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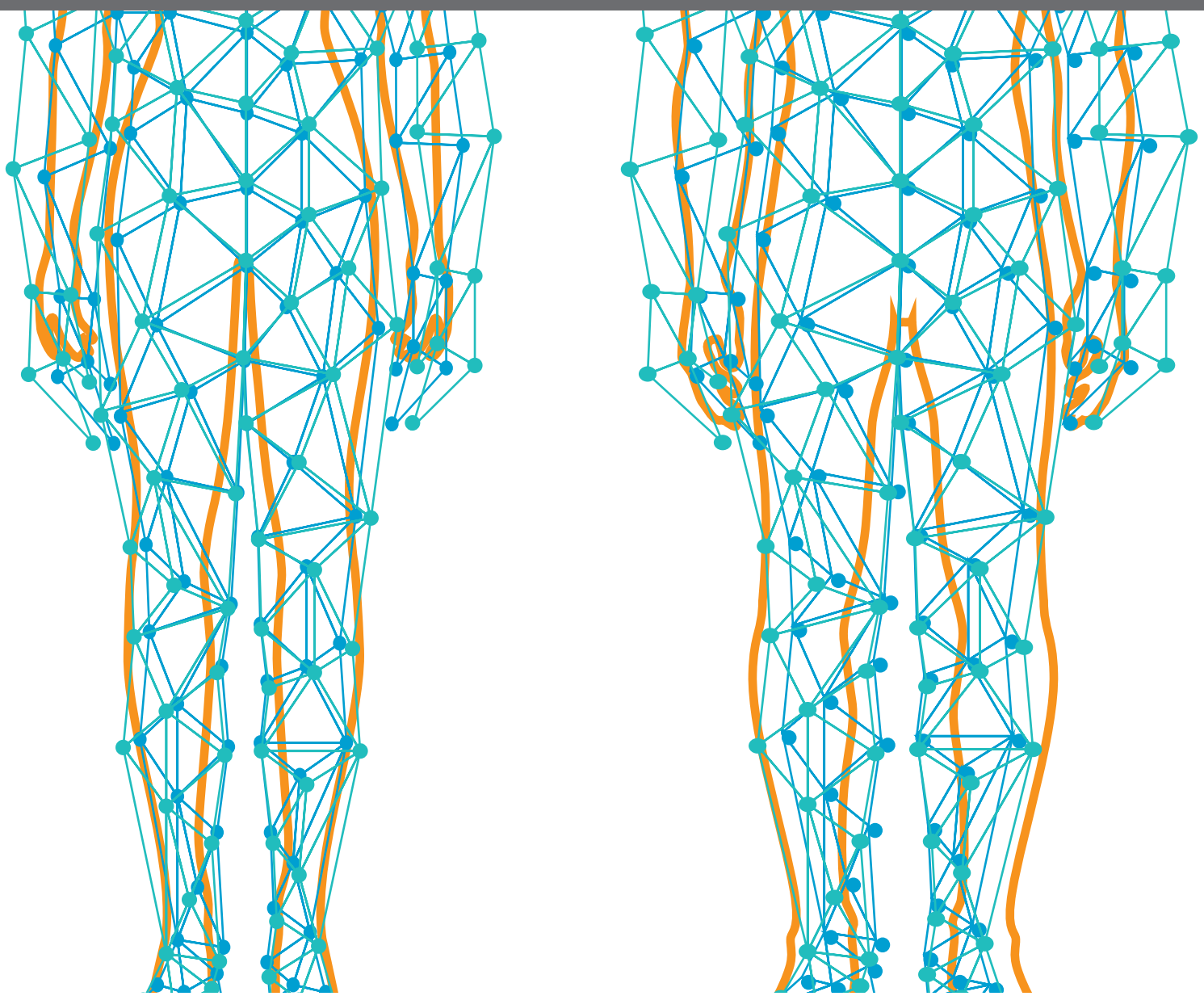

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INSIGHTS IN DERMATOLOGY: 2021

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Table of Contents

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Booster Effect of a Natural Extract of *Polypodium leucotomos* (Fernblock®) That Improves the UV Barrier Function and Immune Protection Capability of Sunscreen Formulations

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Background: Novel approaches to photoprotection must go beyond classical MED measurements, as discoveries on the effect of UV radiation on skin paints a more complex and multi-pronged scenario with multitude of skin cell types involved. Of these, photoimmunoprotection emerges as a crucial factor that protects against skin cancer and photoaging. A novel immune parameter is enabled by the precise knowledge of the wavelength and dose of solar radiation that induces photoimmunosupression. Natural substances, that can play different roles in photoprotection as antioxidant, immune regulation, and DNA protection as well as its possible ability as sunscreen are the new goals in cosmetic industry.

Objective: To analyze the effect of a specific natural extract from *Polypodium leucotomos* (PLE, Fernblock®), as part of topical sunscreen formulations to protect from photoimmunosuppression, as well as other deleterious biological effects of UV radiation.

Methods: The possible sunscreen effect of PLE was analyzed by including 1% (w/w) PLE in four different galenic formulations containing different combinations of UVB and UVA organic and mineral filters. *In vitro* sun protection factor (SPF), UVA protection factor (UVA-PF), contact hypersensitivity factor (CHS), and human immunoprotection factor (HIF) were estimated following the same protocol as ISO 24443:2012 for in vitro UVA-PF determination.

Results: PLE-containing formulations significantly reduced UV radiation reaching to skin. Combination of UVB and UVA filters with PLE increased SPF and UVAPF significantly. PLE also increased UV immune protection, by elevating the contact hypersensitivity factor and the human immunoprotective factor of the sunscreen formulations.

Conclusion: This study confirms the double role of PLE in photoprotection. Together to the biological activity shown in previous works, the UV absorption properties of PLE confers a booster effect when it is supplemented in topical sunscreens increasing the protection not only at level of erythema and permanent pigment darkening but also against two photoimmunoprotection factors.

Keywords: ultraviolet radiation, sunscreens, *Polypodium leucotomos* extract, booster effect, human immunoprotection factor, sun protection factor, UVA protection factor

INTRODUCTION

The skin is the first barrier of the organism against aggression. Biological aggression usually brings to mind pathogens, e.g., viruses or bacteria. However, the skin also protects from mechanical and radiation damage. The latter is crucial due to the constant irradiation of the Earth's surface with sun rays, which contain a significant amount of UV photons. UV radiation comprises photons from ∼100 to 400 nm in wavelength, of which those between 290 and 400 nm have significant biological effects at earth surface. Although some effects on human skin are beneficial [for example, vitamin D synthesis (1)], most are deleterious. Short-term deleterious effects are sunburn, oxidative stress as well as skin pigmentation changes leading in the long-term an increase in photoaging damage as well as the probability of photocarcinogenesis. Sunburn refers to the destruction of epidermal tissue, and includes redness and swelling, blood vessel dilation and inflammation. These processes are collectively known as erythema. Photoaging refers to the inability of the skin to recover its mechanical properties (particularly elasticity) after sun exposure, and it is related to increased metalloprotease and elastase secretion (2), and an overall decrease in the ability of the skin to locally replenish sunburnt populations (3). Finally, photocarcinogenesis refers to the malignant transformation that UV radiation may cause on skin cells, either by direct DNA mutation (mainly formation of T-T dimers) or by indirect means [oxidative damage to the DNA, recently reviewed in Lee et al. (4)].

Since the beginning of the development of skin photoprotection, prevention of the generation erythema is the most extended indicator when measuring the efficacy of photoprotective measures, particularly sunscreens. Different international organizations, including The American Food and Drug Administration (FDA) or European Cosmetics Agency have provided guidelines that control the efficacy of sunscreens by means of *in vivo* and *in vitro* methods, that are finally described in the standards ISO 24444:2019 and the ISO 24443:2012 respectively. Although the European regulatory body (EMA) classifies sunscreens as cosmetic products [Regulation (EC) No 1223/2009], it does require the manufacturer to provide truthful and useful information regarding its use [Regulation (EU) No 655/2013], which, in practical terms, enforces the use of SPF or a similar parameter.

The aforementioned regulations do, in fact, enforce the SPF as the single standardized regulatory element that controls the efficacy and marketability of a given sunscreen or photoprotective measure. However, recent research has clearly demonstrated that sub- Minimal Erythemal Doses (MED) doses of UV radiation, or even longer wavelengths can also have profound effects on the skin (5). These effects range from adaptive responses such as increased melanin production (6) to skin damage. This is particularly true for UVB sub-MED, which may cause cancer (7) and local immunosuppression (8, 9), even at very low (<15% MED) doses (10, 11).

Given that immunosuppression is one of the hallmarks of cancer (12), it is possible that a sunscreen that displays excellent SPF may not prevent photocarcinogenesis due to the combination of subMED skin damage including oxidative stress and immunosuppression, particularly in cancer-prone individuals. Poon et al. (11) demonstrated that prevention of immunosuppression by sunscreens in humans is not related to the MED, as this parameter depends much more strongly on UVB than UVA. This suggests that MED measurements (the basis for SPF determination) do not accurately estimate the dose of UV that may cause immunosuppression. This makes it necessary to widen the type of measurements to ensure that novel formulations exert more biological effects, thereby preventing photoimmunosupression. De Fabo and Noonan described that skin immunosuppression in terms of inhibition of contact hypersensitivity (CHS) in mice depends on the applied wavelength, with a peak between 260 and 290 nm and declining until 320 nm (13). This was done using contact irritants, 2-chloro-l,3,5-trinitrobenzene (TNCB) or 1-fluoro-2,4-dinitrobenzene (DNFB), in the presence of UV light in a murine model (14). The irritants were applied on the ear, then UV of different wavelengths and intensities were applied, and ear swelling was measured. Swelling was a proxy for inflammation, which is a mark of an efficient immune response, and used to determine the UV action spectra at different wavelengths. More recently, another study described that UV radiation induces immunosuppressive effects in human skin using *in vivo* analysis of the nickel model of recall contact hypersensitivity, which works in a similar manner as CHS, but uses nickel as the irritant. Again, swelling is used as a mark of an efficient contact response that is decreased by UV light. In this work, two major bands were identified, one at 300 nm (UVB) and another around

Abbreviations: MED, minimal erythematous dose; UV, ultraviolet; PLE, *Polypodium leucotomos* extract; SPF, sun protection factor; UVA-PF, ultraviolet-A protection factor; LC, Langerhans cells; PMMA, Polymethylmetacrilate; CHS, Contact HiperSensitivity; HIF, Human Immunoprotection Factor; PUVA, psoralens-UVA.

370 nm (UVA) (15). The latter is more pertinent when discussing immunosuppression, so due to the highest solar UVA radiation reaching the earth surface, it can be explained the broadband UV dependence of immunosuppression due to the combined effect of UVA together to UVB. Thus, the assay described above was the basis of the human immune protection factor (HIF) used here. Based on these and other lines of evidence, there is a general trend toward the development of sunscreens containing natural components that may act as physical sunscreens while also providing a biological role as antioxidant or immunomodulator, alone or in combination with chemical sunscreens of proven efficacy to decrease erythema.

Fernblock® (from here on referred to as PLE) is a hydrophilic natural extract from *Polypodium leucotomos* with proven efficacy over other extracts of the same fern due to the extraction method (16). It has been extensively studied in photobiology of the skin due to is due to its antioxidant properties against reactive oxygen species production induced by UV radiation, protective activity to DNA damage, and prevention of UV-mediated apoptosis, necrosis and degradative matrix remodeling as well as acting as a potent immunomodulator [reviewed in Parrado et al. (17)]. The presence of a high percentage of phenolics (mainly benzoates and cinnamates, like caffeic acid and its derivative ferulic acid) confers also UV absorption properties of PLE (18), PLE exerts a dual role on skin, acting as a biological agent with active properties and as a sunscreen.

This work aims to analyze the absorption properties of PLE and its combination with organic and mineral sunscreens to enhance the sunscreen capability of the organic and mineral component of the formulation, and whether its inclusion in galenic formulations boosts immunoprotective parameters used as ISO standards.

MATERIALS AND METHODS

PLE Formulation

Fernblock®, PLE, is a controlled hydrophilic extract from the leaves of *P. leucotomos* (16). PLE was provided as lyophilized powder by Cantabria Labs, Madrid, Spain. The powder was stored at room temperature shielded from light following the supplier's instructions. Stock solutions were prepared at a concentration of 6.25, 12.5, 25, and 50 μg/ml mg/ml in distilled water.

Preparation of Sunscreen Formulation

PLE extract was included in four experimental galenic formulations similar to those used in sunscreen formulations, containing different types of UVB and UVA organic and mineral filters together with PLE at 1% (**Table 1**). For each full sunscreen formula, three different compositions were assayed in each case: (1) PLE alone; (2) Filters; (3) Full sunscreen: PLE + filters.

Absorbance Properties of PLE Analysis

To analyze the potential of PLE as sunscreen, four different concentrations of PLE (6.25, 12.5, 25, and 50 μg/ml) were diluted in distilled water under constant stirring at 25–30°C and their absorbance in the UV-visible (250–700 nm) were measured in quartz UV-transparent cuvette in a UV-visible spectrophotometer Shimazdu UV-1607 (Shimazdu Co., Kioto, Japan).

TABLE 1 | Different combinations of UVB and UVA organic and mineral filters used to prepare the experimental sunscreens used throughout the study.

SAMPLE 1	Ethylhexyl Salicylate, Octocrylene, Butyl Methoxydibenzoylmethane, Ethylhexyl Triazone, Diethylamino Hydroxybenzoyl Hexyl Benzoate, Phenylbenzimidazole, Sulfonic Acid, Tris-Biphenyl Triazine (nano), Decyl Glucoside, Butylene Glycol, Disodium Phosphate, Xanthan Gum, Aqua.
SAMPLE 2	Phenylbenzimidazole, Sulfonic Acid, Disodium Phenyl Dibenzimidazole Tetrasulfonate, Octocrylene, Butyl Methoxydibenzoylmethane, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Cyclopentasiloxane, Titanium Dioxide (nano), Polyglyceryl-3 Polydimethylsiloxyethyl Dimethicone, Aluminum Hidroxide, Stearic Acid, Tris-Biphenyl Triazine (nano), Decyl Glucoside, Butylene Glycol, Disodium Phosphate, Xanthan Gum, Aqua.
SAMPLE 3	Ethylhexyl Salicylate, Ethylhexyl Triazone, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Diethylamino Hydroxybenzoyl Hexyl Benzoate, Cyclopentasiloxane, Titanium Dioxide (nano), Polyglyceryl-3 Polydimethylsiloxyethyl Dimethicone, Aluminum Hidroxide, Stearic Acid, Zinc Oxide (nano), Triethoxycaprylylsilane, Tris-Biphenyl Triazine (nano), Decyl Glucoside, Butylene Glycol, Disodium Phosphate, Xanthan Gum, Aqua.
SAMPLE 4	Ethylhexyl Methoxycinnamate, Octocrylene, Diethylamino Hydroxybenzoyl Hexyl Benzoate, Butyl Methoxydibenzoylmethane, Ethylhexyl Triazone, Zinc Oxide (nano), Triethoxycaprylylsilane, Titanium Dioxide (nano), Alumina, Simethicone, Aqua.

PLE was analyzed including a concentration of 1% of PLE in the four formulations.

Protection Factors of Sunscreen Formulations

The spectral transmittance of the different formula containing only PLE, filters or full sunscreen were calculated as well as the spectral absorbance of them. Absorbance was calculated for each wavelength in the interval of 290–400 nm following the formula:

$$\text{Absorbance} = -Log(\text{Transmittance})$$

The protection factor of each formulation were calculated *in vitro* by measuring the spectral transmittance of formulas in the UV range (290–400 nm) in PMMA plaques (Schönberg, Hamburg, Germany), following the protocol indicated in ISO 24443:2012 for the analysis of the UVA protection factor for sunscreens (19).

Briefly, transmittance spectra was determined by evenly spreading 1.3 mg/cm^2 of the product over a 5 × 5 cm^2 PMMA plate. The plate had a roughness simulating that of real skin relief, as indicated by the aforementioned ISO regulation. After 15 min in the darkness, the sample was placed on the sensor (Ulbrich sphere type) of a Macam SR-2210 double monochromator spectroradiometer (Macam, Scotland), and illuminated with a 300 W Oriel solar simulator (Oriel, Newport Corporation, Irvine, US). Spectral transmittance spectrum was analyzed at 1 nm intervals in the range 290–400 nm, referred to the spectral transmittance of the blank PMMA plate coated with glycerol.

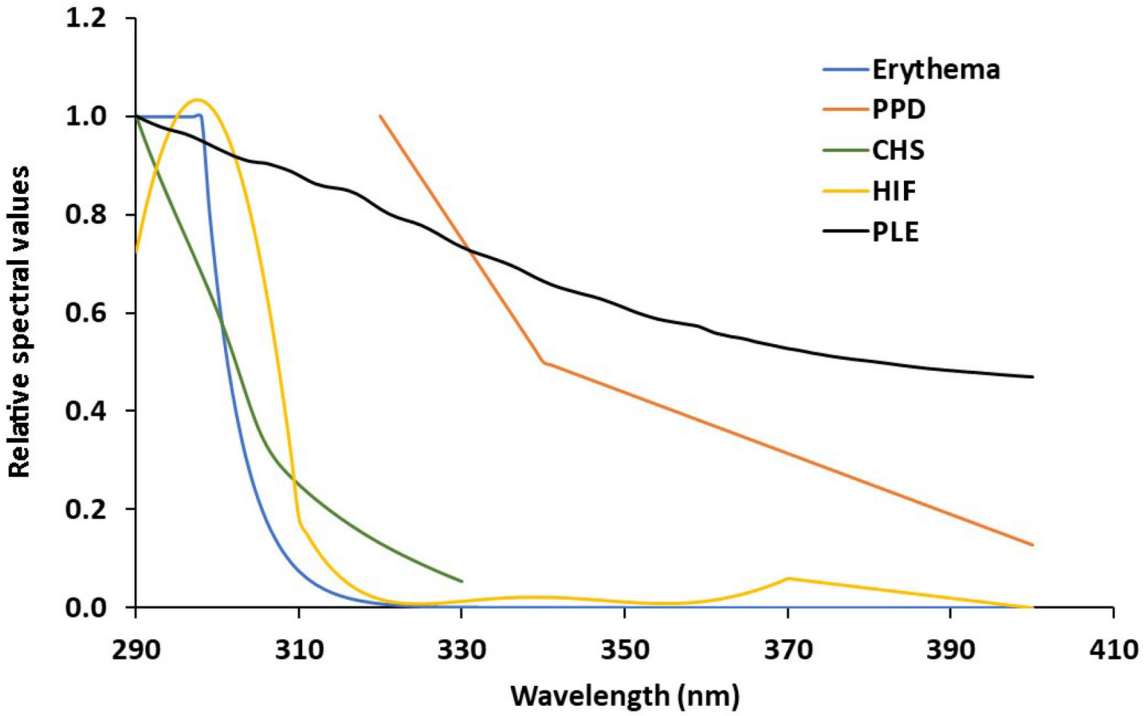

FIGURE 1 | Spectral absorbance of PLE related to the different action spectra analyzed (Erythema; PPD, Persistent Pigment Darkening; CHS, Contact Hypersensitivity factor; HIF, Human Immunoprotection Factor; PLE, *Polypodium leucotomos* extract, Fernblock®).

Sun protection factor (SPF) was calculated as the protection potential against skin erythema (14) using the following formula:

$$SPF = \frac{\int_{290}^{400} (E_\lambda \times \varepsilon_\lambda)}{\int_{290}^{400} (E_\lambda \times \varepsilon_\lambda \times T_\lambda)}$$

In which SPF, sun protection factor; E, spectral irradiance of solar simulator; ε, relative effectiveness for erythema; T, Transmittance of the sample.

UVA protection factor was also calculated by determining the action spectrum of Persistent Pigment Darkening as described in ISO 24443:2012. To determine protection against photo immunosuppression, sample transmittance in the UV region was pondered by the action spectra published for the contact hypersensitivity (14), and human skin photoimmunosuppression (15). The action spectra data was analyzed at 1 nm intervals in the range 290–400 nm from cubic spline interpolation between the data points of the respective action spectrum to provide values of 1 nm increments. The integral in the equation was replaced by the sum of the data obtained at each step of 1 nm. Spline interpolation was carried out using Table curve 2D 5.0. Error in the interpolation and 1 nm-step data sum is estimated to be <5%. The action spectrum of erythema, Persistent Pigment Darkening, contact hypersensitivity, and human skin photoimmunesupression are shown, compared to the absorbance of aqueous extracts (50 μg/ml) of PLE are shown in **Figure 1**.

Critical wavelength was also determined. Critical wavelength defines the performance of a sunscreen in the whole UV solar spectrum and it is identified as the upper limit of the spectral range from 290 nm on, covering 90% of the area under the extinction curve of the whole UV range between 290 and 400 nm. When the critical wavelength is 370 nm or greater, the product is considered broad spectrum, which denotes balanced protection throughout the UVB and UVA ranges.

Statistics

Data regarding Protection Factor for different UV skin biological effects (erythema, PPD, CHS and HIF) as well as critical wavelength, based on UV transmittance was determined in three different places of 25 cm^2-PMMA plaques. Three plaques were used for each treatment (glycerol, base formula + PLE extract 1% and full formula with combination of PLE with sunscreens). Protection factors are determined using a total of nine sub-replicates. From the nine replicates, the mean ± SD was calculated. In order to accept the final protection factor with this number of replicates, the confidence interval of 95% had to be lower than 17% with respect to the mean value. Booster effects have been analyzed in terms of % of change of biological factors between the full formulations compared to PLE 1% alone in base formula. Comparison

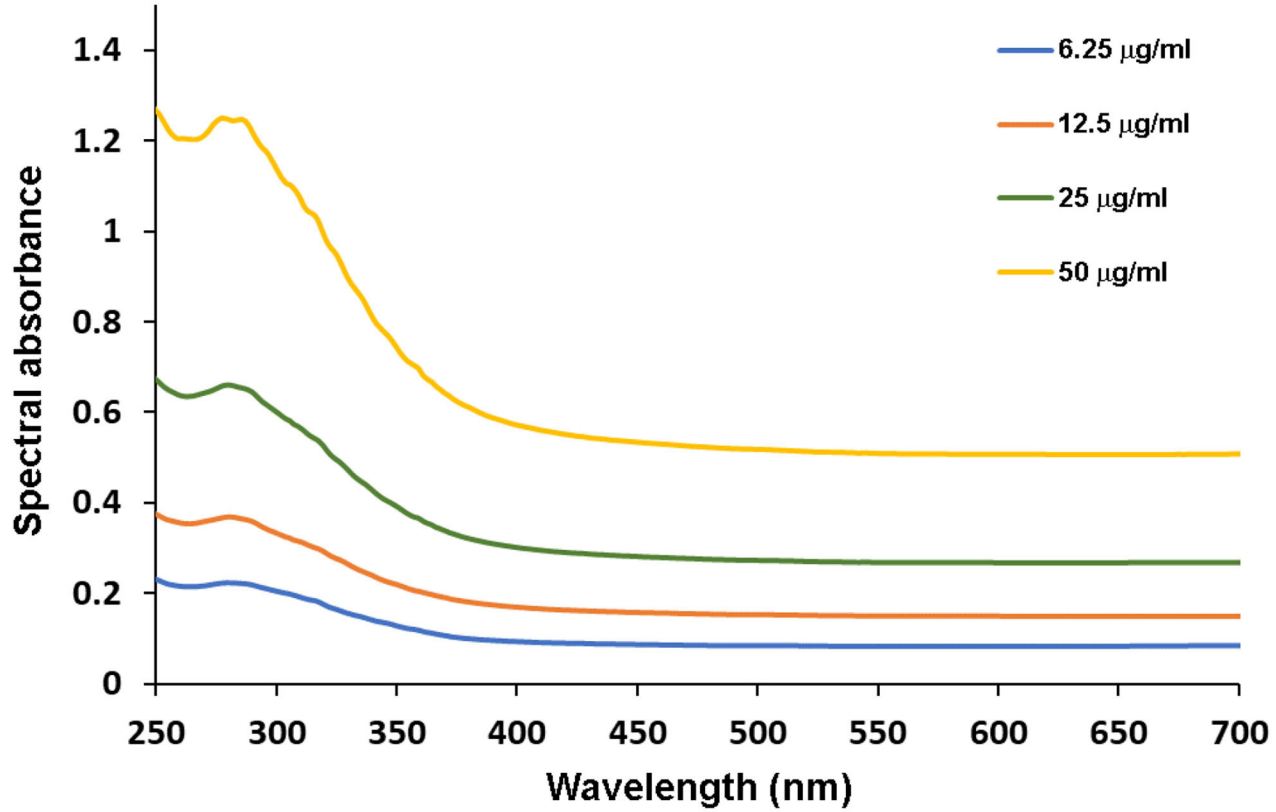

FIGURE 2 | Spectral absorbance in the UV and visible spectral regions (250–700 nm) of different concentrations of the PLE extract diluted in distilled water at different concentrations (6.25, 12.5, 25, and 50 μg/ml). Data is representative of three independent experiments made in triplicates.

of the mean protection factors between PLE alone with respect to the full sunscreen formula has been made using Student's *t*-test. Significance was considered ≤ 0.05 as per the standard of the field. Statistics were performed using 2019 Excel Program.

RESULTS

UV Absorbance of PLE

The different concentrations of PLE diluted in distilled water increased absorbance in the UV spectrum, gradually from 250 to 400 nm, reaching a peak around 290 nm (**Figure 2**). Due to the brownish color of the different concentrations of PLE extract in water, their absorbance in the visible region also increased, with values reaching 0.6 absorbance units along the entire visible spectrum (400–750 nm; **Figure 2**).

PLE Booster Effect in Different Sunscreen Galenic Formulations

The booster effect of PLE in galenic formulations of full sunscreens is shown in **Figure 3**. 1% PLE alone (in the same excipient formula as that of full sunscreen) displayed a gradual decrease in UV transmittance from 290 to 400 nm, reaching the bottom value at ≈310 nm (**Figures 3A–D**). The combinations of filters alone significantly decreased UV transmittance up to 400 nm, with a wider range of low values from 290 to 390 nm. The booster effect of PLE is clearly observed when absorbance is analyzed for all four different combinations of UV filters (**Figures 3E–H**). One percent of PLE alone (in the same excipient formula as that of full sunscreen) displayed an absorbance peak at 308 nm of ≈0.4 absorbance units in the different galenic formulas. When PLE was combined with the UV filters, the absorbance curve was significantly enhanced in all cases, leading to absorbances >2 as shown in **Figures 3E–H**.

Next, we used the transmittance curves to calculate the protection factor by ponderation with the different action spectra. Results are shown in **Table 2**. PLE markedly increased SPF in the different formulas. In case of formulation 1, thought the PLE alone has a SPF of 2.52 when PLE is included in the final formulation increased SPF from 37.99 to 42.22. In case of sample 3, PLE showed a SPF of 1.55 but in this case, when it is combined with filters, SPF is increased over 20%. So, the average booster effect in SPF obtained from the four different combinations was 14.16% (**Table 2**).

When we estimated UVA-PF, the enhancer effect of PLE in full sunscreen was lower than that obtained for SPF, but still significant, with a medium UVA-PF increase of 9.34%. This is consistent with the lower absorbance of PLE

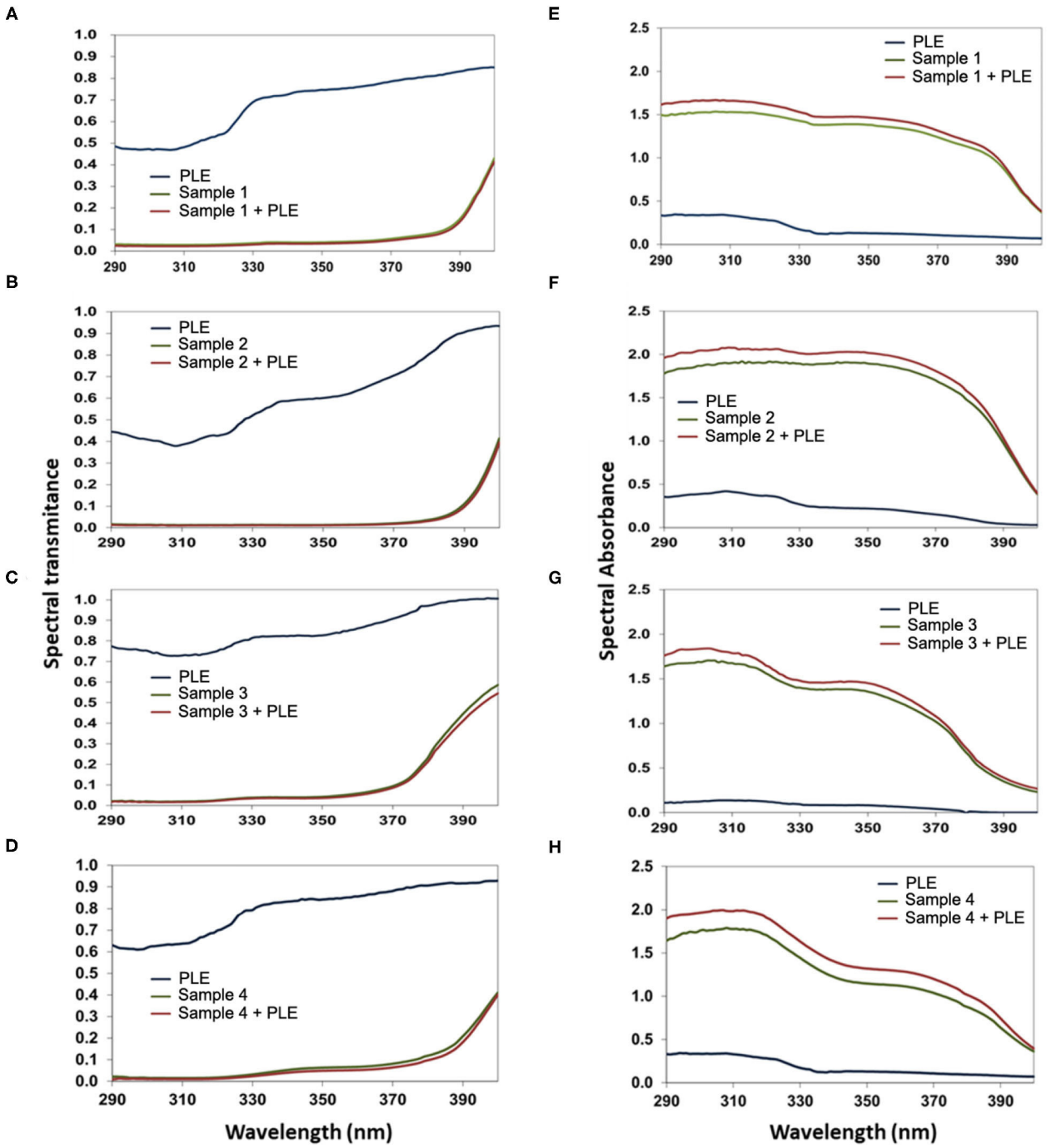

FIGURE 3 | Spectral transmittance **(A–D)** and absorbance **(E–H)** of PLE alone, sample 1 **(A,E)**, 2 **(B,F)**, 3 **(C,G)**, and 4 **(D,H)** without PLE, or a combination of both compared to the formula containing (Sample 1–4) only filters and the formula containing only PLE (Sample 1–4+PLE). Please refer to the Materials and Methods section and **Table 1** for details on the formulations used in each case.

in this region of the light spectrum. Nevertheless, all the formulas analyzed showed critical wavelengths over 370 nm. Thus, PLE maintains the typical broad spectrum of these sunscreens formulas.

PLE Boosts Photo Immunoprotection-Related Action Spectra

We next examined the ability of these preparations to prevent photoimmunosuppression. To do this, we analyzed two different

TABLE 2 | Solar protection factors, UVA protections factors, the relation between UVA/UVB, the critical wavelength (CW), the contact hypersensitivity factor (CHS), and the human immunoprotection factor (HIF) for different combinations of filters with PLE (full sunscreen) compared with the formula containing only filters and the formula containing only PLE.

SAMPLES		SPF	CHS	HIF	UVAPF	CW
Sample 1	**Filters**	37.99 ± 3.58	38.91 ± 3.88	27.44 ± 3.4	18.82 ± 2.72	383 ± 0.15
	PLE	2.52 ± 0.10	2.37 ± 0.017	1.90 ± 0.12	1.63 ± 0.17	380 ± 0.30
	Full sunscreen	42.22 ± 5.12	42.95 ± 5.28	30.09 ± 2.73	20.68 ± 1.23	383 ± 0.21
	Boost (%)	**11.13**	**10.38**	**9.65**	**9.88**	–
Sample 2	**Filters**	67.17 ± 9.44	71.03 ± 10.81	51.23 ± 5.14	30.09 ± 2.71	383 ± 0.20
	PLE	2.36 ± 0.06	2.35 ± 0.06	1.79 ± 0.15	1.52 ± 0.19	371 ± 0.22
	Full sunscreen	75.62 ± 9.55	82.84 ± 7.54	60.23 ± 6.15	32.38 ± 2.21	382 ± 0.18
	Boost (%)	**12.58**	**16.62**	**17.56**	**7.61**	–
Sample 3	**Filters**	38.53 ± 3.07	39.43 ± 3.78	15.79 ± 1.28	8.52 ± 0.31	376 ± 0.25
	PLE	1.55 ± 0.05	1.51 ± 0.05	1.53 ± 0.04	1.42 ± 0.01	375 ± 0.21
	Full sunscreen	46.49 ± 3.53	47.71 ± 3.63	17.49 ± 1.36	9.44 ± 0.44	378 ± 0.01
	Boost (%)	**20.66**	**21.00**	**10.77**	**10.80**	–
Sample 4	**Filters**	66.85 ± 6.15	70.72 ± 3.21	25.85 ± 2.61	15.78 ± 1.27	378 ± 0.31
	PLE	1.48 ± 0.01	1.48 ± 0.01	1.56 ± 0.02	1.48 ± 0.03	378 ± 0.30
	Full sunscreen	75.05 ± 10.79	79.18 ± 11.71	27.10 ± 3.47	17.21 ± 1.97	378 ± 0.22
	Boost (%)	**12.26**	**11.96**	**4.83**	**9.06**	–
Average boost (%)		**14.16**	**14.99**	**10.70**	**9.34**	–

action spectra. First, we estimated its effect on CHS (14). CHS photoprotection displayed by the four different formulas was quite similar to that of SPF; the addition of PLE to the formula led to increased CHS protection factor (14.99%), suggesting that the booster effect of PLE in CHS is comparable to that of SPF. We also estimated the HIF index, which has a higher contribution of UVA wavelengths than that of erythema and CHS (15). Thus, we found an improvement degree of protection in the sunscreen combinations, though less than the CHS index. The enhancer effect of PLE was lower compared to the other biological effects. UVA absorption of the product allows us to predict a mean enhancer effect ≈9.34% (**Table 2**).

DISCUSSION

The present study demonstrates that PLE has broad absorption spectrum with a gradual increase up to 290 nm that correlates with that of the erythematous spectrum. It also correlates well with photoimmunoprotection spectra at different UV wavelengths. The fact that PLE absorbs UV photons by itself (**Figure 1**) allows us to predict that it will display broadband protection along the UV spectrum, although this is likely to be more significant at UVB wavelengths. A concentration of 1% PLE alone in the formula leads to a mean SPF, CHS, and HIF around 2, which could be considered as a booster effect. Strikingly, the addition of PLE to different combinations of organic and mineral sunscreens has a booster effect with a mean increase of SPF, CHS and HIF factor over 10 arbitrary units (sample 2, **Table 2**) and more than 10% of average boost of all factors.

Use of natural products in cosmetics is a current trend; thus, the discovery of new UV natural absorbing compounds will reduce need for high concentrations of organic chemical sunscreens in formula and reinforce the biological protection. This is important as some organic components used may have deleterious effects on both humans and the environment. Also, the reduction of these kinds of ingredients improves the galenic formulations and consequently could enhance the photoprotection adherence. Other natural compounds similar to the PLE extract used here may function as UV filters against induced damage in keratinocytes (20); some isoflavones, like genistein and daidzein, also block UVB induced skin burns in human and provide protection against photocarcinogenesis and photoaging (21). Other natural sunscreens are mycosporine-like amino acids synthetized by marine algae, fungi, and lichens. The compounds are endowed with extremely high UVB/UVA extinction coefficients and display negligible toxicity, high photo-stability and antioxidant properties (22–24).

The significant barrier activity of PLE complements the current state of the art of this compound, which is mainly related to photoprotection in terms of erythema, DNA protection and permanent pigmentation darkening (PPD). The data contained herein strongly suggests that it provides an additional layer of protection by curbing photoimmunosuppression. Validation of the evaluation of action spectra to provide relevant biological information also suggests the potential immunoprotective usefulness of other biological sunscreens, e.g., mycosporine-like amino acids (25). The overarching concept is to incorporate these biologically active natural sunscreens to a global strategy that includes oral photoimmunoprotection and use of multi-functional sunscreens.

In this regard, Schalka and Donato recently reported that the PLE incorporation to sunscreens markedly decreased UV-mediated sunburn and CD1a+ depletion in human volunteers

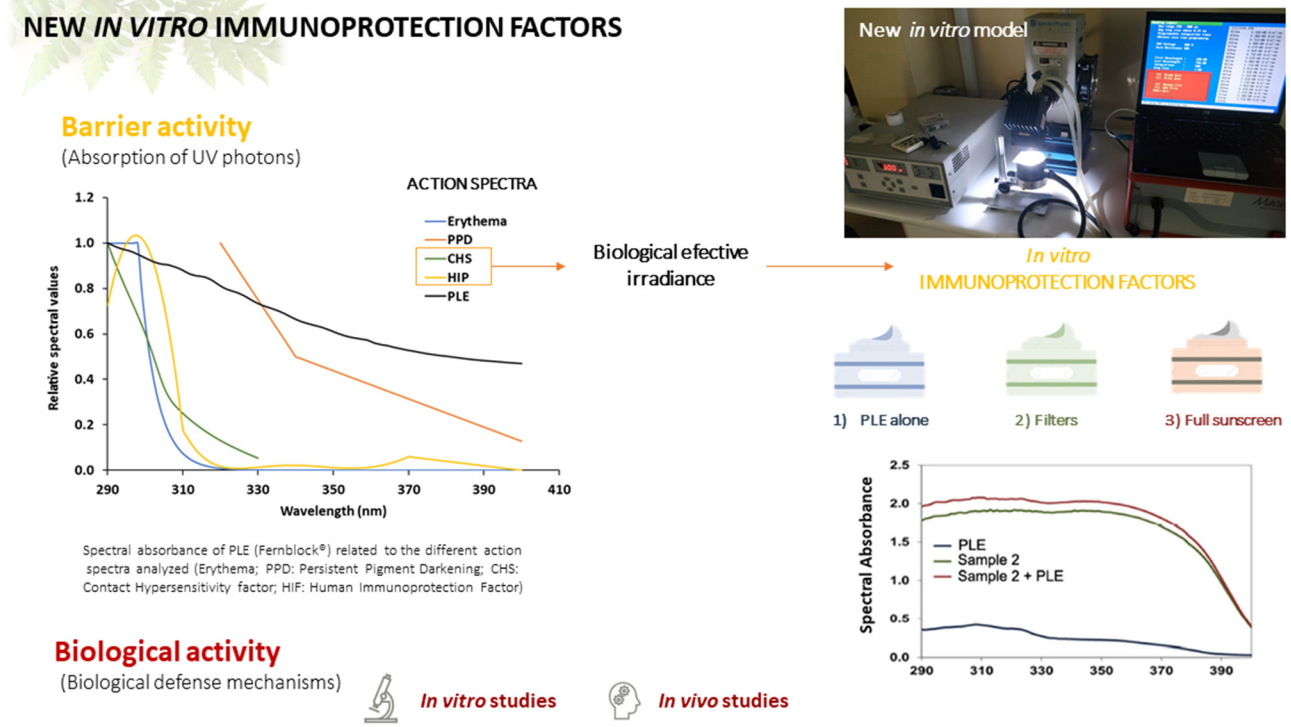

FIGURE 4 | Summary of the effect of PLE (Fernblock®) on diverse action spectra related to erythematous photoprotection and photoimmunoprotection. PLE is endowed with both types of activity when incorporated to canonical sunscreen formulations.

(26). Although this work did not analyze the absorption of PLE across the skin, the data confirms the potentially beneficial effect of incorporating PLE into sunscreen formulations in order to reduce the clinical and biological deleterious effects caused by cutaneous exposure to solar radiation.

In all, the enhancer effect of PLE and its ability to boost both erythemal and photo-immunoprotection potential of conventional sunscreens confirms the data obtained using orally ingested PLE. It is important to highlight that immunosuppression, although more severe at UVB wavelengths in *in vitro* settings, is actually more relevant at UVA wavelengths, due to the fact that many more UVA photons reach the surface of the Earth (15). This is the main difference between the CHS measurements derived from the data published in De Fabo and Noonan (14), referred here as CHS; and the findings of Damian et al. (15), which form the basis of the HIF index. CHS was determined in the 250–320 nm range, which is UVB and correlates with erythema. Conversely, HIF includes the contributions of UVB (in this part of the UV spectrum, it is indeed comparable to CHS), but also UVA, which is likely more significant for immunosuppression despite inducing much less erythema than UVB.

Even at lower effective concentrations, PLE has a positive effect that predicts not only its efficacy as a sunscreen, but also has biological value. *In vitro*, PLE protects human skin cells subjected to UV irradiation (27). Such protection extends to dendritic cells (28). Importantly, *trans*-urocanic acid isomerization to the *cis* form as been proposed as a crucial feature of immunosuppression not only by UVB photons, but also by UVA photons in the presence of psoralens (29). In good agreement with its photoimmunoprotective effect, PLE decreases trans-UCA isomerization (30). It is feasible that PLE absorbs some of the deleterious UV photons *in situ*, while providing positive feedback signals that protect immune cells, contributing to the photo immunoprotective effect described here.

Taken together with the evidence of oral photoprotection displayed by PLE, the data herein suggest a paradigm change in which physical sunscreens, while efficient, would not be sufficient. Indeed, some evidence indicates that photoaging and photo immunosuppression are not sufficiently curbed by physical photon blockers due to a strong influence of UVA photons in the generation of these biological effects. New generation sunscreens need to promote additional effects, not only with filters, but with compounds that promote both regeneration and/or immunoprotection. Evidently, more research in human patients is needed to complete the assessment of this PLE for incorporation in topical sunscreen formulations, but this early evidence indicates that this could be a mechanism to promote additional beneficial effects, leading to a multi-pronged protection network that includes barrier/photon blocking function as well as anti-inflammatory, anti-aging and immunoprotective biological activity (**Figure 4**).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SG, JA, and AR-L: conceptualization. JA, MG, and EH-C: methodology, investigation, and resources. JA: software, data curation, and formal analysis. SG, MG, EH-C, and AR-L: validation. MV-M, JA, SG, and AR-L: writing—original draft preparation and writing—review and editing. MG, EH-C, SG, and AR-L: supervision. AR-L: project administration. AR-L and SG: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: AR-L belongs to the Innovation and Development Department of Cantabria Labs, which produces Fernblock®. SG is a consultant for Cantabria Labs.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Serum Troponin T Concentrations Are Frequently Elevated in Advanced Skin Cancer Patients Prior to Immune Checkpoint Inhibitor Therapy: Experience From a Single Tertiary Referral Center

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Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of several human malignancies, particularly metastatic skin cancer. However, immune-related myocarditis (irM), an immune-mediated adverse event (irAE), is often fatal. In the absence of a reliable biomarker, measurement of pre-ICI therapy serum troponin concentration has been proposed to identify patients at risk of developing irM, although real-world studies examining this strategy are lacking. Thus, we retrospectively analyzed the case records of all patients who commenced ICI therapy between January 2018 and December 2019 in a single university skin cancer center ($n = 121$) to (i) determine the incidence of irM, (ii) establish the frequency of pretreatment serum hsTnT elevations, and (iii) to establish whether this identified patients who subsequently developed irM. Only one patient developed irM, resulting in an overall incidence of 0.8%. Pretreatment hsTnT was measured in 47 patients and was elevated in 13 (28%). Elevated serum hsTnT concentrations were associated with chronic renal failure ($p = 0.02$) and diabetes ($p < 0.0002$). Pretreatment hsTnT was not elevated in the patient who developed fulminant irM. Pre-immunotherapy serum hsTnT concentrations were often asymptomatically elevated in patients with advanced skin cancer, none of whom subsequently developed irM during ICI therapy. However, large studies are required to assess the positive and negative predictive values of hsTnT for the development of irM. In the meantime, elevated hsTnT concentrations should be investigated before initiation of immunotherapy and closely monitored during early treatment cycles, where the risk of irM is greatest.

Keywords: myocarditis, immune checkpoint inhibition, melanoma, non-melanoma skin cancer, troponin

INTRODUCTION

Immunotherapy, targeting specific immune checkpoints including cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD1), and programmed cell death ligand 1 (PD-L1) has revolutionized the treatment of both locally advanced and metastatic melanoma and non-melanoma skin cancer (1, 2). As a result, there have been dramatic improvements in progression-free (PFS) and overall survival (OS), particularly in metastatic melanoma, with 5-years OS rates of over 50 and 44% for those treated with combined anti-CTLA4 and anti-PD1 therapy or anti-PD-1 monotherapy, respectively (3). Furthermore, the use of checkpoint inhibitors to prevent melanoma recurrence (4, 5), the adjuvant setting, is already leading to their increased use.

However, any decision to commence immune checkpoint inhibitor treatment must include a careful assessment of treatment-associated risks, particularly in the adjuvant setting where there is no radiological evidence of residual tumor. In fact, due to the lack of reliable biomarkers, it is not currently possible to predict which individual patients with fully resected high-risk metastatic melanoma will develop disease recurrence. Reassuringly, the safety profile of pembrolizumab is similar irrespective of whether it is administered in the adjuvant or palliative setting (5) and adjuvant nivolumab has a superior safety profile to ipilimumab in resected stage III and IV melanoma (4).

Immune-related adverse events (irAEs), side effects due to the removal of immune checkpoint inhibition, can essentially affect any tissue but commonly involve the gastrointestinal, endocrine, integumentary, hepatic, and respiratory systems with varying frequencies (6, 7). The majority of these irAEs can be managed with systemic corticosteroids. While cutaneous irAEs are common (8) and may even correlate with treatment response, (9) cardiac irAEs are rare. However, along with neurological irAEs, they account for almost 50 % of fatalities following ICI (10).

Cardiac irAEs often present early during treatment. There is also evidence that the incidence of immune-related myocarditis (irM), with mortality that can exceed 50%, is increasing (10–14). Although the incidence of irM is often cited as <1%, this may in fact be underestimated due to its non-specific initial presentation and rapidly fatal clinical course (15–18). Indeed, the endomyocardial biopsy, the gold standard for the diagnosis of immune-related myocarditis (irM), may also fail to confirm the diagnosis due to the patchy nature of the T-cell infiltrate, centered on areas of myocardial necrosis (19). Given the nonspecific clinical presentation of irM, combined with the lack of highly sensitive and specific diagnostic tests, a recent expert consensus statement emphasized the need for increased clinical awareness of irM (19).

Due to the lack of specific biomarkers for irM, there have been efforts to identify which patients may be most at risk. Lyon et al. (20) suggested that immune combination therapy (anti-PD1 plus anti-CTLA4), preexisting cardiac disease, previous autoimmune disease, and the expression of cardiac antigens in the tumor tissue may all predispose patients to immune checkpoint-mediated cardiotoxic effects (20). The extent to which preexisting cardiac disease predisposes to the development of irM remains unclear (2). For example, although this is often cited as a potential risk factor, a database analysis of over 100 patients with irM did not reveal widespread reporting of preexisting cardiac comorbidities (21). Several studies have reported that more than two-thirds of the cases of irM are in men, suggesting that the male sex may also be an important risk factor (16, 22).

The difficulty in identifying at-risk patients is confounded by the varied clinical presentation of irM, which may result in diagnostic delay. In fact, irM may be asymptomatic or present with symptoms ranging from non-specific fatigue and dyspnea to dysrhythmia and fulminant cardiogenic shock (23, 24). Interestingly, in contrast to several other irAEs, irM often presents shortly after treatment initiation, with the median time from the first infusion to initial symptoms being just over 1 month (25). Moslehi et al. reported that 64% of patients with irM developed the symptoms after the first or second dose of immune checkpoint therapy, although presentation after 33 treatment cycles has been reported (21, 22). Based on a pro-and retrospective register of patients who developed irM, Mahmood et al. found elevated high-sensitivity Troponin T (hsTnT) levels and an abnormal ECG in 94 and 89% of patients, respectively (16). Just over half of the patients had a normal left ventricular ejection fraction on echocardiography, and two-thirds of patients had raised serum n-terminal pro-brain natriuretic peptide (NT-proBNP) levels (16). While cardiovascular MRI using the Lake Louise Criteria has become the widely accepted clinical standard for diagnostic imaging of acute myocarditis (26, 27), its diagnostic performance in irM is still the subject of research and warrants larger studies (19). Given the limited specificity and sensitivity of electrocardiographic, echocardiographic, biochemical, radiological, and histological investigations in suspected irM, making the diagnosis of irM requires a high index of suspicion (19).

In the absence of an evidence-based surveillance strategy for the early detection of irM, routine measurement of serum Troponin concentrations prior to ICI therapy, and prior to cycles 2–4 in high-risk patients, has been proposed (20). Therefore, given that we introduced routine serum hsTnT testing prior to immune checkpoint therapy in 2019, we retrospectively analyzed all patients treated with immune checkpoint therapy between 2018 and 2019 to (i) investigate the incidence of irM, (ii) establish the frequency of pretreatment hsTnT elevations, and (iii) establish whether this identified patients who subsequently developed irM.

METHODS

In order to determine the incidence of irM in our center, we retrospectively analyzed the case notes of all patients in whom treatment with immunotherapy was initiated for locally advanced and/or metastatic melanoma, in both the adjuvant and palliative settings, and non-melanoma skin cancer in 2018 or 2019. All data were anonymized and collated and analyzed after approval by the ethics committee of the University of Luebeck and according to the Declaration of Helsinki principles (AZ 20-216). In addition to routine measurement of serum creatine kinase levels, we began

routinely measuring serum hsTnT concentrations in all patients prior to immunotherapy in 2019. Serum NT-proBNP levels were determined depending on the existence of preexisting cardiac disease and when clinically indicated as part of the assessment of symptoms and signs which may have suggested heart failure. Data on sex and preexisting cardiac disease were collated given that these may be potential risk factors for the development of irM. In addition, age, cancer type, treatment type (anti-PD1, anti-PD-L1, combined anti-CTLA4/anti-PD1) and setting (adjuvant vs. palliative), and baseline electro- and/or echocardiography findings were also recorded. Overall survival (OS) was also calculated and compared between patients with normal vs. elevated serum hsTnT concentrations. Finally, any therapeutic consequences and the treatment of irM were noted. All statistical analyses were performed using Microsoft Excel (version 2019), and survival analyses were calculated using GraphPad Prism (version 8). $P < 0.05$ were considered statistically significant.

RESULTS

Between the 1st of January 2018 and the 31st of December 2019, a total of 121 patients received ICI therapy for locally advanced or metastatic melanoma and non-melanoma skin cancer (**Flowchart**). Eighty-one patients were male, and 40 patients were female, with a mean age of 74 years. The vast majority of the patients (96%) were treated for melanoma. Of these 116 patients, almost two-thirds were treated in the palliative setting for high-risk resected melanoma (stage IV), and the remaining third received ICI therapy in the adjuvant context (**Table 1**). Of the 77 patients receiving palliative treatment, 47 received combined anti-CTLA4 and anti-PD1 therapy, with the remaining patients receiving monotherapy with pembrolizumab (9) or nivolumab (21). Five patients with non-melanoma skin cancer were treated with immune checkpoint inhibitors, two with locally advanced squamous cell carcinoma (cemiplimab, anti-PD1), and three with metastatic Merkel cell carcinoma (avelumab, anti-PD-L1).

As expected, the overall incidence of irM was low (0.8%) and in line with that reported in the published literature (16, 20). Only a single patient developed irM which developed 16 days after the first dose (350 mg i.v.) of cemiplimab for locally advanced squamous cell carcinoma (**Figure 1**). The patient presented with generalized myalgia and malaise. Admission ECG was unremarkable, but the serum hsTnT concentration was markedly elevated at 457 ng/l. Creatine kinase and NT-proBNP were also elevated at 4596 U/L and 901 pg/ml, respectively. His peak hsTnT and NT-proBNP levels reached 2238 ng/l (normal limit < 14) and 1366 pg/ml (normal limit < 486) at 32 and 44 days, respectively, after the first dose of cemiplimab. An echocardiogram revealed left ventricular dysfunction. The patient was admitted to the coronary care unit for monitoring and high-dose immunosuppression with intravenous prednisolone (2 mg/kg). Although the patient declined an endomyocardial biopsy, cardiac MR imaging demonstrated a focal transmural, almost global subendocardial myocardial edema, and an epi- to mid-myocardial enhancement with pericardial involvement, consistent with irM (**Figure 2**). Despite an initial improvement, the patient's condition deteriorated and additional immunosuppression with mycophenolate mofetil (3 g/d) was commenced. The patient's recovery was complicated by *Staphylococcus aureus* sepsis and reactivation of cytomegalovirus infection. Following antibiotic and antiviral treatment, along with tapering of his immunosuppressive therapy, the patient was discharged to a rehabilitation unit after 68 days of in-patient care. Following 4 weeks of rehabilitation, the patient was discharged home but died 4 weeks later of cardiac failure, some 20 weeks after the administration of cemiplimab.

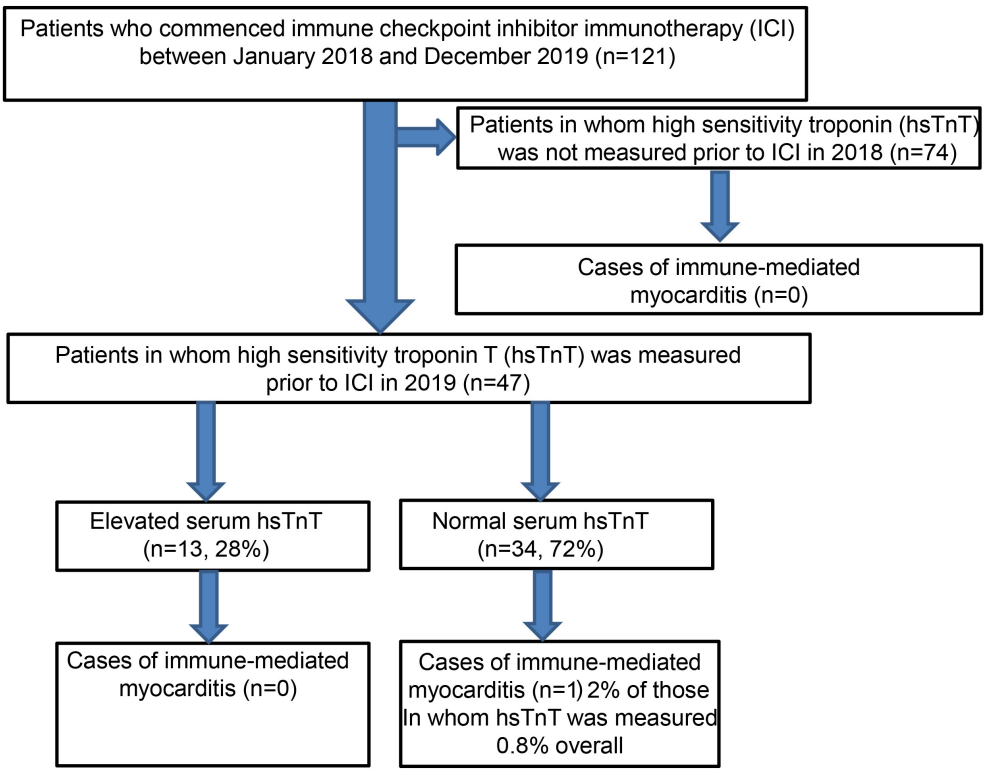
Fifty-six out of 121 patients had preexisting cardiac comorbidities before initiating immunotherapy (**Figure 3A**). Baseline echocardiography was available for 59 patients, which were abnormal in 33 patients. Given that we introduced routine pre-immunotherapy baseline hsTnT measurement in 2019, based on the American Society of Clinical Oncology (ASCO) guidelines (28), we were able to collect data for 47 patients (**Table 2**). HsTnT was measured using the Elecsys Assay (Roche), according to the manufacturer's instructions, and was elevated in 28% of patients (13 out of 47) in the absence of any clinical symptoms. Ten had preexisting cardiac comorbidities (77%), including arrhythmias, chronic heart failure, and coronary artery disease. Five of those patients had additionally elevated baseline creatinine levels (38%), and 46% had elevated NT-proBNP natriuretic-peptide concentrations.

Each patient with elevated serum hsTnT concentration was assessed, often on an emergency basis, and serial hsTnT measurements, ECGs, and echocardiography were performed to exclude acute ischemia (**Table 3**). There was no evidence of acute ischemia in any of the patients, and immunotherapy was subsequently initiated as planned after cardiological evaluation. Reassuringly, none of the patients with elevated pretreatment hsTnT concentrations developed any signs of cardiotoxicity in general or myocarditis in particular during ICI therapy.

Of the 34 patients with normal pretreatment hsTnT concentrations, one patient developed myocarditis. Preexisting diabetes and ischemic heart disease were significantly associated with an elevated serum hsTnT level concentration ($p = 0.02$ and $p < 0.0002$, respectively). There was no association between hsTnT concentration and sex or BRAF status (in patients with melanoma) (Fisher's exact test). Patients with elevated hsTnT levels were significantly older (**Figure 3B**) and had significantly increased serum creatinine levels (**Figure 3C**). HsTnT did not affect OS, although changes in cancer survival were not expected due to the relatively short follow-up period (**Figure 3D**).

DISCUSSION

Immunotherapy can produce significant and durable antitumor responses in a range of locally advanced and metastatic skin cancers (29). The increasing use of immunotherapy is likely to result in clinicians from several specialties being confronted with potentially fatal irAE (30). The life-threatening nature of irM, compounded by the difficultly of prompt recognition to initiate rapid treatment, makes it one of the most challenging irAEs to manage successfully (16). Given that myocarditis frequently



FLOW CHART | Study population.

TABLE 1 | Distribution of sex, cancer type, and therapy setting of all patients.

Sex	**Males-80**	**Females-41**	
Cancer	Melanoma-116	Squamous cell carcinoma-2	Merkel cell carcinoma−3
Therapy setting	Palliative-79	Adjuvant-42	

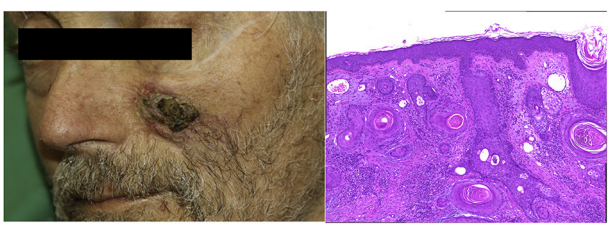


FIGURE 1 | Clinical presentation and histopathology of squamous cell carcinoma. **(A)** 3 × 3 cm solitary subcutaneous hardened plaque with central ulceration. **(B)** Squamous cell carcinoma (H&E staining, 200×).

occurs shortly after initiation of immunotherapy, it is possible that certain patient groups are more susceptible, potentially related to preexisting cardiac risk factors (31).

Evidence from animal models suggests that both CTLA-4 and PD-1 may have protective effects against stress (32–34) and that PD-1 ligands can protect the myocardium. For example, CTLA-4 knockout mice reportedly develop autoimmune myocarditis caused by CD8+T cells, whereas knockout of PD-1 is associated with anti-cTn autoantibody-mediated myocarditis (31). The extent to which pharmacological manipulation of the PD-1/PD-L1 pathway influences the treatment of immune-mediated cardiac inflammation is unclear (31, 35). Consistent with the published literature, irM was rare in our cohort.

Several recent publications have recommended close hsTnT surveillance before the initiation of ICI therapy and during the early treatment cycles, particularly when combined anti-CTLA4 and anti-PD1 therapy is planned (28, 36, 37). In our cohort, this recommendation identified asymptomatic elevations of serum hsTnT levels in 28% of patients with advanced skin cancer. In the single case of irM which occurred, baseline biochemical (including serum hsTnT levels), ECG, and echocardiographic findings were unremarkable. The only identifiable potential risk factor in this patient was being male (2, 22). Importantly, the patient had no history of renal impairment, cardiac disease, or diabetes. Recent studies, both cross-sectional and longitudinal, have highlighted the association between elevated hsTnT levels and diabetes mellitus, consistent with our findings (38, 39). HsTnT has even been proposed as a predictor of incident diabetes (40). The mechanism underlying this association is currently unclear but may be mediated by concurrent chronic renal impairment or reflect microangiopathy-associated structural nerve damage in type II diabetes mellitus (41, 42).

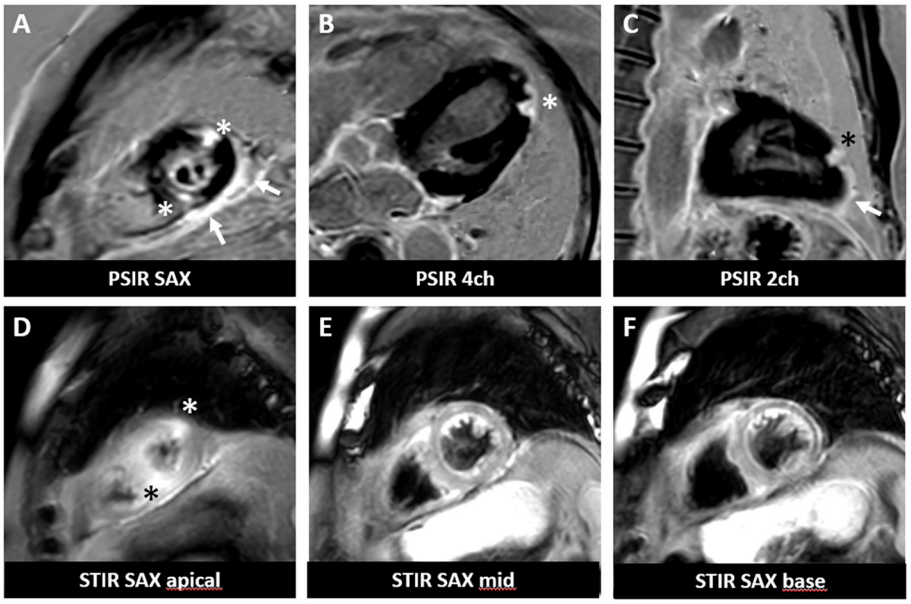


FIGURE 2 | Cardiac magnetic resonance imaging of a patient with irM following a single infusion of cemiplimab. Cardiac MR revealed focal subepicardial to mid myocardial delayed gadolinium enhancement **(A–C)** associated with edema **(D–F)** at the lateral and inferoseptal apex (asterisks) involving the pericardium (arrows) in a delayed gadolinium enhancement sequence performed according to clinical standard. PSIR, phase-sensitive inversion recovery; STIR, short tau inversion recovery; SAX, short-axis view; 4ch, 4-chamber view; 2ch, 2-chamber view.

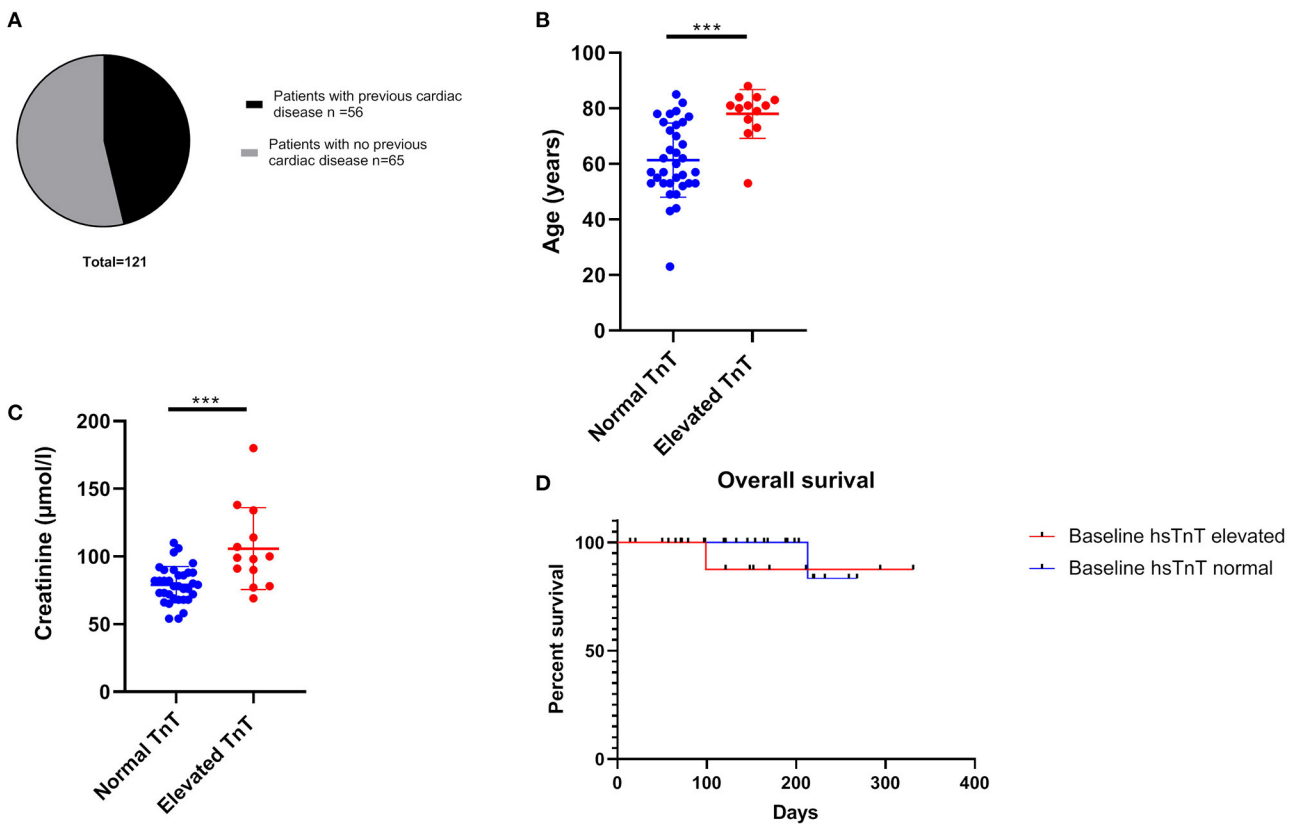


FIGURE 3 | Cardiac co-morbidity status and factors associated with elevated hsTnT concentrations. **(A)** Almost 50% of all patients had pre-existing ischaemic heart disease. Age (**B**) and elevated baseline creatinine concentration **(C)** were significantly associated with increased hsTnT levels ***$p < 0.001$. **(D)** overall survival was not significantly different between the elevated and normal hsTnT groups.

TABLE 2 | Demographics and factors associated with normal and elevated baseline hsTnT concentrations.

Patients' baseline characteristiscs	Troponin elevated	Troponin normal
Sex		
Male	9	22
Female	4	12
Age		
Mean	78	61.4
Range	53–88	23–85
Tumor type		
Melanoma	13	33
Squamous cell carcinoma	0	1
Baseline hsTnT		
Mean (ng/l)	25.5	7.04
Range (ng/l)	14–50.7	5–13.4
Baseline creatinine		
Mean (μmol/l)	105.8	79.1
Range (μmol/l)	69–180	54–110
Echocardiography		
Abnormal echocardiography	7	3
Normal echocardiography	2	13
Not performed	4	18
Previous cardiac disease		
	10 out of 13	8 out of 34
Immunotherapy		
First combinated therapy, afterwards PD-1 Inhibitor	6	13
Nivolumab monotherapy	6	7
Pembrolizumab monotherapy	1	13
Cemiplimab	0	1
BRAF mutation		
BRAF positive	2	13
BRAF negative	11	21
Diabetes mellitus		
Co-existing Diabetes mellitus Type 2	4	1
No history of Diabetes mellitus Type 2	9	33
Therapeutic setting		
Adjuvant	4	18
Palliative	9	16
Immunotherapy related myocarditis (irM)		
Events	0	1

Elevated cardiac biomarkers, including hsTnT, have been reported in cancer patients prior to anticancer therapy and are strongly related to all-cause mortality. However, the studies to date have largely included patients with breast, lung, and hematological malignancies (43–45). In one study of over 550 cancer patients, only two (0.4%) patients with advanced skin cancer were included (45). It is therefore of note that over a quarter of the patients in our study had asymptomatic elevated hsTnT levels, the vast majority of whom had metastatic melanoma. The extent to which metastatic melanoma *per se* is associated with increased serum hsTnT concentrations needs to be confirmed in larger studies. Although there was no difference in overall survival between the group with normal and that with elevated hsTnT concentrations, the observation period was too short to allow any conclusions to be drawn on whether patients with elevated pretreatment hsTnT concentrations had a poorer overall prognosis, potentially independent of the development of irM.

In this context, it is particularly interesting to note that the association between irAEs and response to treatment with ICI may be compounded by both a publication and an immortal time bias. Therefore, prospective studies in the adjuvant treatment setting may be best placed to conclusively determine the relationship between toxicity and response in patients undergoing ICI (46). Future multicenter studies should examine the extent to which elevated serum hsTnT concentrations may identify "at-risk" patients not only for irM but also for all-cause mortality. Our study was neither designed nor powered to evaluate the positive or negative predictive value of pretreatment elevated serum hsTnT for the development of irM, which would also require large multicenter studies. Additional limitations of our study include the predominance of a single cancer type (melanoma), the single-center setting, its retrospective nature, and that only one patient developed irM. Moreover, as we only measured pretreatment serum hsTnT concentrations our study does not allow any conclusions to be drawn about the sensitivity or specificity of serum hsTnT concentrations in the diagnosis of irM. Finally, the patient declined an endomyocardial biopsy, which may have shed light on the extent and nature of the immune-cell infiltrate.

Nevertheless, in our experience, pre-therapeutic elevated hsTnT concentrations were not associated with the development of irM. This may provide some reassurance to treating physicians and patients. Given the dramatic increase in the number of cancer patients who are now eligible for treatment with immune checkpoint inhibitors (47), there will inevitably be more patients who develop irAEs. A key challenge over the next decade will be the identification of biomarkers not only to maximize the benefit of immunotherapy among patients receiving it but also to maximize patient safety and optimize treatment of irAEs, especially those associated with significant morbidity and mortality. To this end, interleukin 6, C-reactive protein, and melanoma inhibitory activities have recently been reported to correlate with the onset of irAEs (48). Should these results be confirmed, a role for anti-IL-6R antibodies in the treatment of irAEs may emerge.

In summary, we confirm that irM is rare and report that pre-ICI treatment hsTnT concentrations were frequently elevated in patients with advanced skin cancer in the absence of acute ischemia. Following cardiac evaluation, immunotherapy was administered as planned and none of the patients with an elevated hsTnT concentration developed irM, although this was not expected given the sample size. Nevertheless, pre-ICI treatment hsTnT concentrations should be routinely performed before the initiation of immune checkpoint inhibition (28, 36, 37) and thoroughly investigated when elevated. Following cardiological assessment and the decision to initiate ICI therapy, pre- and early-treatment serum hsTnT concentrations should be measured and closely monitored especially during the initial treatment cycles where the risk of irM is greatest, particularly in

TABLE 3 | Cardiological assessment in patients with elevated hsTnT concentrations.

Patient	Initial hsTnT (ng/l) Normal range <14 ng/l	Follow-up hsTnT (ng/l) Normal range <14 ng/l	NT-proBNP (ng/l) Normal range <486 ng/l	ECG	Echocardiography performed	Creatinine (μmol/l) Normal range 59–104 μmol/l	Cardiological Evaluation
1	37.2	36	-	No evidence of acute ischaemia	Yes	138	hsTnT elevation due to chronic renal impairment
2	15	13.2	1,216	No evidence of acute ischaemia	Yes	98	hsTnT due to pre-existing cardiac disease
3	25.9	18.9	1,654	No evidence of acute ischaemia	Yes	134	hsTnT due to pre-existing cardiac disease/chronic renal impairment
4	25	23.2	-	No evidence of acute ischaemia	No	77	No evidence of ischaemic heart disease
5	34.8	34.0	4,081	No evidence of acute ischaemia	Yes	100	hsTnT due to pre-existing chronic cardiac failure
6	32.5	30.5	1,395	No evidence of acute ischaemia	Yes	69	No evidence of ischaemic heart disease
7	28.4	28.8	-	No evidence of acute ischaemia	Yes	78	No evidence of ischaemic heart disease
8	18.2	14.0	-	No evidence of acute ischaemia	No	180	hsTnT elevation due to chronic renal impairment
9	15.2	14.5	-	No evidence of acute ischaemia	No	112	hsTnT elevation due to chronic renal impairment
10	50.7	45.8	700	No evidence of acute ischaemia	Yes	91	No evidence of ischaemic heart disease
11	21.9	17.6	-	No evidence of acute ischaemia	No	120	hsTnT elevation due to chronic renal impairment
12	20.9	18.9	1,800	No evidence of acute ischaemia	Yes	95	hsTnT due to pre-existing chronic cardiac failure
13	14.0	-	-	No evidence of acute ischaemia	Yes	107	hsTnT due to pre-existing cardiac disease

patients with additional risk factors for irM, including the male sex, diabetes, a history of heart disease, and those undergoing combined anti-PD1 and anti-CTLA4 immunotherapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Lübeck, Ref 20-216. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JK, EL, and PT conceptualized the study and analyzed the data. JK recorded the data. UG and AF reported the MRI result and provided the images. KB evaluated the histology and provided the images. EL and JK wrote the manuscript. All co-authors reviewed and revised it.

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Long-Term Course of Polymorphic Light Eruption: A Registry Analysis

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Background: Little is known about the long-term course of polymorphic light eruption (PLE).

Objective: To predict disease course, a questionnaire was sent to patients whose PLE had been diagnosed between March 1990 and December 2018 and documented in the Austrian Cooperative Registry for Photodermatoses.

Methods: In January 2019, 205 PLE patients were contacted by mail and asked to complete a questionnaire on their disease course, including whether the skin's sun sensitivity had normalized (i.e., PLE symptoms had disappeared), improved, stayed the same, or worsened over time. Patients who reported normalization of sun sensitivity were asked to report when it had occurred.

Results: Ninety-seven patients (79 females, 18 males) returned a completed questionnaire. The mean (range) duration of follow-up from PLE onset was 29.6 (17–54) years for females and 29.4 (16–47) years for males. The disease disappeared in 32 (41%) females after 17.4 (2–41) years and in 4 (24%) males after 11.8 (5–26) years. Twenty-nine (37%) females and 6 (35%) males reported improvement of symptoms over time; 15 females (19%) and 7 males (41%) reported no change; and 3 females (4%) and no males reported worsening of symptoms. Kaplan-Meier analysis revealed that after 20 years 74% (95%CI, 64–82%) of patients still suffered from PLE. PLE lesion persistence (>1 week) tended to predict a prolonged course of PLE.

Conclusions: PLE usually takes a long-term course over many years though in most patients its symptoms improve or disappear over time. How improvement relates to the pathophysiology of the disease remains to be determined.

Keywords: polymorphic light eruption, disease course, persistence, predictive factors, remission

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WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Polymorphic light eruption (PLE) has a long-term course.

WHAT DOES THIS STUDY ADD?

PLE symptoms improve or disappear over time in approximately three quarters of patients although it takes 20 years until one quarter of patients has normalized from the disease. A long persistence of PLE lesions under daily life conditions may predict a poor prognosis for clinical disease remission.

INTRODUCTION

Polymorphic light eruption (PLE) is the most common and prevalent photodermatosis, particularly among young women in temperate climates (1–4). In a pan-European study, the average PLE prevalence was 18% (4). Similar to autoimmune diseases, PLE affects women approximately four times more often than men and usually has its onset within the first three decades of life (2, 5, 6). Several hours to days after initial exposure to intense sunlight, usually in spring or early summer, itchy skin lesions of variable morphology appear on sun-exposed skin. Many patients also experience flares during summer holidays (4). If further sun exposure is avoided, skin lesions subside without scarring within days. However, repeated exposure to sunlight reduces susceptibility to PLE. As summer progresses, many individuals experience a hardening effect after repeated exposure (2, 7, 8), making skin lesions less likely to occur or less severe. Unfortunately, this natural photohardening effect as well as the hardening effect of prophylactic medical phototherapy are lost in winter; consequently, PLE lesions recur the next year and often for years to come (2, 9, 10).

Recently, the pathophysiology of PLE has become much better understood. This includes initial triggers (11–14); concurrent resistance against induction of UV-induced immune suppression, linked to an imbalanced micromilieu marked by low levels of IL-4, IL-10, and TNF-alpha (15, 16); failure of Langerhans cell emigration from the skin and neutrophilic infiltration into the skin (17–21); disturbances in Treg levels and function (22–24); and potential involvement of CD11b/IL-31+ cells (25), mast cells (26, 27) or plasmacytoid dendritic cells (28, 29). Also better understood now are the therapeutic mechanisms of photohardening (19, 23, 27, 30–34) and other preventive measures (35–38). However, little is known about the initial and long-term course of the disease.

The aim of our study was to investigate the course of PLE and to identify potential predictive factors for the course and duration of the disease. Data for the analysis were available from standard questionnaires collected over a period of 30 years on a routine basis from patients with PLE and documented in the Cooperative Registry for Photodermatoses at the Medical University of Graz. In order to identify potential predictive factors for the course of the disease, patients were invited to report in an additional new questionnaire the course of their disease over the years and whether symptoms had improved, vanished or worsened.

PATIENTS AND METHODS

Study Setting

This study and the Austrian Cooperative Registry for Photodermatoses from which its data were extracted were approved by the ethics committee of the Medical University of Graz (application no. 30-089 ex 17/18). All patient data recorded in the registry were extracted from patient charts (paper or electronic) and from parts of a questionnaire designed for patients with photodermatoses that was routinely completed by those visiting the Outpatient Photodermatology Unit, Medical University of Graz. The questionnaire contained questions concerning patient demographics and disease characteristics. A key question for this study was whether the skin's sun sensitivity disappeared, improved, stayed the same, or worsened over time. If the answer was normalization of sun sensitivity (i.e., cessation of PLE symptoms), the patient was asked to report when or over what time interval the normalization had occurred.

Study Population

In January 2019, 205 of 213 patients who were already enrolled in the Cooperative Registry for Photodermatoses and who had visited our Outpatient Photodermatology Unit between March 1990 and December 2018 were contacted by mail and asked to complete a questionnaire on their disease course. Ninety-seven of them (79 females and 18 males) returned completed questionnaires and their data were analyzed. The flow chart showing patient selection is presented in **Figure 1**.

Statistical Analysis

Descriptive statistics were used to report and compare patient demographics. An unpaired, two-tailed Student's *t*-test, chi-square test, or Fisher exact test was administered to determine statistical differences between females and males with PLE. Persistence of PLE was analyzed by survival analysis, considering normalization of PLE as event of interest. Patients who had not normalized until the completion of the questionnaire were considered as censored. In order to assess risk factors for normalization Kaplan-Meier curves and univariate and multivariate Cox models were calculated. The logrank test criterion was used. The patient or disease characteristics under study were sex, age at disease onset, skin phototype, seasonal occurrence of skin lesions, and lesion occurrence (within 24 h after sun exposure) and duration (more than 1 week). Statistical analyses were performed and graphical illustrations were created using Prism 6 for Mac OSX V 6.0f, USA, GraphPad Prism V.8.4.1, USA and SPSS V25.0.0.1, IBM, USA, and R 4.0.2 (www.r-project.org) using packages survival 32-11 and survminer 0.4.9.

RESULTS

Patient Characteristics

Our study population for data analysis included 97 patients, most of them (81.4%) female (**Table 1**). Except for body site distribution of PLE lesions, there were no statistically significant sex-specific differences in demographics, disease characteristics, or follow-up. The mean age at disease onset was 25.9 years for females and 28.1 years for males (**Table 1**). Disease onset occurred between age 15 and 40 years in most females (56/76, 74%) and most males (11/17, 65%; **Figure 2**). However, it occurred before age 15 years in 12 (16%) females and 3 (18%) males. This included a boy who was 5 years old at disease onset and 8 years old at initial (and effective) prophylactic photohardening with 311-nm narrowband UVB light. Disease onset occurred after age 40 years in 8 (11%) females and 3 (18%) males (**Figure 2**). By sex, the most common morphological type of PLE was macular in females (63%) and papular in males (60%), with overlap among the other different morphological types in

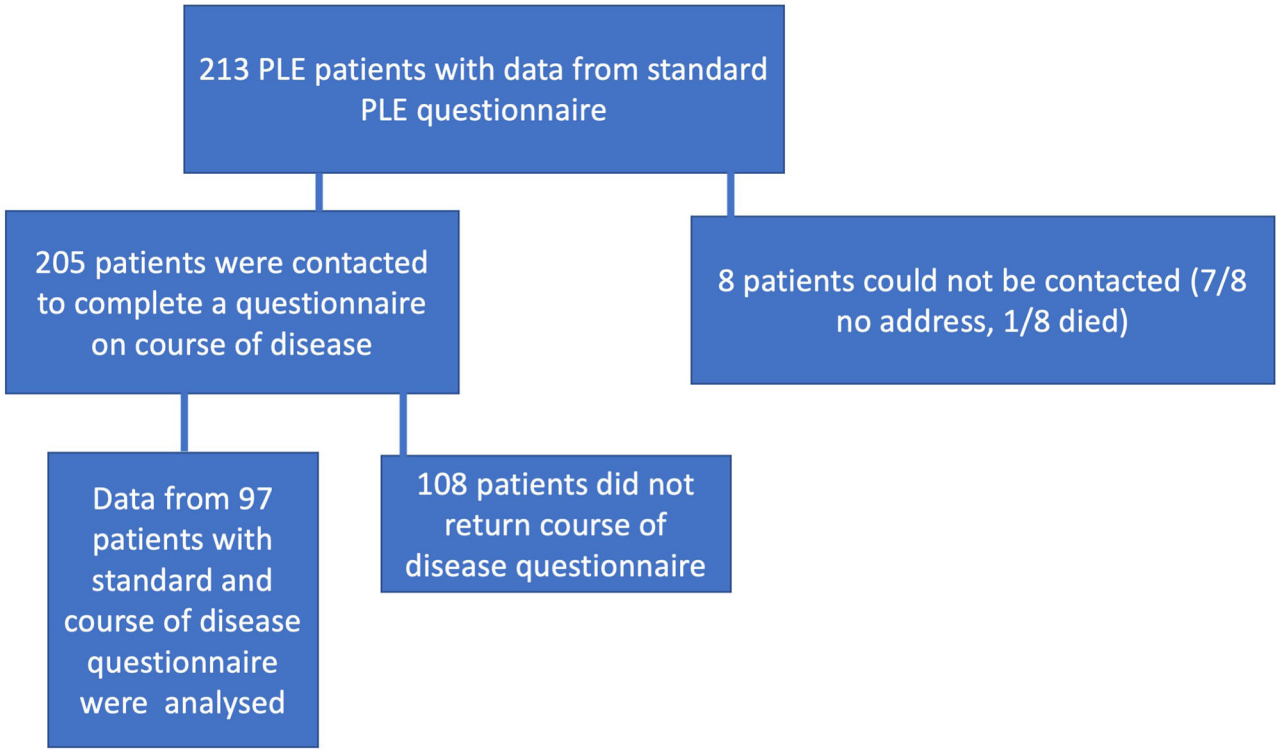

FIGURE 1 | Patient flow chart.

many patients (**Table 1**). Significantly more females than males reported PLE involvement of the V-neck (90 vs. 39%; $p < 0.0001$) (**Table 2**). Females tended to have a lower skin phototype than did men (type I/II, 44 vs. 7%; $p = 0.0671$) (**Table 1**). Results of antinuclear antibody (ANA) serum testing were available for 37 females and 8 males. Apart from one female (ANA titer of 1:80) and one male (ANA titer of > 1:80), all patients had negative test results. The clinical follow-up (including testing for antinuclear antibodies) revealed no suspicion for LE in any patients with a long persistence of skin lesions included in this study (data not shown).

Disease Course and Prognostic Factors

Data on disease course are presented in **Table 3**. The mean (range) follow-up period (from disease onset to last follow-up) was 29.6 (17–54) years for females and 29.4 (16–47) years for males. Thirty-two females (41%) and four males (24%) reported normalization of sun sensitivity (i.e., cessation of PLE symptoms) after a mean time of 17.4 (2–41) years and 11.8 (5–26) years, respectively. In those patients, the mean disease-free observation period was 12.2 (2–24) years for the females and 15 (10–21) years for the males (**Table 3**).

Twenty-nine (37%) females and 6 (35%) males reported improvement of symptoms over time; 15 females (19%) and 7 males (41%) reported no change; and 3 females (4%) and no males reported worsening of symptoms. The long-term duration of PLE symptoms is plotted for individual patients in **Figure 2**. Persistence of PLE was analyzed by survival analysis and results are blotted in **Figure 3**. After 20 years 74% (95%CI, 64–82%) of patients still suffered from PLE. No median time of persistence could be given as the lowest point of the Kaplan-Meier curve was at 52%. However, it took 20 (95%CI, 13–26) years until one quarter of patients had normalized from PLE. It took 25 (95%CI, 18–41) years until one third of patients had normalized from PLE. Univariate and multivariate analysis (after Bonferroni *p*-value adjustment) revealed no statistical significance for the patient characteristics under study including sex, age at disease onset, skin phototype, seasonal occurrence of skin lesions, and lesion occurrence after sun exposure (**Figure 3**; data for age at disease onset not shown). However, there was a trend for PLE lesion persistence (more than 1 week) predicting a prolonged course of PLE (**Figure 3F**). The hazard ratio for lesion persistence was 2.47 (95%CI, 0.75–8.13). There was no statistical significance in the omnibus test for the set of risk factors in consideration ($p = 0.3$).

DISCUSSION

Previous studies have shown that in most PLE-affected subjects the disease is persistent and slow to improve (39, 40). Jansen et al. contacted patients of a cohort 7 years after an original study and reported a significant reduction of sun sensitivity in 64 of 114 subjects (56%), including 12 subjects (11%) who achieved total absence of appearance of lesions over time (40). In a subsequent

TABLE 1 | Patient characteristics.

	Females	Males	*p*-value
Number/total number of patients (%)	79/97 (81.4%)	18/97 (18.6%)	
Age at disease onset (years), median, mean (SD), range	24.0 25.9 (±12.4) 1–62	30.0 28.1 (±15.0) 4–53	0.534
Age in years at providing the standard questionnaire: median, mean (SD), range	34.0 35.01 (±11.6) 15–64	37.5 35.6 (±11.2) 9–55	0.846
Skin phototype, number (percentage)	I 4 (5%) II 31 (39%) III 39 (49%) IV 5 (6%) Na 0	I 0 (0%) II 1 (7%) III 11 (79%) IV 2 (14%) Na 4	0.067
Type of PLE, number (percentage) patients	Mac: 48 (63%) Ves: 23 (30%) Pap: 29 (38%) Urt/plaq: 39 (51%) Na 3	Mac: 8 (53%) Ves: 4 (27%) Pap: 9 (60%) Urt/plaq: 7 (47%) Na 3	0.636
Lesions occurring in spring, summer, fall, winter. Number (percentage) patients	Spring 35 (49%) Summer 67 (94%) Fall 11 (15%) Winter 7 (10%) Na 8	Spring 6 (50%) Summer 12 (100%) Fall 1 (8%) Winter 3 (25%) Na 6	0.551
Persistence of skin lesions, hours (≤24 h), days (>1d-≤7d), weeks (>7d)	Hours: 19 (26%) Days: 43 (58%) Weeks: 12 (16%) Na 5	Hours: 1 (8%) Days: 7 (54%) Weeks: 5 (38%) Na 5	0.113
Occurrence of skin lesions within hours (≤24 h), days (>24 h)	Hours: 47 (69%) Days: 21 (31%) Na 11	Hours: 10 (91%) Days: 1 (9%) Na 7	0.169

Mac, macular; Ves, vesicular; Pap, papular; Urt/plaq urticarial/plaques.; Na, no answer. P-values were determined by student's t-test and chi-square, or Fisher's exact test, whatever was the most appropriate.

study of the same cohort with a mean follow-up duration of 32 years after the onset of PLE, 23 of 94 (24%) became disease free, 48 (51%) experienced improvement of symptoms (less frequent or severe), and 23 (24%) showed equal or worse symptoms (39).

In our study, PLE symptoms vanished in 32 of 79 females (41%) and 4 of 17 males (24%) after a mean disease duration of 17 and 12 years, respectively (**Table 3**). When improvement in PLE symptoms was included, those rates increased to 61 of 79 females (77%) and 10 of 17 males (59%) (**Table 3**). However, Kaplan-Meier analysis revealed that in overall it took 20 years until one quarter of patients had normalized from PLE and 25 years until one third of patients had normalized from PLE. There was trend for PLE lesion persistence (>1 week) predicting a prolonged course of PLE by a hazard ratio of 2.47 (95%CI, 0.75–8.13) (**Figure 3F**). How this relates to the pathophysiology of PLE such as disturbed neutrophil infiltration (41) remains to be determined. Meanwhile, a longer PLE lesion persistence may indicate a pathophysiologic relationship with lupus erythematosus (LE). Indeed, some groups have suggested that PLE and LE share a common pathogenesis and that PLE can progress to LE (42–44). However, long term follow up studies of PLE patients have shown no increased risk of transition to LE (39, 40), although PLE lesions may precede the development of LE (45). Photosensitivity is one of the pathognomonic features of LE, and in some cases the sun-related skin rash seen in lupus can be virtually indistinguishable from PLE (42, 45–47). However, in our study, results of ANA testing were negative in all patients (except for one patient of each sex), and follow-up revealed no instances of suspected LE in any patients, including those with persistent skin lesions.

Our study also indicated that disease onset usually occurred between young adulthood and middle age, at a mean age of 25.9 years in females and 28.1 years in males (**Table 1**). Moreover, we found that in most cases (74% of females and 65% of males), the onset of disease (PLE symptoms) occurred between the ages of 15 and 40 years (**Figure 2**). Whether the quality or quantity of the microbiota present on humans during different periods of life plays a role in this needs to be determined. We recently hypothesized a potential link between disturbances in the microbiome and UV-induced immune suppression (48–51) and PLE formation (11) and reported an age-dependent skin microbiota and a potential role of sex hormones (52) and cited herein.

Consistent with previous studies, the female/male ratio in our study (4.39) was high (2, 10, 39). However, there were no significant sex-based differences other than in the body site of PLE involvement. Significantly more females than males reported

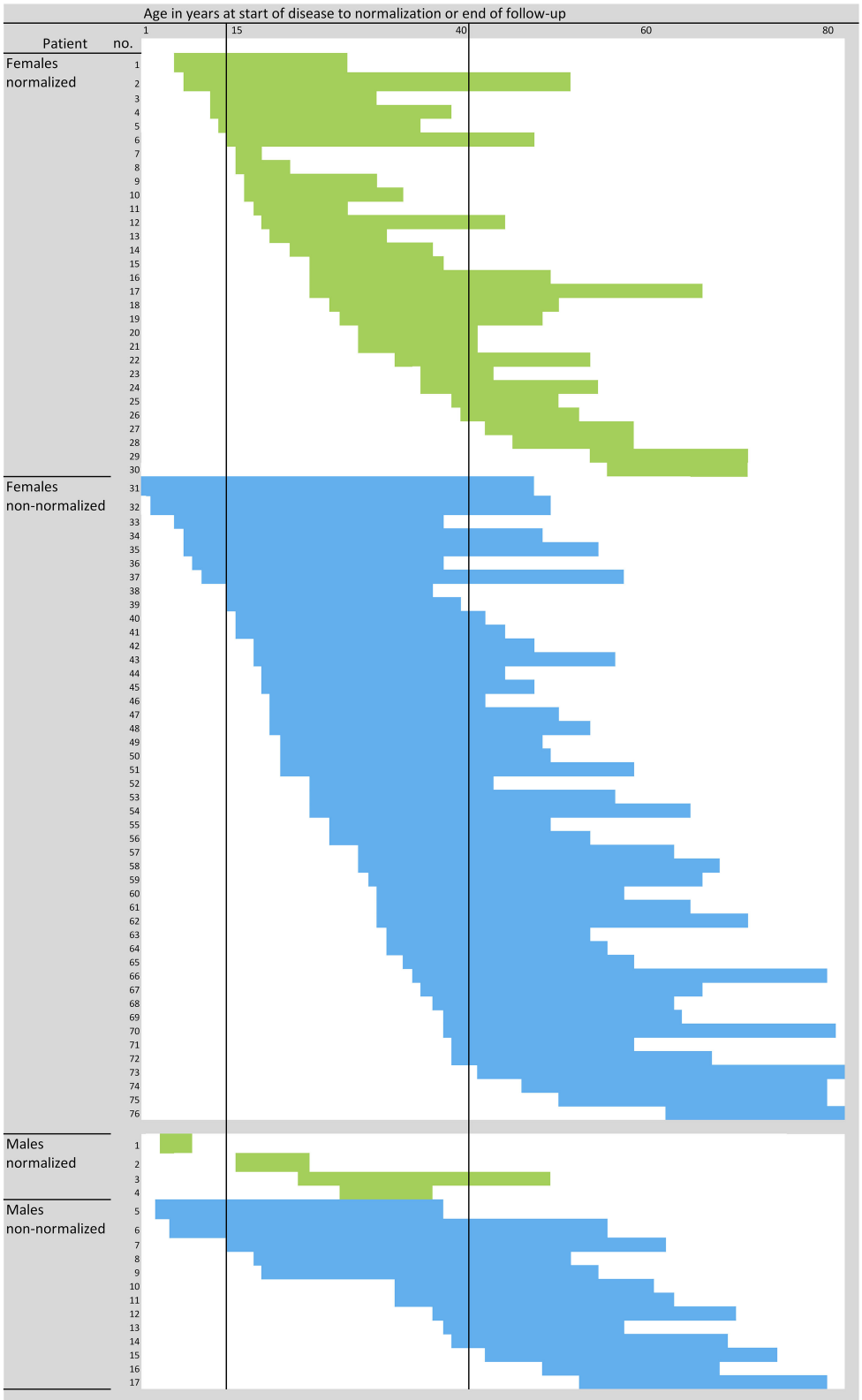

FIGURE 2 | Course of disease in individual PLE patients. Blue and green represent individual patients and their time span from onset of disease to normalization of sun sensitivity (i.e., cessation of PLE symptoms) (green), being considered as event, or the end of the follow-up (not-normalized, blue), being considered as censored. $N = 97$ patients; three women did not exactly report the start and/or cessation or improvement of symptoms, and one man did not answer the question on the course of the disease at all, and thus the data for these four patients were not plotted.

V-neck lesions (90 vs. 39%; $p \leq 0.0001$) (**Table 2**). This difference may be due to sex-based differences in seasonal changes in clothing style and exposure of the skin of this body site. Perhaps women experience more sudden changes in clothing style and exposure in spring, after a long fall and winter, resulting in more frequent occurrence of V-neck lesions. Alternatively, a difference in how women and men perceive this body site may account for the reported difference.

TABLE 2 | Body site involvement in PLE.

Body site of PLE involvement	Females ($n = 79$)	Males ($n = 18$)	p-value
Face	25 (32%)	4 (22%)	0.5714
V-neck	70 (90%)	7 (39%)	**<0.0001**
Neck	24 (31%)	6 (33%)	0.9999
Back	19 (24%)	8 (44%)	0.1431
Upper chest	32 (41%)	11 (61%)	0.1878
Abdomen	21 (27%)	5 (28%)	0.9999
Upper arm	42 (54%)	7 (39%)	0.3017
Forearm	46 (59%)	13 (72%)	0.4217
Thigh	29 (37%)	6 (33%)	0.9999
Lower leg	32 (41%)	7 (39%)	0.9999
Dorsum hand	24 (31%)	6 (33%)	0.9999
Dorsum feet	22 (28%)	5 (28%)	0.9999
na	1	0	na

na, not available. P-values were determined by chi-square, or Fisher's exact test, whatever appropriate. Significant rates are printed in bold.

Fitzpatrick skin phototype has been associated with the likelihood of developing PLE, skin type I posing the highest risk and skin type IV or higher posing the lowest (4). In our study, most patients had skin type III (49% of females and 79% of males), and skin type I/II was not a significant predictor of PLE course (**Figure 3**). Moreover, age at onset of disease, sex, and occurrence of lesions in certain seasons (spring and/or summer exclusively) and the time period of occurrence of lesions after sunlight exposure also had no predictive value with regard to the course of the disease (**Figure 3**).

Our study had several limitations. One was the relatively low rate of return of completed disease-course questionnaires from the patients we contacted (only 47%). Another limitation was that patients were asked to score the interval between sunlight exposure and occurrence as well as persistence of PLE lesions in a photosensitivity questionnaire (characteristics that were not determined/confirmed in a clinical photoprovocation assay) and also had to recall their disease course retrospectively. A third limitation was the introduction and use of better sun protection measures (including more effective broadband sunscreens with high UVA protection) during the period covered by our study and their possible contribution to the notion among some of our patients that PLE (most often caused by UVA wavebands) (10) had improved or even disappeared over time. Finally, the relatively low number of males in our study population limited the statistical power of our sex-based comparisons. Nonetheless, this study matches well in size and follow-up with the largest previous study so far on the course of PLE (39). However, in contrast to that previous study, in which some of the 94 patients developed associated diseases (including LE, actinic reticuloid PLE, or unusual forms of PLE

TABLE 3 | Course of PLE.

Course of disease	Females			Males		
	Number (%)	Years until cessation of disease: median, mean, range	Years of follow up: median, mean, range	Number (%)	Years until cessation of disease: median, mean, range	Years of follow up, median, mean, range
Worse symptoms	3 (4)		30.0 31.0 23–40	0 (0)		
Equal symptoms	15 (19)		32.0 31.3 17–43	7 (41)		29.0 33.3 24–47
Less symptoms	29 (37)		26.5 28.7 18–45	6 (35)		30.0 26.5 17–32
Normalized	32 (41)	15.5 17.4 2–41	28.0 [11.5]* 19.5 [12.2] 17–54 [2–24]	4 (24)	8.0 11.8 5–26	23.5 [14.5] 26.8 [15.0] 16–44 [10–21]
All courses	79 (100)		28.0 29.6 17–54	17 (100)		29.0 29.4 16–47
na	0			1		

Numbers in square brackets indicate time of follow up after cessation of disease. na, no answer available. One man did not answer the question on the course of the disease, and two women did not report the start; one woman did not report the time of cessation of symptoms, and thus the data for these four patients could not be included in the analysis of the follow-up and disease duration (see also footnote in **Figure 2).*

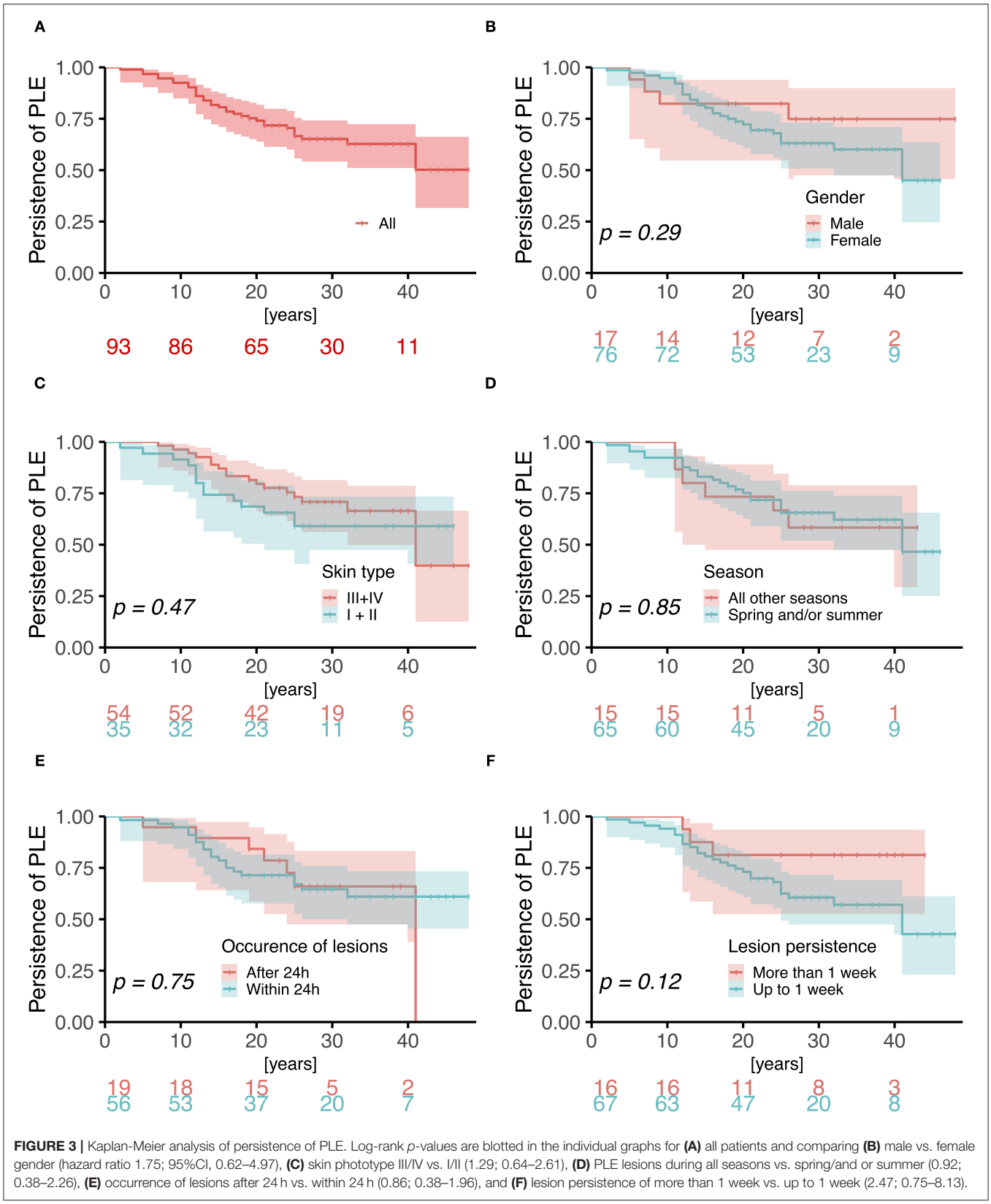

FIGURE 3 | Kaplan-Meier analysis of persistence of PLE. Log-rank *p*-values are blotted in the individual graphs for **(A)** all patients and comparing **(B)** male vs. female gender (hazard ratio 1.75; 95%CI, 0.62–4.97), **(C)** skin phototype III/IV vs. I/II (1.29; 0.64–2.61), **(D)** PLE lesions during all seasons vs. spring/and or summer (0.92; 0.38–2.26), **(E)** occurrence of lesions after 24 h vs. within 24 h (0.86; 0.38–1.96), and **(F)** lesion persistence of more than 1 week vs. up to 1 week (2.47; 0.75–8.13).

such as prurigo-, solar urticaria-, or hydroa vaccinforme-like PLE) over time (39), our study had a more uniform PLE patient population.

In summary, this analysis revealed a long-term course of PLE. Though the disease improved in a substantial number of patients (i.e., 77% of females and 59% of males) over the years, it took 25 years until one third of patients had normalized from PLE. The persistence of skin lesions for more than 1 week under daily life conditions may predict a prolonged course of the disease over the years. However, the strength of lesion persistence as predictive factor needs to be assessed in further studies, possibly by combining data from different centers in a registry, like the Austrian Cooperative Registry for Photodermatoses. Such studies should also access the success or failure of photohardening and how this affects the long-term course of the disease. Moreover, how this all relates to the pathophysiology of the disease (for example, the failure of neutrophilic infiltration and other disturbances) (41) remains to be determined.

DATA AVAILABILITY STATEMENT

The questionnaires of the study and raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Graz. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG-W: conceptualization-equal, data curation-equal, formal analysis-equal, investigation-equal, project administration-equal, validation-equal, writing-original draft-equal, and writing-review and editing-equal. TS: data curation, investigation-equal, project administration-supporting, and writing-review and editing-supporting. TG: data curation, formal analysis-equal, investigation, validation-equal, visualization-equal, and writing-review and editing-equal. FL: data curation, investigation, and writing-review and editing-equal. HR: data curation-supporting, investigation-supporting, and project administration-supporting. AH: data curation-equal, investigation-equal, and writing-review and editing-equal. FQ: formal analysis-equal, validation-equal, visualization-equal, writing-review and editing-equal. PW: conceptualization-lead, data curation-equal, formal analysis-lead, investigation-lead, methodology-lead, project administration-lead, resources-equal, supervision-lead, validation-lead, visualization-lead, writing-original draft-equal, and writing-review and editing-lead. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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The Impact of SARS-CoV-2 (COVID-19) Pandemic on International Dermatology Conferences in 2020

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To limit the spread of the SARS-CoV-2 (COVID-19) outbreak, humans have been significantly restricted in their ability to travel and interact with others worldwide. Consequently, dermatology conferences were forced to adapt to such changes. The aim of this study is to investigate the impact of COVID-19 on international dermatology conferences. We retrospectively investigated decisions made for international dermatology conferences scheduled for 2020. Thirty-three major conferences were analyzed. Their data were obtained from their respective websites (data was accessed 2 June 2021). Among 33 conferences analyzed, 13 (39.4%) were conducted as scheduled, nine (27.3%) were canceled, eight (24.3%) were postponed to 2021 or 2022, and three (9.1%) were delayed but conducted in 2020. The number of the cancellation (44.4%) and postponement (75%) was the largest in the second quarter of the year. During the fourth quarter, most conferences were held on schedule (70%) but were run virtually. Eight out of 13 virtual conferences shortened their duration (61.5%). Most (90.9%) conferences have decided on the schedule of their meetings for 2021 or 2022 while three (9.1%) remain undecided. Twelve (40%) are planned to run virtually, eight (26.7%) have opted for a hybrid form, five (16.7%) are planned to run in-person, four (13.3%) have not decided on the format, and one (3.3%) has been canceled. Virtual and hybrid conference formats have facilitated people to share knowledge despite the travel restrictions posed by the COVID-19 pandemic. Such formats are environmentally friendly, are able to attract a large audience, and save delegates time and costs involved in attending. Therefore, virtual platforms should continue to be integrated within conferences in the post-pandemic era.

Keywords: COVID-19, conference, virtual, dermatology, coronavirus, pandemics, congress, SARS-CoV-2

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) forced innumerable events to make significant adjustments in 2020 (1). Cancellation, postponement or online reformatting of major events, such as the Olympics and major film festivals, prevented expected attendees from participating in-person.

International conferences facilitate thousands of delegates to meet and discuss ideas and update each other on their topics of interest (2). However, as gatherings and international travel significantly increase the risk of viral transmission, governments worldwide have implemented strict quarantine and social distancing restrictions. Consequently, conferences have been forced to cancel, postpone or reformat their meetings in order to protect their attendees and local communities (3, 4). International dermatology conferences were no exception. In this study, we analyzed the decisions made due to COVID-19 by the major dermatological conferences regarding their meetings scheduled for 2020.

METHODS

Study Design

We searched for international dermatology conferences arranged in 2020. Thirty-three major conferences were analyzed. Their data were obtained from their respective websites. Data collected included the venue, originally planned date, decision on cancellation or postponement and relevant details, original meeting format (in-person or virtual), change in meeting duration, date and format of the next meeting [in-person, virtual or hybrid (mix of in-person and virtual)], and the number of confirmed and deceased COVID-19 cases during 2020 in the host country (**Table 1**, last accessed 2 June 2021).

For the conferences of which the upcoming meeting dates are confirmed, their final schedules are described in **Table 1**. We applied "Not Determined (ND)" for the undecided schedules. The format of subsequent meetings was also marked as "ND" if the conferences did not decide whether they would be in-person, virtual or hybrid. Furthermore, we recorded the official World Health Organization (WHO) reported total number of confirmed and deceased COVID-19 cases in the hosting countries until December 31, 2020. This study was exempted from ethics review as it investigated publicly available data.

Classification of the Decision Made

We classified the decisions made for each conference into four categories: "Conducted on original date", "Conducted on delayed date", "Postponed (to 2021 or 2022)", or "Cancelled". "Conducted on original date" refers to the meetings that were hosted on the originally planned date. "Conducted on delayed date" stands for the conferences that were held on delayed dates within 2020. If an annual conference which is always held in one country is postponed a year, it was classified as "Cancelled". Indefinitely postponed conferences were classified as "Cancelled" as well. The 20th Edition of Dubai World Dermatology and Laser conference and the Australasian Melanoma Conference 2020 (6th and 27th on **Table 1**) were such cases. However, if a conference which is held in a different country each time is postponed for >1 year, it was marked as "Postponed (to 2021 or 2022)" as long as the hosting country remained the same.

RESULTS

Overall Fate of Conferences in 2020

Out of the 33 international dermatology conferences, 13 (39.4%) were conducted as scheduled, nine (27.3%) were canceled, eight (24.3%) were postponed to 2021 or 2022, and three (9.1%) were delayed but conducted in 2020. Among 16 meetings held in 2020, 13 (81.25%) were held virtually, and three (18.75%) were held in-person. All in-person meetings were held in January 2020.

Change in Conference Schedules per Quarter

In each quarter of 2020, 6, 12, 5, and 10 conferences were originally scheduled to be held. Out of the conferences scheduled January–March, three (50%) were conducted on their original dates, two (33.3%) were canceled and one (16.6%) was conducted on delayed dates. Out of the conferences scheduled April–June second quarter, six (50%) were postponed, four (33.3%) were canceled, one was (8.3%) conducted on its original date and one (8.3%) was delayed but conducted in 2020. Out of the conferences scheduled July–September, two (40%) were conducted on their original dates, two (40%) were canceled and one (20%) was conducted on a delayed date. Out of the conferences scheduled October–December, seven (70%) were conducted on their original dates, two (20%) were postponed and one (10%) was canceled.

The number of conferences conducted on their original dates was the largest in the fourth quarter of the year (53.8%), followed by the first quarter (23.1%), the third quarter (15.4%) and the second quarter (7.7%). The number of canceled conferences was the largest in the second quarter (44.4%), followed by third (22.2%), first (22.2%) and fourth (11.1%). COVID-19 appears to have had the most significant impact on conferences in the second quarter of 2020, when the World Health Organization (WHO) declared it as a pandemic. All the conferences held on their original dates in the fourth quarter were held virtually. Three conferences which were delayed but conducted in 2020 ran virtually.

Duration of Conferences Held

Of the 16 completed meetings, eight (50%) were shortened, seven (43.75%) were conducted as scheduled and one (6.25%) was lengthened. All in-person conferences in January 2020 were run as scheduled, while most virtual meetings (eight out of 13, 61.5%) shortened their duration (the original duration: 3.70 ± 0.9, the changed duration: 3.31 ± 1.1 days, mean $\pm$ standard deviation).

Decision on Upcoming Meetings

Most (93.9%) conferences have decided on the schedule of their meetings for 2021 or 2022 while two (3.1%) remain undecided. Of the 31 arranged conferences, 12 (38.7%) are planned to run virtually, eight (25.8%) have opted for a hybrid format, five (16.1%) are planned to run in-person, four (12.9%) are

TABLE 1 | Summary of major dermatology conferences in 2020.

	Conference	City and country	Original date	Decision	Details	Meeting format	Period shortened	Next meeting schedule	Next meeting format	Confirmed cases** (Deceased)
1	Melanoma 2020: 30th Annual Cutaneous Malignancy Update	San Diego, USA	24–26 January	Conducted on original date		In-person	No	23–24 January 2021	Virtual	19,346,790 (335,789)
2	Maui Derm for Dermatologists 2020	Maui, Hawaii	25–29 January	Conducted on original date		In-person	No	25–29 January 2021	Hybrid	21,459 (286)
3	International Master Course on Aging Science (IMCAS) World Congress 2020	Paris, France	30 January−1 February	Conducted on original date		In-person	No	27–29 January 2022	Hybrid	2,556,708 (64,004)
4	14th International Congress of Aesthetic Dermatology (ICAD)	Bangkok, Thailand	3–4 February	Conducted on delayed date	Postponed to 20–22 November 2020 and later merged with '18th Aesthetic & Anti-aging Medicine World Congress (AMWC) Global – The Virtual Edition' and held on November 5–6, 2020	Virtual	No	18–20 November 2021	In-person[#]	6,690 (61)
5	20th Edition of Dubai World Dermatology and Laser conference (Dubai Derma)	UAE, Dubai	16–18 March	Canceled*	Postponed initially to 16–18 June 2020 and later to 2–4 March 2021 and finally to 6–8 July 2021	-	No	6–8 July 2021	Hybrid	206,092 (665)
6	2020 Annual Meeting of the American Academy of Dermatology (AAD)	Denver, USA	19–23 March	Canceled		-		Canceled	Canceled	19,346,790 (335,789)
7	16th European Association of Dermato-Oncology (EADO) Congress	Vilnius, Lithuania	20–25 April	Conducted on delayed date	held on 12–14 October 2020	Virtual	Yes (3 days)	15–17 April 2021	Virtual	140,579 (1,458)
8	International Society of Atopic Dermatitis (ISAD) 2020	Seoul, South Korea	22–24 April	Postponed to 2021	postponed to 19–20 April 2021 and provided 3 hours of live streaming on 3 September 2020 instead	-	Yes (1 day)	19–20 April 2021	Hybrid	60,734 (900)
9	7th Continental Congress of Dermatology (CCD)	Mexico City, Mexico	22–25 April	Canceled		-		2022 (Final dates to be determined)	ND[#]	1,401,529 (123,845)
10	16th spring symposium of the European Academy of Dermatology and Venereology (EADV)	Poro, Portugal	30 April−2 May	Canceled		-		20–22 May 2021	Virtual	406,051 (6,830)
11	38th Annual Meeting of Latin American Dermatologists (RADLA)	Asunción, Paraguay	1–4 May	Postponed to 2021	Postponed to 15–18 April 2021	-	No	15–18 April 2021	Virtual	106,136 (2,220)

(Continued)

TABLE 1 | Continued

	Conference	City and country	Original date	Decision	Details	Meeting format	Period shortened	Next meeting schedule	Next meeting format	Confirmed cases** (Deceased)
12	2nd World Congress of Trichoscopy	Sorrento, Italy	6–8 May	Postponed to 2021	Postponed to 9–11 October 2021	-	No	9–11 October 2021	ND	2,083,689 (73,604)
13	53rd Annual Meeting of the Australian College of Dermatologists (ACDASM)	Adelaide, Australia	6–9 May	Postponed to 2021	Postponed to 9–11 April 2021	-	Yes (1 day)	9–11 April 2021	Virtual	28,381 (909)
14	20th European Society for Pediatric Dermatology (ESPD) Annual Meeting	Vienna, Austria	11–13 May	Postponed to 2021	Postponed to 12–14 May 2021	-	No	12–14 May 2021	Virtual	356,351 (6,086)
15	78th Annual Meeting of the Society for Investigative Dermatology (SID)	Arizona, USA	13–16 May	Conducted on original date	Free virtual meeting of selected content of the original program	Virtual	No	3–8 May 2021	Virtual	19,346,790 (335,789)
16	15th World Congress of International Academy of Cosmetic Dermatology (IACD)	Dresden, Germany	18–20 June	Canceled	Postponed initially to 1–3 July 2021 and later canceled	-	No	ND	ND	1,719,737 (33,071)
17	24th International Pigment Cell Conference (IPCC)	Yamagata, Japan	18–21 June	Canceled		-		May/June 2023(Final dates to be determined)	ND	230,304 (3,414)
18	18th World Congress on Cancers of the Skin (WCCS)	Buenos Aires, Argentina	24–27 June	Postponed to 2021	Postponed initially to 3–6 November 2021 and later to 2–5 November 2022	-	No	2–5 November 2022	ND	1,602,163 (43,018)
19	100th Annual Meeting of the British Association of Dermatologists (BAD)	Manchester, UK	7–9 July	Conducted on delayed date	Held on 1–3 September 2020	Virtual	No	6–8 July 2021	Virtual	2,432,892 (72,548)
20	45th Annual Meeting Society for Pediatric Dermatology Annual meeting (SPDA)	Asheville, USA	9–12 July	Conducted on original date	Held on 10–12 July 2020	Virtual	Yes (1 day)	8–10 July 2021	Virtual	19,346,790 (335,789)
21	72nd Annual Meeting of the Pacific Dermatologic Association (PacDerm)	San Francisco, USA	30 July−2 August	Canceled		-		19–22 August 2021	Hybrid	19,346,790 (335,789)
22	American Academy of Dermatology (AAD) 2020 Summer Meeting	Seattle, USA	13–16 August	Canceled		-		5–8 August 2021	In-person	19,346,790 (335,789)

(Continued)

TABLE 1 | Continued

	Conference	City and country	Original date	Decision	Details	Meeting format	Period shortened	Next meeting schedule	Next meeting format	Confirmed cases** (Deceased)
23	12th 5-Continent-Congress (5CC) World Congress	Barcelona, Spain	27–30 August	Conducted on original date	Held on 28–30 August 2020	Virtual	Yes (1 day)	4–5 September 2021	Virtual	1,893,502 (50,442)
24	American Society for Dermatologic Surgery (ASDS) Annual Meeting 2020	Washington DC, USA	8–11 October	Conducted on original date	Held on 9–11 October 2020	Virtual	Yes (1 day)	14–17 October 2021 (In person) 19–21 November 2021(Virtual)	Hybrid	19,346,790 (335,789)
25	41st Annual Meeting of the International Society for Dermatologic Surgery (ISDS)	Cairo, Egypt	20–24 October	Conducted on original date	Held on 21–23 October 2020	Virtual	Yes (1 day)	ND	ND	136,644 (7,576)
26	Australasian Melanoma Conference (AMC) 2020	Sydney, Australia	23–24 October	Canceled*	Postponed to 19–20 November 2021	-	No	19–20 November 2021	In-person	28,381 (909)
27	29th Congress of the European Academy of Dermatology and Venereology (EADV)	Vienna, Austria	28 October−1 November	Conducted on original date	Held on 29–31 October 2020	Virtual	Yes (2 days)	29 September-2 October 202113-17 October 2021	Virtual	356,351 (6,086)
28	17th International Congress of the Society for Melanoma Research (SMR)	New Orleans, USA	29 October−1 November	Conducted on original date	Held on 28 October 2020	Virtual	Yes (3 days)	28–31 October 2021	Hybrid	19,346,790 (335,789)
29	8th World Congress of Teledermatology, Imaging, and Artificial Intelligence for Skin Diseases	Seville, Spain	5–6 November, 2020	Conducted on original date	Held on 5–6 November, 2020	Virtual	No	ND	ND	1,893,502 (50,442)
30	57th American Society of Dermatopathology (ASDP) Annual Meeting	Chicago, USA	5–8 November	Conducted on original date	Held on 5–11 November 2020	Virtual	Lengthened (3 days)	20–24 October 2021	Virtual	19,346,790 (335,789)
31	9th Dermatologic & Aesthetic Surgery International League (DASIl) World Congress	Mexico City, Mexico	11–14 November	Conducted on original date	Held on 13–15 November 2020	Virtual	Yes (1 day)	27–30 October 2021	In-person	1,401,529 (123,845)
32	4th Inflammatory Skin Disease Summit (ISDS)	New York, USA	18–21 November	Postponed to 2021	Postponed to 3–6 November 2021	-	No	3–6 November 2021	Hybrid	19,346,790 (335,789)
33	6th Eastern Asia Dermatology Congress (EADC)	Gyeongju, South Korea	25–27 November	Postponed to 2022	Initially delayed to 7–9 July 2021 and later delayed to 8–10 December 2022	-	No	8–10 December 2022	In-person	60,734 (900)

**When the annual conference which always takes the same venue was postponed one year, we classified it as "Cancelled" even though it announced postponement. When the conference, which rotates its venue internationally, is postponed for more than one year, we marked it as "Postponed to next years (2021 or 2022)" as long as the venue is still the same.*

***Confirmed and deceased cases refer to those of the host countries; #ND stands for "not determined".*

TABLE 2 | Advantages and disadvantages of running conferences virtually.

Advantages	Disadvantages
Allow moderators to better control the flow of sessions	Cannot conduct hands-on learning
Can record talks for future reference	Have technical issues: weak internet connection, poor audio and video quality
Can host a large number of attendees	Limit mentorship and interaction between experts and residents or students
Can allow delegates to attend regardless of location	Lose human contact, affections and emotions (5)
Reduce carbon footprint of meeting travel (6)	Lose networking opportunities amongst delegates
Reduce or eliminate registration fees becoming more affordable	Restrict interaction with dermatology-related industries (e.g., cosmetics, laser, pharmaceutical)
Reduce costs for hosting organizations (e.g., venue hire, staffing)	Prevent speakers from sufficiently engage with audience
Save travel and accommodation costs for delegates	Prevent delegates of developing countries with poor internet connection from participating

undecided, and two (6.5%) have been canceled. Among nine meetings scheduled for the first half of 2021, seven (77.8%) were virtual and two (22.2%) were hybrid. Of the 15 conferences scheduled for the second half of 2021, five (33.3%) are scheduled to run virtually, five (33.3%) have opted for a hybrid format, four (26.7%) are planned to run in-person and one (6.7%) remains undecided.

DISCUSSION

In this study, we analyzed how major dermatology conferences in 2020 adapted to restrictions set by the COVID-19 pandemic. The results denote close association between the date and the decisions made by the conferences. The WHO declared the outbreak of COVID-19 on January 30, 2020. Before the declaration, all three conferences in January were conducted in-person. However, all 30 conferences planned from February to December 2020 were canceled, rescheduled or switched to virtual form.

COVID-19 had the most significant impact on conferences during the second quarter of 2020 when the WHO declared it as a pandemic. Eleven out of 12 conferences planned for the second quarter deferred or canceled their meetings. The second quarter accounted for the largest percentage of cancellations (44.4%) among four quarters. In contrast, seven out of 10 meetings originally scheduled for the fourth quarter were run as scheduled but in virtual form. These results show how the conference hosts with meetings scheduled near the end of the year had sufficient time to re-organize and run their events virtually to adapt to COVID-19 restrictions. Success of these virtual conferences was enabled by audio-visual e-platforms, such as Zoom (Zoom Video Communications, California, U.S.), Cisco Webex (Cisco Webex, California, U.S.) and Google Hangout (Google, California, U.S.), which developed rapidly due to the exponential increase in demand during the pandemic.

Running conferences virtually has several advantages and disadvantages (**Table 2**). The greatest advantage is that virtual conferences have significant flexibility in timing and location. Thus, they can host a much larger number of attendees compared to in-person conferences, thereby offering economy of scale to reduce registration fees (7). Running conferences virtually may be more profitable for the hosting organizations as they may reduce costs on venue hire and staffing (8). Affordable fees can make meetings more accessible for a larger audience (9). Talks may even be recorded and transmitted via delayed streaming to let attendees choose their best time to view the lecture. (5) In addition, virtual conferences are more environmentally friendly as they can reduce the carbon footprint of traveling (10, 11). Finally, given that much of dermatology is image-based, it is well suited to this virtual method of knowledge distribution. (12).

However, in-person conferences have characteristics which cannot be mimicked by virtual means. In-person conferences allow attendees of all career stages to interact, share ideas and learn from one another (5, 13). Furthermore, virtual conferences cannot provide opportunities for hands-on learning, such as dermatologic surgery skills, or mentorship between leading dermatology experts and junior doctors as well as students. Virtual meetings are, by nature, not as engaging as in-person interactions, as audience members are reduced to names on screens. In our data, alteration to virtual format was accompanied by shortening of conference duration in the majority of conferences. The average conference duration decreased from 3.7 to 3.3 days. This may be due to the deletion of activities only feasible in-person, such as workshops and welcome receptions, which further reduces networking opportunities for attendees.

Technical issues including intermittent connection, poor audio and video quality significantly disrupt delegates' ability to distribute information and interact with one another (14). Hyper-efficient telecommunication networks and optimal image quality are prerequisites for real-time video and audio interaction. Therefore, attendees from underdeveloped societies may not be able to participate, leading to an imbalance of knowledge distribution and opportunities. Virtual conferences also restrict dermatology experts from interacting with dermatology-related industries, such as cosmetics, pharmaceutical and laser companies, and helping them manufacture evidence-based products.

It is likely that most conferences in 2021 will run virtually due to the COVID-19 pandemic. All nine conferences scheduled for the first half of 2021 were run virtually (77.8%) or in hybrid form (22.2%). For the second half of 2021, 10 (66.7%) out of 15 conferences are planned to be held in virtual or hybrid formats. Some organizations have even launched independent virtual conferences, rather than temporarily adopting virtual platforms to run their in-person conferences. For example, the American Academy of Dermatology (AAD) canceled their 2020 Annual

Meeting. Instead, they launched the Annual Meeting of the American Academy of Dermatology Virtual Meeting Experience (AADVMX), which ran live from June 12 to 14, and academic content was made accessible until December 31, 2020. AADVMX was held from 23 to 25 April 2021 as well.

Our study has a few limitations. First, not all conferences were analyzed due to the absence of a platform that shows every dermatological conference at a glance. We however attempted to include all major gatherings that attract hundreds of attendees nationally and internationally. Second, biennial conferences which were not scheduled for 2020 but for 2021 were not included. Despite these limitations, this study sufficiently captures the effect of COVID-19 on the 2020 dermatological society and informs future decision-making for overcoming travel restrictions when organizing internationall conferences, especially when facing another pandemic.

CONCLUSION

The restrictions posed by COVID-19 provided a unique opportunity for conference hosts to experiment running their events virtually. Although virtual conferences have limitations, such as technical issues and loss of networking opportunities, they allow participants across the globe to overcome physical limitations and congregate to share knowledge. Removing the need for delegates to travel long distances is also beneficial for the environment and saves delegates' time and costs when compared to attending in-person conferences. By optimizing the technicalities of virtual platforms and increasing opportunities for more liberal interaction amongst delegates, conferences should continue integrating virtual experiences for their future meetings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

EH, JH, and J-HM contributed to data acquisition and contributed to data analysis. All authors contributed equally to the concept, design, and contributed to the drafting and critical revision of the manuscript.

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REVIEW
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A Review of the Efficacy and Safety for Biologic Agents Targeting IL-23 in Treating Psoriasis With the Focus on Tildrakizumab

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Psoriasis is a chronic and debilitating inflammatory immune-mediated skin disorder. Several cytokines including interleukin (IL)-23 were demonstrated to play a central role in the pathogenesis of this disease. Treatment options for psoriasis range from topical to systemic modalities, depending on the extent, anatomical locations involved and functional impairment level. Targeting cytokines or their cognate receptors that are involved in disease pathogenesis such as IL-12/23 (i.e., targeting the IL-12p40 subunit shared by these cytokines), IL-17A, IL-17F, IL-17RA, and TNF-α using biologic agents emerged in recent years as a highly effective therapeutic option for patients with moderate-to-severe disease. This review provides an overview of the important role of IL-23 signaling in the pathogenesis of psoriasis. We describe in detail the available IL-23 inhibitors for chronic plaque psoriasis. The efficacy, pharmacokinetic properties, and the safety profile of one of the most recent IL-23 biologic agents (tildrakizumab) are evaluated and reviewed in depth.

Keywords: psoriais, treatment, tildrakizumab, guselkumab, IL-23, risankizumab, mirikizumab, ustekinumab

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INTRODUCTION

Psoriasis is a T-cell mediated autoimmune inflammatory disease that primarily affects the skin but can also affect the joints and other organs. The prevalence of psoriasis in the developed countries is between ∼1–5% (1), with the most common clinical form being the chronic plaque subtype. The underlying etiology of psoriasis is multifactorial and is comprised of genetic predisposition, immunologic, environmental, and endogenous factors (2). These factors ultimately affect various components of innate and adaptive immunity to result in dysregulated keratinocyte proliferation and the development of psoriatic lesions. Psoriasis is a heterogenous disease, where >80 genes and alleles were described to increase disease susceptibility, including *HLA-Cw6, PSOR1-15, CCHCR1, CDSN* along with the range of inflammatory molecules regulated by the TNF-α signaling pathway in T helper (Th) cells (**Figure 1**) (3, 4).

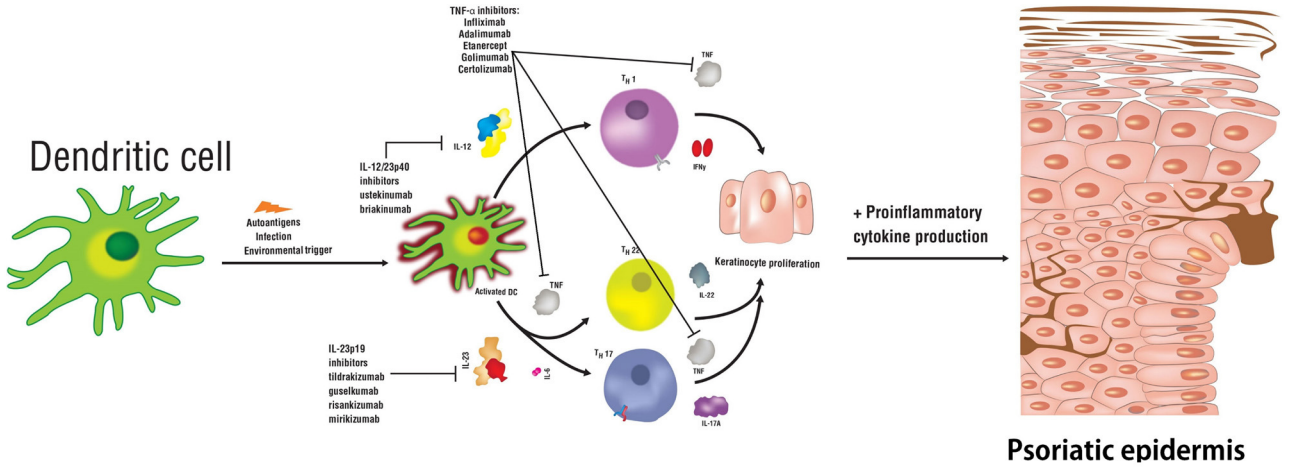

FIGURE 1 | Schematic representation of relevant cytokines and T helper cell subsets involved in the pathogenesis of psoriasis. Biologic therapies used to treat this disease are indicated along with the signaling pathways targeting specific cytokines.

THE ROLE OF INTERLEUKIN-23 SIGNALING IN THE PATHOGENESIS OF PSORIASIS

IL-23 has been shown to play a fundamental role in the pathogenesis of psoriasis (2). IL-23 is a heterodimeric cytokine composed of two subunits p19 and p40 (**Figure 2**). The p19 subunit is unique to the structure of IL-23, a 4-fold helical core with a disulfide bond, which is attached to the p40 subunit (5, 6). The p40 subunit is shared with IL-12, where it dimerizes with the p35 subunit (7). Genomic studies have confirmed that IL-23p19 is found on chromosome 12q13.2; the gene is composed of four exons and three introns, whereas, IL-23p40 is located on chromosome 11q1.3, composed of eight exons and seven introns (5–8). Antigen-presenting cells (APCs) including Langerhans cells, macrophages, and tissue-resident or recruited inflammatory myeloid CD11$^+$ dendritic cells (DC) produce IL-23. Keratinocytes were also shown to produce mRNA transcripts for IL-23p19 and IL-23p40 (9). Various immune factors are involved in the expression of IL-23 by APCs including lipopolysaccharides, CpG, and PolyI:C (10). These factors bind to toll-like receptors (TLRs) to induce the activation of transcription factors AP-1 and NF-kB, which then further leads to the upregulation of IL-23 (11).

A key immunologic function of IL-23 is to drive the differentiation process of naïve T-helper (Th) cells into Th17 cells, primary producers of IL-17. Studies demonstrate that the presence of IL-6, IL-1β, or TGF-β is not sufficient for Th17 differentiation and that concomitant IL-23 stimulation is essential. IL-23 inhibits the differentiation of regulatory T (Treg) cells that produce IL-10 and inhibit inflammation, and thus restrict Th17 differentiation (12, 13). IL-6, IL-1 β, and TGF-β are essential for the expression of IL-17A, IL-17F, and IL-23 receptors (IL-23R) (6, 14). IL-23 binds to a receptor complex to induce biological inflammatory responses (**Figure 2**). The receptor complex is comprised of two parts, IL-12Rβ1 and IL-23R

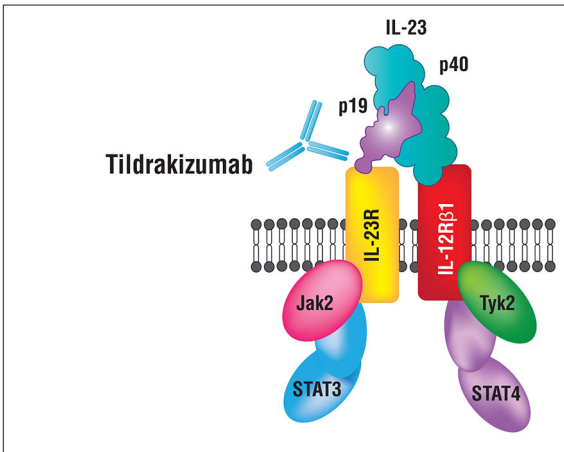

FIGURE 2 | IL-23 and its receptor complex. IL-23 is a heterodimeric cytokine composed of p40 and p19 subunits.

and is expressed by several immune cells including natural killer, dendritic and memory T-cells, macrophages, and keratinocytes (14–16). Upon binding to the receptor complex, specifically on naïve Th cells, IL-23 activates Signal Transducer and Activator of Transcription (STAT3), which then dimerizes, translocates into the nucleus and binds/transactivates the promoters of IL-17A and IL-17F (17). IL-17 is an essential cytokine involved in linking T-cell activation to neutrophil mobilization and activation of the Th17 inflammatory pathway in several autoimmune conditions including psoriasis (7, 8, 18). IL-23 and IL-12 together activate Th17 and Th1 cells that release IL-22 and TNF-α (19). IL-22 is an effector cytokine of the Th17 lineage and works cooperatively with IL-17A and IL-17F (20). Furthermore, IL-23 plays a role in promoting differentiation of CD8$^+$ T cells into cytotoxic T 17 cells (Tc17). Tc17 cells along with mast cells, neutrophils, and IL-23R$^+$ T cells further increase IL-17 production upon stimulation

by IL-23 (21–24). Intriguingly, recent data from studies in mice indicates that tissue-resident innate lymphoid 3 cells (ILC3) also produce IL-17 and IL-22 cytokines in response to IL-23 signaling, which contributes to dermal inflammation in psoriasis (25).

Thus, IL-23 stimulation and the expression of downstream cytokines secreted by T cells, $CD4^+$-T cells, regulatory T cells, cytotoxic T cells, natural killer cells, type 3 innate lymphoid cells, neutrophils, and mast cells are observed in psoriasis (26). T-cell activation inhibitors are known to significantly ameliorate psoriatic lesions, albeit, none are used for the treatment of disease due to significant adverse effects (27–30). Deregulation of genes related to the IL-23/Th17 signaling axis increases the risk of developing psoriasis. Psoriatic skin lesions have consistently demonstrated increased levels of IL-23 (specifically IL-23p19 and p40 mRNAs), IL-17, IL-22, and infiltration of epidermal Th17 cells as well as dermal Tc17 cells (22, 31–33). IL-23 protein levels were also higher in psoriatic skin, when compared to non-lesional skin (34). Intradermal injection of IL-23 in murine skin models led to histological changes consistent with psoriatic lesions. Consistent with this finding, experimental imiquimod-induced psoriasis models are dependent on IL-23 and IL-17 production (35–37). Blocking of the IL-23/IL-17 signaling axis using anti-IL-23 antibodies was shown to suppress the onset of psoriasis in experimental animals (38). IL-23p19 and IL-17RA deficient mice showed an amelioration in erythema, scaling, and skin thickening (37). Injections of recombinant IL-23 into mice stimulated epidermal hyperplasia and psoriasis plaques formation through IL-17 and IL-22 signaling, which was not observed in IL-17 and IL-22 deficient mice (39). IL-22 is known to directly induce keratinocyte proliferation and migration (40). IL-17A increases proliferation of keratinocytes and downregulates the expression of molecules involved in their differentiation. IL-17A and IL-22 interact with TNF-α to upregulate the expression of IL-36, a cytokine that further augments the function of Th17 cytokines creating a feedback loop observed in pustular psoriasis (41).

As detailed above, IL-23 and IL-12 share the same p40 subunit that binds to their receptor complexes to initiate an immune response. IL-12 binds to $CD4^+$ T cells via the IL-12 receptor complex, which triggers the differentiation of naïve T cells into Th1 cells. Th1 cells release IFN-γ and TNF-α. Together with IL-23, IL-12 increases the production of pro-inflammatory cytokines involved in the pathogenesis of psoriasis (19).

In summary, in the pathogenesis of psoriasis, IL-6, IL-1β, and TGF-β initiate the differentiation of naïve Th17 cells, alongside IL-23, which is required for Th17 activation and maintenance, and secretion of pro-inflammatory cytokines (**Figure 1**). IL-23 is crucial for the survival and proliferation of Th17 cells, primary producers of IL-17. IL-17 protein is observed at high levels in blood and skin samples from psoriasis patients. IL-23 signaling also leads to the release of IL-22, which together with IL-17, further stimulates keratinocytes to produce chemokines and antimicrobial peptides to recruit additional Th17 cells, therefore, sustaining the inflammatory response (42, 43). Concomitantly, IL-12 induces the differentiation of the Th1 cells and triggers the release of IFN-γ and TNF-α (7, 19, 22, 39, 41, 44–47).

TABLE 1 | Summary of status of approval for the treatment of psoriasis by Health Canada, the Food and Drug Administration (FDA), and the European Medicines Agency (EMA) of biologic agents presented in this review.

Biologic agent	Approved by health Canada (62)	Approved by the Food and Drug Administration (63)	Approved by the European Medicine Agency (64)
Ustekinumab	Yes	Yes	Yes
Briakinumab	No	No	No
Guselkumab	Yes	Yes	Yes
Risankizumab	Yes	Yes	Yes
Mirikizumab	Trials ongoing	Trials ongoing	Trials ongoing
Tildrakizumab	Under review	Yes	Under review
Etanercept	Yes	Yes	Yes
Infliximab	Yes	Yes	Yes
Adalimumab	Yes	Yes	Yes
Certolizumab pegol	Yes	Yes	Yes
Golimumab (for psoriatic arthritis only)	Yes	Yes	Yes
Secukinumab	Yes	Yes	Yes
Ixekizumab	Yes	Yes	Yes
Bimekizumab	Under review	Under review	Under review
Brodalumab	Yes	Yes	Yes

INHIBITION OF THE IL-12P40 SUBUNIT SHARED BY THE IL-12/23 CYTOKINES FOR THE TREATMENT OF PSORIASIS

The key role of IL-23 in the pathogenesis of psoriasis makes this cytokine an intriguing therapeutic target (48–52). Clinical studies have shown that inhibition of IL-23 effectively treats symptoms of psoriasis, as several other key inflammatory cytokines including IL-17, IL-22, TNF-α, and IL-36 are inhibited (2). Although, the focus of this review is on IL-23 inhibition and particularly on tildrakizumab (53–55), we briefly discuss inhibitors targeting TNF-α, IL-17/IL-17RA, and IL-12/23. TNF-α inhibitors include etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab (the latter used off-label to treat psoriasis) (56); IL-17 inhibitors include secukinumab, ixekizumab, and bimekizumab; IL-17RA inhibitor–brodalumab (19, 57–61); Inhibitors of IL-12p40 subunit, which affect the IL-12 and IL-23 signaling include ustekinumab and briakinumab. The status of regulatory approval by Health Canada, the U.S. Food and Drug Administration (FDA), and the European Medicine Agency (EMA) for these drugs is summarized in **Table 1**.

Ustekinumab

Discovery of elevated expression of the p40 subunit in psoriatic lesions combined with biologic plausibility prompted the development of targeted biologic therapies. The first agent was an entirely humanized antibody, ustekinumab (48). Ustekinumab targets IL-23 and IL-12 by neutralizing IL-23p40 to treat chronic plaque psoriasis and psoriatic arthritis. Ustekinumab was

approved by the FDA at the dose of 45 or 90 mg as an injection depending on the patient's weight. A randomized controlled clinical trial demonstrated that ustekinumab demonstrated superior efficacy than etanercept in treating psoriasis over a 12-week period (50). Two large randomized controlled clinical trials with the total of 1,996 patients with moderate-to-severe psoriasis demonstrated that ustekinumab 45 and 90 mg achieved a 75% reduction in the psoriasis area and severity index (PASI; PASI75) more significantly than the placebo (51, 52). Further clinical trials have assessed the long-term safety and efficacy of ustekinumab and have produced similar results (50, 65–67). Specifically, one long-term study illustrated that 76.5 and 78.6% of patients were demonstrating a PASI75 response after a 5-year period of ustekinumab 45 and 90 mg treatment, respectively (65). The adverse events (AEs) of this drug were studied across a 3-year period demonstrating comparable findings between the placebo vs. 45 and 90 mg doses of ustekinumab (50).

Briakinumab

Briakinumab is another entirely humanized antibody that was developed to inhibit p40 subunit, however drug development was discontinued (2). Initially, clinical trials suggested that this agent was effective and safe (68, 69). A randomized controlled study, where 347 chronic plaque psoriasis patients were given briakinumab, etanercept, or placebo, showed that briakinumab was superior to etanercept (68). Another randomized controlled, double-blind clinical trial demonstrated that briakinumab was more effective than methotrexate. However, concern about increased occurrence of serious AEs including infections, malignancies, and, importantly, cardiac events led to the discontinuation of briakinumab's development (40).

TARGETED INHIBITION OF IL-23 SIGNALING AS A RELIABLE SYSTEMIC TREATMENT STRATEGY FOR PSORIASIS

Therapeutic agents specifically targeting IL-23p19 subunit include guselkumab, tildrakizumab, risankizumab, and mirikizumab.

Guselkumab

Guselkumab is a humanized IgG1 lambda monoclonal antibody used to treat moderate-to-severe chronic plaque psoriasis (70). The dosage is 100 mg administered at weeks 0, 4 and then every 8 weeks thereafter (71–73). An initial randomized controlled trial with 24 participants at week 12 demonstrated a PASI75 response in guselkumab treated patients at a significantly higher rate than in patients receiving a placebo (73). Two randomized controlled trials (VOYAGE 1 and VOYAGE 2) compared the efficacy and safety of guselkumab 100 mg, adalimumab (a TNF-α inhibitor), a commonly used biologic at that time for chronic plaque psoriasis, and a placebo. In VOYAGE 1 trial, 73.3% of patients using guselkumab achieved a PASI90 disease response at week 16, when compared to 49.7% of patients using adalimumab. VOYAGE 2 trial demonstrated a PASI90 response of 70 and 2% for guselkumab vs. placebo groups, respectively. Investigator Global Assessment (IGA 0/1) improvement was also significantly greater for the guselkumab compared to the adalimumab and placebo groups, with 85 vs. 65.9% and 7% of patients achieving IGA 0/1, respectively, at week 16. Both studies showcased the long-term efficacy of guselkumab up to 48 weeks. AEs were comparable across all groups (72, 74). Another randomized controlled trial included patients receiving ustekinumab 45 or 90 mg at weeks 0 and 4. At week 16, patients with inadequate responses to ustekinumab (defined as maintaining an IGA score of $\geq$2) were re-randomized to receive guselkumab 100 mg or they continued the same ustekinumab treatment. This trial illustrated that at week 28, 48.1% of patients after switching to guselkumab achieved a PASI90 response rate in comparison to 22.6% of patients continuing to receive ustekinumab. IGA improvements for the guselkumab vs. ustekinumab arms of the study were observed in 31 and 14% of the patients, respectively, at week 28. Thus, guselkumab was shown to be a superior alternative for ustekinumab in patients, who do not respond to IL-12/23 p40 inhibitor. However, 66.4% of patients receiving guselkumab had an AE compared to 55.6% treated with ustekinumab; the most frequent being common non-severe infections (75).

The systematic review and Bucher indirect comparison of tildrakizumab and guselkumab demonstrated that one treatment is not superior to the other, according to the results from the reSURFACE 1/2, and VOYAGE 1/2 trials. There were no statistically significant differences between the two biologic agents in achieving PASI75 and 90 scores or serious AEs (76). The rates of discontinuation at weeks 12 to 16 and 24 to 28 were comparable between the drugs (76). The data for the outcomes of the placebo groups for weeks 24 to 28 was imputed from weeks 12 to 16 due to the discontinuation of the placebo arm after week 16. The authors assumed that changes are not expected in the placebo arm beyond weeks 12 to 16, which is a limitation of this study design.

Risankizumab

Risankizumab is a human monoclonal antibody of IgG1 class that also targets the IL-23p19 subunit for the treatment of psoriasis (a dosing schedule of 150 mg at weeks 0, 4, and subsequently every 12 weeks) (77). A phase III randomized controlled trial compared the efficacy of risankizumab with adalimumab in patients with moderate-to-severe chronic plaque psoriasis (78). In total, 605 patients were enrolled in this study and randomized to receive risankizumab or adalimumab. Seventy two percent of patients in the risankizumab group achieved a PASI90 score compared to 47% of patients in the adalimumab group at week 16. Subsequently, 66% of patients in the adalimumab group were able to achieve a PASI90 score at week 44, after switching to receive risankizumab treatment, while only 21% of patients, who continued the treatment with adalimumab, achieved a PASI90 score. AEs were similar across all groups. Two phase III multicenter trials (ultIMMa-1 and ultIMMa-2) were further conducted to compare risankizumab 150 mg *vs.* placebo *vs.* ustekinumab (79). Both trials demonstrated risankizumab to be more effective than the placebo and ustekinumab; ultIMMa-1 trial illustrated that 75.3% of patients achieved a PASI90 score at week 16 using risankizumab compared to 4.9 and 42% of patients

in the placebo and ustekinumab groups, respectively. At week 52, 82, and 56% of patients receiving risankizumab achieved PASI90 and PASI100 scores in the ultIMMa-1 trial, similar to 81 and 60%, respectively in the ultIMMa-2 trial. Treatment-emergent AEs were consistent across all groups, most of which included the upper respiratory tract infections (URTIs), fatigue, headache, injection-site reaction, and dermatophyte infections. A 2-year trial further assessed the efficacy and safety of continuous use of risankizumab. Participants receiving risankizumab achieved a PASI90 clearance at a significantly higher rate than the placebo group: 73.2 vs. 2% of patients, respectively, at week 16. The rates of AEs remained stable and were comparable to those observed in the placebo arm over the 2 years (80). An immunohistochemical analysis of 81 psoriasis patients treated with risankizumab for 4 weeks showed a significant decrease in immunohistochemical marker staining associated with psoriasis including K16, Ki67, CD3, and CD11c in 69% of patients receiving 180 mg dosing. Similar molecular changes were observed in only 29% of patients treated with ustekinumab (81).

Mirikizumab

More recently, mirikizumab, a humanized monoclonal IgG4-variant antibody, was developed as an IL-23 antagonist. This biologic agent is currently being studied for its potential use in psoriasis and Crohn's disease/Ulcerative colitis patients. A multicentre phase II randomized controlled trial assessed the efficacy and safety of mirikizumab in treating moderate-to-severe chronic plaque psoriasis. In total, 205 patients were randomized into either a placebo *vs.* mirikizumab 30 mg, 100 mg, or 300 mg groups, where injections were administered at weeks 0, 8, and then every 8 weeks thereafter. At week 16, 67 and 59% of patients in the mirikizumab 100 and 300 mg groups, respectively, achieved a PASI90 score, compared to 0% in the placebo group. AEs were similar across all groups. Hypertension was observed in 5 patients receiving mirikizumab 100 mg and 300 mg groups, along with viral infections/URTIs, injection-site pain and diarrhea, and were similar across all dosage groups. Serious AEs included suicidal tendencies, observed once in both placebo and mirikizumab groups, and alanine aminotransferase and aspartate aminotransferase enzyme elevation >10 times of the upper limit of normal, observed once in the mirikizumab group. Further studies are required to demonstrate that this biologic agent is an effective and safe therapeutic option for psoriasis (82).

Tildrakizumab

Tildrakizumab is a high affinity humanized monoclonal IgG kappa IL-23p19 antibody (83–94). Tildrakizumab (SCH-900222, MK03222) was developed by Merck, Sun Pharmaceutical Industries and approved by the FDA in March 2018 for the treatment of moderate-to-severe chronic plaque psoriasis in adults (95–97). Tildrakizumab was the second IL-23p19 inhibitor approved by the FDA after guselkumab (98). Tildrakizumab binds to IL-23p19 and inhibits its interaction with the IL-23 receptor. The recommended dose is 100 mg administered on 0, 4 weeks, and then every 12 weeks thereafter. However, it is up to the physician's discretion to escalate the dose to 200 mg, when necessary (99). Tildrakizumab is recommended as the first line monotherapy for moderate-to-severe psoriasis (100). This antibody is available in 1 mL syringes at 100 mg/ml concentrations. The pre-filled syringes should be stored in a refrigerator and left at room temperature for 30 min before use.

In 2015, a phase 1, randomized placebo-controlled trial evaluated the efficacy of tildrakizumab in treating chronic plaque psoriasis. This initial trial has demonstrated PASI75 score in all subjects treated with intravenous tildrakizumab 3 and 10 mg/kg by day 196 in two out of the three parts of this phase 1 trial (101). These successful results were followed by a phase 2b trial assessing the safety and efficacy of subcutaneous tildrakizumab in moderate-to-severe chronic plaque psoriasis (102). Tildrakizumab's efficacy and safety was superior to placebo, maintaining response for 52 weeks of treatment and persisting for 20 weeks after cessation. However, this trial was limited due a small sample size, requiring a larger phase 3 trial assessing the safety and tolerability of tildrakizumab. In 2017, the results from two phase 3 trials were published. These studies illustrated that tildrakizumab 100 and 200 mg doses are more effective and well-tolerated compared to the placebo and etanercept in treating moderate-to-severe chronic plaque psoriasis (103). However, these trials were limited because comparisons with more effective TNF-α inhibitors or ustekinumab have not been conducted. The non-responders treated with tildrakizumab discontinued therapy before part 3, which started at week 28 of the trial. This resulted in lower dropout rates in these treatment arms within 28 weeks. The authors also noted that 12 weeks may have been too early to assess the efficacy of tildrakizumab adequately. Thus, in-between-treatment analyses for tildrakizumab 100 mg were not conducted at several endpoints, including PASI75 and PGA responses at 28 weeks. Currently, four other trials are ongoing to assess the efficacy and safety of tildrakizumab. These include the extension phase 3 reSURFACE 1 and reSURFACE 2, two multinational, phase 2 trials, a multiple-dose phase 2b study in patients with active psoriatic arthritis, and a phase 2a study in patients with active ankylosing spondylitis or non-radiographic axial spondylarthritis. The extensions of reSURFACE 1 and 2 are observational studies designed to further assess the efficacy profile of tildrakizumab and its adverse events (103, 104).

EFFICACY OF TILDRAKIZUMAB IN THE TREATMENT OF PSORIASIS: DETAILED REVIEW OF CLINICAL TRIAL DATA

As highlighted above, a phase I, randomized controlled trial with 77 subjects demonstrated a PASI75 response in participants treated with the 3 and 10 mg/kg intravenous tildrakizumab after 196 days from the first dose. This study also included a histological, immunohistochemical, and gene expression analyses of psoriatic skin following the treatments. Individuals treated with 3 mg/kg and 10 mg/kg of intravenous tildrakizumab experienced a resolution of thickened psoriatic skin lesions and demonstrated reduced epidermal hyperplasia as well as a decrease of vascular and inflammatory cell infiltrate parameters. All of the groups had a significant reduction in the histopathological

psoriasis severity score, a mean reduction of 67%. Proliferation markers including Ki67 and keratin 16, apparent in psoriasis, also normalized upon treatment, along with the inflammatory infiltrating cells (epidermal $CD4^+$ and $CD8^+$ T-cells, dermal myeloid DCs, plasmacytoid DCs, and $CD15^+$ neutrophils). Tildrakizumab treatment reduced and normalized the levels of IL-19, IL-20, CCL20 ligands (CCL20 is overexpressed in psoriasis and binds to Th17 chemokine receptors), and CXCL8/IL-8 (overexpressed in psoriasis and binds to neutrophil CXCE1/2 receptors) in the lesional skin (101).

A phase II randomized controlled trial with 355 patients affected by chronic plaque psoriasis demonstrated that subcutaneous injections of tildrakizumab resulted in PASI75 clearance that was maintained through 1 year. The most potent response was produced using the tildrakizumab 200 mg treatment, where PASI75 clearance was achieved in 74.4% of patients at week 16, compared to 66.3% in patients receiving 100 mg dosing and 4.4% in the placebo group (102). Two randomized controlled phase III trials (reSURFACE 1 and reSURFACE 2) were conducted to compare the efficacy and safety of tildrakizumab ($n = 1{,}863$ subjects). In part 1 of the reSURFACE 1 trial, participants received tildrakizumab 100, 200 mg, or placebo treatments subcutaneously at 0 and 4 weeks. In part 2, tildrakizumab treated patients received doses at week 16, and the placebo group patients were re-randomized to receive either tildrakizumab 100 or 200 mg for weeks 12 and 16 doses. In the reSURFACE 2 trial, during part 1 participants received tildrakizumab 100, 200 mg, a placebo treatment, or etanercept 50 mg (50 mg twice a week for 12 weeks then 50 mg once weekly for 16 weeks). In part 2 of this trial, tildrakizumab group patients received doses at week 16, while the re-randomized placebo group patients received tildrakizumab 100 or 200 mg for weeks 12 and 16 doses. In part 3 of both trials, responders and partial responders (PASI $\geq$ 75 and PASI $\geq$50 or PASI <75, respectively) to tildrakizumab treatment were re-randomized to continue the same regimen, an alternative tildrakizumab dosing, or a placebo treatment for subsequent doses. Patients with missing data were treated as non-responders and in these cases data imputation was carried our. However, for secondary analyses, the full-analysis-set observed data (i.e., all randomized participants who received one or more doses of treatment and had baseline and one or more post-baseline efficacy measurements) was conducted.

The results demonstrated at week 12, that tildrakizumab 100 and 200 mg treatments were significantly more effective than the placebo and etanercept groups in achieving PASI75 clearance. In the reSURFACE 2 trial, 61% and 66% of patients receiving tildrakizumab 100 mg or 200 mg, respectively, achieved a PASI75 response score compared to 48, and 6% in etanercept and placebo groups, respectively. AEs were similar and occurred at low frequency across all groups (103).

Combined data from phase IIb and III trials demonstrated that PASI75 was achieved using tildrakizumab 200 mg (62–74%), 100 mg (61–64%), 25 mg (59%), 5 mg (24%) doses, in comparison to a placebo and etanercept: 4–6 and 48%, respectively at week 12. The phase III reSURFACE trials also demonstrated that ∼70% of tildrakizumab patients achieved a Physician Global Assessment (PGA) score of clear or almost clear. A review of phase II and III trial data using tildrakizumab established that the most common AEs included common, non-threatening infections.

Recently the data became available highlighting 5-year efficacy and safety outcome based on long-term extension of the reSURFACE 1 and 2 trails (105). The results highlighted that patients who responded to tildrakizumab (i.e., achieved PASI 75 at week 28) 100 mg treatment demonstrated PASI 75/90/100 response at week 244 at the rate of 88.7, 65.9, and 32.8%, respectively. For the 200 mg treatment, responders at week 28 continued to demonstrate clinical benefit at week 244 as 92.5% of patients achieved PASI75, while 69.5 and 40.8% of patients achieved PASI90 and PASI100 responses, respectively. Subjects that demonstrated a partial response to etanercept and non-responders were switched to receive tildrakizumab 200 mg treatment. These patients benefitted and achieved PASI75/90/100 and at rates of 81.3, 49.5, and 21.5%, respectively. Five-year analysis of safety data was comparable to findings of shorter time studies, where the most frequent treatment related AE was nasopharyngitis. Several severe AEs were observed in both tildrakizumab 100 mg and 200 mg groups and were deemed not related to treatment (105). Hence, long-term continuous dosing or switching from another biologic agent could be part of the psoriasis management regimen using tildrakizumab.

Furthermore, the impact of patient demographic and disease characteristics on tildrakizumab efficacy was studied. PASI75 and 90 scores were achieved slightly more frequently (not reaching statistical differences) in patients, who were <65 years of age, and had a bodyweight of <90 kg, no evidence of arthritis, and no prior biologic exposure. The efficacy of tildrakizumab did not differ based on sex, race, and prior failure of conventional systemic treatments (106). To further assess the efficacy of tildrakizumab 100 mg treatment on scalp, head and neck psoriasis disease at week 28 a *post-hoc* analysis was conducted using the data from the reSURFACE 1 trial. A PASI head component score (PASIh) (range 0.0–7.2) was used. Rapid, progressive reduction in PASIh score was noted at week 28. Tildrakizumab's efficacy for scalp, head and neck clearance has shown to be similar to secukinumab and adalimumab treatments, however, there are no direct comparison studies available (107). A *post-hoc* analysis also demonstrated that tildrakizumab treated patients with PASI > 75 at week-28 maintained their improvement at week 52, and >50% of the partial responders at week 28 improved their PASI scores to more than 75 at week 52 (108). Gordon et al. further evaluated supplementing dichotomous efficacy with residual disease activity and found that disease activity was more reliably estimated by PASI scores than PASI improvements by percentages. At week 12, the median PASI score was 2.9 and the response rate for PASI 90 was 36.9%, whereas, at week 28, the median PASI was 1.7 and the response rate for PASI 90 was 51.9% (109). Another *post-hoc* analysis assessed the time and predictors leading to relapse in patients treated with tildrakizumab 100 and 200 mg. The median time to loss of PASI 75 from 28 weeks was 142 and 172 days with 100 and 200 mg dosing, respectively.

Increase in body mass index and an increase in disease duration were associated with relapse (110).

COST EFFECTIVENESS

Tildrakizumab has been shown to be cost-effective. The introduction of tildrakizumab with a 1% annual uptake over 5 years can potentially reduce the cost of treating psoriasis patients based on the data from the United States. In a population of 1,048 psoriasis patients treated with tildrakizumab, the total health plan costs decreased by $964,763 over the span of 5 years. Tildrakizumab is one of the most cost-effective first-line psoriasis treatments. It has been shown to be more cost-effective than risankizumab, secukinumab, guselkumab, ixekizumab, adalimumab, ustekinumab, etanercept, and certolizumab pegol (111–113).

PHARMACOKINETIC PROPERTIES OF TILDRAKIZUMAB

The bioavailability of tildrakizumab is ∼73–80% following an injection (96). The half-life of tildrakizumab is ∼20.2–28.2 days, with the low volume of distribution of ∼10.8 L. Intravenous administration of tildrakizumab 0.1, 0.5, 3, or 10 mg/kg produced mean half-life times of 29.4, 29.7, 26.9, and 24.6 days, respectively (104). Dosing with 100 mg of tildrakizumab on weeks 0, 4, and every 12 weeks thereafter resulted in a steady state achieved by week 16, where the mean steady-state concentration ranged from 1.22 ± 0.94 to 1.47 ± 1.12 mcg/mL (99). Tildrakizumab is most likely cleared via catabolic pathways that degrade this immunoglobulin into small peptides and amino acids. However, the pharmacokinetic properties of tildrakizumab and its use in geriatric, pediatric, breastfeeding, or pregnant female populations have not been extensively studied (96, 99). Other pharmacokinetic parameters including maximum concentration and area under the curve of tildrakizumab increase proportionally from doses of 50–200 mg. Increased body weight resulted in lower area under the plasma concentration-time curve at steady state (114). The pharmacokinetic properties of tildrakizumab are similar to other monoclonal antibodies and do not require dosage adjustments.

To better understand IL-23 pharmacokinetic parameters, the degree of target suppression associated with clinical efficacy, accelerator mass spectrometry was used to measure the concentration of human recombinant [^{14}C]-IL-23 in cynomolgus monkeys. It was found that the predicted rank order of reduction of free IL-23 was consistent with the reported rank order of PASI100 scores in clinical efficacy trials; the rankings were ustekinumab < tildrakizumab < guselkumab < risankizumab (115).

It was also found that the pharmacokinetic factors such as half-life, maximum concentration, drug exposure over time, and median time to drug concentration were comparable across different races and/or ethnicities including Chinese, Japanese and Caucasian. The overall geometric mean area under the receiver operating curve was 6.15, 6.05, and 6.32-day ×μg/mL/mg for Japanese, Caucasian and Chinese subjects, respectively, upon treatment with tildrakizumab (116). Across all three populations, 10 mg/kg dosing was well-tolerated. Other studies demonstrated that 50 mg of tildrakizumab dosing had a bioavailability of 80% and 200 mg dosing had a bioavailability of 73% (101, 116–118).

The effect of tildrakizumab on cytochrome P450 metabolism was studied in psoriasis patients, as changes in systemic inflammation have been shown to alter cytochrome P450 metabolism. Tildrakizumab showed no clinically relevant effects on the pharmacokinetic properties of the probe substrates. There were also no changes in the IL-6 or high-sensitivity C-reactive protein levels (119).

A few studies have assessed the immunogenicity of tildrakizumab evaluating antidrug antibody (ADA) production. Between 8 and 18% of patients tested positive for an ADA after a treatment with tildrakizumab. Two of the studies demonstrated decreased levels of tildrakizumab in patients with positive ADAs, and another demonstrated a decrease in tildrakizumab half-life in ∼30% of subjects with ADAs. However, further studies are required to understand the immunogenicity of tildrakizumab and the relevance of antibody suppressants in ADA positive patients (102, 116, 118). Finally, another study evaluating ADA development in psoriasis patients established a dose-dependent relationship, where 6.5 and 8.2% of treatment-emergent ADAs occurred using tildrakizumab 100 mg and 200 mg dosing regimens, respectively. Specifically, the incidence of treatment-emergent ADA-positive *neutralizing* antibodies was 2.5 and 3.2% for tildrakizumab 100 and 200 mg, respectively. In patients with a positive ADA, when compared to a negative ADA status, the efficacy of tildrakizumab decreased. At week 52, the mean PASI score improvement in treatment-emergent neutralizing antibody-positive vs. ADA negative patients were 76% (n = 10) vs. 91% (n = 342) for the 100 mg of tildrakizumab dosing regimen. Thus, participants with treatment-emergent ADAs and neutralizing antibodies showed reduced efficacy and lower serum levels of tildrakizumab (120).

SAFETY PROFILE OF TILDRAKIZUMAB

As highlighted by the data from clinical trials, tildrakizumab is a reliable treatment leading to only minor AEs, including an increased risk of nasopharyngitis/URTIs (99). To test safety, 29 healthy subjects were randomized to receive either 0.1, 0.5, 3, or 10 mg/kg doses of tildrakizumab, or a placebo treatment intravenously. Of the subjects receiving intravenous tildrakizumab, 83% reported at least one AE, 50% in 0.1 mg/kg; 100% in 0.5 mg/kg; 88% in 3 mg/kg; 100% in 10 mg/kg; and 71% in the placebo groups. The most common AEs were URTIs, headaches, injection-site reactions, and fatigue. Serious AEs included upper airway obstruction observed in the placebo group, and rhinal surgery observed in the 10 mg/kg treatment group (117). In a different study, 37 healthy subjects were randomized to receive 50 or 200 mg of tildrakizumab, or placebo subcutaneously. Subcutaneous injections resulted in AEs in 65% of participants; 64% in 50 mg; 57% in 200 mg; and 78% in the placebo group. Common AEs included URTIs and headaches,

and no serious AEs were observed (117). Also, while the product monograph advises to evaluate patients for a possible latent or active tuberculosis infection, as per the typical "biologic classification," because of the targeted nature of this treatment, the risk of reactivating or increasing susceptibility to tuberculosis remains low (121).

The incidence of serious gastrointestinal disorders, including inflammatory bowel disease (Crohn's disease and ulcerative colitis), were assessed in detail using the data from phase IIb and III trials (118, 122, 123). The *post-hoc* analysis based on 28 weeks of clinical trial data concluded that tildrakizumab did not induce or worsen inflammatory bowel disease in patients with psoriasis. This is in contrast to the clinical trials using IL-17 and IL-17RA inhibitors that demonstrated new cases and exacerbation of inflammatory bowel disease in psoriasis and Crohn's disease patients (124).

Furthermore, as mentioned above the long-term safety and tolerability of tildrakizumab has been evaluated using the data from tildrakizumab clinical trials for up to 244 weeks (105). Consistent with our review, frequencies of treatment-emergent AEs, serious AEs, discontinuations due to AEs, major adverse cardiovascular events, and severe infections were comparable between tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and etanercept groups in the reSURFACE 1 and 2 trials. There were no AEs of inflammatory bowel disease or suicides reported up to 244 weeks of tildrakizumab use. Candida skin infections were infrequent with rates of 0.1, 0.3, 0.0, and 0.0% for the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo and etanercept groups, respectively (105, 125).

Psoriasis is associated with the metabolic syndrome and portends a higher risk of cardiovascular disease (126). A *post-hoc* analysis of the tildrakizumab trials demonstrated that the efficacy, safety, and drug survival were comparable and similar in psoriasis patients with or without a metabolic syndrome (127). A recent study demonstrated that the cardiometabolic risk factors for patients receiving tildrakizumab 100 mg or 200 mg doses differed at week 52 and 64 compared to the baseline. To evaluate cardiometabolic risk, fasting serum glucose, low/high-density lipoprotein-cholesterol, total cholesterol, triglyceride levels, body weight, and blood pressure were studied (128). It was confirmed that patients with psoriasis treated with tildrakizumab 100 or 200 mg doses up to 3 years were not susceptible to increased cardiovascular risk (129).

Another important consideration is the use of tildrakizumab during pregnancy. A recent consensus paper regarding the management of chronic plaque psoriasis with biologic therapies in women of child-bearing potential stated that tildrakizumab could be transported across the placenta and there is a possibility that it can be present in breast milk. A *post-hoc* analysis of clinical trials analyzed 14 women who received tildrakizumab and became pregnant. The outcomes included 6 cases of fetal loss (2 spontaneous and 4 elective abortions) and 8 live births. There were no congenital anomalies observed. This study does not demonstrate a clear association, as it is unknown whether tildrakizumab led to the spontaneous abortions in the aforementioned 2 cases. It is worth noting that ∼10–15% of all natural pregnancies end in recognized spontaneous abortions (130). Hence, 2/14 spontaneous abortion rate is comparable to that in the general population. Nevertheless, female patients should use contraceptive measures, when treated with tildrakizumab and should refrain from using this biologic agent if pregnant until more data becomes available (131). To our knowledge, there are no studies conducted evaluating the safety of tildrakizumab during breast feeding. Due to tildrakizumab's large molecular structure, it is unlikely to be absorbed by the infant and is likely to be metabolized by the infant's gastrointestinal tract (132, 133).

The safety profile of tildrakizumab was also assessed using a cynomolgus monkey model. Cynomolgus monkeys were treated with 100 mg/kg of tildrakizumab every 2 weeks up to 9 months and the drug was found to be well-tolerated at systemic exposures approximately 90 times higher than what is recommended for human patients. Treatment with tildrakizumab 100 mg/kg in pregnant monkeys did not lead to embryofetal developmental abnormalities (134).

Tildrakizumab is contraindicated in patients with a previous serious hypersensitivity to this drug or to any of the excipients. If a hypersensitivity reaction occurs, use should be discontinued. The use of live vaccines should also be restricted. Prior to initiating tildrakizumab, age-appropriate immunizations should be completed according to the immunization guidelines (99).

COMPARING EFFICACY AND SAFETY PROFILES OF TILDRAKIZUMAB

There are no direct head-to-head comparison clinical studies evaluating the efficacy and safety of tildrakizumab to other biologic agents aside from etanercept, as presented earlier. In **Tables 2–4** and Table 1 in **Appendix**, we compared the efficacy/safety of tildrakizumab in treating psoriasis with clinical trials conducted using other biologic agents: IL-23 inhibitors [i.e., guselkumab (72, 74), risankizumab (79), mirikizumab (82)], IL-23/12p40 inhibitor [i.e., ustekinumab (51, 52)], IL-17/IL-17 receptor inhibitors [i.e., secukinumab (135), ixekizumab (123), brodalumab (136), and bimekizumab (137)], and TNF-α inhibitors [i.e., etanercept, infliximab (138), adalimumab (139), certolizumab pegol (140), and golimumab (141)]. We indicated PASI75, 90, and 100 scores, PGA measures, common adverse and serious AEs from each pivotal clinical trial and compared demographic parameters of the study population.

A recent systematic review of IL-17, IL-17RA, IL-12/23, and IL-23 inhibitors demonstrated that tildrakizumab 100 and 200 mg dosing ranked higher than guselkumab 100 mg, ustekinumab 45 mg, and brodalumab 140 mg dosing in achieving a PASI75 response short-term (142). However, this review had several limitations including the lack of detail on randomization sequence generation, allocation concealment, and blinding in the trials, most of the analyses were indirect comparisons, and the medical histories of patients were not accounted for. Tildrakizumab 100 and 200 mg treatments ranked the lowest for short-term risk of AEs but ranked higher than risankizumab 150 mg in short-term risk of serious AEs. One study compared the safety profiles of tildrakizumab, guselkumab,

TABLE 2 | Summary of the demographic data of patients enrolled in clinical trials testing the efficacy of IL-23, IL-23/12, IL-17, IL-17RA, and TNF-α inhibitors.

References	Phase	Biologic	Dosing scheme	Endpoint week	Total (*n*)	Age (years)	Male (%)	Weight (kg)	BMI (kg/m ∧ 2)	Disease duration (years)	% body surface
Resurface 1 (103) (dosing scheme summary only from part 1)	3	Tildrakizumab	100 mg, week 0, 4	12	309	46.4	67	88.5			29.7
		Tildrakizumab	200 mg, week 0, 4	12	308	46.9	73	88.9			30.9
		Placebo		12	154	47.9	65	87.5			29.6
Resurface 2 (103) (dosing scheme summary only from part 1)	3	Tildrakizumab	100 mg, week 0, 4	12	307	44.6	72	89.4			34.2
		Tildrakizumab	200 mg, week 0, 4	12	314	44.6	72	88.4			31.8
		Etanercept	50 mg, week 0, 4	12	313	45.8	71	88			31.6
		Placebo		12	156	46.4	72	88.7			31.3
Papp et al. (102)	2b	Tildrakizumab	5 mg, week 0, 4	12	42	43.2	74		28.9		
		Tildrakizumab	25 mg week 0, 4	12	92	46.3	65		28.5		
		Tildrakizumab	100 mg week 0.4	12	89	45.5	85		29		
		Tildrakizumab	200 mg week 0, 4	12	86	43.2	76		28.5		
		Placebo		12	46	45.9	83		29.5		
Kopp et al. (101)	1	Tildrakizumab	3 mg/kg–weeks 0, 4	28	7	52.7	100	90.27			
		Tildrakizumab	10 mg/kg–weeks 0, 4	28	6	46.2	67	94.25			
		Placebo		28	20	45.5	80	102.46			
Voyage 1 (72)	3	Guselkumab	100 mg–week 0, 4	16	329	43.9	72.9		29.7	17.9	28.3
		Placebo		16	174	44.9	68.4		28.9	17.6	25.8
Voyage 2 (74)	3	Guselkumab	100 mg–week 0, 4	16	496	43.7	70.4		29.6	17.9	28.5
		Placebo		16	248	43.3	69.8		29.6	17.9	28
UltIMMa-1 (79)	3	Risankizumab	150 mg–week 0, 4	16	304	48.3	70	87.8			26.2
		Placebo		16	102	49.3	77	88.8			27.9
UltIMMa-2 (79)	3	Risankizumab	150 mg–week 0, 4	16	294	46.2	69	92.2			26.2
		Placebo		16	98	46.3	68	92.2			23.9
Reich et al. (82)	2	Mirikizumab	100 mg–week 0, 8	16	51	46	69	86.4		18.6	26.5
		Mirikizumab	300 mg–week 0, 8	16	51	47.5	71	87.9		18.1	21.3
		Placebo		16	52	46	81	89.1		18	26.4
Phoenix-1 (51)	3	Ustekinumab	90 mg–week 0, 4	12	256	46.2	67.6	93.8		19.6	25.2
		Placebo		12	255	44.8	71.8	94.2		20.4	27.7
Phoenix-2 (52)	3	Ustekinumab	90 mg–week 0, 4	12	411	46.6	66.7	91.5		20.3	27.1
		Placebo		12	410	47	69	91.1		20.8	26.1
FIXTURE (135)	3	Secukinumab	150 mg–weeks 0–4 then every 4 weeks thereafter	12	327	45.4	72.2	83.6		17.3	34.5
		Secukinumab	300 mg–weeks 0–4 then every 4 weeks thereafter	12	327	44.5	68.5	83		15.8	34.3
		Placebo		12	326	44.1	72.7	82		16.6	35.2
		Etanercept	50 mg–weeks 0–4 then every 4 weeks thereafter	12	326	43.8	71.2	84.6		16.4	33.6
UNCOVER-1 (123)	3	Ixekizumab	160 mg × 1, 80 mg (q2w)	12	433	45	67.2	92		20	27
		Ixekizumab	160 mg × 1, 80 mg (q4w)	12	432	46	66.9	92		19	28
		Placebo		12	431	46	70.3	92		20	27
AMAGINE-1 (136)	3	Brodalumab	140 mg q2w	12	219	46	74	90.6		19	27.4
		Brodalumab	210 mg q2w	12	222	46	73	91.4		20	25.1
		Placebo		12	220	47	73	90.4		21	26.9
BE ABLE 1 (137)	2b	Bimekizumab	160 mg q4w	12	40	43.4	65.1	91.6		15.9	24
		Bimekizumab	320 mg q4w	12	43	42.6	74.4	86.9		15.9	24
		Placebo		12	42	46.7	59.5	88.8		15	25.5

(Continued)

TABLE 2 | Continued

References	Phase	Biologic	Dosing scheme	Endpoint week	Total (*n*)	Age (years)	Male (%)	Weight (kg)	BMI (kg/m ∧ 2)	Disease duration (years)	% body surface
EXPRESS II (138)		Infliximab	5 mg/kg	14	314	44.5	65	92.2		19.1	28.7
		Placebo		14	208	44.4	69.2	91.1		17.8	28.4
REVEAL (139)	3	Adalimumab	40 mg q2w	15	814	44.1	67.1	92.3		18.1	25.8
		Placebo		15	398	45.4	64.6	94.1		18.4	25.6
CIMPACT (140)	3	Certolizumab pegol	200 mg q2w	16	165	46.7	68.5	89.7		19.5	28.1
		Placebo		16	57	46.5	59.6	93.7		18.9	24.3
GO-VIBRANT (141)	3	Golimumab	2 mg/kg, weeks 0, 4 then every 8 weeks thereafter	16	241	45.7	53.1			6.2	
		Placebo		16	239	46.7	50.6			5.3	

and risankizumab using phase III clinical trials. The biologic treatments evaluated did not show any significant safety concerns and the overall safety profiles were comparable. The most common AE amongst all evaluated biologic agents was the occurrence of nasopharyngitis/URTIs (143).

A systematic review on the rapidity of onset of action for IL-17 and IL-23 inhibitors for psoriasis demonstrated that the time to onset of action for brodalumab was 2.1–2.6, and 2.2–2.3 weeks for ixekizumab, which were quicker than tildrakizumab (5.6–5.7 weeks), secukinumab (3.0–4.3 weeks), and guselkumab (3.8 weeks) (144). The onset of action was defined by the weighted mean time needed for 25 and 50% of patients to achieve a PASI90 score. A network meta-analysis compared the efficacy of biologic therapies for psoriasis using PASI75, 90, and 100 responses. Specifically, 62 randomized controlled trials were evaluated, and it was determined that tildrakizumab, adalimumab, brodalumab, certolizumab pegol, guselkumab, risankizumab, secukinumab, and ustekinumab were comparable with respect to short-term efficacy and tolerability in comparison to the placebo and methotrexate at 10–16 weeks (145), however, this analysis did not include data beyond 16 weeks of treatment. This study also calculated the numbers needed to treat to benefit/harm (NNTB/NNTH) as the reciprocal of the corresponding risk; thus, the NNTB/NNTH for tildrakizumab vs. placebo was 3 (95% CI: 2–4) and non-significant for tildrakizumab vs. adalimumab in achieving PASI90 clearance during weeks 10–16. Similarly, another Bayesian and Frequentist network meta-analyses using 32 phase III clinical trials demonstrated that brodalumab and ixekizumab had the quickest treatment effects based on PASI75 response at weeks 2, 4, and 8 as well as based on PASI90 and PASI100 scores at weeks 2, 4, 8, and 12. The PASI score changes of tildrakizumab were negligible for the initial 2 weeks of therapy (146). The speed of onset and level of skin improvement between ixekizumab and guselkumab, tildrakizumab, and risankizumab in patients with moderate-to-severe plaque psoriasis were also compared. Matched adjusted indirect comparisons demonstrated that ixekizumab was superior to guselkumab, tildrakizumab, and risankizumab short term (week 2–12) with respect to the onset and clinical efficacy (147). A study comparing the speed of onset and level of improvement between ixekizumab, tildrakizumab, guselkumab, and risankizumab further demonstrated that ixekizumab provided a quicker onset of response and clinical benefit than the IL-23 inhibitors using matched adjusted indirect comparisons from clinical trials (147). Ixekizumab showed favorable results over tildrakizumab based on the data from weeks 2–12 evaluating PASIs 75, 90, and 100 scores. A network meta-analysis comparing the efficacy and safety of risankizumab, guselkumab, tildrakizumab, and ustekinumab to treat moderate-to-severe psoriasis also illustrated that risankizumab 90 and 180 mg doses were more effective than tildrakizumab 5, 25, 100, and 200 mg treatment (148). This study used indirect comparisons and the surface under the cumulative ranking curve. The safety was comparable between all IL-23 inhibitors and placebo.

Another network meta-analysis compared the efficacy and safety of systemic agents including tildrakizumab, guselkumab as well as IL-12/23 and TNF-α (149). The study demonstrated that at class level, all of the interventions including tildrakizumab were significantly more effective than the placebo at reaching PASI90 clearance for chronic plaque psoriasis. However, there was significant difference between the anti-IL-17 agents (brodalumab, ixekizumab, and secukinumab), tildrakizumab and guselkumab when comparing the PASI90 scores. Results from the ranking analysis for quality of life with the surface under the cumulative ranking curve demonstrated that tildrakizumab was inferior to ixekizumab, guselkumab, ustekinumab, and superior to etancercept. Ranking analysis for PGA 0/1 further suggested that tildrakizumab was superior to ixekizumab, secukinnumab, brodalumab, ustekinumab, but was inferior to certolizumab. Ranking analysis for PASI75 further demonstrated that tildrakizumab was superior to ustekinumab but inferior to ixekinumab, secukinumab, and brodlumab. Following the placebo treatment, tildrakizumab demonstrated the best safety profile with regards to the number of adverse events, followed by guselkumab and certolizumab. This network meta-analysis also found no significant differences in serious adverse events between tildrakizumab and other IL-23, IL-17, and 12/23 inhibitors. However, the authors indicated that the number of studies

TABLE 3 | Summary of AEs and serious AEs that occurred in clinical trials evaluating the efficacy and safety of IL-23, IL-23/12, IL-17, and TNF-α inhibitors.

References	Biologic	Dose	Sample Size	Week #	>/= 1 AEs reported %	Common AE types listed	>/= 1 SAEs reported %	Common SAE types listed
Resurface 1 (103)	Tildrakizumab	100 mg	309	12	47	8%Nasopharyngitis; 3% URTIs; 1% psoriasis	2	<1% severe infection; <1% confirmed major adverse cardiovascular events
		200 mg	308	12	42	2% discontinued use; 6% nasopharyngitis; 5% URTIs	3	<1% severe infection; <1% Drug-related hypersensitivity
	Placebo	n/a	154	12	48	1% discontinued use; 5% nasopharyngitis; 6% URTIs; 5% psoriasis	1	
Resurface 2 (103)	Tildrakizumab	100 mg	307	12	44	1% discontinued use; 1% injection site erythema; 13% nasopharyngitis	1	<1% death; <1% malignancies; <1% non-melanoma skin cancer; <1% drug-related hypersensitivity
		200 mg	314	12	49	1% discontinued use; 1% injection site erythema; 11% nasopharyngitis	2	<1% severe infections <1% malignancies; <1% non-melanoma skin cancer
	Etanercept	50 mg	313	12	54	2% discontinued use; 1% injection site erythema; 8% nasopharyngitis	2	1% severe infections; 1% drug-related hypersensitivity
	Placebo		156	12	55	1% discontinued use; 1% injection site erythema; 11% nasopharyngitis	3	1% severe infections; 1% drug-related hypersensitivity
Papp et al. (102)	Tildrakizumab	5 mg	42	16	71	2% discontinued use	0	
	Tildrakizumab	25 mg	92	16	61	2% discontinued use; 1% injection site reaction	1	1% bacterial arthritis
	Tildrakizumab	100 mg	89	16	65	1% discontinued use; 1% serious infections	1	1% death
	Tildrakizumab	200 mg	86	16	63	1% discontinued use	2	1% ovarian cyst; 1% lymphoedema
	Placebo		46	16	69	1% discontinued use; 1% injection site reaction	0	
Kopp et al. (101)	Tildrakizumab	3 mg/kg	6	16	71	14% headache; 14% cough; 14% nasopharyngitis; 14% arthralgia; 14% back pain; 14% hypertension		
	Tildrakizumab	10 mg/kg	5	16	33			
	Placebo		20	16	75	15% headache; 15% cough; 10% nasopharyngitis; 15% arthralgia; 5% back pain; 5% hypertension; 15% URTI; 5% oropharyngeal pain; 10% fatigue; 5% pruritis; 15% sinusitis; 10% psoriasis		Only 1 serious AE (convulsions) was deemed possibly related to tildrakizumab
Voyage 1 (72)	Guselkumab	100 mg	329	16	51.70	9.1% nasopharyngitis; 7.6% URTIs; 1.8% injection-site erythema; 3.6% headache; 3.3% arthralgia; 1.5% pruritis; 1.8% back pain	2.40	0.3% NMSC; 0.3% MACE
	Placebo		174	16	49.40	9.8% nasopharyngitis; 5.2% URTIs; 4% headache; 1.7% arthralgia; 5.7% pruritis; 1.1% back pain	1.70	
Voyage 2 (74)	Guselkumab	100 mg	496	16	47.60	7.1% nasopharyngitis; 5.1% headache; 3.2% URTIs; 21.5% infections	1.60	0.2% serious infections
	Placebo		248	16	44.80	6.5% nasopharyngitis; 2.8% headache; 4% URTIs; 18.5% infections	1.20	0.4% serious infections
UltIMMA-1 (79)	Risankizumab	150 mg	304	16	49.7	24.7% infections;	4.3	0.3% serious infection; 0.3% malignancies
	Placebo		102	16	51	16.7% infections	7.8%	1% malignancies

(Continued)

TABLE 3 | Continued

References	Biologic	Dose	Sample Size	Week #	>/= 1 AEs reported %	Common AE types listed	>/= 1 SAEs reported %	Common SAE types listed
UltIMMA-2 (79)	Risankizumab	150 mg	294	16	45.6	19% infections	4.40	1% severe infections; 0.3% malignancies; o.3% deaths
	Placebo		98	16	45.9	9.2% infections	2	
Reich et al. (82)	Mirikizumab	100 mg	51	16	47	25% infections; 20% URTIs; 4% injection site pain; 6% hypertension 2% diarrhea	0	
	Mirikizumab	300 mg	51	16	47	25% infections; 9% URTIs; 4% injection-site pain; 4% hypertension; 6% diarrhea	2	
	Placebo		52	16	48	23% infections; 7% URTIs; 2% injection-site pain; 2% diarrhea	2	
Phoenix-1 (51)	Ustekinumab	90 mg	256	12	51.4	6.3% URTIs; 8.2% nasopharyngitis; 2.4% arthralgia; 5.1% headache	1.6	25.9% infections; 0.8% serious infections
	Placebo		255	12	48.2	6.3% URTIs; 8.6% nasopharyngitis; 2.7% arthralgia; 2.4% headache	0.8	26.7% infections; 0.4% serious infections
Phoenix-2 (52)	Ustekinumab	90 mg	411	12	47.9	2.4% arthralgia; 1% cough; 4.6% headache; 1.5% injection-site erythema; 3.4% URTI; 6.8% nasopharyngitis	1.20%	22.4% infection; 0.2% serious infection; 0.2% skin cancer; 0.2% CV event
	Placebo		410	12	49.8	2.9% arthralgia; 1.7% cough; 4.1% headache; 0.2% injection-site erythema; 7.1% nasopharyngitis; 3.4% URTIs	2%	20% infections; 0.5% serious infections; 0.2% cutaneous cancer; 0.2% non-cutaneous cancer
FIXTURE (135)	Secukinumab	150 mg	327	12	58.4	13.8% NP; 4.9% Headache; 3.7% diarrhea; 3.7% pruritis; 4.3% arthralgia; 3.1% URTI; 2.4% back pain; 1.5% cough; 3.1% hypertension; 1.8% nausea; 1.5% oropharyngeal pain	2.10%	30.9% infections
	Secukinumab	300 mg	323	12	55.5	10.7% NP; 9.2% Headache; 5.2% diarrhea; 2.5% pruritis; 1.5% arthralgia; 2.1% URTI; 2.5% back pain; 3.4% cough; 1.5% hypertension; 2.5% nausea; 2.8% oropharyngeal pain	1.20%	26.7% infections
	Etanercept	50 mg	323	12	57.6	11.1% NP; 7.1% Headache; 3.4% diarrhea; 2.5% pruritis; 3.7% arthralgia; 2.2% URTI; 2.8% back pain; 1.2% cough; 1.5% hypertension; 1.2% nausea; 1.2% oropharyngeal pain	0.90%	24.5% infections
	Placebo		324	12	49.8	8% NP; 7% Headache; 1.8% diarrhea; 3.4% pruritis; 3.1% arthralgia; 0.9% URTI; 1.8% back pain; 1.2% cough; 1.2% hypertension; 2.1% nausea; 2.1% oropharyngeal pain	1.80%	19.3% infections
UNCOVER-1 to 3 (123)	Ixekizumab	160 mg × 1, 80 mg × q2w	1,167	12	58.4	9.5% nasopharyngitis;4.4% URTI; 10% injection site reaction; 2.5% Arthralgia; 4.4% headache	1.7	27% infections; 0.1% cancer; 0.2% nonmelanoma skin cancer; 0.1% Chron's disease
	Ixekizumab	160 mg × 1, 80 mg × q4w	1,161	12	58.8	9% nasopharyngitis; 3.9% URTI; 7.7% injection site reaction; 1.9% arthralgia; 4.3% headache	2.2	27.4% infections; 0.2% Mace; 0.1% Crohn's disease; 0.2% cancer; 0.1% non-Melanoma skin cancer
	Placebo		791	12	46.78	8.7% nasopharyngitis; 3.5% URT; one point 1% injection site reaction; 2.1% arthralgia; 2.9% headache	1.5	22.9% infections; 0.1% Mace; 0.1% cancer; 0.1% non-Melanoma skin cancer

(Continued)

TABLE 3 | Continued

References	Biologic	Dose	Sample Size	Week #	>/= 1 AEs reported %	Common AE types listed	>/= 1 SAEs reported %	Common SAE types listed
AMAGINE-1 (136)	Brodalumab	140 q2w	219	12	57.5	0.5% depression; 1.4% injection site reaction; 0.5% neutropenia; 9.1% nasopharyngitis; 8.2% URTI; 5.5% headache	2.7	0.9% serious infectious episode
	Brodalumab	210 q2w	222	12	59	0.5% depression; 0.5% injection site reaction; 9.5% nasopharyngitis; 8.1% URTI; 5% headache	1.8	0.5% serious infectious episode
	Placebo		220	12	50.9	0.5% depression; 10% nasopharyngitis; 6.4% URTI; 3.2% headache	1.4	
BE ABLE 1 (137)	Bimekizumab	160 mg q4w	40	12	55.8	7% nasopharyngitis; 4.7% URTI; 7% glutamyl transferase increase; 2.3% hypertension 2.3%; respiratory tract infection; 4.7% tonsillitis; 2.3% rhinitis	0	
	Bimekizumab	320 mg q4w	43	12	60.5	14% nasopharyngitis; 4.7% URTI; 2.3% arthralgia; 2.3% glutamyl transferase increase; 2.3% respiratory tract infection; 4.7% neutropenia	0	
	Placebo		42	12	35.7	4.8% nasopharyngitis; 2.4% URTI; 2.4% glutamyl transferase increase; 2.4% rhinitis; 7.1% hypertension; 2.4% respiratory tract infection	2.4	
EXPRESS II (138)	Infliximab	5 mg/kg	314	14	68.8	13.4% URTI; 12.1% headache; 5.1% pharyngitis; 3.8% nausea; 4.5% pain; 6.4% sinusitis; 2.9% pruritis; 1.9% coughing; 2.9% rhinitis; 2.2% hypertension; 1.6% psoriasis	2.9	30.9% infections
	Placebo		208	14	56	14% URTI; 5.3% headache; 3.4% pharyngitis; 3.9% nausea; 4.3% pain; 1.4% sinusitis; 4.3% Pruritis; 1.4% coughing; 0.5% rhinitis; 3.9% hypertension; 4.8% psoriasis	2.4	30% infections
REVEAL (139)	Adalimumab	40 mg	814	15	62.2	28.9% infections; 7.2% URTI; 5.3% nasopharyngitis; 4.9% headache	1.8	0.6% serious infection; 0.2% malignancies; 0.5% non-melanoma skin cancer;
	Placebo		398	15	55.5	22.4 infections; 3.5% URTI; 6.5% nasopharyngitis; 3.8% headache	1.8	1% serious infection; 0,3% malignancy; 0.3% non-melanoma skin cancer
CIMPACT (140)	Certolizumab pegol	200 mg	165	12	47.3	8.5% nasopharyngitis; 3.6% URTI; 0.6% depression	0.6	26.7% infection and infestations
	Placebo		57	12	56.1	8.8% nasopharyngitis; 10.5% URTI	8.8	28.1% infection and infestations
GO-VIBRANT (141)	Golimumab	2 mg/kg	241	24	46.3	0.4% demyelinating events; 0.8% injection site reaction	2.9	45% infections; 0.4% serious infections
	Placebo		239	24	40.6		3.3	0.8% serious infections; 0.8% malignancies; 0.8% deaths; 15.5% infections

included for tildrakizumab was low, thus this conclusions should be interpreted with caution.

Also, Armstrong et al. recently published an additional network meta-analysis assessing the short and long-term efficacy of biologic treatments in managing moderate-to-severe chronic plaque psoriasis (150). This analysis demonstrates that the short-term PASI90 and 100 response rates (10–16 weeks after study initiation) were higher for ixekizumab, risankizumab, and brodalumab compared to tildrakizumab 200 mg and 100 mg, guselkumab and secukinumab. Guselkumab and secukinumab also had significantly higher response rates compared to tildrakizumab 100 and 200 mg. This analysis did not present data for the long-term efficacy of tildrakiuzmb which was denoted as 48–52 weeks after study initiation.

TABLE 4 | Summary of PASI75, 90, and 100 responses evaluating biologic agents in Phase III clinical trials for IL-23, IL-23/12, IL-17, and TNF-α inhibitors.

Biologic	Dose	PASI 75		PASI 90		PAS 100	
Tildrakizumab (103)	100 mg	64% at 12 wks	80% at 28 wks	35% at 12 wks	52% at 28 wks	14% at 12 wks	24% at 28 wks
	200 mg	62% at 12 wks	82% at 28 wks	35% at 12 wks	59% at 28 wks	14% at 12 wks	32% at 28 wks
Tildrakizumab (103)	100 mg	61% at 12 wks	73% at 28 wks	39% at 12 wks	56% at 28 wks	12% at 12 wks	23% at 28 wks
	200 mg	66% at 12 wks	73% at 28 wks	37% at 12 wks	58% at 28 wks	12% at 12 wks	27% at 28 wks
Guselkumab (72)	100 mg	91.2% at 16 wks		73.3% at 16 wks		37.4% at 16 wks	
Guselkumab (74)	100 mg	86.3% at 16 wks		70% at 16 wks		34.1% at 16 wks	
Risanzikumab (79)	150 mg	86.8% at 12 wks		75.3% at 16 wks		35.9% at 16 wks	
Risanzikumab (79)	150 mg	88.8% at 12 wks		74.8% at 16 wks		50.7% at 16 wks	
Mirikizumab (82)	100 mg	78% at 16 wks		59% at 16 wks		31% at 16 wks	
Mirikizumab (82)	300 mg	75% at 16 wks		67% at 16 wks		31% at 16 wks	
Ustekinumab (51)	90 mg	66.4% at 12 wks	78.6% at 28 wks	36.7% at 12 wks	55.6% at 28 wks	10.9% at 12 wks	29.2% at 28 wks
Ustekinumab (52)	90 mg	75.7% at 12 wks	78.5% at 28 wks	50.9% at 12 wks	54.3% at 28 wks	18.2% at 12 wks	29.5% at 28 wks
Secukinumab (135)	150 mg	67% at 12 wks		41.9% at 12 wks		14.4% at 12 wks	
Secukinumab (135)	300 mg	77.1% at 12 wks		54.2% at 12 wks		24.1% at 12 wks	
Ixekizumab (123)	160 mg q2w	89.1% at 12 wks		70.9% at 12 wks		35.3% at 12 wks	
Ixekizumab (123)	160 mg q4w	82.6% at 12 wks		64.6% at 12 wks		33.6% at 12 wks	
Brodalumab (136)	140 mg	60.3% at 12 wks		42.5% at 12 wks		23.3% at 12 wks	
Brodalumab (136)	210 mg	83.3% at 12 wks		70.3% at 12 wks		41.9% at 12 wks	
Bimekizumab (137)	160 mg	81.4% at 12 wks		67.4% at 12 wks		27.9% at 12 wks	
Bimekizumab (137)	320 mg	93.1% at 12 wks		79.1% at 12 wks		55.8% at 12 wks	
Etanercept (135)	50 mg	44% at 12 wks		20.7% at 12 wks		4.3% at 12 wks	
Infliximab (138)	5 mg/kg	75.5% at 10 wks		45.2% at 10 wks			
Adalimumab (139)	40 mg			37% at 12 wks		14% at 12 wks	
Certolizumab pegol (140)	200 mg	61.3% at 12 wks		31.2% at 12 wks			
Golimumab (141)	2 mg/kg	59.2% at 14 wks		39.3% at 14 wks		16.8% at 14 wks	

OFF-LABEL USE OF IL-23 INHIBITORS INCLUDING TILDRAKIZUMAB

IL-23 inhibitors are indicated in conditions other than the moderate-to-severe psoriasis and have been used off label. Guselkumab is approved for the treatment of psoriatic arthritis (PsA), while risankizumab have shown efficacy in treating this disease based on conducted trials (151, 152). IL-23 induces the production of IL-17, which is involved in the inflammatory pathogenesis of psoriatic arthritis (152). However, a 2018 phase II randomized controlled trial demonstrated that risankizumab did not show clinically significant improvements in treating ankylosing spondylitis (153). Guselkumab has been reported as a second- or third-line therapy for HS in 16 cases (154). Guselkumab has also been shown to be effective in patients with alopecia secondary to psoriasis. A case report demonstrated hair regrowth and improvements in areas of psoriatic erythema upon treatment with guselkumab 100 mg (155). In a randomized controlled trial, guselkumab was also shown to improve the palmoplantar pustulosis in 49 patients (156). Phase II and III randomized controlled trials are also being conducted to assess the efficacy of guselkumab for the treatment of inflammatory bowel disease. Notably, two randomized controlled trials along with the transcriptome-wide-RNA-sequence profiling analysis have demonstrated risankizumab to be an effective therapy for Crohn's Disease. Mirikizumab was also shown to be effective and safe in managing ulcerative colitis and Crohn's Disease (157, 158). Risankizumab treatment was recently shown to result in a significant improvement in the treatment of pyoderma gangrenosum at the dose of 150 mg every 8 weeks (159).

Although the focus of this paper is not on the off label uses of tildrakizumab, **Table 5** summarizes case studies that utilized tildrakizumab off label, demonstrating potential benefits in other clinical settings. Subcutaneous injections of tildrakizumab 100 mg at weeks 0, 4 and then every 12 week thereafter were reported to improve ulceration in a patient with refractory pyoderma gangrenosum and polymyalgia rheumatica with no recorded AEs (160). Tildrakizumab was also effective in treating a case of PASH syndrome, a rare inflammatory condition characterized by pyoderma gangrenosum, acne, and hidradenitis suppurativa (HS). Specifically, tildrakizumab 100 mg administered at weeks 0 and 4 resulted in a significant reduction in abscess and nodule counts (161). Similar to guselkumab, tildrakizumab was shown to be effective in treating HS in 5 patients. Specifically, 100 mg of tildrakizumab was injected in 5 HS patients at weeks 0 and 4, followed by tildrakizumab 200 mg treatment every 4 weeks thereafter. All patients showed significant improvements in abscess and nodule counts; 4 patients had improvements in the Dermatology Life Quality Index (DLQI), and three patients experienced a reduction

TABLE 5 | Clinical cases reported in the literature discussing the off label uses of tildrakizumab.

Case Report	Sample Size	Condition	Tildrakizumab dosage and regimen	Outcome	Adverse events
John and Sinclair (160)	1	Refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica	Tildrakizumab 100 mg; weeks 0, 4, every 12 weeks thereafter	Re-epithelialisation of ulceration, complete resolution	None
Kok et al. (161)	1	Pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH)	Tildrakizumab 100 mg; weeks 0, 4, the tildrakizumab 200 mg every 4 weeks thereafter	Clinical improvement, abscess and nodule count of 5 compared to 68 baseline, DLQI score of 19 compared to 26 baselines	None
Kok et al. (162)	5	Moderate- to-severe hidradenitis suppurativa	Tildrakizumab 100 mg; weeks 0, 4, the tildrakizumab 200 mg every 4 weeks thereafter	All patients demonstrated an improvement, mean reduction of 16.8 ($P = 0.04$) in abscess and nodule count; four patients had DLQI improvement, DLQI, mean difference = 8.0, $P = 0.46$; Three patients had reduction in VAS, mean difference = 1.2, $P = 0.64$	None
Ismail et al. (163)	1	15-year history of treatment-resistant lupus erythematosus tumidus	Tildrakizumab 100 mg, weeks 0, 4, and 16	Improvements in facial plaques	None
Ismail and Sinclair (164)	1	9-month history of biopsy-proven, severe erosive oral lichen planus	Tildrakizumab 100 mg, weeks 0, 4, and 16	complete healing of erosions, with residual fine reticular striations	None
Kerkemeyer et al. (165)	1	15-year history of pruritic lichenoid papules and plaques	Tildrakizumab 100 mg, weeks 0, 4, and 16	Reduction in itch; significant improvement, near-complete clinical resolution after 3 doses	None
Jerjen et al. (166)	1	3-month history of rapidly progressive vitiligo	Tildrakizumab 100 mg; weeks 0, 4, 12, then 3-month intervals	55% reduction in Vitiligo Area Scoring Index, 90% repigmentation in affected areas	None
Ismail et al. (167)	1	Psoriatic nail dystrophy and psoriatic arthritis	Tildrakizumab 100 mg, weeks 0, 4, and 16	Significant improvement; patient noticed reduced time for arthritic pain to ease in the morning	None
Kerkemeyer and Sinclair (168)	10	Alopecia areata	Tildrakizumab 100 mg, weeks 0, 4, and 16	2 patients had a partial response (16–99%); 8 patients had no response; 1 patient with- drew due to no response	Mild; Upper respiratory tract infection, acne
Trindade de Carvalho et al. (169)	1	Recalcitrant lichen planopilaris and frontal fibrosing alopecia	Tildrakizumab 100 mg; weeks 0, 4, every 12 weeks thereafter	Remission and clinical improvements maintained at 13 months	None

in pain symptoms (162). Tildrakizumab was also recently subcutaneously injected for the treatment-resistant lesions of lupus tumidus on the face. Two doses of Tildrakizumab 100 mg significantly improved the facial plaques (163). Another patient with erosive oral lichen planus was treated with tildrakizumab 100 mg injections at weeks 0 and 4, which significantly improved this disease (164). Similarly, near complete resolution of lesions was observed in a patient with recalcitrant lichen planus pemphigoides upon treatment with tildrakizumab 100 mg at weeks 0, 4, and 16 (165). Tildrakizumab has also been employed to induce repigmentation of acrofacial vitiligo. A patient with rapidly progressive vitiligo was treated with tildrakizumab 100 mg at weeks 0, 4, and 12, resulting in a significant repigmentation and improvement of DLQI scores (166). A case of psoriatic nail dystrophy and psoriatic arthritis was also reported, demonstrating a significant improvement in both conditions using tildrakizumab injections at weeks 0 and 4 (167). Treatment of alopecia areata with tildrakizumab 100 mg administered at weeks 0, 4, and 16 has also been reported. Nine patients with alopecia areata were treated with tildrakizumab 100 mg, where 2 patients had a partial response (16–99% improvement) with 2 patients experiencing AEs including URTIs and acne (168). Finally, a patient with recalcitrant lichen planopilaris and frontal fibrosing alopecia demonstrated significant improvement after 4 doses of tildrakizumab 100 mg at weeks 0, 4, and subsequently every 12 weeks. Disease remission was maintained for 13 months (169).

CONCLUSION

Tildrakizumab is a promising biologic that can be used to treat moderate-to-severe chronic plaque psoriasis. The IL-23 inhibitory mechanism of tildrakizumab plays a central role in hindering the pathogenesis of psoriasis. The reSURFACE trials and the *post-hoc* analyses have demonstrated that tildrakizumab is a reliable biologic therapy. Further head-to-head trials are

needed to confirm its efficacy in comparison to other newer biologic agents. Data is also emerging on the off-label use of IL-23 inhibitors making them likely suitable for the treatment of other debilitating skin diseases.

AUTHOR CONTRIBUTIONS

FG, FM, LK, MB, YP, RV, MW, CL, and IL performed the literature review and wrote the paper. CL and IL supervised the project. All authors read and approved the final version for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.702776/full#supplementary-material

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Combinatrix, Connetics, Coria, Dermik Laboratories, Dow Pharmaceutical Sciences, Dusa, Embil Pharmaceuticals, EOS, Ferndale Laboratories, Galderma, Genentech, GlaxoSmithKline, Health Point, Intendis, Innovail, Johnson & Johnson, Laboratory Skin Care, LEO Pharma, 3M, Medical International Technologies, Merck, Medicis Pharmaceutical, Merz, Nano Bio, Novartis, Nucryst Pharmaceuticals, Obagi, Onset, OrthoNeutrogena, Promius, QLT, PharmaDerm, Pfizer, Quatrix, Serono (Merck Serono International SA), SkinMedica, Stiefel, Sun Pharmaceutical Industries, TolerRx, Triax, Valeant Pharmaceuticals Intl, Warner-Chilcott, and ZAGE. YP has received grant funding and honoraria for services as an investigator, speaker, and member of advisory boards from AbbVie, Amgen, Bausch, Janssen-Ortho, UCB Biopharma, and has received grant funding as an investigator from AnaptysBio, Arcutis biotherapeutics, Asana, Astrazeneca, Baxalta, Baxter, Boehringer Ingelheim, Bond Avillion, Bristol Myers Squibb, Celgene, Dermira, Devonian, Galderma, Genentech, Glaxo Smith Kline, Eli Lilly, Incyte, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sun Pharmaceutical Industries, Serono, Takeda. MB an advisory board member and speaker for AbbVie, Amgen, Leo Pharma, and Janssen; a speaker for Astellas and Merck; and an investigator for AbbVie, Astellas, Amgen, Leo Pharma, Novartis, Janssen, Sun Pharma, Lilly, Pfizer, and Celgene. RV was a speaker for AbbVie, Amgen, Celgene, Galderma, Janssen, Leo Pharma, Novartis, and Pfizer, and was an investigator for AbbVie, Amgen, Celgene, Galderma, Janssen, Leo Pharma, Novartis, Sun Pharmaceutical Industries, Pfizer, Lilly, and Merck. MW reports having received honoraria for ad board participation from Novartis, Sun Pharmaceutical Industries and Pfizer. CL was a consultant, speaker, and advisory board member for Amgen, Pfizer, AbbVie, Janssen, Novartis, and Celgene, and was an investigator for Amgen, Pfizer, AbbVie, Janssen, Lilly, Novartis, and Celgene. YP was a speaker and advisory board member for AbbVie, Amgen, and Janssen, and was an investigator for AbbVie, Amgen, Celgene, Centocor, Lilly, Galderma, Incyte, Sun Pharmaceutical Industries, Janssen, Leo Pharma, Merck, Novartis, Pfizer, and Roche. IL received research grant funding from Novartis, Merck, Abbvie, and Bristol Myers Squibb and honoraria from Janssen, Bausch, Galderma, Novartis, Pfizer, Sun Pharmaceutical Industries, Johnson & Johnson, and Actilion. Topics included in this article were based on, but not limited to, broad discussions at an advisory board meeting, which was sponsored and funded by Sun Pharma Canada, Inc. Consultancy fees were paid to meeting participants (LK, MB, YP, RV, MW, CL, and IL). Sun Pharma Canada, Inc., participated in developing the content for the meeting.

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BRIEF RESEARCH REPORT
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Nailfold Capillaroscopy Abnormalities Correlate With Disease Activity in Adult Dermatomyositis

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Objectives: The aim of this study was to determine the relationship between disease activity in adult patients with dermatomyositis (DM) and other biomarkers of disease activity such as C-reactive protein creatinine kinase and nailfold video capillaroscopy (NVC).

Methods: We performed a prospective single center study of 15 adult patients with DM. Study participants underwent two assessments at least 9 months apart including clinical, laboratory and NVC evaluations. Patients received immunosuppressive medications for their dermatomyositis, and ongoing disease activity was measured by the Myositis Intention to Treat Index (MITAX). NVC evaluation included assessment of capillary density, capillary apical diameter (mm), and the number of microhemorrhages per digit.

Results: Microvascular abnormalities were present in most DM patients. Of these, capillary density (4.71 vs. 6.84, $p = 0.006$) and mean apical diameter (56.09 vs. 27.79 μm, $p = 0.003$) significantly improved over the study period in concordance with improving disease control (MITAX 8.53 vs. 2.64, $p = 0.002$). Longitudinal analysis demonstrated that capillary density was independently associated with MITAX ($\beta = -1.49$ [CI −2.49, −0.33], $p = 0.013$), but not other parameters such as C-reactive protein and creatinine kinase.

Conclusions: Nailfold capillary density is a dynamic marker of global disease activity in adult DM. NVC may be utilized as a non-invasive point-of-care tool to monitor disease activity and inform treatment decisions in patients with DM.

Keywords: dermatomyositis, nailfold capillaroscopy, capillary density, disease activity, CK

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INTRODUCTION

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and characteristic cutaneous findings. The diagnosis of DM is based on clinical features, complemented by detection of myositis-specific antibodies (MSAs), elevation in muscle enzymes such as creatinine kinase (CK), muscle biopsy, and/or imaging.

Monitoring response to treatment remains a challenge as no single measure is able to capture global disease activity in DM. The International Myositis Assessment and Clinical Studies Group (IMACS) has developed a core set of disease activity and treatment response criteria for adult DM. In these criteria, monitoring response to treatment is largely clinical, with inclusion of muscle enzyme evaluation as the only biomarker. However, the relationship between disease activity and muscle enzymes is not firmly established (1) and they are therefore assigned low weighting in treatment response criteria (2). The absence of a readily available and reliable marker of disease activity therefore remains a significant gap in our ability to assess disease activity in DM.

The pathogenesis of DM is driven by small vessel vasculopathy wherein perivascular inflammation leads to a reduction in the density of capillaries, resulting in tissue ischemia and dilatation of remaining capillaries. These changes are present in skeletal muscle where they lead to muscle atrophy and weakness as well as in other areas such as the nailfolds where they may be more readily detected.

Nailfold video capillaroscopy (NVC) is a point-of-care tool for directly visualizing microvascular changes associated with connective tissue diseases (3). Detection of these abnormalities has been suggested to have a clinical role in both diagnosis and prognosis, particularly in systemic sclerosis and in patients with Raynaud's phenomenon associated with an inflammatory etiology. While microvascular changes are present in DM, the role of NVC in monitoring disease activity in adult DM has not yet been established. In this study, we performed a prospective analysis of NVC findings and disease activity in adult DM.

METHODS

Study Population

Study participants were prospectively enrolled from the Rheumatology Clinic at the Kaye Edmonton Clinic, Edmonton, Canada. All participants met 2017 EULAR/ACR DM classification criteria (4). All patients were tested for myositis specific autoantibodies. Anti-synthetase syndrome is increasingly recognized as a unique clinical entity with rapidly progressive ILD as a predominant feature. Therefore, in order to study dermatomyositis as an isolated entity, patients with anti-synthetase antibodies were excluded from this study. Patients underwent simultaneous clinical and NVC assessments at the time of enrollment, and then again after an interval ranging from 9 to 15 months. Patients received therapy as directed by their primary DM physician. All participants enrolled provided written consent for study participation which was approved by the University of Alberta Research Ethics Office. The study design did not include patient input.

Nailfold Video Capillaroscopy

All images were captured using a 200X Video Capillaroscope (DS Medica, Italy) by a Rheumatologist trained in NVC, as previously described (5, 6). NVC parameters were recorded as follows: mean capillary density (number of capillaries per mm averaged over 8 digits), apical capillary diameter (μm), and microhemorrhages (number of hemorrhages per digit, averaged over the 8 digits).

Clinical Measures

The Myositis Intention to Treat Index (MITAX), as described by the International Myositis Assessment & Clinical Studies Group, is a disease activity score with seven domains: cutaneous, muscle, constitutional, skeletal, gastrointestinal, pulmonary, and cardiovascular (7). Each domain was scored from 0 to 9, and the total sum is reported giving a total score range of 0–63. The score assigned to a domain integrates both the severity of current dermatomyositis manifestations and their relative improvements or exacerbations over the proceeding 4 weeks. A score of 3 or higher for a single domain generally indicates intention to treat and indication for immunosuppression.

MITAX determination was made at the same time as NVC image acquisition by a single observer. MITAX scoring was confirmed to be consistent with their primary treating physicians' intention to treat with subsequent changes in disease management. Disease activity was considered present for a given domain for any score of one or greater. Detection of myositis specific antibodies was performed by the Mitogen Advanced Diagnostics Laboratory, Calgary, Canada. CRP and CK assays were measured by Alberta Precision Laboratories, Edmonton, Canada using Beckman Coulter DxC 800 Synchron assays. Complete blood counts, alanine aminotransferase and total bilirubin levels were measured in some patients receiving methotrexate for toxicity monitoring. As not all patients were receiving methotrexate, and these results were not routinely measured for all patient and not included in analysis of disease activity.

Statistical Methods

Changes in clinical parameters between the two assessments was analyzed by Wilcoxon signed rank or Fisher's exact tests. The longitudinal relationship between clinical parameters was analyzed used mixed-linear model regression. A series of individual regressions were first used to examine the correlation between parameters across assessments. A combined mixed-linear model regression was then performed using NVC parameters. All analysis was performed using IBM SPSS Statistics 27.0.

RESULTS

Baseline Characteristics

A total of 15 DM patient were prospectively enrolled in the study. Baseline characteristics are summarized in **Table 1**. Our cohort was predominantly female (93%) with a median age of 53. At the time of enrollment, patients had disease duration ranging between 0 and 6 years, with a median duration of 1 year. For six patients, their baseline assessment occurred at the time of diagnosis. The majority of patients were receiving immunosuppressive therapy, with only two patients untreated at the time of initial assessment. Baseline total MITAX ranged from 2 to 16, with a mean of 8.5, indicating that most patients had ongoing disease activity requiring immunosuppression in at

TABLE 1 | Demographic, clinical, and NVC characteristics of patients across two assessments.

	Assessment 1	Assessment 2
Number	15	13
Age at baseline (year), median (range)	52 (35–80)	–
Duration of disease at baseline (year), median (range)	1.0 (0–4.8)	–
Female, *n* (%)	14 (93)	–
Myositis specific antibodies, *n* (%)		
TIF1γ	7 (35)	6 (46)
Mi2	3 (20)	2 (15)
NXP2	2 (13)	2 (15)
SAE	1 (7)	0 (0)
MDA5	3 (20)	3 (23)
Organ Involvement, *n* (%)		
Cutaneous,	12 (80)	7 (54)^{ns}
Muscular	10 (67)	3 (23)*
Skeletal	7 (47)	5 (8)^{ns}
Pulmonary	2 (13)	1 (8)^{ns}
Constitutional	12 (80)	5 (38)^{ns}
Gastrointestinal	3 (20)	1 (8)^{ns}
MITAX, mean (range)	8.5 (2–16)	2.6 (0–10)**
CK (units/L), mean (range)	233 (25–2,370)	98 (49–223)^{ns}
CRP (mg/L), mean (range)	4.1 (0.3–21)	1.5 (0.5–4.9)^{ns}
Nailfold video capillaroscopy		
Decreased Capillary Density, *n* (%)	12 (80)	5 (38)*
Mean Capillary Density (capillaries/mm), mean ± SD	4.71 ± 2.31	6.84 ± 1.29**
Microhemorrhages, *n* (%)	12 (80)	10 (77)^{ns}
Mean Microhemorrhage (count per digit), mean ± SD	0.65 ± 0.54	0.29 ± 0.32^{ns}
Mean Apical Diameter (μm), mean ± SD	56.1 ± 30.5	27.8 ± 8.5**
Therapy, *n* (%)		
Prednisone	4 (27)	0 (0)
Methotrexate	7 (47)	9 (69)
Hydroxychloroquine	6 (40)	6 (46)
Mycophenolate mofetil	3 (20)	3 (23)
Leflunomide	0 (0)	1 (08)
Toficitinib	0 (0)	1 (08)
Leflunomide	5 (33)	6 (46)
No Immunosuppression	2 (13)	0 (0)

*Statistical significance between first and second assessments as measured by Wilcoxon signed rank (means) or Fisher exact (categorical) tests; ns (p > 0.05), *(P < 0.05), **(p < 0.01). Values denoted by (-) were not re-evaluated or applicable to follow-up. MITAX (Myositis intention to treat index), CK (Creatinine Kinase), CRP (C-Reactive Protein).*

least one domain. Active skin (80%), muscle (67%), skeletal (47%) and constitutional (80%) disease was common at baseline, while pulmonary (13%) and gastrointestinal (20%) involvement was less frequent.

Thirteen patients underwent a second evaluation. The follow-up interval had a mean duration of 12 months, ranging from 9 to 15 months, during which time all patients received immunosuppressive therapy as indicated in **Table 1**. Disease activity, as measured by MITAX, was significantly lower in follow up (8.53 vs. 2.64, $p = 0.002$). Indeed, in 12 out of 13 patients, the MITAX score decreased or remained stable. Fewer patients had active muscle disease (67% vs. 23%, $p = 0.01$). Other manifestations were also observed less frequently although they did not reach significance. The mean CK value was 233.4 at baseline and 98.5 at follow-up. The observed difference was largely driven by a single patient who had a CK of more than 2,000 at baseline and was not statistically significance ($p = 0.72$). There were no significant changes in CRP (4.05 vs. 5.89, $p = 0.32$) between assessments.

Nailfold Video Capillaroscopy Findings

NVC abnormalities were detected in most patients at baseline assessment and are summarized in **Table 1** and visualized in **Figure 1**. Frequent abnormalities included both decreased capillary density (80%) and the presence of microhemorrhages (80%). Giant and dilated capillaries were also present with a mean apical density of 56.09 μm (normal <22 μm). In follow-up, fewer NVC abnormalities were observed. There was significant recovery of both capillary density (4.71 vs. 6.84, $p = 0.006$) and capillary dilatation (56.09 vs. 27.79, $p = 0.003$). Fewer microhemorrhages were also detected and approached statistical significance (0.65 vs. 0.29, $p = 0.053$).

Correlates of Disease Activity

Using a series of mixed-linear models, we analyzed the association between DM disease activity, as measured by MITAX, and various clinical parameters over the course of two consecutive assessments (**Figure 2**). No relationship was detected between MITAX and either CRP ($p = 0.62$) or CK ($p = 0.65$). In contrast, both decreasing capillary density and the presence of microhemorrhages were associated with increased disease activity. Those with more active disease also tended to have increased apical capillary diameters, although this did not achieve statistical significance.

To further characterize the relationship between NVC abnormalities and disease activity, we also performed a multiple mixed-linear model regression of NVC parameters and MITAX. Capillary density was independently associated with disease activity ($\beta = -1.49$ [CI -2.49, -0.33], $p = 0.013$), while apical diameter ($\beta = -0.05$ [CI -0.12, 0.02], $p = 0.14$), and microhemorrhages ($\beta = 1.09$ [CI -1.96, 4.13], $p = 0.47$) were not.

Finally, we examined the association between capillary density and individual MITAX components over time in a mixed-linear regression (**Table 2**). In additional to its association with global MITAX, there was a significant association between decreased capillary density and cutaneous, muscle, and constitutional disease. No relationship was detected for capillary density and GI, pulmonary, and skeletal disease activity, all of which were observed infrequently in our cohort.

DISCUSSION

The presence of microvascular abnormalities, including microhemorrhages, giant capillaries, and capillary dropout

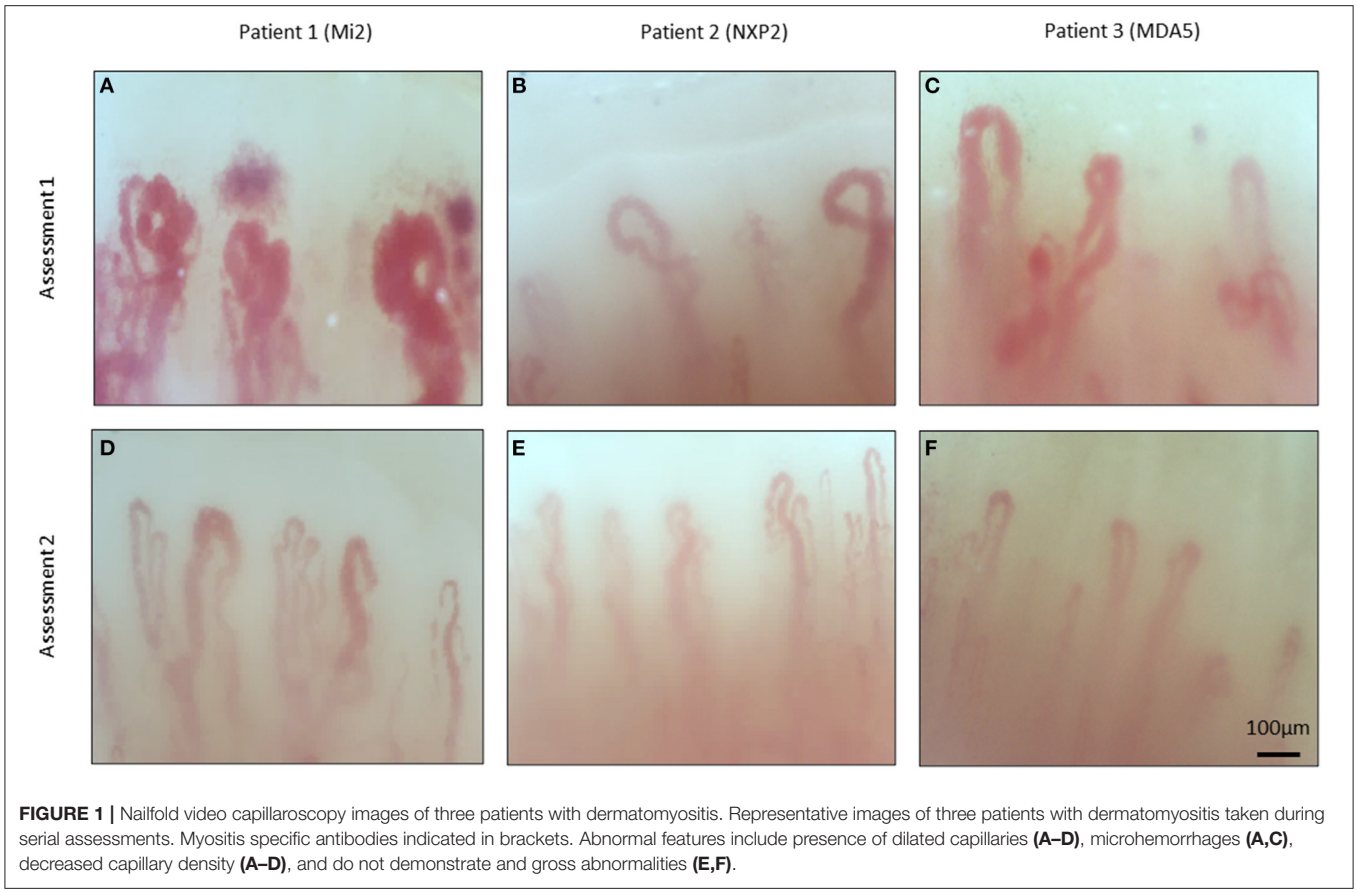

FIGURE 1 | Nailfold video capillaroscopy images of three patients with dermatomyositis. Representative images of three patients with dermatomyositis taken during serial assessments. Myositis specific antibodies indicated in brackets. Abnormal features include presence of dilated capillaries **(A–D)**, microhemorrhages **(A,C)**, decreased capillary density **(A–D)**, and do not demonstrate and gross abnormalities **(E,F)**.

have been well-described in DM (8). These abnormalities are dynamic and change over the course of disease. Patients with DM duration of <6 months had worse capillary drop out and giant capillaries than those with >6 months duration, suggesting that microvascular changes can resolve over time (9). Multiple studies have also demonstrated that the presence of microhemorrhages and decreased capillary density can improve over the course of treatment (10, 11). This is in keeping with our own findings of significant improvement in capillary density and dilatation in follow-up.

Given that small vessel vasculopathies leads to both clinical disease and nailfold capillary abnormalities in DM, it is reasonable to hypothesize that NVC and disease activity may be correlated. To date, there have been variable reports of the association between microvascular abnormalities and disease activity in DM (8). Several studies have reported an association between multiple NVC abnormalities and global DM disease activity (10, 12). By contrast, a cross sectional analysis of 50 DM patients found that NVC abnormalities were significantly associated with active muscle disease and only marginally with global disease activity ($p = 0.56$) (11).

Several studies, however, have not shown a relationship between NVC abnormalities and disease activity. One analysis found that the presence of NVC abnormalities correlated with EMG abnormalities, but not with disease activity in 27 patients with DM (13). Similarly, two cross-sectional studies found no relationship between NVC and disease activity (14, 15).

While small studies have shown variable results in adult DM, the relationship between nailfold capillary abnormalities and disease activities has been well-established in juvenile DM. A prospective analysis of 92 juvenile DM patients with repeated assessments over a period of 5.5 years demonstrated a strong correlation between the capillary density and both skin and muscle disease activity (16). This is corroborated by several other studies in juvenile DM that also report associations between NVC abnormalities and active cutaneous and/or muscle disease (17–19). These findings are congruent with analysis of our cohort, wherein decreased capillary density strongly correlated with disease activity over time. NVC assessment may therefore be useful not only for diagnosis, but for ongoing disease monitoring.

While our study and others have demonstrated that NVC findings correlate with cutaneous and muscle disease, they may also correlate with ILD in DM. The presence of multiple capillary abnormalities was found to be associated with a concurrent diagnosis of ILD (12). It has also been reported the presence of enlarged capillaries correlates with the presence of pulmonary involvement (15). Furthermore, the presence of microhemorrhages have also been correlated with ILD severity in a combined analysis of patients with MDA-5 antibody positive dermatomyositis and anti-synthetase syndrome (20). Ultimately,

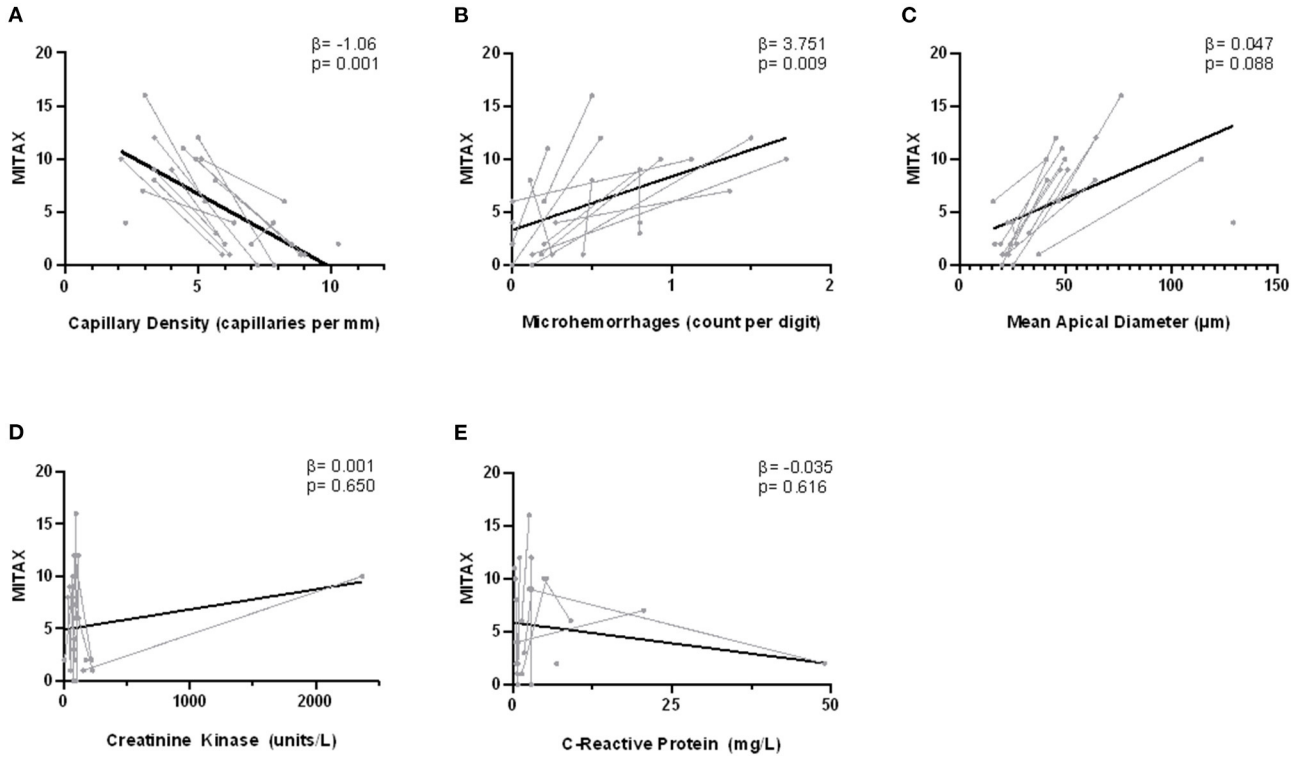

FIGURE 2 | Correlation between nailfold capillary measurements and MITAX. Disease activity is indicated on the y-axis as measured by the Myositis intention to treat index (MITAX). The NVC measurements capillary density **(A)**, microhemorrhages **(B)**, and apical diameter **(C)** as well as biochemical indices creatinine kinase (CK) **(D)** and C-reactive protein (CRP) **(E)** are indicated on the x-axes. Single assessments are indicated in gray, with lines connecting the longitudinal assessments for one individual patient. The overall fitted line is indicated in black. Fixed effect estimates (β) and significance (*p*) are the result of individual mixed-linear models with dependent variable MITAX and time as a random effect.

TABLE 2 | Association of capillary density measurements with individual and composite MITAX scores.

	β	*p*	95% CI
Global MITAX	−1.04	0.001	−1.61, −0.46
Cutaneous	−0.38	0.019	−0.69, −0.07
Muscle	−0.47	0.003	−0.76, −0.17
Constitutional	−0.20	0.006	−0.34, −0.06
Skeletal	0.08	0.099	−0.02, 0.18
GI	0.01	0.774	−0.08, 0.10
Pulmonary	0.01	0.867	−0.16, 0.19

Fixed effect estimates (β), significance (p), and 95% confidence interval (CI) from mixed linear model regression of capillary density with MITAX (Myositis intention to treat index) components and time as a random effect.

only two patients in our cohort had pulmonary involvement and we were likely underpowered to detect a relationship between ILD and NVC.

CK is a marker of muscle damage and is frequently measured during both diagnosis and follow-up of DM. However, in comparison to other inflammatory myopathies CK elevation in DM is relatively modest (21). CK abnormalities are also variable across DM subtypes, with only 41% of those with MDA-5 antibody positive disease having CK elevation, in comparison to 94.5% of those with MDA-5 antibody negative disease (22). In addition, CK elevation in DM is also known to be impacted by patient age, sex, and ethnicity (23).

While CK has been shown to have moderate correlation with muscle disease and is included by IMACS as a core measure of disease activity (24), it may not represent other manifestations and its utility as a biomarker of global disease activity in DM is unclear (1). In particular, for those patients that have resolution of muscle disease and more refractory cutaneous and pulmonary involvement, serial CK measurements may have limited utility in monitoring disease activity. During the creation of the 2016 ACR-EULAR DM response criteria, expert consensus deemed muscle enzymes evaluation to be less meaningful than physician global assessment, patient global assessment, HAQ, manual muscle testing, and assessment of extramuscular manifestations (25). As such, muscle enzyme evaluation has the smallest weighting of all core criteria in the 2016 ACR-EULAR adult DM response criteria, and no weighting in the juvenile DM criteria.

In our cohort, CK did not correlate with disease activity. All patients except one had a normal CK level, including those with active muscle disease. While CK has an established role in the diagnosis of DM, our data does not support its use as a sensitive biomarker of disease activity.

Few other biochemical markers are used clinically in the follow up of DM. While CRP is commonly tracked in DM patients, and has been correlated with the presence of ILD (26), it has not been found to correlate well with global disease activity (27). Similarly, our study found no correlation between overall disease activity and CRP elevation. The limited utility of readily available biochemical assays clearly defines the need for a reliable marker of disease activity.

Limitations

This study is the first to prospectively demonstrate the relationship between longitudinal NVC findings and global disease activity in adult DM. Important limitations include its single-center design and small sample size. Additionally, we were likely underpowered to analyze the association between NVC findings and uncommon manifestations of DM such as pulmonary and GI disease.

CONCLUSIONS

Microvascular changes are present in adult DM and are dynamic over time. Decreased capillary density strongly correlates with global disease activity as measured by MITAX and is more sensitive than traditional biochemical measures such as CK or CRP. Longitudinal NVC assessments may therefore represent an inexpensive and non-invasive measure of DM disease activity. Further studies with larger numbers of patients will be required to confirm these findings as well as understand the relationship between NVC and uncommon manifestations such as ILD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Alberta Research Ethics Office. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design was primarily performed by DJ and MO with contribution from all authors. NM, DR, CP, SK, RG, JC, and MO recruited and assessed study participants. DJ, CE, and MO performed data analysis. DJ and MO wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Alterations of Ultra Long-Chain Fatty Acids in Hereditary Skin Diseases—Review Article

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The skin is a flexible organ that forms a barrier between the environment and the body's interior; it is involved in the immune response, in protection and regulation, and is a dynamic environment in which skin lipids play an important role in maintaining homeostasis. The different layers of the skin differ in both the composition and amount of lipids. The epidermis displays the best characteristics in this respect. The main lipids in this layer are cholesterol, fatty acids (FAs) and ceramides. FAs can occur in free form and as components of complex molecules. The most poorly characterized FAs are very long-chain fatty acids (VLCFAs) and ultra long-chain fatty acids (ULCFAs). VLCFAs and ULCFAs are among the main components of ceramides and are part of the free fatty acid (FFA) fraction. They are most abundant in the brain, liver, kidneys, and skin. VLCFAs and ULCFAs are responsible for the rigidity and impermeability of membranes, forming the mechanically and chemically strong outer layer of cell membranes. Any changes in the composition and length of the carbon chains of FAs result in a change in their melting point and therefore a change in membrane permeability. One of the factors causing a decrease in the amount of VLCFAs and ULCFAs is an improper diet. Another much more important factor is mutations in the genes which code proteins involved in the metabolism of VLCFAs and ULCFAs—regarding their elongation, their attachment to ceramides and their transformation. These mutations have their clinical consequences in the form of inborn errors in metabolism and neurodegenerative disorders, among others. Some of them are accompanied by skin symptoms such as ichthyosis and ichthyosiform erythroderma. In the following review, the structure of the skin is briefly characterized and the most important lipid components of the skin are presented. The focus is also on providing an overview of selected proteins involved in the metabolism of VLCFAs and ULCFAs in the skin.

Keywords: lipids, fatty acids, skin, epidermis, cholesterol, ceramides, dermis

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INTRODUCTION

The skin is a large organ composed of three main layers: hypodermis, dermis, and epidermis. The primary role of the hypodermis is protection against mechanical injury, and thermal insulation. In addition, it provides support and energy for the body [fat cells store triacylglycerols (TAGs), which are produced during lipogenesis] (1, 2). The dermis is involved in the body's immune

defense; it provides elasticity and moisture to the skin (3), and epidermal nourishing and support (1, 3, 4). The dermal-epidermal junction (DEJ) is the connection between the dermis and the epidermis. The DEJ includes complex junctional structures in the dermo-epidermal junction areas. The role of the DEJ is to assist in the adhesion of the epidermis to the dermis and to regulate the exchange of metabolic products. It also plays a role in the migration of keratinocytes during the wound-healing process (1, 3, 4). The outermost layer of the skin, being the actual physical barrier between the body and the environment, is the epidermis.

Among the most important components of human skin are lipids. These hydrophobic molecules are important for the proper functioning of the protective barrier—they prevent the entry of microorganisms and inhibit transepidermal water loss (TEWL).

In the skin, the most abundant lipids are cholesterol, free fatty acids (FFAs) and ceramides (CERs). Very long-chain fatty acids (VLCFAs) and ultra long-chain fatty acids (ULCFAs) are part of the FFA fraction, and major components of ceramides. VLCFAs have chain lengths of 20–25 carbon atoms. FAs which have 26 or more carbon atoms in their chains are called ULCFAs (5, 6). VLCFAs and ULCFAs are responsible for the rigidity and impermeability of membranes, forming the mechanically and chemically robust outermost layer of cell membranes. Any change in the composition and length of the carbon chains of fatty acids (FAs) results in changes in their melting points. Despite playing such an important role, the number of papers concerning VLCFAs and ULCFAs in different tissues is highly limited.

Lipid Composition in Human Skin

The composition of lipids differs in each part of the skin. In the hypodermis two main lipid groups, TAGs and FFAs, can be distinguished (**Table 1**). In the dermis, which is rich in collagen and elastin fibers, high concentrations of TAGs and diacylglycerols (DAGs) are localized in deep areas (**Table 1**). There are also eight classes of ceramides with the predominance of a non-hydroxy FA chain, as well as eleven subtypes of phospholipids (23) (**Table 1**). The lipid content in the epidermis is much more complex, as was described above.

The epidermis consists of 4 layers; counting from the bottom layer: stratum basale (SB), stratum spinosum (SS), stratum granulosum (SG), and stratum corneum (SC) (1). In the skin of the palms and soles, between the SG and SC, there is an additional layer—stratum lucidum (SL) (1). The SB consists mainly of a single layer of cuboidal basal cells, from which epidermal keratinocytes develop. The SB is constantly undergoing cell division. Therefore, old cells are pushed toward higher layers of the epidermis. In the SB, 45% of all lipids are polar, e.g., phosphatidylethanolamine (PE), phosphatidylcholine (PC), phosphatidylserine (PS), sphingomyelin (SM), and lysolecithin (LYS). Trace amounts of sphingolipids, which increase in the higher layers of the epidermis, can also be found (27). The main functions of the SB are proliferation, repair following damage to the epidermis, the reception of stimuli, and the synthesis of vitamin D. The SS is located between the SB and SG, and consists of 8–10 cell layers (1, 28). Keratinocytes are polygonal in shape with large, round nuclei. They are connected to each other by desmosomes so that they adhere more tightly to each other. As the cells migrate away from the SB, they begin to flatten. At the border of the SS and SG, lamellar bodies (LBs) begin to form (29). Involucrin production also begins, and there is an increase in the production of keratin 1 and keratin 10, which are markers of this layer (28). The SB and SS are where the synthesis takes place of cholesterol sulfate, which is a fraction of cholesterol substituted by a sulfoxy group at position 3 (30). The next layer, the SG, is composed of 3–5 layers of spindle-shaped cells with flattened nuclei (1). The cells in this layer contain keratohyalin granules with profilaggrin and loricrin. Profilaggrin is a precursor of filaggrin, involved in the binding of keratin fibers. The products of its degradation are counted among natural moisturizing factors (31). As a result of keratinization, granular cells remove all organelles and transform into corneocytes—dead cells of the epidermis (3). At the same time, there is an increase in the number of LBs, which at the boundary between the SG and SC, by exocytosis, caused by the increasing concentration of Ca^{2+} ions, secrete lipids and some hydrolytic enzymes which, in the intercellular space, form the intercellular lipid matrix (ICL) (2, 32). In the SG a decrease in polar lipids is observed and an increase in sphingolipid levels (**Table 1**) (8). Furthermore, there are the highest concentrations of cholesterol sulfate, which plays an important role in the process of epidermis exfoliation as it inhibits the proteases involved (30). In addition, the stabilization of lipid organization by dissolving cholesterol in the lamellar phases is also important (33). The SL is the intermediate layer between the SG and SC. It can be seen in certain regions of hairless skin. The keratinocytes in this layer are dead—it is considered the first dead layer of the epidermis. It contains lipid-rich protein, which makes it transparent and provides a barrier against water loss (1). The SC is the outermost layer of the epidermis and consists of 15–30 layers of cells—corneocytes.

The lipid bilayer of the cell membrane is converted into a single layer of acylceramides which are cross-linked with cornified envelope (CE) proteins (34). The membrane structure containing CERs bound to proteins is called the corneocyte lipid envelope (CLE) and serves to connect corneocytes to lipid sheets. The structure of the SC can be represented by the "bricks and mortar" model. The bricks are corneocytes immersed in the ICL, which plays the role of cement. The LBs at the interface release lipids to form lipid lamellae. The main ceramide precursors in lipid lamellae are glucosylceramides and SM. They are converted to CERs by β-glucocerebrosidase and sphingomyelinase when released into the extracellular space (35, 36). The SC is crucial for mechanical and biological protection and prevents excessive water evaporation.

The greatest quantities of lipids within the epidermis are cholesterol, FFAs and CERs. Cholesterol makes up 25% of the epidermal lipids. A major source of cholesterol in the skin is endogenous synthesis in this organ. Its main function is to improve the plasticity and rigidity of the membrane (37). It plays an important role in epidermal homeostasis, hence any change in its amount results in impaired barrier function and impaired epidermal exfoliation (38). Increased cholesterol synthesis occurs during permeability barrier repair

TABLE 1 | The composition of skin lipids in particular skin layers.

Layer of skin		Lipids	Individual species	Number of studied subjects	Age	Sex	References
Epidermis	Stratum corneum	Cholesterol esters	nd	22	22–40 y	F	Norlen et al. (7)
		TAG	nd	4 cadavers	nd	nd	Lampe et al. (8)
		FFA from abdomen	C14:0 (3.8%), C16:0 (36.8%), C16:1 (3.6%), C18:0 (9.9%), C18:1 (33.1%), C18:2 (12.5%), C20:0 (0.3%), C20:1 (trace), C22:0 (trace)	nd	Median age of 50 y	M	Lampe et al. (9)
		FFA from leg	C14:0 (10.9%), C16:0 (36.2%), C16:1 (16.6%), C18:0 (10.0%), C18:1 (17.7%), C18:2 (1.4%), C20:0 (2.6%), C20:1 (1.1%), C20:2 (trace), C20:3 (trace), C20:4 (trace), C22:0 (3.5%)	nd	Median age of 50 y	M	Lampe et al. (9)
		FFA from plantar	C14:0 (0.3%), C16:0 (10.5%), C16:1 (1.2%), C18:0 (20.1%), C18:1 (18.8%), C18:2 (6.5%), C20:0 (6.1%), C20:1 (1.5%), C20:3 (3.1%), C22:0 (9.6%), C22:1 (5.8%), C24:0 (16.5%)	nd	nd	M	Lampe et al. (9)
		FFA from face	C14:0 (1.4%), C16:0 (27.9%), C16:1 (6.5%), C18:0 (16.3%), C18:1 (23.5%), C18:2 (11.9%), C20:0 (2.4%), C20:1 (0.1%), C20:2 (0.1%), C20:4 (3.5%), C22:0 (4.4), C22:1 (2.0%)	nd	nd	M	Lampe et al. (9)
		FFA from forearm	**C12:0, C14:0, C16:0, C16:1, C18:0, C19:0, C20:0, C21:0, C22:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0, C30:1, C31:0, C32:0, C32:1, C34:0, C34:1, C36:0, C36:1	22	22–40 y	F	Norlén et al. (7)
		FFA from stripped sample from forearm	C20:0 (5%), C22:0 (11%), C24:0 (39%), C25:0 (10%), C26:0 (23%), C27:0 (3%), C28:0 (8%), C29:0 (1%), C30:0 (2%)	22	22–40 y	F	Norlén et al. (7)
		FA in SC ceramide Cer[NS] from forearm[C]	C24:0 (8.95%), C25:0 (6.97%), C26:0 (10.77%), C27:0 (5.16%), C28:0 (11.99%), C29:0 (5.92%), C30:0 12.59%), C31:0 (7.13%), C32:0 (14.87%), C33:0 (5.77%), C34:0 (10.77%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
		FA in SC ceramide Cer[NDS] from forearm[C]	C24:0 (6.50%), C25:0 (4.72%), C26:0 (13.19%), C27:0 (8.27%), C28:0 (19.69%), C29:0 (9.65%), C30:0 (18.31%), C31:0 (7.48%), C32:0 (12.20%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	FA in SC ceramide Cer[NP] from forearm[C]	C24:0 (9.78%), C25:0 (6.99%), C26:0 (13.17%), C27:0 (7.98%), C28:0 (19.96%), C29:0 (9.98%), C30:0 (17.76%), C31:0 (5.99%), C32:0 (8.38%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[NH] from forearm[C]	C24:0 (7.28%), C25:0 (10.24%), C26:0 (26.95%), C27:0 (10.51%), C28:0 (20.22%), C29:0 (7.55%), C30:0 (17.25%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[AS] from forearm[C]	C15:0 (17.37%), C16:0 (52.63%), C17:0 (11.58%), C18:0 (18.42%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[AP] from forearm[C]	C24:0 (21.08%), C25:0 (11.48%), C26:0 (19.91%), C27:0 (10.54%), C28:0 (21.78%), C29:0 (7.49%), C30:0 (7.73%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[AH] from forearm[C]	C24:0 (21.07%), C25:0 (14.64%), C26:0 (35.71%), C27:0 (10.71%), C28:0 (17. 86%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[EOS] from forearm[C]	C30:0 (6.82%), C31:0 (5.80%), C32:0 (18.77%), C33:0 (11.26%), C34:0 (34.13%), C35:0 (10.92%), C36:0 (12.29%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[EOP] from forearm[C]	C30:0 (13.05%), C31:0 (5.93%), C32:0 (18.10%), C33:0 (13.06%), C34:0 (29.67%), C35:0 (10.09%), C36:0 (10.09%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[EOH] from forearm[C]	C30:0 (24.18%), C31:0 (12.82%), C32:0 (36.63%), C33:0 (11.36%), C34:0 (15.02%)	7	37 ± 13 y	5 F 2 M	Farwanah et al. (10)
	FA in SC ceramide Cer[NS] from forearm	**C16:0, C17:0, C18:0, C19:0, C20:0, C21:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0, C30:1	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[NDS] from forearm	**C16:0, C17:0, C18:0, C19:0, C20:0, C21:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0, C30:1	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[NH] from forearm	**C16:0, C17:0, C18:0, C20:0, C21:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0, C30:1	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[NP] from forearm	**C16:0, C20:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0, C30:1	19	20–50 y	9 F 10 M	Kawana et al. (11)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	FA in SC ceramide Cer[AS] from forearm	**C16:0, C17:0, C18:0, C20:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C30:0	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[AH] from forearm	**C16:0, C17:0, C18:0, C20:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C30:0	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[AP] from forearm	**C16:0, C17:0, C18:0, C19:0, C20:0, C21:0, C22:0, C23:0, C24:0, C25:0, C26:0, C27:0, C28:0, C29:0, C30:0	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[EOS] from forearm	**C28:0, C29:0, C30:0, C31:0, C32:0, C32:1, C33:0, C33:1, C34:0, C34:1, C36:1	19	20-50y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[EOH] from forearm	**C28:0, C29:0, C30:0, C31:0, C32:0, C32:1, C33:0, C33:1, C34:0, C34:1, C36:1	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramide Cer[EOP] from forearm	**C28:0, C29:0, C30:0, C31:0, C32:0, C32:1, C33:0, C34:0, C34:1, C36:1	19	20–50 y	9 F 10 M	Kawana et al. (11)
	FA in SC ceramides from abdomen	C16:0 (7.7%), C18:0 (4.8%), C18:1 (6.3%), C18:2 (14.0%), C20:0 (5.9%), C24:0 (50.8%), C26:0 (10.5%)	nd	Median age of 50 y	M	Lampe et al. (9)
	FA in SC ceramides from leg	C16:0 (10.2%), C18:0 (11.4%), C18:1 (3.6%), C18:2 (1.9%), C24:0 (43.3%), C26:0 (29.6%)	nd	Median age of 50 y	M	Lampe et al. (9)
	FA in SC ceramides from face	C14:0 (0.1%), C16:0 (4.3%), C18:0 (9.8%), C18:1 (4.3%), C18:2 (6.1%), C20:0 (3.8%), C20:4 (0.3%), C22:0 (7.0%), C22:1 (2.0%), C24:0 (43.9%), C24:1 (10.8%), C26:0 (7.7%)	nd	nd	M	Lampe et al. (9)
	FA in SC wax/sterols from abdomen	C16:0 (20.0%), C16:1 (15.9%), C18:0 (5.8%), C18:1 (49.4%), C18:2 (6.6%), C24:0 (0.9%), C24:1 (1.6%)	nd	Median age of 50 y	M	Lampe et al. (9)
	FA in SC wax/sterols from leg	C14:0 (4.21%), C16:0 (21.0%), C16:1 (27.8%), C18:0 (6.2%), C18:1 (32.9%), C18:2 (5.1%), C20:0 (0.9%), C20:1 (0.7%), C20:2 (trace), C24:0 (1.4%)	nd	Median age of 50 y	M	Lampe et al. (9)
	FA in SC wax/sterols from plantar	C14:0 (2.5%), C16:0 (21.4%), C16:1 (5.7%), C18:0 (8.6%), C18:1 (44.2%), C18:2 (15.2%), C20:1 (trace), C20:4 (trace), C22:1 (trace), C24:0 (2.4%)	nd	nd	M	Lampe et al. (9)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	FA in SC wax/sterols from face	C14:0 (0.9%), C16:0 (14.6%), C16:1 (36.9%), C18:0 (4.6%), C18:1 (32.9%), C18:2 (10.0%), 20:0 (trace). C20:1 (trace), C20:4 (trace), C22:1 (trace)	nd	nd	M	Lampe et al. (9)
	FA in SC phosphatidylethanolamines from abdomen	C14:0 (0.8%), C16:0 (15.8%), C16:1 (4.9%), C18:0 (13.5%), C18:1 (38.1%), C18:2 (20.7%), C20:0 (1.3%), C20:1 (1.0%), C20:2 (0.3%), C20:3 (trace), C20:4 (1.6%), C22:0 (0.7%), C24:1 (1.3%)	nd	Median age of 50 y	M	Lampe et al. (9)
	FA in SC phosphatidylethanolamines from leg	C14:0 (3.0%), C16:0 (10.3%), C16:1 (4.0%), C18:0 (13.6%), C18:1 (34.0%), C18:2 (21.6%), C20:0 (trace), C20:1 (trace), C20:2 (1.2%), C20:3 (trace), C20:4 (12.2%)	nd	Median age of 50 y	M	Lampe et al. (9)
	Total FA in SC from mid-abdominal and mid-scapular	C10:0 (0.7%), C11:0 (0.04%), C12:0 (0.7%), C13:0 (0.2%), C14:0 (4.6%), C14:1 + iso-C14 + anteiso-C14 (0.4%), C16:0 (26.3%), C16:1 + iso-C16 + anteiso-C16 (9.0%), C17:0 (2.2%), C18:0 (3.5%), C18:1 + C18:2 + iso-C18 + anteiso-C18 (52.7%)	17 cadavers	M: 49–68 y F: 2 wks−85 y	8 M 9 F	Reinertson et al. (12)
			9 normal human	23–52 y	M	
	Phospholipids	**PE, PS	4 cadavers	nd	nd	Lampe et al. (8)
	Ceramide	Cer [NS] (21.38%), Cer [EOS] (9.45%), Cer [NP] (18.51%), Cer [AS] (25.23%), Cer [AP] (25.43%)	6	nd	F M	Motta et al. (13)
		Cer [NDS] (9.83%), Cer [NT] (1.73%), Cer[NS] (7.44%), Cer [NP] (22.10%), Cer [NH] (14.51%), Cer [AH] (10.77%), Cer [ADS] (1.63%), Cer [AS] (9.58%), Cer [AP] (8.78%), Cer [OH][a] (0.43%), Cer [OP][a] (0.17%), Cer [OS][a] (0.73%), Cer [EOH] (4.26%), Cer [EODS] (0.40%), Cer [EOS] (6.48%), Cer [EOP] (1.14%)	nd	nd	nd	t'Kind et al. (14)

(Continued)

TABLE 1 | Continued

Layer of skin		Lipids	Individual species	Number of studied subjects	Age	Sex	References
			Cer [NDS] (6.2%), Cer [NS] (5.2%), Cer [NH] (23.7%), Cer [NP] (24.2%), Cer [NSD] (0.1%), Cer [AS] (4.3%), Cer [ADS] (0.9%), Cer [AH] (18.0%), Cer [AP] (9.2%), Cer [ASD] (0.2%), Cer [BS] (0.2%), Cer [OS] (0.6%), Cer [ODS] (0.1%), Cer [OH] (0.6%), Cer [OP] (0.3%), Cer [OSD] (0.02%), Cer [EOS] (2.1%), Cer [EODS] (0.1%), Cer [EOH] (3.1%), Cer [EOP] (1.0%), Cer [EOSD] (0.02%),	19	20–50 y	9 F 10 M	Kawana et al. (11)
			Cer [AH] (22%) Cer [EOS] (8%), Cer [NS] (21%), Cer [NP] (13%), Cer [EOH] (4%), Cer [AS] 27%, Cer [AP] (4%), Cer [OS][a] (66%), Cer [OH][a] (33%)	nd	26–45 y	M	Robson et al. (15)
			**Cer [EODS], Cer [EOS], Cer [EOP], Cer [EOH], Cer[NDS], Cer[NS], Cer [NP], Cer [ADS], Cer [AS], Cer [NH], Cer[AP], Cer [AH]	nd	nd	nd	van Smeden et al. (16)
			**Cer [1-O-EAS], Cer [1-O-ENS]	nd	26–45 y	M	Rabionet et al. (17)
			Cer [OS] (72.4%), Cer [OH] (19.5%), Cer [OP] (8.2%)[C]	6	nd	nd	Hill et al. (18)
	Stratum granulosum	TAG (24.7%)	nd	7 cadavers	nd	nd	Lampe et al. (8)
		FFA (9.2%)	nd	7 cadavers	nd	nd	Lampe et al. (8)
		FA in sphingolipids	C14:0 (0.7%), C16:0 (13.1%), C16:1 (1.8%), C18:0 (11.4%), C18:1 (32.3%), C18:2 (18.8%), C20:0 (1.2%), C20:1 (0.4%), C20:4 (1.8%), C22:0 (2.5%), C24:0 (6.8%), C26:0 (9.3%)	nd	nd	nd	Lampe et al. (8)
		FA in neutral lipids	C12:0 (0.3%), C14:0 (3.5%), C16:0 (25.3%), C16:1 (7.4%), C18:0 (16.7%), C18:1 (31.1%), C18:2 (14.3%), C20:0 (0.03%), C20:2 (0.3%), C22:0 (0.4%), C24:0 (0.7%)	nd	nd	nd	Lampe et al. (8)
		FA in phospholipids	C16:0 (9.4%), C18:0 (20.6%), C18:1 (31.0%), C18:2 (26.5%), C20:0 (2.1%), C20:4 (3.6%)	nd	nd	nd	Lampe et al. (8)
		Phospholipids	**PC, PE, LCS, PS, PI	7 cadavers	nd	nd	Lampe et al. (8)
		Ceramide	nd	7 cadavers	nd	nd	Lampe et al. (8)
	Stratum spinosum/ Stratum basale	TAG (12,4%)	nd	5 cadavers	nd	nd	Lampe et al. (8)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	FFA (7,0%)	nd	5 cadavers	nd	nd	Lampe et al. (8)
	FA in neutral lipids	C12:0 (0.03%), C14:0 (1.9%), C16:0 (24.1%), C16:1 (6.7%), C18:0 (10.7%), C18:1 (36.8%), C18:2 (14.5%), C20:0 (0.5%), C20:2 (0.5%), C22:0 (0.9%), C24:0 (3.8%)	nd	nd	nd	Lampe et al. (8)
	FA in phospholipids	C16:0 (25.8%), C18:0 (14.1%), C18:1 (42.1%), C18:2 (12.3%)	nd	nd	nd	Lampe et al. (8)
	Total FA in SS/SB from mid-abdominal and mid-scapular	C10:0 (1.9%), C11:0 (0.1%), C12:0 (0.7%), C14:0 (4.2%), C14:1 + iso-C14 + anteiso-C14 (1.0%), C16:0 (25.2%), C16:1 + iso-C16 + anteiso-C16 (5.3%), C18:0 (5.5%), C18:1 + C18:2 + iso-C18 + anteiso-C18 (57.3%)	17 cadavers	M: 49–68 y F: 2 wks−85 y	8 M 9 F	Reinertson et al. (12)
			9 normal human	23–52 y	M	
	Phospholipids	**PC, PE, LCS, PS, PI	5 cadavers	nd	nd	Lampe et al. (8)
	Ceramide	nd	5 cadavers	nd	nd	Lampe et al. (8)
Epidermis*	Ceramide	Cer [NS] (34.5%), Cer [NDS](11.7%), Cer [NH] (14.3%), Cer [NP] (12.6%), Cer [AS] (3.3%), Cer [ADS] (1.1%), Cer [AH] (5.2%), Cer [AP] (6.3%), Cer [EOS] (8.8%), Cer [EOH] (1.8%), Cer [EOP] (0.4%)	4	33–47 y	F	Kendall et al. (19)
		Cer [OH][a], Cer [OS][a], Cer [OT][a], Cer [1-O-E(EO)S][b], Cer [1-O-E(EO)H][b], Cer [1-O-E(EO)T][b] – nd	nd	nd	nd	Assi et al. (20)
	FA in sphingomyelin	C14:0 (2.6%), C15:0 (1.1%), C16:0 (14.6%), C17:0 (2.0%), C18:0 (6.4%), C18:1 (2.8%), C20:0 (11.6%), C21:0 (1.3%), C22:0 (8.9%), C23:0 (1.6%), C24:0 (18.8%), C24:1 (9.5%), C25:0 (2.0%), C26:0 (5.8%), C28:0 (0.7%)	nd	nd	nd	Gray and Yardley (21)
	FA of epidermal glycosphingolipid	C14:0 (5.1%), C15:0 (3.4%), C16:0 (8.2%), C17:0 (2.4%), C18:0 (4.3%), C18:1 (17.9%), C20:0 (7.7%), C21:0 (1.7%), C22:0 (4.3%), C23:0 (1.7%), C24:0 (10.0%), C24:1 (2.0%), C25:0 (5.2%), C26:0 (5.4%), C28:0 (5.9%), C24:0-OH (2.6%), C26:0-OH (5.6%)	nd	nd	nd	Gray and Yardley (21)
	FA of prostanoids	C20:3 n-6 (10.2%), C20:4 n-6 (88.3%), C20:5 n-3 (1.5%)	8	28–56 y	F	Kendall et al. (22)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	Hydroxy FA	C18:2 n-6 (69.7%), C20:3 n-6 (1.7%), C20:4 n-6 (25.2%), C20:5 n-3 (2.4%), C22:6 n-3 (1.1%)	8	28–56 y	F	Kendall et al. (22)
	FA of N-acylethanolamides	C16:0 (34.7%), C18:0 (11.4%), C18:1 n-9 (11.3%), C18:2 n-6 (5.5%), C18:3 n-3 (1.2%), C20:4 n-6 (13.1%), C20:5 n-3 (6.3%), C22:6 n-3 (16.5%)	8	28–56 y	F	Kendall et al. (22)
	Total FA	C16:0 (23.9%), C18:0 (22.1%), C18:1 n-9 (24.3%), C18:2 n-6 (9.6%), C18:3 n-3 (0.5%), C20:4 n-6 (2.7%), C20:5 n-3 (0.5%), C22:6 n-3 (0.5%)	8	28–56y	F	Kendall et al. (22)
	Total FA in SC from mid-abdominal and mid-scapular	C10:0 (0.7%), C11:0 (0.1%), C12:0 (0.5%), C13:0 (0.1%), C14:0 (3.6%), C14:1 + iso-C14 + anteiso-C14 (0.5%), C15:0 (1.0%), C16:0 (27.7%), C16:1 + iso-C16 + anteiso-C16 (7.6%), C18:0 (3.3%), C18:1 + C18:2 + iso-C18 + anteiso-C18 (54.8%)	17 cadavers	M: 49–68 y F: 2 wks−85 y	8 M 9 F	Reinertson et al. (12)
			9 normal human	23–52 y	M	
	Phospholipids	PC (28.00%), PA (3.36%), Eplas (11.49%), PE (6.97%), PS (9.49%), LPC (3.08%), PI (5.31%), AAPC (11.17%), SM (11.22%), DHSM (9.76%), CL (4.13%)	7	nd	nd	Meneses et al. (23)
	Sterols	Cholest-7-ene-3β-01 ester (nd)	2	nd	nd	Gray and Yardley (21)
	TAG DAG MAG	nd	nd	nd	nd	Nicolaides (24)
	Glycosphingolipids	nd	nd	nd	nd	Gray and Yardley (21)
Dermis	Ceramides	Cer [NS] (53.4%), Cer [NDS] (21.2%), Cer [NH] (7.3%). Cer [NP] (8%), Cer [AS] (3.4%), Cer [ADS] (1.1%), Cer [AH] (2.1%), Cer [AP] (3.5%)	4	33–47 y	F	Kendall et al. (19)
	FA of prostanoids	C20:3 n-6 (8.0%), C20:4 n-6 (90.5%), C20:5 n-3 (1.6%)	8	28–56 y	F	Kendall et al. (22)
	Hydroxy FA	C18:2 n-6 (50.3%), C20:3 n-6 (5.9%), C20:4 n-6 (40.9%), C20:5 n-3 (3.0%)	8	28–56 y	F	Kendall et al. (22)
	FA of N-acylethanolamides	C16:0 (38.7%), C18:0 (11.6%), C18:1 n-9 (18.3%), C18:2 n-6 (6.2%), C18:3 n-3 (1.1%), C20:4 n-6 (8.3%), C20:5 n-3 (4.1%), C22:6 n-3 (11.7%)	8	28–56 y	F	Kendall et al. (22)

(Continued)

TABLE 1 | Continued

Layer of skin	Lipids	Individual species	Number of studied subjects	Age	Sex	References
	Total FA	C16:0 (19.9%), C18:0 (2.9%), C18:1 n-9 (44.8%), C18:2 n-6 (10.7%), C18:3 n-3 (0.7%), C20:4 n-6 (0.7%), C20:5 n-3 (0.1%), C22:6 n-3 (0.2%)	8	28–56 y	F	Kendall et al. (22)
	Phospholipids	PC (37.09%), PA (2.03%), Eplas (9.83%), PE (6.10%), PS (8.82%), LPC (5.53%), PI (5.17%), AAPC (6.56%), SM (15.86%), DHSM (4.58%), CL (2.04%)	7	nd	nd	Meneses et al. (23)
	TAG DAG	nd	nd	nd	F	Sjövall (25)
	Cholesterol esters	nd	nd	nd	nd	Kendall et al. (26)
Hypodermis	TAG	nd	nd	nd	nd	Kanitakis (3)
	FFA	nd	nd	nd	nd	Kanitakis (3)
	Total FA in hypodermis from mid-abdominal and mid-scapular	C10:0 (0.2%), C12:0 (0.6%), C14:0 (3.1%), C14:1 + iso-C14 + anteiso-C14 (0.5%), C16:0 (24.4%), C16:1 + iso-C16 + anteiso-C16 (9.2%), C18:0 (8.9%), C18:1 + C18:2 + iso-C18 + anteiso-C18 (53.8%)	17 cadavers	M: 49–68 y F: 2 wks−85 y	8 M 9 F	Reinertson et al. (12)
			9 normal human	23–52 y	M	

*Classes present throughout the epidermis.

**No data available on concentrations of all these lipids.

[a]Protein-bound ceramide.

[b]EpiSkin human reconstructed epidermis model ceramide.

[C]Values calculated on the basis of the data in the publication.

TAG, triacylglycerol; DAG, diacylglycerol; MAG, monoacylglycerol; Cer, ceramide; FFA, free fatty acid; FA, fatty acid; PC, phosphatidylcholine; PA, phosphatidic acid; Eplas, ethanolamine plasmalogen; PE, phosphatidylethanolamine; PS, phosphatidylserine; LPC, lysophosphatidylcholine; PI, phosphatidylinositol; AAPC, alkylacylglycerophosphocholine; SM, sphingomyelin; DHSM, dihydrosphingomyelin; long-chain bases: DS, dihydrosphingosine; S, sphingosine; P, phytosphingosine; H, 6-hydroxy sphingosine; SD, 4,14-sphingaidene; fatty acid: N, non-hydroxy FA; A, alfa-hydroxy FA; [B], beta-hydroxy FA; [O], ω-hydroxy FA; [EO], esterified ω-hydroxy FA; [P-O], protein-bound FA; [1-O-E], 1-O-acylceramides with three hydrophobic chains; the third chain ester-linked to the primary hydroxyl in position 1 of the sphingoid base; [1-O-E(EO)], ceramides contain an ultra long-chain esterified with a linoleic acid in the N- position and a long to very long acyl chains in the 1-O- position of the sphingoid base; wks, weeks; y, years; M, male; F, female; nd, no data.

(39). Sphingolipids are complex lipids with long-chain bases (LCBs) as their basic element. Most LCBs from sphingolipids have 12–22 carbon atoms with aliphatic amines that have two or three hydroxyl groups. Sphingolipids include CERs, glycosphingolipids, SM and sphingosine 1-phosphate, among others. Sphingolipids are involved in the formation of lipid microdomains and lipid rafts in biological membranes (40), the maintenance and stabilization of the nervous system (41), spermatogenesis (42), and play a role in apoptosis, signaling and proliferation (43). CERs play an important role in the formation and maintenance of the skin barrier (35, 36, 42, 44).

CERs are composed of LCBs and FAs varying in carbon chain length, degree of unsaturation, and position and number of hydroxyl group (45). LCBs have six sphingoid bases: sphingosine (S), 6-hydroxysphingosine (H), dihydrosphingosine (DS), phytosphingosine (P), dihydroxysphinganine (T) (46), and sphinga-4,14-diene (SD) (11). We can also distinguish five types of fatty acids that build ceramides: α-hydroxy fatty acids (A), non-hydroxy fatty acids (N), ω-hydroxy fatty acids (O) (46), and β-hydroxy fatty acids (B) (11). CERs esterified with additional FAs are preceded by the letter E before the base and the FA chain (46). There are 22 free ceramide classes and five protein-bound ceramides in the human epidermis (11, 14) (**Tables 1**, **2**). EOS, EODS, EOH, EOP, and EOSD are the group of acylceramides. Some acylceramides are metabolized into protein-bound ceramides comprising one of the five LCBs and a P-O FA (34). CERs are an essential element in skin homeostasis. Changes in the composition or length of the FA chains that make up CERs can cause severe damage to the epidermal barrier or even lead to death. Acylceramide is essential for maintaining the proper packing of lipid lamellae (10, 48). CERs are involved in epidermal barrier renewal—their synthesis increases with

TABLE 2 | Nomenclature for 22 free ceramide classes and 5 protein bound ceramide classes in human dermis and epidermis.

Fatty acids	Non-hydroxy fatty acid [N]	A-hydroxy fatty acid [A]	ω-hydroxy fatty acid [O]	Esterified ω-hydroxy fatty acid [EO]	B-hydroxy fatty acid [B]	Protein-bound [P-O]
Amino base						
Sphingosine [S]	NS	AS	OS	EOS	BS	P-OS
Phytosphingosine [P]	NP	AP	OP	EOP		P-OP
6-hydroxysphingosine [H]	NH	AH	OH	EOH		P-OH
Dihydrosphingosine [DS]	NDS	ADS	ODS	EODS		P-ODS
4,14-Sphingaidene [SD]	NSD	ASD	OSD	EOSD		P-OSD
Dihydroxysphinganine [T]	NT					

Each ceramide class is represented by a combination of the abbreviations corresponding to its FA and amino base structure (11, 14, 47). [NS], combination of non-hydroxy FA (N) and sphingosine (S); [NP], combination of non-hydroxy FA (N) and phytosphingosine (P); [NH], combination of non-hydroxy FA (N) and 6-hydroxysphingosine (H); [NDS], combination of non-hydroxy FA (N) and dihydrosphingosine (DS); [NSD], combination of non-hydroxy FA (N) and 4,14-sphingaidene (SD); [NT], combination of non-hydroxy FA (N) and dihydroxysphinganine (T); [AS], combination of α-hydroxy FA (A) and sphingosine (S); [AP], combination of α-hydroxy FA (A) and phytoshingosine (P); [AH], combination of α-hydroxy FA (A) and 6-hydroxysphingosine (H); [ADS], combination of α-hydroxy FA (A) and dihydrosphingosine (DS); [ASD], combination of α-hydroxy FA (A) and 4,14-sphingaidene (SD); [OS], combination of ω-hydroxy FA (O) and sphingosine (S); [OP], combination of ω-hydroxy FA (O) and phytosphingosine (P); [OH], combination of ω-hydroxy FA (O) and 6-hydroxysphingosine (H); [ODS], combination of ω-hydroxy FA (O) and dihydrosphingosine (DS); [OSD], combination of ω-hydroxy FA (O) and 4,14-sphingaidene (SD); [EOS], combination of esterified ω-hydroxy FA (EO) and sphingosine (S); [EOP], combination of esterified ω-hydroxy FA (EO) and phytosphingosine (P); [EOH], combination of esterified ω-hydroxy FA (EO) and 6-hydroxysphingosine (H); [EODS], combination of esterified ω-hydroxy FA (EO) and dihydrosphingosine (DS); [EOSD], combination of esterified ω-hydroxy FA (EO) and 4,14-sphingaidene (SD); [BS], combination of β-hydroxy FA (B) and sphingosine (S); [P-OS], protein bound (P) combination of ω-hydroxy FA (O) and sphingosine (S); [P-OP], protein bound (P) combination of ω-hydroxy FA (O) and phytosphingosine (P); [P-OH], protein bound (P) combination of ω-hydroxy FA (O) and 6-hydroxysphingosine (H); [P-ODS], protein bound (P) combination of ω-hydroxy FA (O) and dihydrosphingosine (DS); [P-OSD], protein bound (P) combination of ω-hydroxy FA (O) and 4,14-sphingaidene (SD).

TABLE 3 | Classification of FAs according to carbon chain length and number of multiple bonds (5, 6).

Number of double bonds	Saturated Fatty Acid (SFA)
	Monounsaturated Fatty Acid (MUFA)
	Polyunsaturated Fatty Acid (PUFA)
Carbon chain length	Short chain fatty acid (SCFA) C2–C4
	Medium chain fatty acid (MCFA) C5–C11
	Long-chain fatty acid (LCFA) C12–C20
	Very long-chain fatty acid (VLCFA) C20–C25
	Ultra long-chain fatty acid (ULCFA) ≥ C26

keratinocyte differentiation (49). An excess of CERs leads to an increase in uncontrolled cell death and inflammation (50).

FAs, one of the components of ceramides, are a group of chemical compounds with a great deal of diversity, thus it is difficult to categorize them unequivocally. **Table 3** presents the two most common divisions of acids: the first concerning the presence and number of double bonds and the length of the carbon chain in the molecule (**Table 3**).

VLCFAs and ULCFAs are the most abundant group of FAs in the SC, but they are also present in the retina, meibomian gland, testis and brain. In addition, they can be found in the liver, lung, and kidneys (5, 6). The FA elongation process occurs in the endoplasmic reticulum and consists of four steps: elongation, reduction, dehydration, and reduction (**Figure 1**) (5, 6). Elongation is catalyzed by fatty acid elongase (ELOVL). Seven isoforms can be distinguished in mammals (ELOVL1-7) (51–53). This is a rate-limiting step. Reduction is catalyzed by 3-ketoacyl-CoA reductase (KAR), and NADPH is used as a cofactor (54). Dehydration is catalyzed by 3-hydroxyacyl-CoA dehydratase, which has 4 isoforms (HACD1-4). This is also a rate-limiting step (55, 56). The final step is also reduction, catalyzed by trans-2-enyl-CoA reductase (TER) (54). Each cycle results in the elongation of the carbon chain by two carbon atoms (51, 52).

VLCFAs and ULCFAs are degraded by beta-oxidation, and VLCFA-CoAs and ULCFA-CoAs are transported to peroxisomes where FA chains are converted to shorter acyl-CoAs. The resulting acyl-CoAs are then transported to the mitochondrial matrix where they undergo further steps of beta-oxidation (57).

Very Long-Chain Fatty Acids and Ultra Long-Chain Fatty Acids in Skin Disorders

Considering the abundance of VLCFAs and ULCFAs, it is not surprising that there are plenty of enzymes and other proteins involved alongside them in multiple biochemical reactions and complex interactions. Disruption of these processes due to genetic defects in several genes encoding proteins enrolled in the metabolism of VLCFAs has clinical consequences leading, i.e., to inborn errors of metabolism and neurodegenerative disorders. Some also affect the skin and, in such cases, are referred to as genodermatoses, which are defined as inherited skin diseases. The majority of them are monogenic and can be inherited in an autosomal dominant, recessive or X-linked manner. The skin symptoms are common, but not exclusive, as several genodermatoses are multisystemic disorders. In fact, it is estimated that cutaneous findings can be present in around one third of all hereditary disorders (58). However, in the majority of them, the dysfunction of other organs is of principal clinical concern. Conversely, there are also genodermatoses with isolated skin symptoms only.

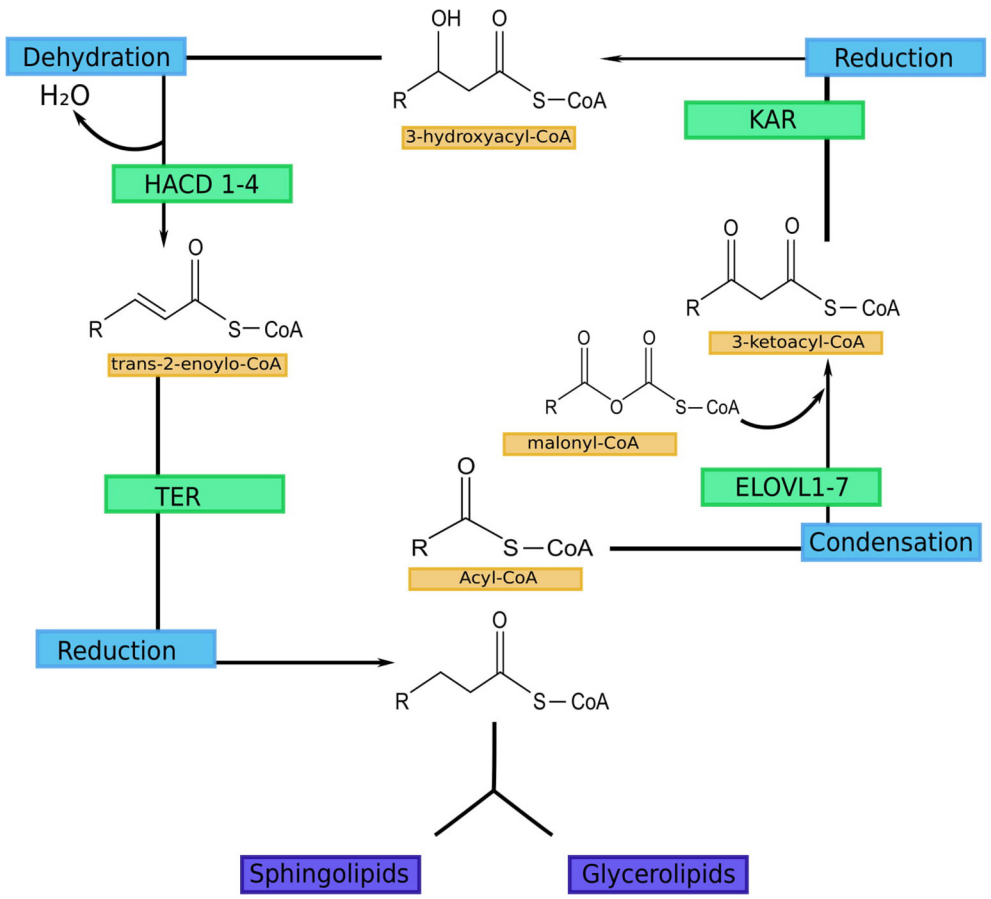

FIGURE 1 | FA elongation cycle with involved enzymes in each step (5). ELOVL1-7-fatty acid elongase 1-7 (ELOVL1 elongates SFA with chain lengths of 18–24 carbons, ELOVL2 elongates PUFA with 20–22 carbon and SFA with 18–20 carbon chains; ELOVL3 elongates SFA with chain lengths of 18–24 carbons; ELOVL4 elongates long-chain PUFA and long-chain SFA of 24 carbon length to VLC-PUFA and VLC-SFA (≥26 carbons; ELOVL5 mediates elongation of long-chain PUFA and long-chain SFA between 18 and 22 carbons in length; ELOVL6 elongates SFA, MUFA and PUFA with 12–18 carbon chains; ELOVL7 elongates SFA with chain lengths of 18–22 carbons); KAR, 3-ketoacyl-CoA reductase; HACD 1-4, 3-hydroxyacyl-CoA dehydratase; TER, trans-2-enoyl-CoA reductase.

As expected, several proteins involved in the metabolism of ULCFAs are located in the epidermis and their mutations often result in an aberrant cornification process clinically manifested as isolated or syndromic ichthyosis or keratoderma. From the diagnostic perspective, the clinical features of those disorders, also referred to as Mendelian Disorders of Cornification, often overlap despite different molecular defects and, conversely, may be highly different even though the pathogenic variants occur in the same gene. Currently, several forms of autosomal recessive non-syndromic ichthyosis, including harlequin ichthyosis, lamellar ichthyosis, congenital ichthyosiform erythroderma and pleomorphic ichthyosis, are comprehensively named autosomal recessive congenital ichthyosis (ARCI). However, the clinical symptoms of ARCI may differ significantly between patients from a severe, even fatal phenotype to a mild outcome.

Herein, we present an overview of selected proteins involved in the metabolism of VLCFAs and ULCFAs in the skin (**Figure 2**) with regard to recent findings connected with their functions and with skin pathology.

Enzymes

ELOVL (elongases) 1-7 (3-ketoacyl-CoA synthases) are key enzymes involved in the elongation of saturated fatty acids (SFAs) and unsaturated FAs, which are essential for the proper functioning of several human systems and organs, the nervous system and the epidermis in particular. ELOVL1, 3 and 4 are enzymes involved in the first step of the elongation of SFAs and monounsaturated fatty acids (MUFAs) to VLCFAs. Each of these enzymes is expressed, among others, in the skin, therefore any disorder related to the mentioned elongases is manifested in the skin.

ELOVL1

Fatty acid elongase 1 (ELOVL1) is an enzyme involved in the cycle of VLCFA formation. It is involved in the first step in the preparation of acylceramide (59) and responsible for the elongation of saturated C18:0- to C26:0-CoA and monounsaturated C18:1- to C22:1-CoA (51, 53). Depending on its location in the epidermis, ELOVL1 interacts with ceramide

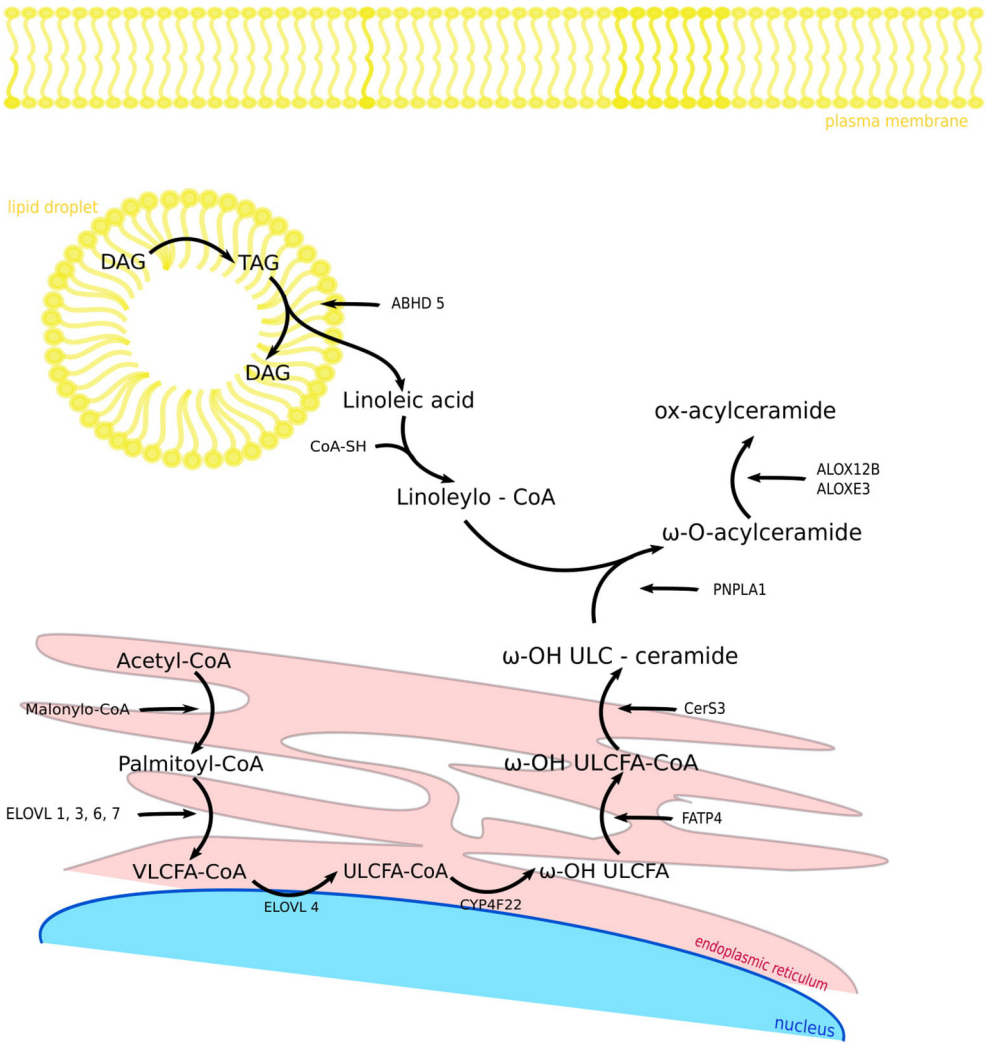

FIGURE 2 | Components and biosynthetic steps of fatty acid modification in the skin. FASN1 catalyzes *de novo* synthesis of fatty acids from acetyl-CoA and malonyl-CoA. After activation to acyl-CoA esters, the acyl chain is elongated to VLCFA-CoA esters. CYP4F22 catalyzes ω-hydroxylation ULCFA-CoA to ω-OH ULCFA and FATP4 synthesize ω-OH ULCFA-CoA. CerS3 enables the synthesis of ω-OH ULC-ceramide. In the same time in lipid droplet TAG is hydrolyzed by ATGL activated by the ABHD5 to linoleic acid, which is synthesize with CoA-SH by receiving Linoleoyl-CoA. PNPLA1 catalyzes as a transacylase the formation of an ester bond between ω-hydroxyceramide and linoleoyl-CoA, so that we get ω-O-acylceramide. ALOX12B and ALOXE3 are responsible for oxidizing linoleic acid when it is attached to acylceramide. FASN1, fatty acid synthase 1; VLCFA-CoA, very long-chain fatty acid CoA; ELOVL, fatty acid elongase; ULCFA-CoA, ultra long-chain fatty acid CoA; CYP4F22, Cytochrome P450 Family 4 Subfamily F Member 22; FATP4, fatty acid transporter 4; CerS3, ceramide synthase 3; ABHD5, abhydrolase domain containing 5; PNPLA1, patatin like phospholipase domain containing 1; ALOX12B, arachidonate 12-lipoxygenase, 12R type; ALOXE3, arachidonate lipoxygenase 3; TAG, triacylglycerol; DAG, diacylglycerol.

synthases: ceramide synthase 2 (CERS2) and ceramide synthase 3 (CERS3). The cooperation of ELOVL1 with CERS2 takes place in the lower layers of the epidermis. ELOVL1 enables the formation of FAs C22:0 and C24:0, which are substrates in the process of obtaining CERs. In contrast, the coexpression of CERS3 takes place in the higher layers of the epidermis and this stimulates ELOVL1 to an additional cycle resulting in the formation of C26:0-CoA, which is further elongated by fatty acid elongase 4 (ELOVL4) (53, 60). The absence of VLCFAs C24:0 and C24:1 causes severe skin lesions. Recently, it was discovered that heterozygous mutations in the *ELOVL1* gene cause ichthyotic keratoderma, spasticity, hypomyelination, and dysmorphic facial features (IKSHD) disease. So far, only one mutation—p.Ser165Phe—was found to arise *de novo* in two unrelated patients of Polish origin (61, 62). Moreover, mice lacking *Elovl1* have an altered lipid lamellae structure, resulting in elevated TEWL (60). It has also been shown that ELOVL1 levels are decreased in psoriasis and atopic dermatitis (AD). In AD, interferon-γ (IFN-γ), which acts on keratinocytes to decrease the expression of the enzyme, is responsible for the downregulation

of ELOVL1 (63, 64). In contrast, tumor necrosis factor α (TNF-α) and type 2 cytokines negatively affect the expression of the enzyme (65, 66).

ELOVL3

Fatty acid elongase 3 (ELOVL3) is involved in the elongation of saturated C16:0- to C22:0-CoA. It is expressed in brown adipose tissue and in the skin (51). In the *Elovl3*-ablate mice model, skin abnormalities can be observed due to a transient decrease in the ability to elongate saturated fatty acyl-CoAs during temporarily decreasing levels of C20:0 and C22:0 (67). The mice also have increased TEWL. The epidermal lipid composition is mildly altered with an increase in neutral lipids. It has also been shown that a lack of functional *Elovl3* in mice causes abnormalities in the SC—abnormal LBs and an abnormal membrane lipid composition. However, the lipid composition itself is not altered despite the altered phenotype (68).

Recently, another study on mice led to the discovery that the ELOVL3 enzyme is involved in the synthesis of C21:0 to C29:0 FAs, including odd and branched chains (69). Interestingly, according to the Human Gene Mutation Database (HGMD), only a single variant of mutation in *ELOVL3* was detected in humans so far. The variant occurred *de novo* and was detected in one child of a large cohort screened for molecular alterations causing autism spectrum disorders (70). A reduced expression of ELOVL3 by interleukin 4/interleukin 13 (IL-4/IL-13) was observed in a keratinocyte culture experiment—this resulted in an accumulation of FAs with shorter chains and a decrease in VLCFAs. A reduced expression of ELOVL3 by IL-4/IL-13 was observed in the SC of AD patients—this resulted in an accumulation of shorter chain FAs and a reduced level of VLCFAs. Moreover, after a siRNA-induced downregulation of ELOVL3/ELOVL6 expression in keratinocytes, the proportion of long-chain fatty acids (LCFAs) globally and in sphingolipids was decreased (71).

ELOVL4

Fatty acid elongase 4 (ELOVL4) is the enzyme responsible for elongating SFAs and polyunsaturated fatty acid (PUFA) ULCFAs-C26:0–C36:0 (51). It is the only elongase that extends the carbon chain beyond 26 carbon atoms. ELOVL4 catalyzes the first step in the preparation of acylceramides, which results in ULCFAs. Since the ULCFAs are components of skin CERs and glucosylceramides, they are essential in providing the hydrophobicity of lipid lamellae in the epidermis, and in the preservation of the water barrier (5, 6). Indeed, certain pathogenic variants occurring in the gene encoding ELOVL4 cause scaly and dry skin. These symptoms are caused by the absence of lamellar membranes in extracellular domains in the SC (72), which in turn are due to the lack of ω-O-acylceramides (72, 73). Similarly, ω-O-acylceramides are also involved in the lipid layer formation in the retina, acting against the evaporation of the aqueous tear film (74). In addition, besides the skin and retina, ELOVL4 is also expressed in the central nervous system and in the reproductive system (74).

The expression pattern of ELOVL4 explains, at least partially, the fact that skin syndromes are not isolated and, so far, were only identified as part of more systemic diseases, e.g., autosomal dominant spinocerebellar ataxia and erythrokeratodermia (75), and autosomal recessive syndromes, referred to as ichthyosis, intellectual disability and spastic quadriplegia (76) or neuro-ichthyotic disorder. Interestingly, among 21 different *ELOVL4* variants published so far, skin involvement was observed only in 8 cases. The majority of *ELOVL4* pathogenic variants led to autosomal dominant: Stargardt disease and spinocerebellar ataxia.

It has been proposed that the phenotype depends on the variant type and location within the gene: pathogenic variants leading to Stargardt disease and neuro-ichthyotic disorder, leading to protein truncation and the absence of the C-termination part, where the ER-retention motif is encoded. In the case of Stargardt disease, those variants tend to locate in exon 6. In spinocerebellar ataxia, missense variants are mainly detected and hence, although changed, still a full-length protein can be produced. The mechanism of Stargardt disease was investigated on a mice model. In transgenic mice expressing a pathogenic variant form of human *ELOVL4*:c.790_794delAACTT (p.Asn264Leufs*9), it was shown that an accumulation of undigested phagosomes and lipofuscin by the retinal pigment epithelium is followed by its atrophy and photoreceptor degeneration (77). Furthermore, Vasireddy et al. (72) observed on their mice model that heterozygous mice harboring a 5bp deletion in the *Elovl4* gene also had progressive photoreceptor degeneration, while in the case of homozygotes, severe skin symptoms were present and death occurred within the first few hours of life (72). This corresponds to severe ichthyosis, intellectual disability and spastic quadriplegia syndrome in humans.

Last but not least, recent studies on normal human cultured keratinocytes of AD and mice models show that IFN-γ significantly reduces ELOVL4, which may be one of the key findings explaining the mechanism of the chronicity of barrier function impairment in AD (63, 64).

CERS3

Ceramide synthase 3 (CERS3) is an enzyme expressed in the testis and skin (78, 79). This enzyme is responsible for the formation of epidermal-specific CERs and is one of the enzymes involved in the synthesis of acylceramides. Importantly, it is the only enzyme with the ability to synthetize ULC-ceramides (78–80). In the epidermis, the expression originates in the SB and increases with keratinocyte differentiation, so the highest amounts of CERS3 are present in the SG and SC. CERS3 cooperates with ELOVL1 and ELOVL4 (49, 60). In the lower epidermal layers, the cooperation of CERS3 and ELOVL1 catalyzes one more elongation cycle and produces C26:0-CoA, which can next be elongated by ELOVL4 (60). The coordinated expression of ELOVL4 and CERS3 is controlled by the peroxisome proliferator-activated receptor (PPAR) factor β/γ (49). CERS3 also has an ability to take over the functions of another ceramide synthase—CERS2 allowing uninterrupted ceramide synthesis (49). CERS3 deficiency results in decreased levels of acylceramides and ULC-CERs (≥C24 CERs) (78, 81), which cause skin barrier damage due to the

impaired formation of intercellular lipid bilayers (82) and the decreased water permeability barrier (WPB) (35, 42).

Although *CerS3*-deficient mice had prominent skin symptoms and died shortly after birth (78), pathogenic variants of *CERS3* in humans are not lethal and the condition of human skin in affected people tends to improve with age. In 2013, the first cases of *CERS3* pathogenic variants in humans were reported (81, 83) and up to now, only 9 different pathogenic variants in this gene are known, according to the HGMD. They cause rare ARCI type 9, which is clinically characterized mainly by a collodion membrane at birth, generalized scaling with fine or large scales, and palmoplantar hyperlinearity. In some patients, large brownish scales on the lower extremities, acrogeria, ectropion, and alopecia may develop (84).

Along with studies on *ELOVL4* gene expression in the context of psoriasis and AD, the involvement of CERS 3 in the elucidation of the pathomechanisms of these disorders is also being investigated (63, 64).

CYP4F22

CYP4F22 is a protein belonging to the cytochrome P450 family 4. It is highly expressed in the epidermis, mainly in the SG (85). It is a fatty acid hydroxylase that catalyzes the ω-hydroxylation of ULCFAs (FAs >C26:0) (86, 87). In a mice *Cyp4f39e* knockout (KO) model (Cyp4f39e is a functional homolog of human CYP4F22), death occurred within 8 h of birth due to severe skin barrier disruptance. An increased thickness of corneocytes, and the presence of corneodesmosomes, which normally disappear in the upper layer of the SC, were observed. Miyamoto et al. (88) demonstrated these mice had reduced ω-OH CERs and they stored ULC-CERs. A significant decrease in acylceramide concentration was also observed (88).

The *CYP4F22* gene was discovered in 2006 (85) and subsequently, pathogenic variants were discovered in patients with ARCI. Around 55 pathogenic variants have been described since then, most of which are missenses. Recently, Nohara et al. (89) investigated CYP4F22 enzyme activity *in vitro* with several missenses and showed that the majority of them led to a marked reduction or loss of ω-hydroxylase activity. In two of the analyzed cases, however, the enzyme activity was comparable to the wild type (89). According to the authors, this could reflect the fact that either these mutations are not pathogenic or that patients with these variants have very mild ichthyosis symptoms. However, these were the results of *in vitro* studies, so the exact effect of those variants *in vivo* could be potentially different. The frequency of mutations in *CYP4F22* differs among the patient cohort and usually reaches 3–8% of ARCI patients (85, 90, 91). In one of the largest ARCI studies comprising 770 families, *CYP4F22* pathogenic variants were found in 54 families (87). The authors made an attempt to find genotype-phenotype correlations in their CYP4F22 cohort, but could not define any (87).

ABHD5

ABHD5 is an enzyme of the hydrolase family, also referred to as CGI-58, and also expressed in the epidermis. The enzyme activates adipose triglyceride lipase (ATGL, also known as PNPLA2) (92), thus providing fatty acids for the ω-O-esterification of CERs to yield acylceramides. Its expression increases during keratinization (93, 94). ABHD5 is involved in the derivation of linoleic acid necessary for the formation of acylceramides (95). Linoleic acid is required for acylceramide synthesis and CLE formation (94, 96). CLE abnormalities cause lethal, postnatal permeability barrier defect, which can be observed in *Abhd5* KO mice (95). Moreover, ABHD5 stimulates PNPLA1 in acylceramide synthesis. ABHD5 targets enzymes to lipid droplets, which facilitates the access of PNPLA1 to the required substrate (97, 98). Hence ABHD5 defects indirectly affect the energetic balance as well.

In humans, mutations in the *ABHD5* gene cause rare, multisystemic Dorfman-Chanarin syndrome (neutral lipid storage disease-NLSD) (99, 100). One of the characteristic (and diagnostic) features of this disease is the presence of ichthyosis and lipid droplets in granulocytes. It has been shown that ATGL inactivation, caused by molecular defects in ABHD5, leads to the accumulation of TAG-rich intracytoplasmic lipid droplets. ABHD5 is a co-activator of the hydrolase activity of ATGL. Lipid droplets can be observed in several tissues, which indeed reflects the multiorganic character of Dorfman-Chanarin syndrome, which includes, i.e., hepatomegaly and muscle weakness (99, 100).

PNPLA1

PNPLA1 represents a family of enzymes containing a patatin-like phospholipase domain (101). In the epidermis its expression occurs in the SG, and PNPLA1 localizes at the interface between the SG and SC layers (98, 102). It participates in O-acylceramide synthesis by catalyzing as a transacylase the formation of an ester bond between ω-hydroxyceramide and linoleate using triglyceride as the linoleate donor (98, 103, 104). PNPLA1 may be involved in the incorporation of ω-OH-Cer FAs as the last step in the production of acylceramides (105). PNPLA1 also plays an important role in keratinocyte differentiation (98). In *Pnpla1* KO mice, an accumulation of substrates required for acylceramide synthesis is observed: ω-OH CERs, ω-OH ULCFA. Consequently, there is excessive transepidermal dehydration. The proliferation of keratinocytes is also delayed. Furthermore, there is a lack of the corneocyte lipid envelope (CLE) associated with corneocytes (103). Mutations in the *Pnpla1* gene in mice also cause the abnormal secretion of compact lamellar granules at the SG and SC interface and the formation of lipid aggregates in corneocytes (98, 105). In addition, lipid lamellae have an abnormal alignment and the organization of intercorneocyte lipids is defective (105). Although PNPLA1 is known to localize on the cytoplasmatic lipid droplets, it has only recently been shown that in the case of mutations in *PNPLA1* genes, the accumulation of lipid droplets in fibroblasts is changed (106, 107). Indeed, mutations in the human *PNPLA1* gene are causative of ARCI (102, 105, 108–110). In patients with mutations in this gene, various skin symptoms occur, e.g., a collodion membrane at birth, erythroderma and ichthyosis; however, atopy and fungal infection tendency were also observed

(111). Recent studies indicate an association between PNPLA1 single nucleotide polymorphism (SNP) rs4713956 and AD. The results suggest that the pathogenesis of AD may be due to a reduction in the combination of esterified ω-hydroxy FAs (EO) and sphingosine (S) (EOS) synthesis and insufficient CLE formation (112). Since the frequency of *PNPLA1* gene mutations among ARCI patients is rather low, there are no sufficient data yet to define a correlation between the genotype and the type of skin lesions (113).

ALOX12B and ALOXE3

2 (R)-lipoxygenase (12R-LOX) and lipoxygenase-3 (eLOX3) belong to the lipoxygenase family and are encoded by ALOX12B and ALOXE3, respectively. They act as dioxygenases in the epidermis (114, 115) and are responsible for oxidizing linoleic acids when they are attached to acylceramides (115, 116). In Alox12b and Aloxe3 KO mice, a decrease in CERs bound to cornified cell envelope (CCE) proteins was observed (115, 117, 118). Alox12b KO mice had a reduced amount of CERs with oxidized linoleic acid, which caused a loss of barrier function without alterations in proliferation, and the stratified organization of keratinocytes (118) and severe skin damage (118, 119). Mutations in ALOX12B and ALOXE3 genes in humans cause ARCI with generally a rather mild clinical manifestation, including erythema, scaling and mild palmoplantar keratoderma. According to a recent meta-analysis by Hotz et al. (120), in about 76 and 36% of patients with ALOX12B and ALOXE3 mutations, respectively, a collodion membrane was present at birth (120). In epidemiological studies, depending on the ethnicity, taken together, mutations in ALOX12B and ALOXE3 are detected in about 15–30% of ARCI patients (121). Moreover, in both genes, hot-spot mutations are known: p.(Pro630Leu) and p.(Arg234*) accounting for 61% of mutated ALOXE3 alleles and p.(Tyr521Cys) present in 22% of all ALOX12B mutated alleles (120).

PHYH

Phytanoyl-CoA hydroxylase (PHYH) is a peroxisomal enzyme involved in the α-oxidation of fatty acids, and converts phytanoyl-CoA to hydroxyphytanoyl-CoA (122, 123). PHYH deficiency in adults results in phytic acid (PA) accumulation (124), which leads to autosomal recessive Refsum disease. The symptoms of this disorder progress with life and include progressive retinitis pigmentosa and hearing loss, anosmia, polyneuropathy, cardiac arrhythmias, unsteadiness of gait, and ichthyosis (125). The symptom affecting the skin becomes apparent relatively late in life, as late as adolescence or even at the age of 30 or 40 years (126). The accumulation of PA in human skin causes an abnormal shape of lamellar bodies, which may cause a change in the organization of lipid lamellae (127). In addition, the complete loss of the CLE was described (127). Accumulated PA can replace linoleic acid in acylceramides, resulting in CLE atrophy (126).

FATP4

Fatty acid transporter 4 (FATP4) is a protein belonging to the membrane-bound FATP family and is encoded by SLC27A4 (128). The expression sites are the upper part of the SS and the SG (129–131). FATP4 is a major fatty acid CoA synthase for the production of ULCFAs by the synthesized ULCFA-CoA in the epidermis and can transport exogenous VLCFAs across the plasma membrane (128, 132–136).

FATP4 is predominant in the fetal epidermis, and is crucial for epidermal barrier formation in mice neonates, but is not important for the maintenance of this barrier in adult skin (130). In mutant mice the presence of severe skin barrier abnormalities causing increased TEWL is manifested by hyperkeratosis and acanthosis (129, 131, 137). Mice with *Fatp4* mutations have impaired lipid lamellae formation and keratinocyte differentiation (137). This is caused by decreased acyl chain ceramides $\geq$26C and increased ceramides $\leq$24C (129, 131), but also by increased levels of FFAs (137). All these changes in the amount and composition of FFAs result in changes in the organization of lipid lamellae, and increased TEWL (138).

FATP4 is encoded by the *SLC27A4* gene, the mutations of which lead to syndromic autosomal recessive ichthyosis prematurity syndrome (IPS), one of the disorders commonly referred to as ARCI (132). IPS is characterized by premature birth, respiratory distress, skin abnormalities at birth, and eosinophilia (139). Although the perinatal complications are life-threatening, the symptoms may alleviate with time (140). IPS is considered to be a rare disorder, being more frequent in Scandinavian countries, probably due to founder mutation (141, 142). However, up to now, 23 distinct pathogenic mutations have been reported worldwide (according to the HGMD) and some authors claim that the frequency of this disease is underestimated (143).

DISCUSSION

Lipids are important building blocks of the skin. Any changes in the amount and composition of lipids cause skin diseases. In this work we focus on VLCFAs and ULCFAs, and mutations in the genes responsible for the metabolism of these FAs. The small number of studies on VLCFAs and ULCFAs may be due to cognitive difficulties related to limitations in the choice of the research model. In most studies, the research model is mice, whose disease symptoms are more severe than in humans. Additionally, some mutations in humans are so rare that the exact pathomechanism of the disease has not yet been worked out. However, the development of research techniques and lipid analysis methods allows us to conclude that advances in the understanding of epidermal ceramide synthesis and metabolism, and especially acylceramides, will contribute to the development of effective, innovative therapies related to functional epidermal lipids in ichthyoses and ichthyosis syndromes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

AM conceived and designed the review and verified the manuscript. AZ and KW-T studied the literature and wrote the manuscript. All authors accepted the final version of the review. All authors have read and agreed to the published version of the manuscript.

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SYSTEMATIC REVIEW
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Systematic Review on the Efficacy and Safety of Oral Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis

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Background: Atopic dermatitis is a chronic, relapsing and remitting disease that can be difficult to treat despite a recently approved biologic therapy targeting IL-4/IL-13 receptor. Oral janus kinase inhibitors (JAKi) represent a novel therapeutic class of targeted therapy to treat moderate-to-severe atopic dermatitis (AD).

Objective: To review the efficacy, safety, and pharmacokinetic characteristics of oral JAKi in the treatment of AD.

Methods: A PRISMA systematic review was conducted using MEDLINE, EMBASE (Ovid), and PubMed databases for studies assessing the efficacy, safety, and/or pharmacokinetic properties of oral forms of JAKi in the treatment of AD in pediatric or adult populations from inception to June 2021.

Results: 496 papers were reviewed. Of 28 articles that underwent full text screening, 11 met our inclusion criteria for final qualitative review. Four studies examined abrocitinib; three studies examined baricitinib; three examined upadacitinib and one examined gusacitinib (ASN002). Significant clinical efficacy and a reassuring safety profile was reported for all JAKi agents reviewed. Rapid symptom control was reported for abrocitinib, baricitinib and upadacitinib.

Limitations: Given the relatively limited evidence for each JAKi and the differences in patient eligibility criteria between studies, the data was not deemed suitable for a meta-analysis at this time.

Conclusion: Given their ability to achieve rapid symptom control with a reassuring safety profile, we recommend considering the use of JAKi as a reliable systemic treatment

option for adult patients with moderate-to-severe AD, who are unresponsive to topical or skin directed treatments.

Keywords: JAK inhibitor, janus kinase, atopic dermatitis, eczema, abrocitinib, baricitinib, gusacitinib, upadacitinib

INTRODUCTION

Atopic dermatitis (AD), is a chronic and relapsing inflammatory skin condition that affects up to 20% of children and 10% of adults (1). Pruritus is the hallmark of the disease (2); other signs include erythema, scaling, papules, lichenification, excoriations, crusting and vesicles. At times the affected skin can become impetiginized and/or infected with Herpes simplex virus (eczema herpeticum) or molluscum contangiosum (3) leading to increased disease morbidity. Other complications of AD are well-recognized and were reviewed elsewhere (4). In addition to the physical burden, patients with AD have higher rates of psychosocial distress and a reduced quality of life (5–7).

AD is thought to be a multifactorial disease that arises due to both genetic and environmental factors, although the complete pathophysiology has yet to be elucidated (6). Indeed, a meta-analysis of genome-wide association studies, demonstrated that *filaggrin*, *Inteleukin-13* (*IL-13),* and *Ovo Like Transcriptional Repressor 1* (*OVOL1)* were found to be the most commonly identified genes associated with an elevated risk of acquiring AD (8). Specifically, IL-13 and OVOL1 regulate filaggrin expression, which is essential for skin barrier protection and plays a crucial role in the pathogenesis of AD. Considering the importance of filaggrin, disruption of the epidermal barrier due to genetic or environmental causes is thought to lead to increased trans-epidermal water loss, making the skin more vulnerable to allergens and pathogen penetration. This, in turn, causes inflammation via the release of chemokines by keratinocytes and subsequent inflammatory cell infiltration (9).

Although historically thought to be a type 2 T helper (Th2) cell driven disease, multiple inflammatory pathways with their respective cytokines have been implicated in AD to varying degrees. These pathways include Th2 (IL-4, IL-5, IL-13, IL-31), Th22 (IL-22), with variable Th1 [interferon (IFN)-γ] and Th17/IL-23 related cytokine involvement (10). These inflammatory pathways have provided potential therapeutic targets for the treatment of AD.

The mainstay for AD management involves the treatment of acute skin flares, management of secondary infections, and prevention of recurrences. General daily skin care for AD includes gentle cleansing of skin, restoration of the skin barrier through the regular use of emollients and avoidance of aggravating factors (11). For acute flares, topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and/or a topical phosphodiesterase-4 (PDE-4) inhibitor are recommended (12). In moderate-to-severe cases of AD, phototherapy and systemic immunosuppressants (corticosteroids, cyclosporine, azathioprine, mycophenolate mofetil, or methotrexate) can be used (12) although none are approved by Health Canada for the treatment of AD, and side effect profiles for certain systemic immunosuppressants can decrease overall adherence to a treatment plan (11, 13). Access to phototherapy is limited for many patients (14). Although multiple therapeutic modalities are available for the treatment of AD, it remains a challenging disease to manage; in a survey conducted by the National Eczema Association, it was reported that 86% of patients were not satisfied with the treatment of AD (15).

Dupilumab, a monoclonal antibody against IL-4 receptor subunit alpha (Rα) has shown efficacy in many patients and was the first approved biologic therapy for AD that revolutionized the treatment landscape (16). However, approximately 4%-14% experience treatment failure with dupilumab due to either AD worsening (in 5%) or side effects such as conjunctivitis (in 3%) and paradoxical facial erythema (17–19). Patients may also discontinue treatment due to a lack of desired response or for other reasons. Therefore, there remains a need for other targeted therapies. Currently, several other monoclonal antibodies are in phase II/III development and/or pending approval for the treatment of AD, including tralokinumab (20) and lebrikizumab (IL-13 receptor signaling inhibitors), nemolizumab (IL-31 receptor signaling inhibitor) (21–23), and etokimab (IL-33 signaling inhibitor) (24). Given the diversity of cytokines implicated in the inflammatory processes of AD, there is a growing interest toward janus kinases inhibitors (JAKi), which could interfere with the signaling of multiple cytokines simultaneously (25).

Janus kinases (JAKs) are signal transduction proteins that are comprised of a family of four proteins: JAK1, JAK2, JAK3, and TYK2 (26). JAKs are recruited to the inflammatory pathways by the binding of cytokines (such as IL-2, IL-4, IL-6, IL-12, IL-21, IL-22, IL-23, or IFN such as IFN- γ) to their cognate receptors that initiate an inflammatory cascade (**Figure 1**). Recruitment and activation of JAKs results in the phosphorylation of tyrosine residues including residues within the cytokine receptor chains (**Figure 1**). Consecutively, transcription factors, signal transducer and activator of transcription (STAT) proteins, are recruited and become activated by JAKs phosphorylation. Activated STAT proteins undergo dimerization, which then enables the translocation of these proteins into the nucleus and allows for the transactivation of a broad range of different genes (26, 27). Given that specific JAKs are selectivity activated by different cytokine receptors, this selectivity enables JAKi to demonstrate a defined specificity and different capacities to block cytokine receptor signaling. For instance, while pan-JAKi have a broad inhibitory effect against multiple cytokines, JAKi that selectively target JAK1, JAK2, or TYK2 proteins exclusively, have a more targeted mode of action (28).

In this systematic review, we aim to present the current literature on the pharmacokinetics, clinical efficacy and safety of topical and oral JAKi that were recently approved or are currently under investigation for AD.

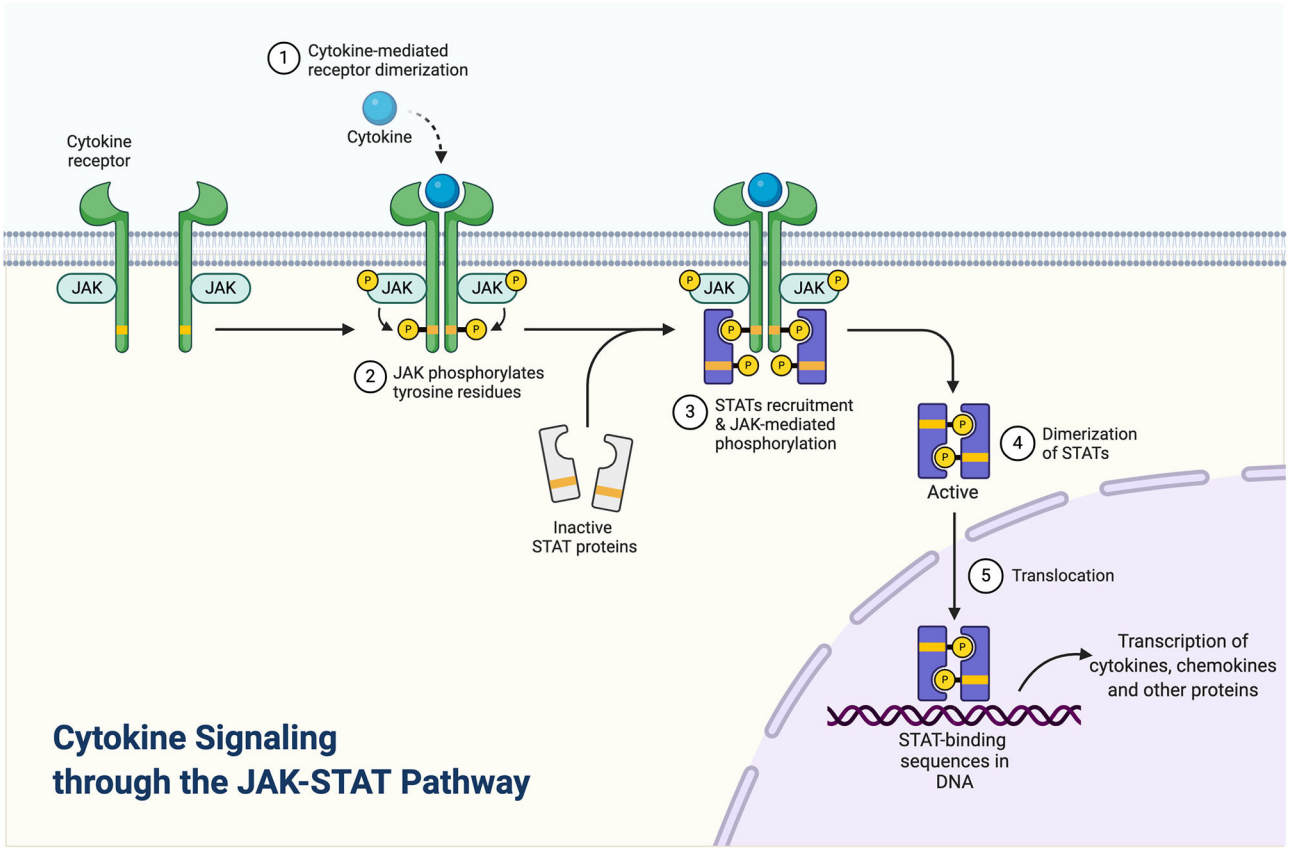


FIGURE 1 | Cytokine signaling through the JAK-STAT pathway. Adapted from "Cytokine signaling through the JAK-STAT pathway," by BioRender.com (2020). Retrieved from https://app.Biorender.com/biorender-templates.

METHODS

Search Strategy

We systematically searched Ovid MEDLINE, EMBASE (Ovid), and PubMed for studies assessing the efficacy, safety, and/or pharmacokinetic properties of oral forms of JAKi in the treatment of AD in pediatric or adult populations from inception to June 2021. We combined free-text search terms for the concept of JAKi ("Janus kinases" OR "JAK inhibitor" or "janus tyrosine kinase inhibitor") and AD ("atopic dermatitis" or "atopic eczema" or "eczema atopica" or "eczema endogenous" or "eczema infantum" or "eczema, infantile" or "endogenous eczema" or "infantile eczema" or "neurodermatitis constitutionalis" or "neurodermatitis disseminata" or "neurodermatitis, atopic constitutional"). A sample of the search strategy is shown in detail (**Supplementary Text 1**).

Study Selection

Two researchers (ML and MB-R) independently assessed study eligibility by title and abstract. When a study was deemed potentially eligible for inclusion, the full text article was obtained and assessed by the reviewers independently. Additional reviewer (FG) was consulted when consensus could not be reached.

We restricted our inclusion criteria to randomized-controlled trials (RCTs) that examined the efficacy or safety of JAKi in the treatment AD as measured by changes from baseline in the Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA) score, and the peak pruritus numeric rating scale (PP-NRS). Specifically, proportion of patients achieving EASI-75 and EASI-50, defined as a 75 and 50% reduction from baseline in the EASI score, respectively; achieving an IGA score of 0 or 1 (i.e., clear or almost clear) with an improvement of $\geq$2 grades from baseline (later referred to as an IGA response); and achieving a PP-NRS score improvement of $\geq$4-point from baseline (later referred to as PP-NRS response), were required as measures of clinical efficacy. Percentage or absolute value changes in these outcomes were accepted. For safety, qualitative reports of adverse events (AEs) and/or side effects were accepted. We set no restrictions on the concentrations or duration of administrations of experimental compounds. As comparators, we accepted any other type of management for AD, including active surveillance.

We accepted studies published in English or French without date restrictions. Non-randomized trials were excluded. Studies were not included if they were only available as abstracts from conference proceedings or if published in a language other than English or French.

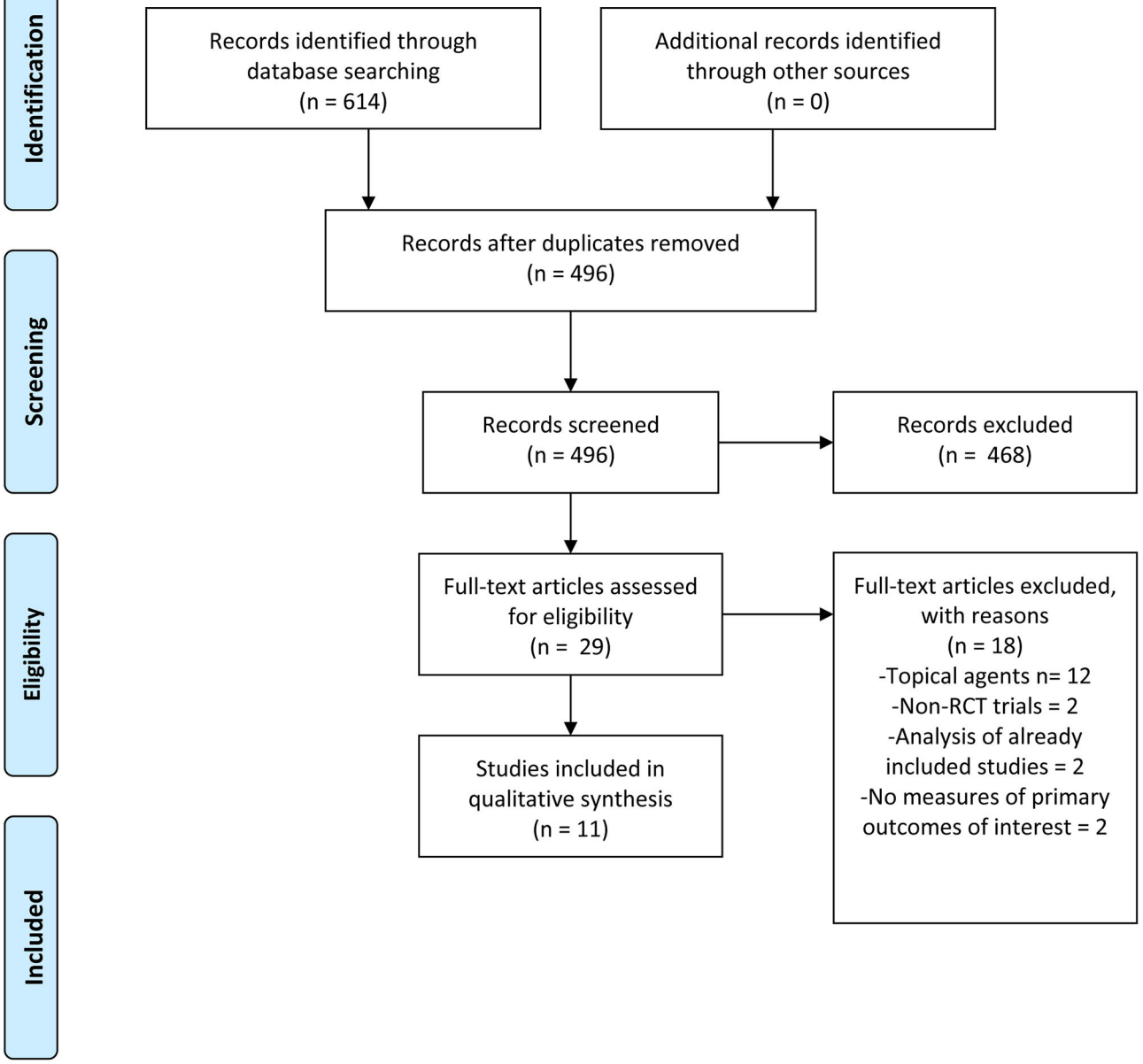


FIGURE 2 | PRISMA Flow Diagram.

Quality Assessment and Data Extraction

Two reviewers (ML and MB-R) independently conducted data extraction and methodology quality assessment for all included studies. We extracted the study type, study time frame, type of population (pediatric vs. adult vs. elderly); method of randomization; whether trial was blinded; sample size; follow-up time; the specific JAKi and comparator treatment employed as well as the dosing and regimens; outcome definitions and method for ascertaining treatment effectiveness; and efficacy. For safety, we extracted the most common and most serious treatment emergent adverse events (TEAEs). As a secondary outcome, we extracted the drug's pharmacokinetic characteristics, when reported.

For all studies, the main measures of interest were the efficacy of JAKi on reducing the severity and extent of involvement of AD compared with any other treatments. If reported, efficacy from intention-to-treat analyses (ITT) was preferred and extracted over per-protocol estimates.

We used the modified Cochrane Collaboration tool to assess risk of bias of RCTs (RoB 2) (29), considered the gold-standard for quality assessment of RCTs (30). The tool is structured into five domains through which bias may be introduced into the results: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of outcome(s); and (5) bias in the selection of reported results (31). The overall bias assessment within each domain is characterized as "low risk," "some concerns," or "high risk of bias," according to responses provided to the signaling questions within each domain (**Supplementary Table 1**).

Data Analysis

We summarized the included reports through descriptive analyses to provide an overview of studies' characteristics, quality, effectiveness, and safety profile of JAKi. Because of the heterogeneity in dosing, length of treatment and length of follow-up, conducting a meta-analysis was not considered. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) in this systematic review reporting (32).

RESULTS

Study Characteristics

Our initial search yielded a total of 614 studies (**Figure 2**). After removing duplicates, 496 articles remained and were screened by title and abstract. Of the 29 articles that underwent full text screening, 11 met our inclusion criteria. Of these, all examined the efficacy of various JAKi in the treatment of moderate-to-severe AD in adults and adolescents: four examined abrocitinib; three baricitinib; three upadacitinib, and one ASN002. In 8/11 studies inclusion criteria were restricted to patients with moderate-to-severe AD, defined as: an EASI score $\geq$ 16, IGA score $\geq$ 3, more than 10% Body Surface Area (BSA) involvement $\pm$ a score of $\geq$ 4 in the PP-NRS (33–38). In the remaining 2 studies, subjects needed to demonstrate an EASI $\geq$ 12, IGA-score $\geq$ 3 and BSA involvement > than 10% for inclusion (**Table 1**). All studies included safety assessment in the form of reported TEAEs (**Table 2**), and two included evaluation of pharmacokinetics. Physicochemical properties of oral JAK inhibitors are listed in **Tables 3**, **4**.

Quality Assessment

Overall, we rated six out of eleven studies as low risk of bias (33, 35, 36, 39–41), and the remainder were considered as higher risk (34, 38, 42–44). All included studies employed a central randomization scheme and stipulated blinding of treatment assignment for investigators, patients and study personnel. Post-randomization, two studies (38, 44) had remaining imbalances between groups in IGA-measured-baseline severity of AD and were thus rated as "higher risk of bias" on the "randomization process" domain of the quality assessment tool. Most studies assessed efficacy of treatment by either an ITT analysis, or a modified version of ITT analysis that included all randomized participants who have received at least one-dose of the study's intervention. A single study (38) reported the per-protocol treatment efficacy estimates and was therefore considered at higher risk of bias for the "deviation from intended intervention" element (**Supplementary Table 1**).

Across all studies, attrition rates were high (9 to 50%, depending on study group) an effect compounded by relatively small sample sizes (range: 36–847). In evaluating the potential effects of missing outcome values on the assessment of treatment efficacy, we considered the stated reasons for attrition within each group. If these reasons differed between groups within a given study, we considered the potential for bias in outcome assessment as "high." If attrition rates were high but reasons for discontinuation were relatively similar between groups, we deemed the risk of bias in measurement as low. With this reasoning, five studies (34, 38, 42–44) were evaluated as having a high risk for bias in the assessment of treatment efficacy. Since most studies abided by an ITT-analysis for the measurement of efficacy, these missing values likely biased the results toward the null hypothesis of no effect. Therefore, efficacy estimates reported in these studies are considered likely to represent an under-estimation, rather than an over-estimation, of the treatment's true efficacy.

ABROCITINIB

Clinical Efficacy

Based on *in-vitro* studies, the JAK1 half maximal inhibitory concentration (IC_{50}) of abrocitinib is 29 nM (45) (**Table 4**). The clinical efficacy of abrocitinib, an oral selective JAK1 inhibitor, was studied in four independent clinical trials, of which three were Phase III trials, while one was a Phase II trial (33, 34, 42) (**Table 1**). In the recent Phase III trial by Bieber et al. (39), a total of 838 adult patients (aged $\geq$18 years) with moderate-to-severe AD, who failed treatment with TCS or TCI or required systemic therapy to control their disease, were enrolled. Moderate-to-severe AD was defined as IGA $\geq$ 3, EASI Score $\geq$ 16, BSA $\geq$ 10%, and PP-NRS $\geq$ 4. Patients were randomized in a 2:2:2:1 ratio to 100 mg abrocitinib, 200 mg abrocitinib, 300 mg dupilumab (every other week), or placebo groups and assessed over 16 weeks. While a significantly higher percentage of patients in the 100 and 200 mg abrocitinib groups achieved an EASI-75 score and IGA response at 16 weeks in comparison to a placebo ($p < 0.001$), this significant increase was not noted when comparing outcome measures with the dupilumab treatment group (**Table 1**). Specifically, an EASI-75 was achieved in 71% of patients in the 200 mg abrocitinib group, 60.3% of the 100 mg abrocitinib group, 65.5% of the dupilumab group and 30.6% of the placebo group at 16 weeks. An IGA response was observed in 47.5% of the 200 mg abrocitinib group, 34.8% of the 100 mg abrocitinib group, 38.8% of the dupilumab group and 12.9% of the placebo group. Interestingly, a significantly higher ($p < 0.001$) proportion of patients achieving a PP-NRS response as early as week 2 was observed in the 200-mg abrocitinib compared to the

TABLE 1 | Summary of clinical efficacy of published oral JAK inhibitor trials.

Author	Study design	Patient eligibility	TCS allowed	Duration	Dose	*N*	EASI-75 (%)	EASI-50 (%)	IGA response (%)	PP-NRS response (%)
Bieber et al. (39)	Multicentre double-blind Phase III RCT	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% PP-NRS ≥ 4 Failed TCS/TCI or requires systemic therapies for control	Yes	16 weeks	Abrocitinib 100 mg	238	60.3 ($p < 0.001$)	–	34.8 ($p < 0.001$)	47.0
					Abrocitinib 200 mg	226	71.0 ($p < 0.001$)	–	47.5 ($p < 0.001$)	62.8
					Dupilumab 300 mg, every other week	243	65.5	–	38.8	57.1
					Placebo	131	30.6	–	12.9	28.7
Simpson et al. (33)	Multicentre double-blind Phase III RCT	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% PP-NRS ≥ 4 Failed TCS/TCI or required systemic tx for AD control	No	12 weeks	Abrocitinib 100 mg	158	40 ($p < 0.0001$)	58	24 ($p = 0.0037$)	38 ($p = 0.0003$)
					Abrocitinib 200 mg	155	63 ($p < 0.0001$)	76	44 ($p < 0.0001$)	57 ($p < 0.0001$)
					Placebo	78	12	22	8	15
Silverberg et al. (34)	Multicentre double-blind Phase III RCT	IGA ≥3 EASI≥16 PP-NRS ≥ 4 Failed TCS/TCI or required systemic tx for AD control	No	12 weeks	Abrocitinib 100 mg	158	44.5 ($p < 0.001$)	68.4	28.4 ($p < 0.001$)	55.3
					Abrocitinib 200 mg	155	61.0 ($p < 0.001$)	79.9	38.1 ($p < 0.001$)	45.2
					Placebo	78	10.4	19.5	9.1	11.5
Gooderham et al. (42)	Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	EASI ≥ 12 IGA ≥ 3 BSA ≥ 10% Failed TCS/TCI	No	12 weeks	Abrocitinib 10 mg QD	46	17.4	26.1	10.9	22.7
					Abrocitinib 30 mg QD	45	13.3	33.3	8.9	33.3
					Abrocitinib 100 mg QD	54	40.7 ($p = 0.004$)	55.6*	29.6 ($p < 0.001$)	50
					Abrocitinib 200 mg QD	48	64.6 ($p < 0.001$)	79.2*	43.8 ($p < 0.001$)	63.6
					Placebo	52	15.4	26.9	5.8	25.5

(Continued)

TABLE 1 | Continued

Author	Study design	Patient eligibility	TCS allowed	Duration	Dose	*N*	EASI-75 (%)	EASI-50 (%)	IGA response (%)	PP-NRS response (%)
Simpson et al. (35)	Multicentre double-blind Phase III RCT (Part 1: BREEZE-AD1)	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% Failed TCS/TCI and/or systemic immunosuppressant therapies	Yes, considered as rescue treatment	16 weeks	Baricitinib 1 mg	127	17.3 ($p \leq 0.05$)	–	11.8 ($p \leq 0.05$)	10.5
					Baricitinib 2 mg	123	18.7 ($p \leq 0.01$)	–	11.4 ($p \leq 0.05$)	12.0
					Baricitinib 4 mg	125	24.8 ($p \leq 0.001$)	–	16.8 ($p \leq 0.001$)	21.5 ($p \leq 0.001$)
					Placebo	249	8.8	–	4.8	7.2
Simpson et al. (35)	Multicentre double-blind Phase III RCT (Part 2: BREEZE-AD2)	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% Failed TCS/TCI and/or systemic immunosuppressant therapies	Yes, considered as rescue treatment	16 weeks	Baricitinib 1 mg	125	12.8 ($p \leq 0.05$)	–	8.8	6.0
					Baricitinib 2 mg	123	17.9 ($p \leq 0.001$)	–	10.6 ($p \leq 0.05$)	15.1
					Baricitinib 4 mg	123	21.1 ($p \leq 0.001$)	–	13.8 ($p \leq 0.001$)	18.7 ($p \leq 0.001$)
					Placebo	244	6.1	–	4.5	4.7
Reich et al. (36)	Double-blind, placebo-controlled, phase 3 RCT	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% Failed TCS	Yes	16 weeks	Baricitinib 2 mg +TCS	109	43	64 ($p < 0.001$)	24	38
					Baricitinib 4 mg +TCS	111	48 ($p < 0.001$)	70 ($p < 0.001$)	31 ($p < 0.001$)	44 ($p < 0.001$)
					Placebo + TCS	109	23	41	15	20
Guttman-Yassky et al. (43)	Phase 2 parallel, double-blind, placebo-controlled RCT	EASI ≥ 12 BSA ≥ 10% Failed TCS/systemicCS/TCI and immunosuppressants	Yes	16 weeks	Baricitinib 2 mg +TCS	37	30	57	22	–
					Baricitinib 4 mg +TCS	38	34 ($p = 0.027$)	61	21	–
					Placebo + TCS	49	20	37	8	–
Reich et al. (41)	Multicentre, double-blind, placebo-controlled, phase 3 RCT	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% PP-NRS ≥ 4 Failed TCS/TCI or requires systemic therapies for control	Yes	16 weeks	Upadacitinib 15 mg + TCS	300	64.6 ($p < 0.0001$)	–	40 ($p < 0.0001$)	51.7 ($p < 0.0001$)
					Upadacitinib 30 mg + TCS	297	77.1 ($p < 0.0001$)	–	59 ($p < 0.0001$)	63.9 ($p < 0.0001$)
					Placebo + TCS	304	26.4	–	11	15

(Continued)

TABLE 1 | Continued

Author	Study design	Patient eligibility	TCS allowed	Duration	Dose	*N*	EASI-75 (%)	EASI-50 (%)	IGA response (%)	PP-NRS response (%)
Guttman-Yassky et al. (40)	Multicentre, double-blind, placebo-controlled, phase 3 RCT (Part 1: Measure Up 1)	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% PP-NRS ≥ 4 Failed TCS/TCI or requires systemic therapies for control	Yes, considered as rescue treatment	16 weeks	Upadacitinib 15 mg	281	70 ($p < 0.0001$)	–	48 ($p < 0.0001$)	52 ($p < 0.0001$)
					Upadacitinib 30 mg	285	80 ($p < 0.0001$)	–	62 ($p < 0.0001$)	60 ($p < 0.0001$)
					Placebo	281	16	–	8	12
Guttman-Yassky et al. (40)	Multicentre, double-blind, placebo-controlled, phase 3 RCT (Part 1: Measure Up 1)	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% PP-NRS ≥ 4 Failed TCS/TCI or requires systemic therapies for control	Yes, considered as rescue treatment	16 weeks	Upadacitinib 15 mg	276	60 ($p < 0.0001$)	–	39 ($p < 0.0001$)	42 ($p < 0.0001$)
					Upadacitinib 30 mg	282	73 ($p < 0.0001$)	–	52 ($p < 0.0001$)	60 ($p < 0.0001$)
					Placebo	278	13 ($p < 0.0001$)	–	5	9
Guttman-Yassky et al. (37)	Phase 2b, double-blind, randomized, parallel-group, dose-ranging trial	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% Failed TCS/TCI	Not specified	16 weeks	Upadacitinib 7.5 mg QD	42	∼28†	∼48†	∼11†	25†
					Upadacitinib 15 mg QD	42	∼49†	∼68	∼28†	59†
					Upadacitinib 30 mg QD	42	∼69†	∼85†	∼47†	55†
					Placebo	41	∼6†	∼18†	∼1†	∼4†
Bissonnette et al. (38)	Phase 1b double-blind, placebo-controlled, RCT	IGA ≥ 3 EASI ≥ 16 BSA ≥ 10% Failed TCS/TCI	Not specified	29 days	Gusacitinib 20 mg	9	0	20	0	–
					Gusacitinib 40 mg	9	71	100 ($p = 0.003$)	43	–
					Gusacitinib 80 mg	9	33	83 ($p = 0.03$)	17	–
					Placebo	9	22	22	11	–

**Values reached statistical significance, however, p-values were not presented in the publication.*

†Values were estimated based on figures presented in the publication as exact values were not available.

AD, Atopic Dermatitis; BSA, Body Surface Area; CS, Corticosteroids; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, peak pruritus numeric rating scale; TCS, Topical Corticosteroids; TCI, Topical Calcineurin Inhibitors; Tx, treatment; RCT, Randomized Controlled Trial.

TABLE 2 | Summary of common TEAEs in published oral JAK inhibitor trials.

Author	Study design	Duration	Dose	*N*	Headache (%)	GI symptoms[a] (%)	Respiratory symptoms[b] (%)	Acne (%)	AD worsening (%)	Cutaneous infections[c] (%)	Elevated Blood Creatinine Phosphokinase (%)	Other TEAEs
Beiber et al. (39)	Multicentre double-blind Phase III RCT	16 weeks	Abrocitinib 100 mg	238	✓ (4.2)	✓ (4.2)	✓ (14.2)	✓ (2.9)	NR	✓ (1.7)	NR	Transient dose-related decreases platelet count was observed in both abrocitinib groups. Most decreases were within normal limits
			Abrocitinib 200 mg	226	✓ (6.6)	✓ (11.1)	✓ (10.6)	✓ (6.6)	NR	✓ (1.8)	✓ (0.4)	
			Dupilumab 300 mg, every other week	243	✓ (5.4)	✓ (2.9)	✓ (13.2)	✓ (1.2)	NR	NR	NR	
			Placebo	131	✓ (4.6)	✓ (1.5)	✓ (11.5)	NR	NR	✓ (0.8)	✓ (0.8)	
Simpson et al. (33)	Multicentre double-blind Phase III RCT	12 weeks	Abrocitinib 100 mg	156	✓ (8)	✓ (9)	✓ (21.8)	NR	✓ (14)	✓ (4.5)	NR	Transient dose-related decreases platelet count was observed in both abrocitinib groups, with a nadir at week 4. Patients in all treatment groups maintained platelet counts within the normal range
			Abrocitinib 200 mg	154	✓ (10)	✓ (20)	✓ (18.8)	NR	✓ (5)	✓ (3.9)	NR	
			Placebo	77	✓ (3)	✓ (3)	✓ (16.9)	NR	✓ (17)	✓ (1.3)	NR	
Silverberg et al. (34)	Multicentre double-blind Phase III RCT	12 weeks	Abrocitinib 100 mg	158	✓ (5.7)	✓ (10.12)	✓ (21.5)	✓ (1.3)	✓ (5.7)	✓ (3.79)	✓ (1.9)	
			Abrocitinib 200 mg	155	✓ (7.7)	✓ (23.2)	✓ (10.9)	✓ (5.8)	✓ (3.9)	✓ (4.5)	✓ (3.2)	
			Placebo	78	✓ (2.6)	✓ (3.84)	✓ (10.2)	0	✓ (15.4)	✓ (5.12)	✓ (2.6)	
Gooderham et al. (42)	Phase IIb, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study	12 weeks	Abrocitinib 10 mg QD	49	✓ (4.1)	✓ (8.2)	✓ (46.9)	NR	✓ (16.3)	NR	NR	Transient decrease in platelet was observed in 30, 100, and 200 mg groups although most decreases were within normal limits
			Abrocitinib 30 mg QD	51	✓ (9.8)	✓ (9.8)	✓ (37.3)	NR	✓ (17.6)	NR	NR	
			Abrocitinib 100 mg QD	56	✓ (8.9)	✓ (10.7)	✓ (42.9)	NR	✓ (14.3)	✓ (1.8)	NR	
			Abrocitinib 200 mg QD	55	✓ (7.3)	✓ (21.8)	✓ (41.8)	NR	✓ (12.7)	NR	NR	
			Placebo	56	✓ (3.6)	✓ (4)	✓ (23.2)	NR	✓ (19.6)	NR	NR	

(Continued)

TABLE 2 | Continued

Author	Study design	Duration	Dose	*N*	Headache (%)	GI symptoms[a] (%)	Respiratory symptoms[b] (%)	Acne (%)	AD worsening (%)	Cutaneous infections[c] (%)	Elevated Blood Creatinine Phosphokinase (%)	Other TEAEs
Simpson et al. (35)	Multicentre double-blind Phase III RCT (Part 1: BREEZE-AD1)	16 weeks	Baricitinib 1 mg	127	✓ (5.5)	✓ (8.7)	✓ (18.1)	NR	NR	✓ (6.3)	✓ (0.8)	
			Baricitinib 2 mg	123	✓ (11.4)	✓ (1.6)	✓ (12.2)	NR	NR	✓ (8.1)	✓ (0.8)	
			Baricitinib 4 mg	125	✓ (8.0)	✓ (8)	✓ (12.8)	NR	NR	✓ (10.4)	✓ (3.2)	
			Placebo	249	✓ (6.4)	✓ (3.6)	✓ (12.9)	NR	NR	✓ (5.6)	✓ (0.8)	
Simpson et al. (35)	Multicentre double-blind Phase III RCT (Part 2: BREEZE-AD2)	16 weeks	Baricitinib 1 mg	125	✓ (4.8)	✓ (4)	✓ (15.2)	NR	NR	✓ (9.6)	✓ (3.2)	
			Baricitinib 2 mg	123	✓ (7.3)	✓ (5.7)	✓ (17.1)	NR	NR	✓ (13)	✓ (0.8)	
			Baricitinib 4 mg	123	✓ (8.9)	✓ (5.7)	✓ (11.4)	NR	NR	✓ (8.9)	✓ (5.7)	
			Placebo	244	✓ (2.0)	✓ (5.7)	✓ (14.3)	NR	NR	✓ (12.3)	✓ (0.4)	
Reich et al. (36)	Multicentre double-blind, placebo-controlled, phase III RCT	16 weeks	Baricitinib 2 mg +TCS	109	NR	✓ (1)	✓ (18)	✓ (1)	NR	✓ (8.3)	✓ (15)	Increased HDL cholesterol levels (≥1.55 mmol/L) observed in 2 mg and 4 mg treatment groups compared to placebo (28, 17, and 10%, respectively)
			Baricitinib 4 mg +TCS	111	NR	✓ (1)	✓ (18.3)	✓ (4)	NR	✓ (11.7)	✓ (22)	
			Placebo + TCS	108	NR	✓ (3)	✓ (13.9)	✓ (1)	NR	✓ (2.8)	✓ (8)	
Guttman-Yassky et al. (43)	Multicentre Phase II parallel, double-blinded, placebo-controlled RCT	16 weeks	Baricitinib 2 mg +TCS	37	✓ (5)	NR	✓ (2.7)	NR	✓ (3)	NR	✓ (3)	
			Baricitinib 4 mg +TCS	38	✓ (13)	NR	✓ (13.2)	NR	NR	✓ (7.9)	✓ (13)	
			Placebo + TCS	49	NR	NR	✓ (4)	NR	✓ (8)	✓ (2)	NR	
Reich et al. (39)	Multicentre, double-blind, placebo-controlled, phase 3 RCT	16 weeks	Upadacitinib 15 mg + TCS	300	✓ (5)	NR	✓ (19)	✓ (10)	✓ (4)	✓ (2)	✓ (4)	Mild-moderate neutropenia observed in 15 and 50 mg treatment groups compared to none in placebo (1, 1% and none, respectively)
			Upadacitinib 30 mg + TCS	297	✓ (5)	NR	✓ (21)	✓ (14)	✓ (1)	✓ (3)	✓ (6)	
			Placebo + TCS	304	✓ (5)	NR	✓ (18)	✓ (2)	✓ (7)	✓ (1)	✓ (2)	

(Continued)

TABLE 2 | Continued

Author	Study design	Duration	Dose	*N*	Headache (%)	GI symptoms[a] (%)	Respiratory symptoms[b] (%)	Acne (%)	AD worsening (%)	Cutaneous infections[c] (%)	Elevated Blood Creatinine Phosphokinase (%)	Other TEAEs
Guttman-Yassky et al. (40)	Multicentre, double-blind, placebo-controlled, phase 3 RCT (Part 1: Measure Up 1)	16 weeks	Upadacitinib 15 mg	281	✓ (5)	NR	✓ (17)	✓ (7)	✓ (3)	✓ (2)	✓ (6)	Transient neutropenia (>500/ microL) observed in 30 mg treatment groups compared to 15 mg treatment and placebo groups (5, 1, and 1%, respectively)
			Upadacitinib 30 mg	285	✓ (7)	NR	✓ (25)	✓ (17)	✓ (1)	✓ (3)	✓ (6)	
			Placebo	281	✓ (4)	NR	✓ (13)	✓ (2)	✓ (9)	✓ (1)	✓ (3)	
Guttman-Yassky et al. (40)	Multicentre, double-blind, placebo-controlled, phase 3 RCT (Part 2: Measure Up 2)	16 weeks	Upadacitinib 15 mg	276	✓ (7)	NR	✓ (13)	✓ (13)	✓ (3)	✓ (3)	✓ (3)	
			Upadacitinib 30 mg	282	✓ (7)	NR	✓ (12)	✓ (15)	✓ (1)	✓ (1)	✓ (4)	
			Placebo	278	✓ (4)	NR	✓ (9)	✓ (2)	✓ (9)	✓ (1)	✓ (2)	
Guttman-Yassky et al. (37)	Multicentre Phase IIb, double-blind, randomized, parallel-group, dose-ranging trial	16 weeks	Upadacitinib 7.5 mg QD	42	✓ (7.1)	✓ (11.9)	✓ (21.4)	✓ (9.5)	✓ (9.5)	NR	NR	Increased frequency of infections were found in treatment groups (41–52%) vs. placebo (20%)
			Upadacitinib 15 mg QD	42	✓ (7.1)	✓ (7.1)	✓ (21.4)	✓ (4.8)	✓ (4.8)	NR	✓ (7.1)	
			Upadacitinib 30 mg QD	42	✓ (9.5)	✓ (7.1)	✓ (19)	✓ (14)	✓ (14)	NR	✓ (9.5)	
			Placebo	40	✓ (2.5)	✓ (7.5)	✓ (12.5)	✓ (2.5)	✓ (5.0)	NR	✓ (5)	
Bissonnette et al. (38)	Multicentre Phase Ib double-blind, placebo-controlled, RCT	29 days	Gusacitinib 20 mg	9	✓ (11)	NR	NR	NR	NR	NR	NR	Mild hypotension observed in one patient receiving 80 mg Gusacitinib
			Gusacitinib 40 mg	9	✓ (44)	✓ (11)	NR	NR	NR	NR	NR	
			Gusacitinib 80 mg	9	✓ (22)	✓ (44)	NR	NR	NR	NR	NR	
			Placebo	9	✓ (33)	✓ (22)	NR	NR	NR	NR	NR	

[a] *Gastrointestinal symptoms include nausea, vomiting, diarrhea, gastroenteritis, and upper abdominal pain.*

[b] *Respiratory tract symptoms include upper respiratory tract infections and nasopharyngitis.*

[c] *Cutaneous infections include viral, fungal bacterial infections including herpes simplex, folliculitis, cellulitis, and tinea. Does not include post-traumatic or post-procedural infections.*

NR, Not reported; QD, daily; RCT, Randomized Controlled Trial; TEAE, Treatment-Emergent Adverse Event; TCS, Topical Corticosteroids.

TABLE 3 | Summary of physicochemical properties of oral JAK inhibitors.

JAK inhibitor	Molecular formula	Molecular weight	Lipophilicity (LogP)
Abrocitinib	$C_{14}H_{21}N_5O_2S$	323.4	1.24
Baricitinib	$C_{16}H_{17}N_7O_2S$	371.4	−0.47
Upadacitinib	$C_{17}H_{19}F_3N_6O$	380.4	2.13
Gusacitinib	$C_{24}H_{28}N_8O_2$	460.5	1.18

TABLE 4 | Summary of half maximal inhibitory concentration (IC50) of oral JAK inhibitors.

IC50 (nM)	JAK1	JAK2	JAK3	TYK2
Abrocitinib	29	803	–	1,253
Baricitinib	5.9	5.7	560	53
Upadacitinib	43	200	2,300	4,700
Gusacitinib*	–	–	–	–

**Data not reported.*

dupilumab group. However, this response was not observed in the 100 mg abrocitinib group.

In another Phase III JADE MONO-1 trial by Simpson et al. (33) a total of 387 patients (aged ≥12 years) with moderate-to-severe AD, defined as IGA ≥ 3, EASI Score ≥ 16, BSA ≥ 10%, and PP-NRS ≥ 4, were enrolled. Patients were randomized to receive either placebo, 100 or 200 mg of abrocitinib daily for a total treatment duration of 12 weeks. At the end of treatment, the authors found that the proportion of patients who had achieved an IGA response, was significantly higher in the abrocitinib 100 mg group than in the placebo group [37 (24%) of 156 patients vs. six (8%) of 76 patients; $p = 0.0037$], and in the abrocitinib 200 mg group compared with the placebo group [67 [(44%) of 153 patients vs. six (8%) of 76 patients; $p < 0.0001$]. Additionally, the proportion of patients who achieved an EASI-75 response was significantly higher in the abrocitinib 100 mg group [62 (40%) of 156 patients vs. nine (12%) of 76 patients; $p < 0.0001$] and abrocitinib 200 mg group [96 (63%) of 153 patients vs. nine (12%) of 76 patients; $p < 0.0001$]. Interestingly, a significant difference in the proportion of patients achieving a PP-NRS response for 100 mg and 200 mg abrocitinib groups vs. placebo was achieved by the second week of treatment [20, 46, and 3%, respectively, with $p = 0.0004$ (100 mg abrocitinib vs. placebo) and $p < 0.0001$ (200 mg abrocitinib vs. placebo)]. This significant difference in PP-NRS response was maintained at week 12 [38, 57, and 15% of patients in the 100, 200 mg abrocitinib and placebo groups, respectively, with $p = 0.0003$ (100 mg abrocitinib vs. placebo) and $p < 0.0001$ (200 mg abrocitinib vs. placebo)] (**Table 1**).

Using the same patient inclusion criteria as the JADE MONO-1 trial, Silverberg et al. (34) also examined abrocitinib at 100 and 200 mg concentrations in adults and adolescent patients (12 to 18 years inclusively) with moderate-to-severe AD. A total of 391 patients were randomized to receive either abrocitinib 100 or 200 mg vs. a placebo intervention for 12-weeks duration. Compared to placebo, the proportion of participants achieving an IGA response were 28.7% higher ($p < 0.001$) for the 200 mg group and 19.3% higher ($p < 0.001$) in the 100 mg group. At the end of the 12-weeks, the 200 and 100 mg groups had achieved an EASI-75 response that was 50.5% ($p < 0.001$) and 33.9% ($p < 0.001$) higher than placebo, respectively. Percentage decreases in EASI scores from baseline were greater for both abrocitinib doses than for placebo at all time points. Significant differences in PP-NRS scores between both doses of abrocitinib and placebo were observed by day 2 of treatment, with decreases of 0.7 [95% Confidence Interval (CI), −0.9–0.5] and 0.6 (95% CI, −0.8–0.4) for the 200 mg and 100 mg doses respectively, vs. 0.1 decrease (95% CI, −0.4–0.2) for placebo.

Similar findings of clinical efficacy were demonstrated in the Phase IIb RCT investigating various dosages of abrocitinib vs. placebo in adult patients (≥18 years of age) with moderate-to-severe AD by Gooderham et al. (42) At week 12, 21 of 48 patients receiving 200 mg of abrocitinib (43.8%; $p < 0.001$), 16 of 54 patients receiving 100 mg of abrocitinib (29.6%; $p < 0.001$), and 3 of 52 patients receiving placebo (5.8%) achieved an IGA response. Additionally, through logistic regression modeling, authors estimated that a greater proportion of patients achieved an EASI-75 response in the 200 mg [estimated 31 of 48 (63.7%), $p < 0.001$] and 100 mg [estimated 22 of 54 (41.6%), $p = 0.004$] groups when compared to a placebo group [estimated 8 of 52 (15.6%)]. Significant differences from placebo in percentage reduction in EASI score from baseline were observed as early as week 1 (first postbaseline assessment) in the 200 mg group [least squares mean (LSM) difference from placebo, −28.3%; $p < 0.001$], and at week 2 in the 100 mg group (−14.9%; $p = 0.03$). Decreases from baseline in EASI score for the 200 mg and 100 mg groups were found to plateau by weeks 4 to 6 and were maintained through week 12.

Safety

In the four trials (33, 34, 39, 42), gastrointestinal and respiratory symptoms were found to be the most frequently reported TEAEs in the abrocitinib 100 and 200 mg groups, followed by a headache. AD worsening was found to be more common in placebo compared to abrocitinib groups. Moreover, in all four trials, transient dose-related numeric decreases in median platelet count were observed in patients receiving abrocitinib, with a nadir observed at week 4 and a return toward baseline values thereafter. Nevertheless, the majority of patients in treatment groups maintained platelet counts within the normal range (**Table 2**).

Specifically, in the Bieber et al. (39) trial, nausea was the most frequently reported TEAE in each of the 100 mg, 200 mg abrocinitib and dupilumab groups. Mild to moderate acne was also more frequently reported in abrocitinib groups (6.6 and 2.9% for 200 and 100 mg abrocitinib, respectively), in comparison to dupilumab or placebo groups (1.2 and 0%, respectively) (**Table 2**). Two malignancies were reported in this study: one cutaneous squamous-cell carcinoma in the in the 200-mg abrocitinib group, and one invasive intraductal breast neoplasia in the dupilumab group. The authors did not comment whether or not these malignancies were considered to be treatment-related. No deaths, or venous thromboembolisms (VTEs) were observed during this trial.

In the Phase III JADE MONO-1 trial (33), the most frequently reported TEAE in the abrocitinib 100 mg and 200 mg groups were nausea (9% in 100 mg and 20% in 200 mg groups) and nasopharyngitis (15% in 100 mg and 12% in 200 mg groups). Other common TEAEs included headache, and upper respiratory tract infection (URTI) symptoms (≥5% in any treatment group). Herpes virus infections were reported in all treatment groups, albeit uncommon [one (<1%) of 156 patients in the abrocitinib 100 mg group, and three (∼2%) of 154 patients in the abrocitinib 200 mg group].

Serious adverse events (SAEs) were reported in five (3%) of 156 patients in the abrocitinib 100 mg group, five (3%) of 154 patients in the abrocitinib 200 mg group, and three (4%) of 77 patients in the placebo group. Among these patients, only two SAEs were considered treatment-related: in one patient receiving the abrocitinib 200 mg, who developed chronic inflammatory bowel disease, abrocitinib was permanently discontinued leading to full recovery; the other patient was in the abrocitinib 100 mg group and developed acute pancreatitis during the treatment period. Thus, abrocitinib was permanently discontinued, and the patient recovered. In this study, no cases of VTE, malignancies, major adverse cardiovascular events, changes in blood creatinine phosphokinase (CPK) levels or deaths were observed.

In Silverberg's Phase III trial of abrocitinib in adults and adolescents (34), the most frequent treatment TEAEs of any causality included nausea in the 200 mg group (14.2%), nasopharyngitis in the 100 mg group (12.7%) and worsening AD in the placebo group (15.4%). Other TEAEs of interest were acne (5.8% in the 200 mg group, 1.3% in 100 mg group and none in placebo group), folliculitis (3.2% in in 200 mg group and 2.6% in placebo group), vomiting (5.2% in 200 mg group, 1.3% in both 100 mg and placebo groups), and upper abdominal pain (3.9% in 200 mg vs. 1.3% and 0 in 100 mg and placebo respectively). SAEs that were considered related to treatment were reported for two patients in the 100 mg group (herpangina and pneumonia) and two patients in the placebo group (eczema herpeticum and a case of staphylococcal infection). None were observed in the 200 mg group. An elderly participant with pre-existing aortic valve sclerosis and untreated hypertension experienced a sudden cardiac death 3-weeks after discontinuation of abrocitinib. The event was not considered related to treatment. Furthermore, no cases of thromboembolisms or malignant neoplasms were reported in any treatment groups. The authors also reported a dose-related increase of ∼10% in high-and-low-density lipoprotein levels, as well as an increase in CPK levels, for both the 200 mg and 100 mg groups compared to placebo (34).

The most frequently reported of TEAEs (≥3 patients in any treatment group) in Gooderham et al. Phase IIb study of abrocitinib included diarrhea, nausea, viral URTI, headache, and worsening atopic dermatitis (42). Two of 267 patients experienced SAEs that were considered related to treatment; one patient in the 200 mg group developed pneumonia during follow-up after initiation of cyclosporine, which was continued, and treated with antibiotics; and one patient in the 100 mg group developed eczema herpeticum during the treatment period, abrocitinib was permanently discontinued. One patient in the 200 mg group reported a pulmonary embolism (PE) after traveling a long distance by car with baseline laboratory values within normal limits. One patient receiving 10mg dose developed a melanoma, which was deemed not related to treatment. No treatment-related trends in serum lipids and transaminase levels were observed in the trial. CPK levels were, unfortunately, not reported.

BARICITINIB

Clinical Efficacy

Baricitinib is an oral selective JAK1 and JAK2 inhibitor that blocks the downstream action of several cytokines in AD pathogenesis, including thymic stromal lymphopoietin, IL-4, IL-5, IL-13, IL-22, and IL-31 (36). According to *in-vitro* analyses, the baricitinib IC_{50} values were reported as 5.9 and 5.7 nM for JAK1 and JAK2 inhibition, respectively (46) (**Table 4**). In the 16-week Phase III independent BREEZE-AD1, BREEZE-AD2 trials by Simpson et al. (35) the efficacy of baricitinib vs. placebo was assessed in a total of 1,239 adult patients with moderate-to-severe AD at varying doses. In both BREEZE-AD1 and BREEZE-AD2 studies, moderate-to-severe AD was defined as IGA ≥ 3, EASI ≥ 16, BSA ≥ 10%. Eligible patients also had to demonstrate an inadequate response to TCS/TCIs and/or systemic immunosuppressant therapies. In total, 624 patients were enrolled in BREEZE-AD1, where they were randomized to daily placebo ($n = 249$), 1 mg ($n = 127$), 2 mg ($n = 123$), or 4 mg ($n = 125$) baricitinib groups. Similarly, a total of 615 patients were enrolled in BREEZE-AD2, where patients were randomized to similar groups [placebo ($n = 244$), 1 mg ($n = 125$), 2 mg ($n = 123$), or 4 mg ($n = 123$)].

In both trials, 2 mg and 4 mg of baricitinib achieved the study's primary efficacy outcome: a significant improvement vs. placebo for the proportion of patients achieving an IGA response at week 16. The percentage of patients achieving IGA response was 4.8% for placebo, 11.4% for baricitinib 2 mg, and 16.8% for baricitinib 4 mg (baricitinib 2 mg, $p \leq 0.05$; baricitinib 4 mg, $p \leq 0.001$ vs. placebo) in BREEZE-AD1, and 4.5% for placebo, 10.6% for baricitinib 2 mg, and 13.8% for baricitinib 4 mg (baricitinib 2 mg, $p \leq 0.05$; baricitinib 4 mg, $p \leq 0.001$ vs. placebo) in BREEZE-AD2 (**Table 1**).

In both studies, 4 mg baricitinib treatment was found to lead to significant improvement for all secondary study endpoints, including a significantly higher proportion of patients achieving a PP-NRS response compared to placebo ($p \leq 0.001$) at weeks 1, 2, 4, and 16; proportion of patients achieving EASI-75; and percentage change from baseline EASI score. Similarly, 2 mg baricitinib treatment also demonstrated a significant improvement for the aforementioned secondary endpoints in both trials, except for the proportion of patients achieving a PP-NRS response compared to placebo at week 1. However, 1 mg of baricitinib treatment led to inconsistent clinical outcomes in primary and secondary endpoints in both trials.

In another Phase III clinical trial by Reich et al. (36) (BREEZE-AD7), a total of 329 patients with moderate-to-severe AD were

randomly assigned (1:1:1) to receive 2 mg of baricitinib once daily ($n = 109$), 4 mg of baricitinib once daily ($n = 111$), or placebo ($n = 109$) for 16 weeks. The use of low-to-moderate potency TCSs as well as TCIs and crisaborole for active lesions was allowed throughout the trial. Rescue therapy with high- or ultrahigh-potency TCSs or systemic therapies were available for patients who experienced worsening and unacceptable AD symptoms after 2 weeks of treatment.

The proportion of patients who achieved the primary endpoint of IGA response at week 16 was significantly higher for patients treated with 4 mg of baricitinib *vs.* placebo [34 of 111 (31%); $p = 0.004$]. Unlike the BREEZE-AD1 and BREEZE-AD2 trials, the primary end point for 2 mg of baricitinib was not met [26 of 109 (24%); $P = 0.08$]. As such, secondary endpoints were only evaluated for the 4 mg of baricitinib group. Specifically, the 4 mg of baricitinib group experienced a significant improvement compared with the placebo group ($p < 0.001$) for a proportion of patients, who achieved an EASI-75 response at week 16 [53 of 111 (48%) in the 4 mg group, vs. 25 of 109 (23%) in the placebo group], proportion of patients who achieved a PP-NRS response at week 4 [52 of 100 (52%) for the 4 mg group vs. 11 of 104 (11%) for the placebo group] and week 16 [44 of 100 (44%) for the 4 mg group, 37 of 97 (38%) vs. 21 of 104 (20%) for the placebo group] (**Table 1**).

Findings of a Phase II RCT investigating the clinical efficacy of 2 mg and 4 mg baricitinib vs. placebo in adult patients with moderate-to-severe AD by Guttman-Yassky et al. (43) demonstrated similar results. In this study, however, moderate-to-severe AD was defined by EASI $\geq$ 12, BSA $\geq$ 10% and eligible patients had to fail treatment with either TCS, TCI, systemic corticosteroids or other conventional immunosuppressants. Additionally, triamcinolone 0.1% cream was used throughout the study according to label instructions or as recommended by the investigator. Significantly more patients who received 4 mg baricitinib, achieved EASI-50 than did patients who were assigned to a placebo arm [61 vs. 37% ($p = 0.027$)] at 16 weeks. However, the proportion of patients achieving EASI-50 in the 2 mg baricitinib group did not reach statistical significance at 16 weeks ($p = 0.065$).

Safety

Overall, the most common TEAEs reported in all baricitinib studies reviewed were respiratory symptoms, headache, cutaneous infections, gastrointestinal symptoms and elevation of blood CPK. Specifically, in the study conducted by Simpson et al. (35), the most frequently reported TEAEs (>2% in any treatment group) were nasopharyngitis, URTIs, CPK elevations and headaches. However, there was no increase in the frequency of nasopharyngitis and URTIs, when comparing baricitinib with placebo. Headaches were reported at similar rates in patients treated with 4 mg baricitinib and placebo in BREEZE-AD1 (8.0 and 8.9%, respectively), while a greater percentage of patients reported headaches in the 4 mg baricitinib group compared to placebo in the BREEZE-AD2 trial (6.4 and 2.0%, respectively). Nevertheless, reported headaches were mild (76% of reported cases) and short-lived (median duration of $\leq$ 5 days), with none requiring study-drug interruption or discontinuation. Herpes simplex was also observed more frequently with baricitinib in BREEZE-AD1 trail. Most cases were of mild or moderate severity in both studies and did not cause SAEs or required drug discontinuation. Although CPK elevations were common, most cases (16 of 20) were asymptomatic and either resolved to below the upper limit of normal or were resolving during the study without treatment interruptions. Three patients treated with baricitinib had temporary treatment interruption with resolution of CPK elevations and one patient discontinued the study. No changes in serum lipids were reported. No deaths or VTEs (including PE and Deep Venous Thrombosis [DVT]) were reported in any group. There were no malignancies reported in baricitinib treatment groups.

In the BREEZE-AD7 trial, the most frequently reported ($\geq$2% in any treatment group) TEAEs for 4 mg and 2 mg baricitinib doses compared with placebo were nasopharyngitis, folliculitis, oral herpes, URTI, acne, diarrhea, and back pain (36). One 51-year-old female patient in the 4 mg baricitinib group experienced a PE in the context of receiving oral contraceptives and having a previous history of smoking (7 pack-years). The patient subsequently discontinued treatment and recovered from the event. No major adverse cardiovascular events, malignant tumors, or deaths were reported.

CPK levels were elevated with baricitinib compared with placebo, with most increases being classified as Common Terminology Criteria for Adverse Events (CTCAE) grades 1 and 2 (increase of CPK of <2.5 times and 2.5–5 times the upper limit of normal, respectively) (36). Additionally, CPK elevations were not associated with evidence of muscle injury (e.g., rhabdomyolysis). Although changes were seen in lipid levels, including increases in high-density lipoprotein (HDL) level ($\geq$60 mg/dL; 4 mg group, 28%; 2 mg group, 17%; and placebo group, 10%), changes in low-density lipoprotein (LDL) levels were similar in all groups ($\geq$160 mg/dL; 4 mg group, 3%; 2 mg group, 3%; and placebo group, 4%).

Similarly, in the phase II trial by Guttman-Yassky et al. headaches and nasopharyngitis were reported as common TEAEs (43). Additionally, it was noted that infections were not increased in the groups treated with 2 mg or 4 mg baricitinib compared with those who received a placebo. In both 2 mg and 4 mg baricitinib-plus-TCS groups, the authors observed asymptomatic increases in CPK levels of $\geq$ 30 U/L at week 16 (43). No deaths, VTEs or malignancies were reported.

UPADACITINIB

Clinical Efficacy

The clinical efficacy of upadacitinib, a selective JAK1 inhibitor, has recently been determined by two Phase III studies by Reich et al. (41) and Guttman-Yassky et al. (40). In the study by Reich et al. (41) the efficacy of upadacitinib at 15 and 30 mg daily with TCS vs. placebo with TCS was assessed in 901 adolescent (aged 12 to 17 years old) and adult (aged 18 to 75 years) patients with moderate to severe atopic dermatitis, as defined by the Hanefin and Rajka criteria. At 16 weeks, authors found that the proportion of patients who had achieved an EASI-75, was significantly higher in the 15 mg and 30 mg upadacitinib with

TCS treatment groups than in the placebo with TCS group (64.6, 77.1, and 26.4%, respectively; $p < 0.0001$; **Table 1**). Additionally, a significantly higher proportion of patients achieved an IGA response at week 16 in both 15 and 30 mg upadacinitib with TCS treatment groups in comparison to placebo alone (**Table 1**).

The proportion of patients achieving a PP-NRS response as early as 1 week was significantly higher in patients receiving 15 and 30 mg upadacitinib with TCS treatments than in the placebo with TCS treated group (12.2, 19.2, 3.1%, respectively; $p < 0.0001$). A similar trend was noted in the proportion of patients achieving an EASI-75 score at 2 weeks. Reich et al. (41) documented 31.0% of patients achieving an EASI-75 score in the 15 mg upadacitinib with TCS group, 44.1% in the 30 mg upadacitinib with TCS group, and 6.9 % in the placebo with TCS group treatment ($p < 0.0001$ when comparing 15 and 30 mg upadacitinib with TCS treatment groups *vs.* placebo).

In the study by Guttman-Yassky et al. (40), the efficacy of upadacitinib at 15 and 30 mg daily vs. placebo were assessed in Measure Up 1 and Measure Up 2 replicate Phase III RCTs. A total of 1,683 adolescent (aged 12 to 17 years old) and adult (aged 18 to 75 years) patients with moderate-to-severe AD, defined as IGA $\geq$ 3, EASI $\geq$ 16, BSA $\geq$ 10%, and PP-NRS $\geq$ 4 were enrolled in both studies.

Eight hundred forty-seven patients participated in Measure Up 1, where they were Randomized to daily placebo ($n = 281$), 15 mg ($n = 281$, or 30 mg ($n = 285$) upadacitinib treatment groups. Eight hundred thirty-six patients participated in Measure Up 2, where patients were randomized to placebo ($n = 278$), 15 mg ($n = 276$), or 30 mg ($n = 282$) upadacitinib treatment groups.

In both Measure Up 1 and 2 trials, patients in the 15 and 30 mg upadacitinib groups demonstrated important efficacy outcomes. Namely, the study showed a significantly higher ($p < 0.0001$ in all cases) proportion of patients in the 15 or 30 mg of upadacitinib groups achieving an EASI-75 score (coprimary endpoint), IGA response (coprimary endpoint) and PP-NRS at week 16 vs. placebo (**Table 1**).

Interestingly, a significantly higher proportion ($p < 0.0001$) of patients in both 15 mg and 30 mg upadacitinib treatment groups achieved a PP-NRS response as early as 1 week in comparison to placebo, in the Measure Up 1 and Measure Up 2 Trials (Measure Up 1: 15.0% in the 15 mg upadacitinib group, 19.6% in the 30 mg group, and 0.4% in the placebo group; Measure Up 2: 7.4% in the 15 mg upadacitinib group, 15.7% in the 30 mg group, and 3.6% in the placebo group). Similarly, a significantly higher proportion ($p < 0.0001$) of patients in both 15 mg and 30 mg upadacitinib treatment groups achieved an EASI-75 score as early as 2 weeks in comparison to placebo, in the Measure Up 1 and Measure Up 2 Trials (Measure Up 1: 38.1% in the 15 mg upadacitinib group, 47.4% in the 30 mg group, and 3.6% in the placebo group; Measure Up 2: 33.0% in the 15 mg upadacitinib group, 44.0% in the 30 mg group, and 3.6% in the placebo group).

In another recent study by Guttman-Yassky et al. (37), the clinical efficacy of the selective JAK 1 inhibitor, upadacitinib, was investigated over a period of 16 weeks in this Phase IIb, double-blinded, randomized, parallel-group, dose-ranging trial. Patients with moderate-to-severe AD, defined by IGA $\geq$ 3, EASI $\geq$ 16, BSA $\geq$ 10%, and who failed treatment with TCSs/TCIs were randomized 1:1:1:1 to once-daily upadacitinib oral monotherapy 7.5, 15, or 30 mg or placebo groups. Results at 16 weeks demonstrated that EASI-50, EASI-75, and EASI-90 responses were also achieved at week 16. EASI-100 was achieved by 2.4% (1 of 42; $p = 0.43$), 9.5% (4 of 42; $P = 0.05$), and 24% (10 of 42; $p = 0.001$) of patients in the upadacitinib 7.5-, 15-, and 30 mg groups, respectively, vs. none (0 of 41) in the placebo group. Each upadacitinib dose level was significantly superior to placebo for achieving an IGA response and patient assessment of pruritus (achievement of PP-NRS response) at week 16. Interestingly, efficacy at the studied doses was generally demonstrated by weeks 1 to 4, with peak values reached and maintained after weeks 4 or 8.

Pharmacokinetics

In the study by Guttman-Yassky et al. (37), pharmacokinetic measures were investigated, where it was found that upadacitinib exposures were approximately dose proportional over the 7.5- to 30 mg dose range. Upadacitinib median (interquartile range) plasma concentrations around peak and trough periods were consistent with exposures previously observed for the evaluated doses in healthy volunteers [7.5 mg dose: 10.6 (0.8–21.0) and 2.8 (1.4–4.5) ng/mL, respectively; 15 mg dose: 32.5 (22.7–39.3) and 3.6 (1.8–7.0) ng/mL; 30 mg dose: 57.0 (28.1–94.8) and 8.1 (6.6–16.6) ng/mL] (37).

Safety

In both the Reich et al. (41) and Guttman-Yassky et al. (40) Phase III studies, TEAEs were reported more frequently in the upadacitinib treatment groups than the placebo group (**Table 2**). The most common reported TEAEs (>5% in any treatment group) were acne, respiratory symptoms, headache, elevation in CPK and worsening of AD. The majority of patients who reported treatment-emergent acne had mild to moderate symptoms consisting of inflammatory papules, pustules, comedones, with few cysts and nodules. While in the Reich et al. (41) study, none of the acne events were considered as severe and did not lead to treatment discontinuation, in the Guttman-Yassky et al. (40) study, one acne event was severe, involving >30% of body surface area. Additionally, among patients in the Measure up 1 and 2 trials, one patient in the upadacitinib 15 mg group and one patient in the upadacitinib 30 mg group discontinued study drug because of moderate acne.

With respect to potentially clinically important laboratory findings, most reports of elevations in CPK levels were asymptomatic and associated with exercise. In the Reich et al. (41) study, the elevated CPK levels were reported to be dose related. In the Guttman-Yassky et al. (40) study, only one case of elevated creatinine phosphokinase levels was reported in the upadacitinib 15 mg group, which led to treatment discontinuation. Transient, mild to moderate, neutropenia was also observed more frequently in upadacitinib groups in comparison to placebo in both Phase III studies. Only one event, occurring in the Reich et al., study lead to discontinuation of 30 mg upadacitinib treatment.

No treatment-related deaths or VTEs were reported in the upadacinitib groups in both Phase III RCTs. In the Reich et al. (41) study, two malignancies were reported in the upadacitinib

30 mg with TCS treatment group: one non-melanoma skin cancer (a keratoacanthoma) identified on treatment day 45 and one adenocarcinoma of the colon identified on treatment day 7. The case of colon adenocarcinoma was considered as a non-treatment-related, serious adverse event that lead to the discontinuation of upacitinib. In the Guttman Yassky et al. (40) study, six cases of malignancy were reported in the upadacitinib groups, all of which were determined not to be treatment-related [squamous cell skin carcinoma ($n = 2$), basal cell skin carcinoma ($n = 1$), breast cancer ($n = 1$), gastric cancer ($n = 1$), and anal cancer ($n = 1$)].

In the Guttman-Yassky et al. (37) Phase IIb study, TEAEs were reported in 71% (30 of 42), 74% (31 of 42), and 79% (33 of 42) of patients receiving upadacitinib 7.5, 15, and 30 mg, respectively, vs. 63% (25 of 40) of patients receiving a placebo (**Table 2**). The most frequently reported TEAEs were gastrointestinal and URTI symptoms, followed by acne and AD worsening, all of which were reported as mild or moderate in severity. Additionally, in the 15 mg and 30 mg groups, increased blood CPK was observed in 7.1 and 9.5%, respectively. Nevertheless, the CPK elevations were asymptomatic in patients receiving upadacitinib and reported to be mild to moderate in severity. There was no relationship noted between the dose of upadacitinib and the occurrence of particular TEAEs.

Two patients in the upadacitinib 7.5 mg group had SAEs, namely worsening AD (skin infection and exacerbation of AD) in the context of contact dermatitis and a lower jaw pericoronitis due to recurring tooth infections, not thought to be associated with the treatment. One patient in the upadacitinib 15 mg group had appendicitis. All SAEs in patients who received upadacitinib resolved with treatment.

There were no deaths, opportunistic infections, malignancies, gastrointestinal perforations, herpes zoster, renal dysfunction, active or latent tuberculosis reactivation, adjudicated cardiovascular events, or VTEs. While infections were more common with upadacitinib than with placebo, there were fewer serious infections with upadacitinib.

GUSACITINIB

Clinical Efficacy

Bissonnette et al. (38) were the first to demonstrate gusacitinib (ASN002) as an effective AD treatment in a double-blinded, placebo-controlled Phase Ib RCT. Gusacitinib is an oral dual inhibitor of JAK and tyrosine-protein kinase SYK (also known as spleen tyrosine kinase). Patients included had a diagnosis of moderate-to-severe AD defined by an IGA ≥ 3, EASI ≥ 16, BSA $\geq 10\%$. In this study, 36 patients were randomized at a 3:1 ratio, gusacitinib or placebo, whereby 9 patients were included in the 20, 40, and 80 mg gusacitinib once daily and placebo groups. Each patient received either gusacitinib or placebo once daily for 28 days. In the context of our systematic review, clinical efficacy was determined via EASI-50 and EASI-75 tools over 29 days. Gusacitinib was found to be significantly superior to placebo for the proportion of patients achieving EASI-50 in the 40 mg and 80 mg dose groups at end of treatment ($p = 0.003$ and $p = 0.03$, respectively) (**Table 1**). However, the same efficacy could not be demonstrated in the 20 mg gusacitinib group. The proportion of patients achieving EASI-75 was also greater in the 40 and 80 mg gusacitinib groups compared to placebo, although the difference did not reach statistical significance ($p = 0.06$ and $p = 0.65$, respectively).

Pharmacokinetics

The trial by Bissonnette et al. (38) also reported the pharmacokinetic parameters of gusacitinib in AD patients (38). For 20 mg gusacitinib, the mean maximum concentration (C_{max}) was found to be 67.8 ng/ml, and half-life of 6.62 h. For 40 mg gusacitinib the mean C_{max} was found to be 136 ng/ml, and half-life of 9.10 h. For 80 mg gusacitinib the mean C_{max} was found to be 186 ng/ml, and half-life of 11.2 h.

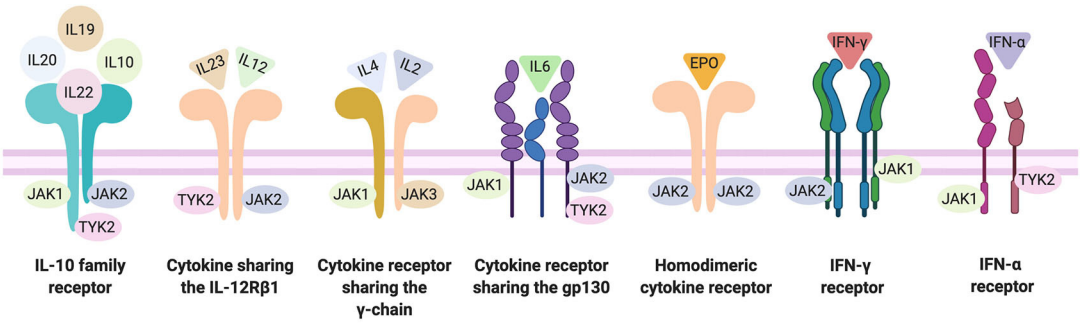
Safety

The most common TEAEs were headache and nausea in 7 and 5% of patients who received gusacitinib, respectively (**Table 2**) (38). There were 2 TEAEs that led to discontinuation including a subject with mild hypertension and another with low lymphocyte counts. The event of mild hypertension was reported in a patient receiving 80 mg gusacitinib and was classified as being possibly related to treatment. The patient with lymphopenia had had low pre-treatment lymphocyte levels and the AE was not considered to be related to treatment. No clinically significant changes in lipid profile were observed in the study. CPK levels were not reported in this trial. Additionally, no VTEs, malignancies or deaths were noted (38).

DISCUSSION

AD is a common and debilitating inflammatory skin disease driven by barrier dysfunction and abnormal Th cell activation. Multiple inflammatory pathways and their respective cytokines are believed to be involved in the chronicity and relapsing nature of the disease. The JAK-STAT and SYK pathways have been shown to assert a downstream modulating effect on AD-associated cytokines. Therefore, JAKi have introduced a promising novel area of therapeutics in the treatment of AD, as well as in other cytokine-mediated autoimmune and inflammatory diseases. With the growing number of clinical trials evaluating the efficacy of various JAKi for the treatment of AD, we sought to systematically review the literature to synthesize and evaluate the available evidence on efficacy and safety of these new compounds. We identified 11 RCTs evaluating the efficacy and safety of four compounds: abrocitinib, baricitinib, upadacitinib, and gusacitinib. A summary of the physicochemical properties of JAKi discussed are provided in **Table 3**. Given the relative paucity of evidence for each individual compound and the differences in patient eligibility criteria among studies, the data was not deemed suitable for a meta-analysis at this time. Nevertheless, the presented review provides a comprehensive summary of the evidence, most of which lends support to the use of JAKi in the treatment of AD.

Abrocitinib, baricitinib, and upadacitinib were the most extensively studied JAKi for the treatment of moderate-to-severe AD to date with Phase III data available. While abrocitinib and upadactinib are oral selective JAK1 inhibitors, baricitinib is an oral selective JAK1 and JAK2 inhibitor. This selectivity



	IL-10 family receptor	Cytokine sharing the IL-12Rβ1	Cytokine receptor sharing the γ-chain	Cytokine receptor sharing the gp130	Homodimeric cytokine receptor	IFN-γ receptor	IFN-α receptor
Pan-JAK Inhibitor Gusacitinib (ASN002)	+	+	+	+	+	+	+
JAK1 JAK2 Inhibitor Baricitinib	+	+	+	+	+	+	+
JAK1 Inhibitor Abrocitinib, Upadacitinib	+	-	+	+	-	+	+

FIGURE 3 | JAKi selectivity toward cytokine receptors. Created and retrieved from https://app.Biorender.com/biorender-templates.

enables JAKi to demonstrate specificity and different capacities to block cytokine receptor signaling (**Figure 3**). Given that baricitinib is a JAK1/2 inhibitor, it has the capacity to inhibit the signaling of multiple cytokine receptors including the IL-10 family receptor, cytokine sharing IL-12Rß1, IFN-γ receptor, homodimeric cytokine receptor, among others. By contrast, JAK1 inhibitors can inhibit most cytokine receptors inhibited by JAK1/2 inhibitors except for the cytokine sharing IL-12Rß1 and the homodimeric cytokine receptor (**Figure 3**). Among the other small molecules reviewed, gusacitinib is a dual JAK/SYK inhibitor.

From the studies reviewed, the clinical efficacy of treatment, as defined by achieving a 4-point reduction in PP-NRS score, was achieved with 100 and 200 mg of abrocitinib, 15 and 30 mg of upadacitinib, and 4 mg of baricitinib as early as week 1 (abrocitinib and upadacitinib) and week 2 (baricitinib), respectively (33–36, 39–41). Notably, 200 mg abrocitinib dose was found to be superior to dupilimab in improving itch response at 2 weeks (39). Two mg baricitinib was also found to be effective in quickly controlling pruritus (35). This rapid efficacy is especially welcome for patients with moderate-to-severe AD, who require prompt symptom control. Similar to cyclosporine, JAKi are able to produce a fast response while demonstrating a side effect profile superior to cyclosporine. Summary of JAKi clinical efficacy by multiple outcome measures are presented in **Figure 4**.

The safety profile for reviewed JAKi small molecules is reassuring with most TEAE being mild and transient in nature, and amenable to symptomatic treatment. Nevertheless, it is important to note that asymptomatic increases in serum CPK levels were observed in the trials with all JAKi (34, 37, 43). These increases mirror the findings from previous studies of JAKi, including tofacitinib (47, 48), baricitinib (49), and upadacitinib (50–52), used in the treatment for a range of other inflammatory diseases. In all previous trials, CPK increases have not been associated with clinically overt myopathy or rhabdomyolysis. However, a recent case report from Australia described two patients with rheumatoid arthritis (RA), who were treated with baricitinib and developed muscle pain and joint swelling coupled to moderate CPK elevation (53). In both cases, clinical and biochemical resolution occurred rapidly after baricitinib discontinuation (53). Increases in serum lipids were also reported in response to abrocitinib and baricitinib in studies included in this review (34, 36). These findings are congruent with previous reports, particularly in response to tofacitinib (54) and baricitinib (55). Yet, while both compounds increase both LDL and HDL cholesterols, they do not appear to alter the LDL:HDL ratio (54, 56). Thus, further evaluation of cardiovascular event rates during long-term treatment is warranted to elucidate the clinical implications of these findings. Overall, it appears that the increases of CPK and lipid levels likely represent class effects, although minor differences deserving special attention in future trials might exists between JAKi compounds.

Two studies within our review reported cases of thromboembolic TEAEs after treatment with 200 mg abrocitinib or 4 mg baricitinib. In both cases, the patients had pre-existing risk factors, and one case also had a history of immobilization. Thromboembolism was first identified as a potential clinically important TEAE of JAKi during the baricitinib approval process for RA (57). In 2017, the European Medicines Agency moved to include DVT and PE as possible side effects of baricitinib, cautioning against its use in patients with risk factors for DVT or PE (58). In 2019, the Food and Drug Administration (FDA) issued a safety warning regarding the preliminary results of safety trial of tofacitinib in the treatment of RA. In patients with RA and at least one cardiovascular risk factor (CVRF), the 10 mg dose of tofacitinib given twice daily was associated with higher rates of thrombosis and all cause-mortality compared to 5 mg given twice daily or TNF-α inhibitors (59). In the absence of a mechanistic

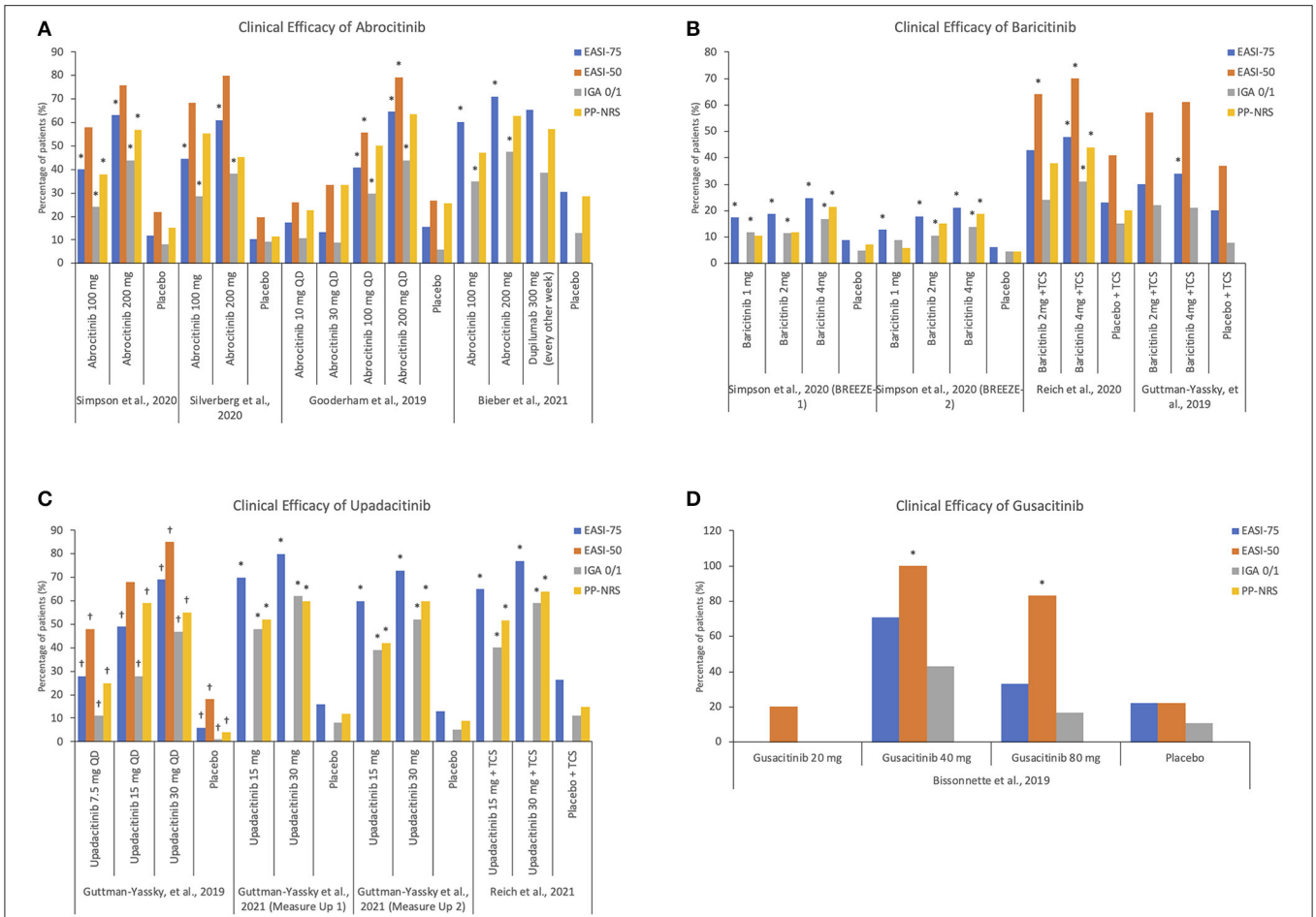


FIGURE 4 | Summary of JAKi clinical efficacy by multiple outcome measures. **(A)** Clinical efficacy of abrocitinib **(B)** Clinical efficacy of baricitinib **(C)** Clinical efficacy of upadacitinib **(D)** Clinical efficacy of gusacitinib. *Values reached statistical significance; †Values were estimated based on figures presented in the publication as exact values were not available. EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale.

explanation for the observed increase in thromboembolic risk in patients with pre-existing CVRFs, regulatory health bodies have moved toward broadening the black box warning to include other JAKi, such as upadacitinib (which is currently approved for RA). The warning is also expected to be added to all future JAKi entering the market, including abrocitinib and gusacitinib. While there is sufficient evidence to conclude that JAKi increase the risk of thromboembolic events, it has been challenging to quantify the magnitude of this association. In one large systematic review and meta-analysis, Oliviera et al. examined the safety of JAKi in patients with inflammatory bowel disease or other immune-mediated diseases (60). Risk of DVT was assessed in 17 studies, including a total of 24,128 patients exposed to a JAKi. The overall incidence rate of VTEs was 0.31 per 100 patient-years, but the results differed between compounds. In healthy individuals, the frequency of thromboembolic events is cited at around 0.1 to 0.2 cases per 100 patient-years, increasing to about 0.5 per 100-patient-years in those aged ≥75. With such low-level frequency rates in the general population, only very large field studies could offer enough evidence for robust conclusions as to the strength of this association. Until then, JAKi should be used judiciously in patients with pre-existing cardiovascular comorbidities.

While no clinical trials within our review reported definitive treatment-related malignancies in JAKi treatment groups, a squamous cell carcinoma and keratoacanthoma were diagnosed in two patients receiving abrocitinib and updacitinib, respectively (39, 41). Nevertheless, we were unable to accurately evaluate the risk of malignancy given that these clinical trials were limited in duration. Previous studies have suggested a link between the use of tofacitinib for RA and the development of malignancies. Of 5,677 adult patients who participated in phase II, phase III and long-term extension studies of tofacitinib, 107 patients were found to develop malignancies [excluding non-melanoma skin cancer (NMSC), also known as keratinocyte carcinomas] (61, 62). The most common was lung cancer ($n = 24$), followed by breast cancer ($n = 19$), lymphomas ($n = 10$), and gastric cancer ($n = 6$). The overall incidence rate (IR) for all malignancies (excluding NMSC) in patients with RA treated with tofacitinib was 0.85 (95% CI, 0.70–1.02). Nevertheless, the incidences of all malignancies (excluding NMSC) were similar in the tofacitinib users compared with the general population (Standardized IR,

1.17; 95% CI, 0.96–1.41) (62). Consistent with this, a subsequent study following patients for 9.5 years of tofacitinib treatment documented no increased risk of malignancy in comparison to the reference population (63). Another study investigating the long-term safety of baricitinib in RA determined that incidences of malignancy (excluding NMSCs) were 0.8 (95% CI 0.4–1.5) per 100 patient-years for 2 mg baricitinib and 1.0 (95% CI 0.5–1.7) per 100 patient-years for 4 mg baricitinib, although there was no significant difference in the incidence of malignancy compared to the placebo group (64). Further long-term studies are required to appropriately determine the risk of developing malignancies when JAKi are used in AD patients. Occurrence of transient neutropenia and acne are additional important side effects to consider in the treatment with JAKi.

In conclusion, given its rapid symptom control combined with the reassuring safety profile, the use of abrocitinib, baricitinib, and upadacitinib can be considered as an important reliable systemic treatment option for adult patients with moderate-to-severe AD who are unresponsive to topical/skin-directed therapies. For abrocitinib, baricitinib, and upadacinitib, close observation of TEAEs is required as well as serial complete blood cell count with differential for neutrophil and platelet monitoring, CPK levels and lipid assessment. Hence, while needle-phobic patients may prefer an oral pill option, regular blood tests will be needed to monitor therapy. Additionally, as a clinical measure of drug efficacy, it has been hypothesized that acne as a TEAE may be due to the pharmacological effect of JAK inhibition.

Although gusacitinib has also demonstrated promising clinical outcomes in the treatment of moderate-to-severe AD, future large-scale phase III trials are required prior to considering their integration in current treatment guidelines. To the best of our knowledge, active clinical trials involving JAKi include phase III trials investigating the use of abrocitinib, baricitinib, and upadacitinib in pediatric populations. Additionally, a phase II clinical trial investigating the safety and efficacy of Jaktinib, a JAK1/2/3 inhibitor, in the treatment of moderate-to-severe AD is currently underway (ClinicalTrials.gov Identifier: NCT04612699).

JAKi represent a new therapeutic class to optimize AD treatment. As more clinical studies confirming the safety and efficacy of JAKi emerge, clinician education regarding this novel treatment will be important.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ML, MB-R, and FG assessed study eligibility. ML and MB-R conducted data extraction and prepared figures. ML, MB-R, FG, MB, LF, MG, LG, SH, HH, IL, PL, DM, MW, JY, CL, and IVL reviewed included studies and the extracted data and wrote the paper. CL and IVL supervised the project. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.682547/full#supplementary-material

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REVIEW
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Lichen Planus

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Lichen planus (LP) is a T cell-mediated disease affecting the stratified squamous epithelia of the skin and/or mucus membrane. Histologically, the disease is characterized by a lichenoid inflammatory infiltrate and vacuolar degeneration of the basal layer of the epidermis. LP has three major subtypes: Cutaneous, mucosal and appendageal LP. Rarely, it may affect the nails in the absence of skin and/or mucosal changes. LP may also be induced by several drugs, typically anti-hypertensive medication or be associated with infections, particularly viral hepatitis. The diagnosis is based on the clinical presentation and characteristic histological findings. Although the disease is often self-limiting, the intractable pruritus and painful mucosal erosions result in significant morbidity. The current first-line treatment are topical and/or systemic corticosteroids. In addition, immunosuppressants may be used as corticosteroid-sparing agents. These, however are often not sufficient to control disease. Janus kinase inhibitors and biologics (anti-IL-12/23, anti-IL17) have emerged as novel future treatment options. Thus, one may expect a dramatic change of the treatment landscape of LP in the near future.

Keywords: lichen planus, skin disease, inflammation, T-cell mediated, treatment

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INTRODUCTION

The term lichen planus (LP) stems from the Greek word "*leichen*," which means "tree moss," and the Latin word "*planus*," which means "flat," which aptly describes the surface of the cutaneous lesion (1). LP is a group of chronic inflammatory diseases affecting stratified squamous epithelia. Recently, LP is perceived as a T cell-mediated autoimmune disease, in which cytotoxic CD8+ T-cells are recruited into the skin and subsequently lead to an interface dermatitis (2–8). Viruses, drugs and contact allergens have all been reported to be possibly associated with development of LP (9–19). Clinically, LP is hallmarked by characteristic lesions, affecting the skin, hair, nails and/or mucous membranes. The classical skin changes are pruritic, purple, polygonal, flat-topped (planar) papules crossed by fine white lines, while erosions are seen on the mucous membranes (**Figure 1**). The latter may be associated with pain and/oral burning sensation (1). An overview of clinical subtypes and rare variants are listed in **Table 1**. LP preferentially affects middle-aged adults, with no known gender pre-disposition (1, 14). Whilst the clinical features are relatively characteristic, histological confirmation of the diagnosis is recommended to exclude potential differential diagnoses. The typical band-like lymphocytic infiltrate and interface dermatitis are the characteristic findings—irrespective of skin location or disease subtype. In addition to routine histology, direct immunofluorescence (IF) microscopy may demonstrate C3 and/or IgG at the dermal-epidermal junction and deposition of IgM as so-called colloid bodies (20). The overall goal of treatment is symptom control and resolution of the skin lesions. Selection of treatment should be based on the severity of the disease, the extent of the subjective symptoms, as well as taking into

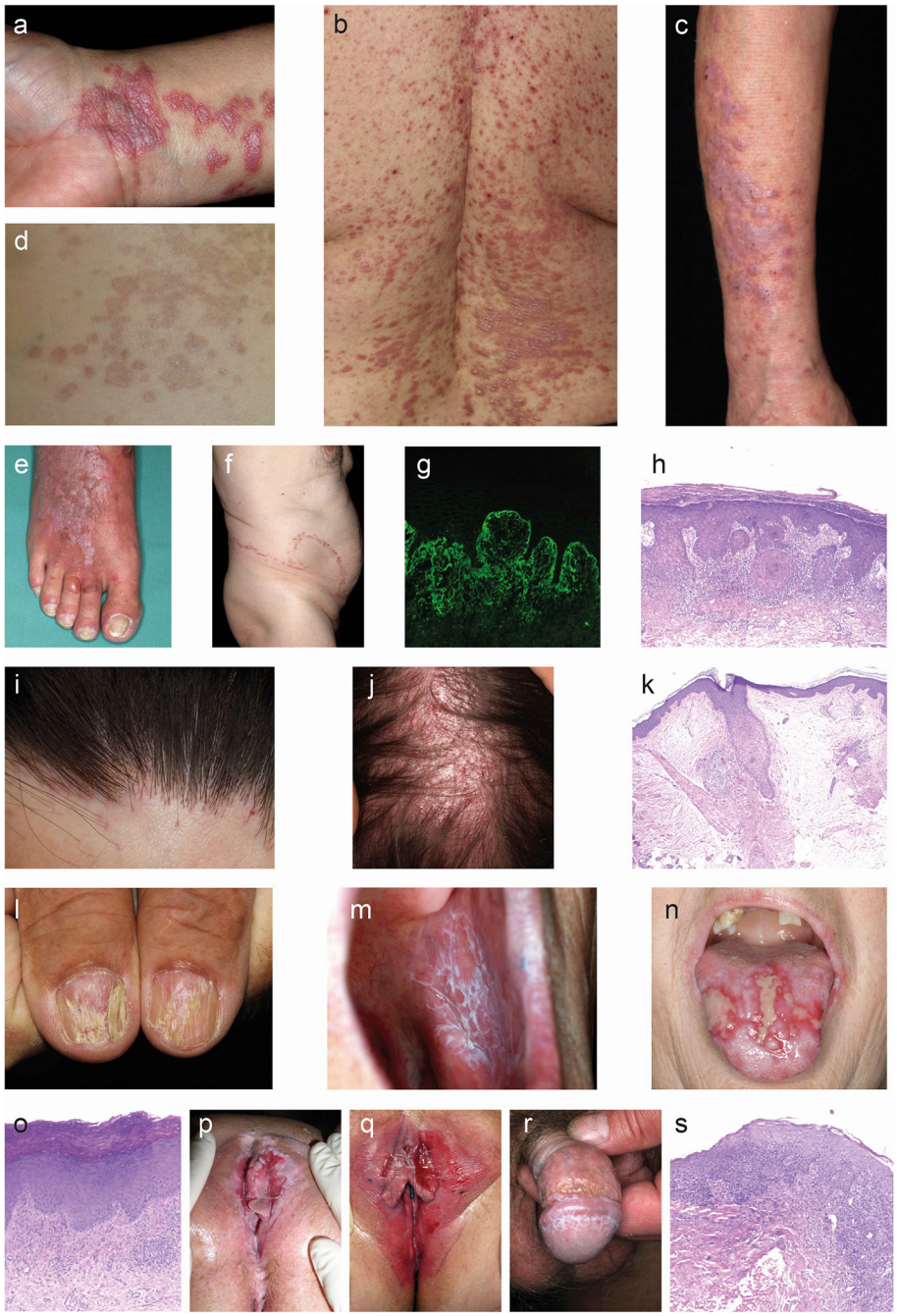

FIGURE 1 | Clinical and histological hallmarks of lichen planus. **(a–f)** Cutaneous lichen planus (LP). **(a)** Polygonal, flat-topped, violaceous confuting plaques with fine white scales on the inner wrist in a patient with localized LP. **(b)** Symmetric red plaques on the back of a patient with generalized cutaneous LP. **(c)** Thick reddish-brown plaques on the arms of a patient with hypertrophic LP. **(e)** Blister on the 3rd toe along with widespread red plaques with whit streaks in a patient with lichen planus pemphigoides. **(f)** Linear lichen planus. **(g)** Direct immunofluorescence microcopy staining with fibrin deposition in the epidermis (400×). **(h)** The histology from a skin biopsy from a lichen planus lesion characteristically shows an irregularly epidermis with saw-toothed rete ridges, hypergranulosis, liquefaction degeneration of the dermal-epidermal junction and a lichenoid (band-like) lymphocytic infiltrate (H&E staining, 200×). **(i–l)** Appendageal LP. **(i)** Scaring alopecia and inflammation around hair follicles along the frontal scalp hair margin in a patient with frontal fibrosing alopecia. **(j)** Image from a patent with lichen planopilaris. **(k)** Lichenoid interface dermatitis of the hair infundibulum and apoptotic keratinocytes (Civatte bodies) and fibrous tracts in a biopsy from a patient with frontal fibrosing alopecia. **(l)** Grooved and ridged nails in a patient with nail LP. **(m–s)** Mucosal LP. **(m)** Wickham striae in the oral mucosa of a patient with oral LP. **(n)** Severe ulcera of the tounge in a patient with erosive oral LP. **(o)** Parakeratosis, acanthosis. band of inflammatory cells just beneath the epidermis, plasma cells in infiltrate in an oral biopsy from a patient with oral LP. **(p)** Severe vulval ulcerations in a patient with vulval LP. **(q)** Erythema and erosions in a patient with vulval LP. **(r)** Wickham striae on the glans penis in a patient with penile LP. **(s)** Occasional parakeratosis, irregularly thickened epidermis, apoptotic basal keratinocytes, lymphohistiocytic infiltrate in a biopsy from a patient with genital LP.

TABLE 1 | Overview of clinical subtypes and rare variants.

Cutaneous lichen planus	• Localized cutaneous lesions of LP	
	• Generalized cutaneous LP	
	• Hypertrophic LP	
	• Palmoplantar LP	
	• Atrophic LP	
	• Actinic LP	
	• Vesiculobullous LP	
	• Annular LP	
	• Erosive and ulcerative LP	
	• Annular LP	
	• LP pigmentosus	
	• Lichen planus pemphigoides	
	• Linear LP	
	• Follicular LP	
Mucosal lichen planus	• Oral LP	◦ LP plaque-like or erosive
		◦ Atrophic LP lesions of the oral mucosa
		◦ Bullous LP of the mucosa
	• Genital LP	◦ Papular genital LP
		◦ Hypertrophic genital LP
		◦ Chronic erosive LP lesions in genitalia
	• Esophageal LP	
	• Laryngeal LP	
Appendageal lichen planus	• Lichen planopilaris (LPP)	◦ Classic form LPP
		◦ Frontal fibrosing alopecia
		◦ Graham-Little-Piccardi-Lasseur Syndrome
	• LP of the nails	
Other forms of LP	• Drug-induced lichen planus	
	• Overlap syndromes: LP erythematosus	
	• Lichenoid reaction of graft-vs.-host disease	
	• Lichenoid keratosis	
	• Ocular LP	
	• Aural and urethral LP	

account relevant co-morbidities (14). Cutaneous LP is usually self-limiting and resolves within 6 months in over 50% of patients and within 18 months in up to 85% of patients (14, 21). By contrast, mucosal LP is often chronic and may be refractory to treatment (22, 23). LP with hypertrophic cutaneous lesions and isolated nail or scalp involvement is also often chronic in nature. Persistent cutaneous and mucosal lesions are considered as a premalignant condition. Thus, patients should be followed up regularly for both, adjustment of treatment, and screening for the development of malignancies.

EPIDEMIOLOGY

The prevalence of LP is 0.89% in the general population and 0.98% in patients seeking dermatological care according to a recent meta-analysis of 46 studies (24). The prevalence of cutaneous LP was reported to range between 0.2 and 1.0% of the adult population, and it is outnumbered by oral LP in most study populations (1, 9). The incidence of LP is less well-characterized and displays considerable geographical heterogeneity as it ranges between 14 and 250 cases/100,000 person-years (25–29). This variability more likely mirrors methodological differences in the sampled populations rather than the existence of an ethnic pre-disposition. Moreover, the aforementioned studies adopted various eligibility criteria and pooled patients with oral and cutaneous LP together. While oral LP affects females more frequently than males (24, 30), cutaneous LP does not demonstrate a prominent sex predilection (21). Cutaneous LP tends to manifest during the fifth and sixth decades of life, with almost two-thirds of patients presenting with the disease between the ages of 30 and 60 years (9, 31, 32). Oral LP tends to develop 10 years later than cutaneous LP (33). While no ethnic predilection is renowned in LP, a recent meta-analysis revealed that the pooled prevalence of oral LP was lower among patients of Asian ancestry (24). The epidemiology of LP remains to be fully delineated as the current knowledge stems mainly from scattered small-scale retrospective studies. Given that the care of patients with LP spreads across different medical specialties, in both primary and specialized healthcare, precise estimation of its incidence and prevalence is methodologically challenging.

PATHOGENESIS

Genetics

The observation of familial LP (34), the occurrence of LP in monozygotic twins (35) and HLA-based susceptibility association studies all point toward a genetic pre-disposition for LP. Several HLA alleles are associated with LP, for example between HLA-B27, HLA-B51, HLA-Bw57 (oral LP in English patients), HLA DR1 (cutaneous/oral LP), HLA-DR9 (oral LP in Japanese and Chinese patients), HLA DR6 (HCV-associated oral LP), and HLA DRB1*11 and DQB1*03 alleles (lichen planopilaris) (17, 36–40). So far, only one genome-wide association study (GWAS) has been published in LP. In total, 261 patients with hepatitis C infection with ($n = 71$) or without ($n = 190$) LP were genotyped. The findings were validated in a small group of patients ($n = 45$), of which only 7 were affected by LP. In addition to the association with the HLA, single-nucleotide polymorphisms (SNP) in loci encoding for *NRP2* and *IGFBP4* that increase or reduce risk of LP association, respectively, were found (37). Recently, a phenome-wide association study confirmed the HLA association in LP and additionally found two additional SNPs to be associated with LP. These SNP encode for three genes: *TSBP1*, *HCG23,* and *BTNL2* (41). Further gene associations had been described for several cytokines (IFN-γ, TNF, TNFαR, IL-4, IL-6, IL-18) and others (NFκB, PGE2, Prothrombin) (40).

Environmental Factors

Several environmental factors have been implemented to trigger LP. Systemic viral infection, such as hepatitis C, may modify self-antigens on the surface of basal keratinocytes, or alter the immune balance, promoting a lichenoid inflammation (15–18, 42). The association between LP and hepatitis C has recently

been substantiated in a large cohort study. Here, the prevalence of chronic inflammatory skin disease, including LP, was contrasted in over 23,000 patients with hepatitis C and a 3-fold greater number of non-hepatitis controls. In this study, the adjusted hazard ratio (HR) for subjects with hepatitis C to develop LP was 13.14 (95% CI: 7.10–24.31), indicating a significantly higher risk to develop LP for patients with hepatitis C. Among all evaluated chronic inflammatory skin diseases, the HR to develop LP for patients with hepatitis C was the second highest (43). Other viruses that are associated with triggering LP are members of the human herpesvirus (HHV) family, specifically (HHV)-6 and HHV-7 (44). However, studies relating to HHV-6 were not validated in other studies (45). Moreover, localized skin disease due to herpes simplex, varicella zoster, or human papilloma virus 16 (46–52) may cause LP. There are also reports that vaccine administration, including influenza and hepatitis B virus vaccines, may be associated with the development of LP (53). Additional environmental factors have been implicated in the development of oral LP. These include changes in the oral microbiome (e.g., *Candida* sp., various other bacterial infections) and dental metals precipitating allergic contact reaction (54–57). In line with this observation, the diversity of the skin bacterial communities may be involved in LP pathogenesis. Under steady-state conditions, a low diversity of bacterial communities on the skin are associated with an increased expression of proinflammatory cytokines (TNFα and CXCL1) and CD11c, pointing toward an increased infiltration with macrophages (58). These cytokines, as well as macrophages are also found in lesional LP skin (59–61). Thus, a low diversity of cutaneous bacterial communities may generate a pro-inflammatory state, even under steady-state conditions, that shares features of LP (**Figure 2**); thereby, potentially lowering the threshold for LP to develop. Among metals that may be associated with oral LP include amalgam (mercury), copper, and gold. Drugs may also elicit lichenoid-like reactions, which may be both clinically and histologically indistinguishable from classic LP. The most commonly implicated drugs (**Table 2**) are angiotensin-converting enzyme inhibitors, thiazide diuretics, antimalarials, anti-inflammatory drugs, antimicrobials, antihypertensives, psychiatric drugs, antidiabetics, PD-1-inhibitors, quinidine, penicillamine, and metals (62–65). Another peculiar potential environmental trigger for LP is UV-filters in sunscreens and hair-care products that have been noted to be associated with frontal fibrosing alopecia and lichen planopilaris (66, 67).

CELLULAR AND MOLECULAR PATHOGENESIS

Most of the findings on LP pathogenesis are based on morphology. Only a limited number of studies also demonstrated a functional impact of cells and/or molecules on LP pathogenesis. A cell-mediated immune response is at the core of LP pathogenesis, with cytotoxic, CD8+ T-cells in the center (**Figure 2**). Yet, both CD4+ and CD8+ T-cells accumulate in the dermis and oral mucosa, whilst a CD8+ T-cell-dominant infiltrate is seen within the epidermis (3, 4). Other groups have reported that CD8+ and CD45RO+ T-cells are the major cell type in the inflammatory infiltrate and that the T cell receptor (TCR) αβ, and to a lesser extent TCR γδ, are expressed (68). The functional contribution of T-cells to LP pathogenesis is further supported by a recent study that showed granule exocytosis with the release of perforin and granzyme B. In this context, to a lesser extent, the Fas/Fas-ligand system appears to be involved, the main pathway of cytotoxicity by CD4+ and CD8+ T-cells in humans (5). In addition to T-cells, mast cells may contribute to LP pathogenesis given that they are often found in the inflammatory infiltrate and show signs of activation (69–72). Immunohistochemistry of oral LP also demonstrated the presence of dendritic cells (73). The fact that CD8+ T-cells and mast cells are detected in lesions of LP patients led to the conclusion that non-specific mechanisms like mast cell degranulation and protease activation are involved in the pathogenesis of LP. These mechanisms may combine to cause T-cell accumulation in lesions and induce keratinocyte apoptosis (74). In line, an increased protease expression has been described in LP lesions that potentially contributes to the disruption of the basement membrane gelatinases (e.g., MMP-2, MMP-7, and−9), chymase, tryptase, capthepsins and caspase-3 (74–79).

Several alterations in the expression of cytokines and chemokines in lesions or serum of patients with LP have been described. Serum levels of interleukin (IL)-5, IL-6, IL-8, IL-9, IL-10, IL-12 IL-17, IL-22, tumor necrosis factor-α, transforming growth factor-β, interferon (IFN)-γ, CXCR-3, CXCR-4, CXCL-10, CXCL-12, CCR1, CCR3, CCR4, CCL5-CCR5, and CCL17-CCR4) have been found elevated (80–89). In addition, an increased expression IFN-γ and IL-17 in the skin of LP lesions has been described (81, 90)—albeit some other studies refuted these observations (91). Case reports indicated that off-label treatment of LP with Janus kinase (JAK) inhibitors (JAKi), such as tofacitinib, led to marked improvement of the disease (92–94). As IFN-γ-induced signaling centers on the activation of JAK (95), IFN-γ and JAK are likely to be central to the pathogenesis of LP. Functional evidence for a pathogenic contribution of IL-17, including the IL-17 pathway, stems from the observation of increased IL-17 and IL-23 expression in LP (84), as well as the clinical improvement following off-label treatment of LP patients with the anti-IL-17 antibody secukinumab, or the IL-12/23-targeting ustekinumab or the IL-23 inhibitor guselkumab. Of note, clinical improvement of LP following IL-17 or IL-23 blockade was accompanied by a strong reduction of the Th1 and Th17/Tc17 cellular mucosal and cutaneous infiltrates (96). This supports the previously mentioned notion that these T-cell subsets may be key effector cells in LP.

ANIMAL MODELS

The relative lack of functional insights into LP pathogenesis may be due to the limited number of pre-clinical model systems. So far, only one mouse model has been established that resembles aspects of LP pathogenesis. This model is based on the intradermal transfer of autoreactive CD4+ T-cells producing IFN-γ and TNF into syngeneic mice, inducing cellular infiltrates

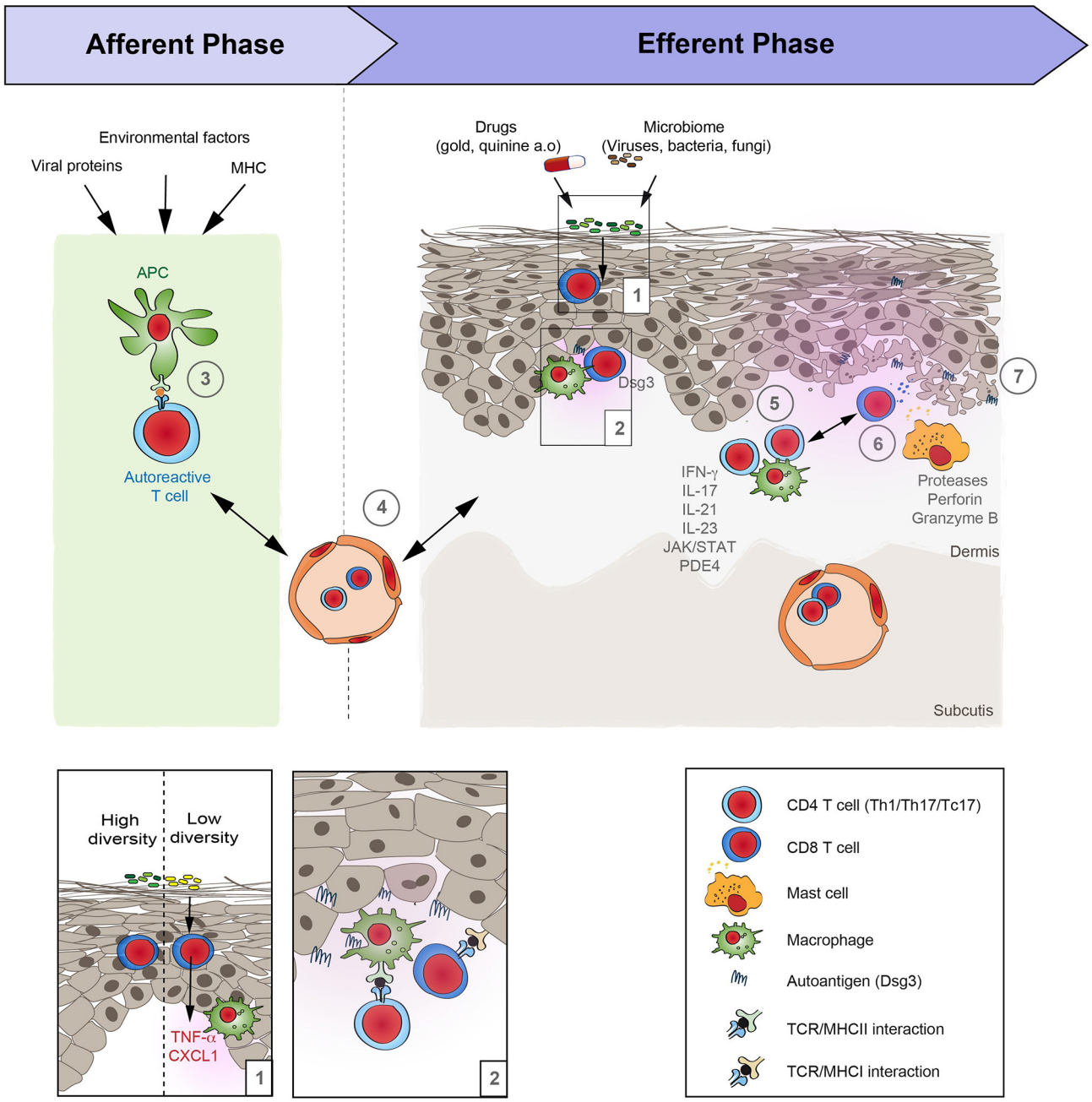

FIGURE 2 | Schematic overview of lichen planus pathogenesis. Based on the increasing evidence of the autoimmune nature of lichen planus (LP), its pathogenesis may be divided in two distinct phases: Afferent phase, where tolerance to autoantigens is lost, and the efferent phase that is characterized by a T cell-driven skin inflammation. (1) Under steady state conditions the diversity of the cutaneous microbiome can alter the "inflammatory state" of the skin. If the diversity of the bacterial communities on the skin is low, this is associated with an increased expression of pro-inflammatory cytokines such as TNFα and CXCL1, as well as an increase of CD11c, suggesting an increased presence of macrophages. (2, 3) Following this presumed injury, the loss of tolerance in LP occurs in the context of an association with the MHC that may additionally be shaped by associated viral infections and other environmental factors. The site of the APC/T-cell interaction is so far unknown. It may occur locally and/or in skin draining lymph nodes. (4) Next, autoreactive T cells reach the skin by extravasation from the blood vessels. (5) Within the skin, T cells become activated by binding to the specific autoantigens. Effector functions of cytotoxic T cells is mediated by (6) proteases, such as granzyme B, as well as perforin. In addition, (7) mast cells become activated and may further aggravate inflammation in LP. However, the precise sequence of events and their interactions are only incompletely understood.

with epidermotropism with basal vacuolar degeneration and colloid bodies (2). Furthermore, desmoglein (Dsg) 3-specific T-cells are also capable of inducing histologically LP-like changes (97). Transfer of Dsg3-specific T-cells into immunodeficient mice induced an interface dermatitis (a distinct form of T-cell–mediated autoimmunity) in mice. The induction of the interface

TABLE 2 | Drugs associated with lichen planus like eruptions.

Antidiabetics			
Chlorpropamide	Glyburide	Tolazamide	Tolbutamide
Antihypertensives			
Captopril	Enalapril	Labetalol	Methyldopa
Propanolol	Diazoxide	Doxazosin	Nifedipine
Prazosin			
Antimalarials			
Chloroquine	Hydroxychloroquine	Quinacrine	
Antimicrobials			
Ethambutol	Griseofulvin	Isoniazid	Ketoconazol
Primethamine	Streptomycin	Sulfamethoxazole	Tetracyclines
Diuretics			
Chlorothiazide	Furosemid		
Hydrochlorothiazide	Spironolactone		
Metals			
Gold salts	Aresenic	Mercury	Bismuth
Palladium			
NSAIDs			
Acetylsalicylic acid	Difunisal	Fenclofenac	Flurbiprofen
Benoxaprofen	Ibuprofen	Indomethacin	Naproxen
Suldinac			
TNF-α inhibitors			
Etanercept	Infliximab	Adalimumab	Lenercept
Others			
Allopurinol	Amiphenazole	Anakinra	Cinnarizine
Cyanamide	Dapsone	Gemifrozil	Hydroyurea
Imatinib	Interferon-α	Iodides	Isotretinoin
Levamisole	Lithium	Mercapto-propiomglycine	Mesalamine
Methycran	Nivolumab	Omeprazole	Orlistat
Prembrolizumab	Penicillamine	Procainamide	Propylthiouracil
Pyrithioxin	Simvastatine	Quidine	Quinine
Rituximab	Sildenafil	Sulfasalazine	Trihexyphenidyl

dermatitis depended on the specificity of the T-cell receptor as well as IFN-γ (97).

DISEASE ASSOCIATIONS

Besides systemic viral infection, several other diseases were shown to be associated with LP. A high prevalence of thyroid disease is found amongst patients with oral LP (98), whereas the association between LP and diabetes mellitus is less well-established (99). In addition to the association with chronic inflammatory diseases, patients with LP present a higher risk for dyslipidaemia, which could be explained by the cytokines involved in the pathogenesis of the disease, such as TNF-α, IL-6, IL-10, and IL-4 (100, 101). Autoimmune diseases such as alopecia areata, ulcerative colitis, vitiligo, morphea, lichen sclerosus and myasthenia gravis are over-represented in patients with LP (14).

DIAGNOSIS

Clinical Manifestations

Over 20 different clinical manifestations of LP are described (**Table 1**). Herein, we focus on the most common variants, as well as LP pemphigoides, lichenoid GVHD and lichenoid drug eruptions.

Cutaneous Lichen Planus

The hallmark of cutaneous LP are purple or violet, polygonal, shiny, flat-topped, firm, papules, and plaques with white streaks (Wickham striae) (40). Wickham striae are best visualized by dermoscopy (102, 103). The cutaneous lesions may vary in size from several millimeters to more than one centimeter. The lesions may be clustered or disseminated and whilst the typical locations are the wrists, lower back, and ankles, a distribution in photo-exposed areas is also well-recognized (**Figures 1a–c**). Skin conditions may also appear following the lines of trauma (isomorphic response, **Figure 1f**). The dominant subjective symptom is pruritus, which may be severe and refractory to standard anti-pruritic therapies.

Mucosal Lichen Planus

The typical lesions of mucosal LP are painful and persistent erosions (erosive LP) or diffuse erythema and peeling of the mucosa (desquamative LP) (40). In addition, Wickham striae may be present in a lacy or fern-like pattern. Mucosal LP can be further subclassified into oral LP, affecting the buccal mucosa, the tongue, and to a lesser extend the gums and lips (**Figures 1m,n**) or genital LP, affecting the glans penis, labia majora, labia minora and vaginal introitus (**Figures 1p–r**). Chronic disease may result in scarring, with the formation of adhesions, resorption of labia minora and ultimately introital stenosis. Penile LP usually presents with papules around the glans penis, white streaks and erosions. In rare cases, mucosal LP may also affect the lacrimal glands, eyelids, external ear canal, esophagus, larynx, bladder, and anus.

Lichen Planopilaris

Lichen planopilaris (LPP) presents as tiny red spiny follicular papules and extending smooth areas on the scalp or less often, elsewhere on the hair-bearing regions body areas (104, 105). Destruction of the hair follicles leads to permanently bald patches characterized by sparse "lonely hairs" (**Figures 1i,j**). Frontal fibrosing alopecia is a variant of LPP that affects the anterior scalp, forehead and eyebrows. Another subtype of LPP is Graham-Little-Piccardi-Lasseur Syndrome with the following characteristics: multifocal, patchy, cicatricial alopecia present on the scalp, non-cicatricial alopecia of the axillae, non-cicatricial alopecia of the perineum, and follicular hyperkeratosis of the trunk and extremities (106).

Nail Lichen Planus

LP may affect one or more nails (**Figure 1l**), sometimes in the absence of skin involvement. LP thins the nail plate, which may become grooved and ridged. The nail may darken, thicken or lift off the nail bed (onycholysis). Sometimes, the cuticle is

destroyed and forms a scar (pterygium). The nails may shed or stop growing altogether, and they may rarely, completely disappear (anonychia). An important clinical feature of nail LP is the occurrence of a dorsal pterygium.

Lichen Planus Pemphigoides

LP pemphigoides is clinically characterized by the simultaneous occurrence of lichenoid and bullous skin lesions. By some, LP pemphigoides is considered as an autoimmune dermatosis with autoimmunity toward type XVII collagen (COL17). By contrast, others consider LP pemphigoides the co-occurrence of 2 independent skin diseases, or as a variant of LP (14, 107, 108).

Lichenoid Graft-vs.-Host-Disease

Graft-vs.-host disease (GVHD) is the primary complication of allogeneic bone marrow transplantation and the skin is the most commonly involved organ. The clinical picture varies and often is similar to autoimmune or inflammatory diseases. Cutaneous GVDH can imitate classical lichen planus with purple, polygonal, pruritic papules (but without Wickham striae) or lichen planus pigmentosus (109, 110). GVHD refers to the inflammatory manifestations, when immunocompetent T-cells from a donor recognize and react against "foreign" tissue antigens in an immunocompromised host, this autoreactive pre-condition leads to a Th2 immune response induced interface dermatitis (109).

Lichenoid Drug Eruptions

Lichenoid drug eruptions often mimic idiopathic lichen planus although there can be features that may help to distinguish them, which may include: symmetrical rash on the trunk and limbs, predominantly in sun-exposed areas. Skin features do normally not show Wickham striae, nail and mucous membrane involvement is missing. Medications reported to trigger a lichenoid drug eruptions are, exemplary (14): ACE inhibitors, beta-blockers, nifedipine, methyldopa, hydrochlorothiazide, frusemide, spironolactone, non-steroidal anti-inflammatory drugs (NSAIDs), carbamazepine, phenytoin, ketoconazole, 5-fluorouracil, imatinib, hydroxychloroquine, sulfonylurea, dapsone, mesalazine, sulfasalazine, allopurinol, iodides and radiocontrast media, interferon-α, omeprazole, penicillamine, tetracycline, infliximab, etanercept, adalimumab, imatinib, misoprostol, sildenafil, and herpes zoster/influenza vaccines.

Contact allergies also may mimic lichen planus: Oral lichenoid lesions may be associated to type-IV-sensitization to mercury or dental amalgam (111, 112); lichenoid skin lesions usually result from contact with rubber, chemicals used in clothing dyes or chemicals in wine industries (113).

Confirmation of Diagnosis

Histopathology

A skin/mucosal biopsy is recommended to confirm the diagnosis of LP. The typical histological findings are acanthosis and hyperkeratosis, wedge-shaped hypergranulosis, vacuolic degeneration of the basal layer, alteration or loss of rete ridges resulting in a sawtooth appearance and a dense, band-like lymphocytic infiltrate in the upper dermis along the dermal-epidermal junction (**Figures 1h,k,o,s**). Apoptotic keratinocytes are often seen near the basal layer and are termed colloid bodies. For LP affecting the scalp, for example LPP, shows beside the penitent LP features often the destruction of hair follicle root sheaths and follicular plugging as well as the loss of sebaceous glands as well (114) (**Figure 1k**).

Immunofluorescence

Additionally, a lesional biopsy for direct IF microscopy can be a useful, especially when trying to differentiate between LP and other autoimmune diseases, such as pemphigus vulgaris, mucous membrane pemphigoid, or lupus erythematosus (LE) (115, 116). In LP, direct IF microscopy (**Figure 1g**) may reveal globular deposits of IgA, IgM, IgG, C3, or fibrinogen mixed with apoptotic keratinocytes (117, 118).

DIFFERENTIAL DIAGNOSES OF LP

Cutaneous Lichen Planus

The differential diagnosis of cutaneous LP is broad and includes graft-vs. host-disease, psoriasis vulgaris, guttate psoriasis, secondary syphilis, pityriasis lichenoides, pityriasis rosea, lichen nitidus, lichen simplex chronicus, lichen sclerosus, lichen striatus, linear epidermal naevus, eczema, prurigo nodularis, erythema dyschromicum perstans, eczematid-like purpura, drug eruption, granuloma annulare, lichen amyloidosus, Kaposi sarcoma and lupus erythematosus. In most cases, histology permits a reasonable differentiation between these diseases and inflammatory disorders.

Mucosal Lichen Planus

Similarly, an extensive list of differential diagnoses should be considered when diagnosing LP of the oral cavity including pemphigus vulgaris, mucous membrane pemphigoid, lupus erythematosus, secondary syphilis, traumatic patches, and candidiasis. Vulval/penile LP can be difficult to distinguish from lichen sclerosis, mucous membrane pemphigoid, psoriasis, intraepithelial neoplasia, graft-vs.-host disease, erosive dermatitis, and intertrigo. Histology and direct IF microscopy should allow a definite diagnosis of LP and the exclusion of other diseases.

Lichen Planopilaris

Various diseases may appear similar to LPP, especially when the destruction of the hair follicles leads to permanently bald or even scarring patches without inflammation or tiny red spiny follicular papules, such as patchy alopecia in systemic LE, alopecia areata, diffuse alopecia due to secondary syphilis or severe folliculitis. Brunsting-Perry cicatricial pemphigoid is rare variant of mucous membrane pemphigoid associated with scarring on the head and neck region. Differentiating them can be difficult, besides punch biopsy trichometric analysis, fungal culture, blood tests are recommended to find the underlying medical condition.

Nail Lichen Planus

Nail LP can be challenging to differentiate from psoriasis, atopical dermatitis, alopecia areata and onychomycosis. For the later, appropriate laboratory testing for presence of fungi is recommended.

MANAGEMENT

The ultimate aim of treatment is the resolution of the skin lesions and their associated symptoms. This is particularly important in oral LP where painful erosions can result in significant malnutrition and weight loss. Drug-induced LP should always be considered and excluded prior to commencing immunosuppressive therapy (14) and the responsible drug discontinued or substituted. An LP-associated diseases should be checked in each patient. Hypertrophic and mucosal LP lesions are potentially premalignant and regular follow-up and biopsies should be considered to exclude malignant transformation (**Table 3**).

TABLE 3 | Management of lichen planus.

	First-line	Second-line	Third-line
Cutaneous lichen planus (LP)	• Topical steroids • Intralesional steroids • Systemic corticosteroids • Acitretin/ isotretinoin • Cyclosporine	• Topical calcineurin inhibitors • Phototherapy (UVB or PUVA) • Combination of phototherapy and acitretin • Sulphasalazine	• Hydroxychloroquine • Azathioprine • Mycophenolate mofetile • Methotrexate • Apremilast • Ustekinumab • Topical calcipotriol • Antibiotic treatment (trimethoprim–sulphomethoxazole, metronidazole) • Antifungal therapy (traconazole, terbinafin, griseofulvin) • Cyclophosphamide • Thalidomide • Adalimumab • Interferon a2b • Alitretinoin • Low molecular weight heparin • Photodynamic therapy • Extracorporeal photochemotherapy • Laser
Mucosal LP	• Topical steroids • Intralesional steroids • Systemic corticosteroids • Acitretin/ isotretinoin • Topical retinoids • Cyclosporine	• Topical calcineurin inhibitors • Hydroxychloroquine • Azathioprine • Sulphasalazine • Mycophenolate mofetile • Methotrexate • Adalimumab • Etanercept	• Cyclophosphamide • Thalidomide • Antibiotic treatment (metronidazole, trimethoprim–Sulphomethoxazole, tetracycline, doxycycline) • Antifungal therapy (traconazole, griseofulvin) • Dapsone • Low molecular weight heparin • Interferon • Topical tocopherol • Photodynamic therapy • Extracorporeal photochemotherapy • Laser

Treatment recommendations shown in the table are based on the European S1 guidelines (14).

Cutaneous Lichen Planus

The first-line treatments for limited LP are (super)potent topical steroids, with intralesional steroid injection reserved for hypertrophic and/or unresponsive lesions (14, 119, 120). For disseminated disease, systemic corticosteroids can be considered, either as oral therapy or intravenous "pulse" therapy, to achieve disease control. Thereafter, the oral dose can be tapered or the interval between intravenous administrations extended (14, 121, 122). Other first-line therapies include systemic retinoids (acitretin/isotretinoin) or cyclosporine (14, 123–126). If diffuse cutaneous LP remains unresponsive, second-line therapy should be considered. These include sulphasalazine, and phototherapy such as broadband/narrowband UVB or psoralen and UVA (PUVA), and the combination of UV/PUVA with retinoids (14, 121, 127–130). For topical treatment of limited and diffuse cutaneous LP calcineurin inhibitors can be used to reduce side-effects of topical steroids (14, 131). Third-line treatments include hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, or biologics targeting IL-12/23 (14, 121, 130, 132–136). Based on the fact that in LP proinflammatory signaling pathways result in T-cell-dependent immune response, oral JAKi may represent a future treatment option (137). Oral antihistamines may be helpful to minimize the itch (14). Topical antipruritic agents such as menthol, camphor, or polidocanol can be prescribed as an adjuvant to the main treatment (14). The majority of patients with cutaneous lesions spontaneously clear within 12–24 months (21); however, relapses are common. Healing may also be complicated by the development of post-inflammatory hyperpigmentation (1, 9).

Mucosal Lichen Planus

Mucosal LP is often difficult to treat, particularly when extensive erosions are present. Long-term follow-up is necessary to monitor disease activity and to exclude malignant transformation of erosive lesions (14). The mainstay of treatment of mucosal LP are topical corticosteroids (14, 138). Superpotent steroids can be applied topically (in the form of an adhesive paste) twice daily for 1–2 months, and then administered as required (14). Intralesional steroid injections are worth considering when lesions are particularly painful and fail to respond to topical therapy (14, 138, 139). Systemic corticosteroids are reserved for patients with severe erosive mucosal LP (recalcitrant, multi-site, ulcers) and to more rapidly induce a remission (14). Further systemic first-line treatments are retinoids (acitretin/isotretinoin) and cyclosporine (14). Second-line treatments include sulphasalasine, azathioprine, hydroxychloroquine, methotrexate, mycophenolate mofetil, and/or use of topical calcineurin inhibitors (14, 133, 140–147). Third-line treatment may include cyclophosphamide, thalidomide, metronidazole, trimethoprim–sulphomethoxazole,

antibiotic treatment, itraconazole, griseofulvin, dapsone and extracorporeal photochemotherapy (ECP) (14, 148–156).

In the management of **oral LP**, lidocain solution as mouthwash may be helpful to reduce pain. Amphotericin B solution as mouthwash several times daily (after food consumption) may prevent secondary candida infection. Patch tests may be recommended for patients with oral lichen planus affecting the gums and who have fillings with amalgam, to assess for contact allergy to thiomersal, a mercurial compound (14). Mucosal LP may clear spontaneously within 5 years, but typically it is a chronic disease with a remitting and relapsing course (22, 23).

The general principles of the management of **genital LP** are similar to those of LP confined to the oral mucosa (14). Most cases of papulosquamous genital LP are self-limited, and treatment with emollients and mid-potency steroids for a few weeks leads to complete remission. First-line treatment for erosive LP of the vulval or penile mucosa are superpotent topical corticosteroids (14, 157), which can be gradually tapered (14). Calcineurin inhibitors (tacrolimus/pimecrolimus) are a further topical treatment option (14). The aim for the treatment of erosive genital lesions is the prevention or limitation of scarring. In women, synechia formation with vaginal stenosis may be prevented by the use of vaginal dilators and application of intra-vaginal steroids to treat mucosal inflammation (14). In uncircumcised men, circumcision is usually recommended to avoid phimosis (14). Local anesthetic gel, low-dose tricyclic antidepressants or anticonvulsants may relieve itch and ease discomfort and nystatin cream can prevent secondary fungal infections (14).

Lichen Planopilaris

The aim of the treatment is disease control to prevent permanent hair loss due to scarring (14). Furthermore, treatment can reduce itching and burning of the scalp. Topical steroids are treatment of first choice (97, 158–160). Intralesional steroid injections may improve response rates (161). Topical calcineurin inhibitors may be used as monotherapy or as an adjuvant to systemic therapy proved effective (162). Systemic steroids are the mainstay of treatment for rapidly progressive disease to prevent scarring (163), while introducing cyclosporine, methotrexate, or hydroxychloroquine as steroid sparing agents (160, 164–168). Suggested second-line options are retinoids (acitretin/isotretinoin), tetracycline/doxycycline, mycophenolate mofetil, adalimumab, pioglitazone, thalidomide, or rituximab (160, 162, 165, 167, 169–175).

Nail Lichen Planus

LP of the nails is generally difficult to treat and the prognosis is poor (14). LP affecting the nails frequently leads to permanent destruction of the nail matrix and bed with functional limitations. Therefore, early treatment is essential, even in mild cases of nail LP (176). Potent topical steroids under occlusive dressings are the preferred, first-line topical treatment (14). Due to the poor short-term efficacy of topical steroids and long-term side effects, triamcinolone acetonide injections (intralesional) should be considered as further first-line therapies (176, 177). Oral prednisone 0.5 mg/kg for 3 weeks demonstrated a marked improvement and is useful when multiple nails are affected (14). Oral retinoids are second-line choices (178–180), and immunosuppressive agents may also be considered (14, 181, 182). In a case series, topical tacrolimus ointment 0.1% was successfully used in treatment of nail LP (183).

Lichenoid Graft-vs.-Host-Disease

Corticosteroids are the backbone the treatment of cutaneous lichenoid GVHD, but ∼30% need additional immunosuppressant such as cyclosporine. cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, pentostatin, or high-dose thalidomide and hydroxychloroquine (184). Another option for skin involvement might be phototherapy, while extracorporeal photochemotherapy may improve cutaneous as well as systemic involvement (184).

Lichenoid Drug Eruptions

The triggering agent should be stopped (14); improvement of the skin lesions can take weeks to months. Commonly flat pigmented freckles persist and fade more slowly. Steroids (topical/systemically) may be supportive to give relief or rapid resolution.

Emerging Treatments

In LP, new therapeutic options currently stem from case reports and/or case report series. These have set the rationale for the planning of current clinical trials in LP (**Table 4**). The molecular targets currently persued for LP can be categorized into biologics targeting cytokines and small molecules blocking intracellular signaling. In addition, photodynamic therapy has consistently been reported to have favorable outcomes in LP patients (185).

Currently licensed (for other indications than LP) biologics targeting IL-17 or the IL-17R are secukinumab, ixekizumab and brodalumab. In 2017, occurrence of oral LP was noted in a psoriasis patient treated with secukinumab. As concurrently oral candidiasis, a relatively common adverse event under anti-IL-17 treatment, was present, the causality of IL-17 inhibition and induction of oral LP remained ambiguous (186). In addition to this case, 3 more cases of cutaneous/oral lichenoid eruptions associated with IL-17 inhibition were noted, albeit (oral) LP was not formally diagnosed (187–189). By contrast, response to IL-17 inhibition has been reported in a total of 5 LP patients (96, 190, 191). Grounded on the latter observations, as well as the increased serum and tissue IL-17 expression in both oral and cutaneous LP (83, 192, 193), two clinical studies currently evaluate the impact of IL-17 inhibition using secukinumab or ixekizumab in patients with LP (NCT04300296, NCT05030415).

Biologics targeting either IL-12 and/or IL-23 (ustekinumab) or IL-23 alone (risankizumab, tildrakizumab and guselkumab) have so far not been associated with the induction of LP. However, one report noted a failure of LP to respond to ustekinumab (194). Later observations noted a response of IL-12/23 inhibition on one

TABLE 4 | Selected clinical studies in lichen planus.

Study	Lichen planus	Intervention	Target	Design	Phase	Status
NCT03697460	Cutaneous LP	INCB018424 (Ruxolitinib)	JAK1/2	Single center, exploratory, open-label, single-arm	2	Completed (2021)
NCT03656666	Genital erosive LP	Apremilast	PDE4	Double-blinded, randomized, placebo-controlled	2	Recruiting (2021)
NCT05030415	Lichen planopilaris and LP	Ixekizumab	IL17A	Open-label		Recruiting (2021)
NCT04300296	Lichen planopilaris, oral and cutaneous LP	Secukinumab	IL17A	Multicenter, randomized, double-blind, placebo-controlled	2	Active, not recruiting (2021)
NCT03417141	Lichen planopilaris	Mechlorethamin (Valchlor)	–	Open-label	2	Completed (2021)
NCT04409041	Lichen planopilaris and frontal fibrosing alopecia	Naltrexone	Opiate-receptor	Open-label	2	Completed (2021)
NCT03858634	Pruritus, CIU, LP, Lichen simplex chronicus, plaque psoriasis	Vixarelimab (KPL-716)	Oncostatin M receptor beta	Quadruple -blinded, randomized	2	Completed (2020)
NCT04976673	Oral LP	PDT	–	Double-blinded, randomized	2	Completed (2021)
NCT01282515	Female genital erosive LP	PDT	–	Single (investigator)-blinded, randomized	2/3	Completed (2021)
NCT04991012	Oral LP	PDT	–	Double-blinded, randomized	2	Completed (2021)

A search on clinicaltrials.gov was conducted on September 25th, 2021 with the key word "lichen planus". A total of 116 clinical studies were identified. We focused on studies with a molecular target. A total of 14 completed interventional studies with molecular targets were updated since 2020. In addition, 2 studies with a defined molecular target (status: not recruiting/recruiting, enrolling by invitation/active, not recruiting) were found. We also included completed (with updates since 2020) and ongoing studies using photodynamic therapy. Number in brackets in the Status column indicate the last year, the study was updated in clincaltrials.gov. CIU, Chronic idiopathic urticarial; LP, Lichen planus; PDT, Photodynamic therapy.

patient with LP pemphigoides (195), and three patients with LP (96, 196). Use of IL-12/23 was grounded on the observation of increased IL-23 expression in oral LP (84), as well as an increased serum concentration of IL-23 in LP patients (197). Of note, we are not aware of any study addressing the impact of IL-12/23 inhibition in LP.

By contrast to IL-17 and IL-23, blockade of TNF-α has not emerged as a promising therapeutic target in LP. There are several reports on lichenoid drug eruptions following TNF-α inhibition (198, 199), and only one report on a successful treatment of lichen planus with the anti-TNF-α antibody adalimumab (135). On the expression level, increased TNF-α expression has been noted in the skin and serum of LP patients (60, 90). In line, a study evaluating the impact of the TNF-α inhibitor etanercept of LP was terminated due to slow recruitment in 2018 (NCT00285779).

Recent work showed that the inflammation in LP is dominated by an IFN-γ and an IL-21 signature, along with an increased expression of phospho-STAT1 in the dermal infiltrate (200). In another T-cell mediated inflammatory skin disease, namely alopecia areata, the identification of an IFN gene signature in affected skin identified JAK inhibitors as potential new treatments for alopecia areata, which showed efficacy in phase 2 clinical trials (201, 202). Based on these morphological observations and considerations, the authors concluded that use of JAK inhibitors may be beneficial in LP (200). Successful treatment of a treatment-refractory LP patient with the JAK1/3-selective JAKi tofacitinib supports this notion. Furthermore, in 2 independent case series, tofacitinib used as either monotherapy or adjunctive therapy led to clinical improvement in 11/13 patients (95, 96). In line with these observations, a clinical trial currently investigated the impact of topical ruxolitinib in LP patients. The trial was completed in 2020. Results are shown at clinicaltrial.gov: 12 patients were enrolled, 3 were lost to follow-up, most likely related to the Covid-19 pandemic, and no serious adverse events occurred (NCT03697460).

Grounded on the broad anti-inflammatory activity of the PDE4 inhibitor apremilast, the safety and efficacy of the drug in LP patient's refractory to topical corticosteroid treatment was evaluated in an investigator-initiated, single-center, non-randomized, open-label, pilot study in 2013. Patients were treated with 2 × 20 mg apremilast per day for 12 weeks. The primary endpoint was achieving a 2-grade or more in Physician Global Assessment (PGA) at 12 weeks. While all patients demonstrated a significant clinical improvement, 3/10 met the primary endpoint (137). Subsequently, a total of 5 LP patients, mostly with treatment-refractory disease, were reported to improve when treated with apremilast (203–205). Based on these reports, apremilast is currently evaluated in a randomized placebo-controlled clinical trial in women with genital erosive lichen planus (206). Currently, patients are recruited to this study (NCT03656666).

Other clinical trials are evaluating the impact of topical mechlorethamine, a topical chemotherapy used for the treatment of cutaneous T cell lymphoma (207), in LP. The study was

completed in 2019, but so far results have not been published (NCT03417141). A study treating LP patients with the opiate opioid receptor antagonist naltrexone was recently completed (NCT04409041). Again, results are pending to be published. In this line, a small case series reported on the beneficial outcome of naltrexone in LPP (208).

Most of non-pharmacological interventions for LP that are currently evaluated in clinical trails focus on the use of photodynamic therapy (PDT) (NCT04976673, NCT01282515). Both studies are completed, while the results have not been published so far. Up to date, a total of 5 controlled studies has addressed the impact of PDT in oral LP (209–213). In most studies, topical steroids were used as an active comparator. In 3/5 studies, no difference between the 2 treatment modalities (that both led to a reduced severity of LP) was observed (209, 211, 212), whilst in 2/5 studies, a superior effect of PDT was noted (211, 213). In an open study using PDT in oral LP, a significant change of molecular disease markers (reduced numbers of CD4+ and CD8+ T-cells in the lesions, reduced numbers of activated T cells in the circulation) were observed in parallel to the clinical improvement (214).

In addition, a recent retrospective investigation and review of the impact of narrowband UVB phototherapy and psoralen plus UVA (PUVA) photochemotherapy as second-line treatment of LP showed a relatively good response (complete responses in a little over 70% for both narrow-bad UVB and PUVA), whereby adverse events were only observed in patients treated with oral PUVA (215).

Previous reports also indicated a good response of recalcitrant LP to extracorporeal photochemotherapy (ECP) (155, 216, 217). In a larger case series, 9/12 patients showed complete remission and 3/12 a partial response. In follow-up, relapse occurred frequently when ECP sessions were less frequent or stopped (216). Since 2010, no more reports on the use of ECP in LP were published. Hence, ECP may be used in LP cases refractory of several previous therapies, and additional treatments should be administrated to maintain the (presumed) initial good response to ECP.

OUTLOOK

Overall, LP is an under-recognized dermatosis, whose epidemiology and pathogenesis is only partially understood, the disease is associated with significant morbidity, and current treatment options are limited in their success. Given the lack of double-blind randomized control trials, treatment is often based on clinical experience and the results of retrospective meta-analyses (121, 218). Biological treatments (93) and JAKi (96) hold significant promise as future therapeutic options. The lack of animal models underscores the importance of a comprehensive understanding of the pathogenesis of LP elucidating human phenotype-genotype correlations facilitating renewed efforts to unravel the cellular and molecular changes underlying the disease (219). Still, with the emergence of biological treatment options and of JAKi that both derived from careful clinical observations, the treatment landscape of LP will hopefully improve in the near future.

AUTHOR CONTRIBUTIONS

KBo, EL, KK, RL, and KBi wrote the manuscript. All authors read, commented, and approved the final version of the manuscript.

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The Global, Regional, and National Burden of Psoriasis: Results and Insights From the Global Burden of Disease 2019 Study

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Background: Psoriasis is a common, chronic, inflammatory, debilitating, systemic disease with a great impact on healthcare systems worldwide. As targeted therapies have transformed the therapeutic landscape, updated estimates of the Global Burden of Disease (GBD) imposed by psoriasis are necessary in order to evaluate the effects of past health care policies and to orient and inform new national and international healthcare strategies.

Methods: Data were extracted from the GBD 2019 study, which collates a systematic review of relevant scientific literature, national surveys, claims data, and primary care sources on the prevalence of psoriasis. Prevalence data were combined with disability weight (DW) to yield years lived with disability (YLDs). Measures of burden at global, regional, and national levels were generated for incidence, prevalence, and YLDs, due to psoriatic disease. All measures were reported as absolute numbers, percentages, and crude and age-adjusted rates per 100,000 persons. In addition, psoriasis burden was assessed by socio-demographic index (SDI).

Findings: According to the GBD 2019 methodology, there were 4,622,594 (95% uncertainty interval or UI 4,458,904–4,780,771) incident cases of psoriasis worldwide in 2019. The age-standardized incidence rate in 2019 was 57.8 (95% UI 55.8–59.7) per 100,000 people. With respect to 1990, this corresponded to a decrease of 20.0% (95% UI −20.2 to −19.8). By sex, the age-standardized incidence rate was similar between men [57.8 (95% UI 55.8–59.8) per 100,000 people] and women [(57.8 (95% UI 55.8–59.7) per 100,000 people]. With respect to 1990, this corresponded to a decrease by 19.5% (95% UI −19.8 to −19.2) and by 20.4% (95% UI −20.7 to −20.2) for men and

women, respectively. The age-standardized incidence rate per 100,000 persons was found to vary widely across geographic locations. Regionally, high-income countries and territories had the highest age-standardized incidence rate of psoriasis [112.6 (95% UI 108.9–116.1)], followed by high-middle SDI countries [69.4 (95% UI 67.1–71.9)], while low SDI countries reported the lowest rate [38.1 (95% UI 36.8–39.5)]. Similar trends were detected for prevalence and YLDs.

Conclusion: In general, psoriasis burden is greatest in the age group of 60–69 years, with a relatively similar burden among men and women. The burden is disproportionately greater in high-income and high SDI index countries of North America and Europe. With advances in psoriasis therapeutics, objective evaluation of psoriasis disease burden is critical to track the progress at the population level.

Keywords: psoriasis, prevalence, incidence, years lived with disability (YLDs), epidemiology, global health

INTRODUCTION

Psoriatic disease is a complex, chronic, systemic, immune-mediated disease that represents a wide clinical spectrum ranging from cutaneous psoriasis to psoriatic arthritis, including dactylitis, enthesitis, psoriatic axial spondyloarthritis, and psoriatic onychopathy (1–4).

Epidemiological data on psoriatic disease are uncertain, with estimates of psoriasis prevalence ranging from 0.91 to 8.5% in adults and 0.0 to 2.1% in children (5). The global psoriasis prevalence rate is around 2–3% of the world population (6), reaching 8–11% in some Northern European countries (7). Remarkably, concerning the full spectrum of psoriatic disease, several observational studies pointed out that the proportion of undiagnosed psoriatic arthritis ranges from 10.9 to 29.0% in patients with psoriasis from European countries (8, 9), thereby suggesting that the real burden generated by psoriasis is significantly underestimated/under-reported. All the different manifestations of psoriatic disease share a similar pathogenetic, immunological (10, 11), and metabolic signature (12). Due to systemic inflammation, the psoriatic disease is often associated with other comorbidities that negatively impact social and private life, resulting in overall poor quality of life (13–15).

Furthermore, the increase in life expectancy, as well as the advent of targeted therapies and the improvement of healthcare services, could have increased the burden of the disease. Moreover, the dramatic demographic changes that occurred over the last four decades, including population growth and aging, could have impacted the burden of psoriatic disease as well; therefore, reliable, statistically robust, and updated estimates of psoriatic disease burden are necessary in order to evaluate the impact of past healthcare policies and, at the same time, to orient and inform new healthcare strategies in a data-driven, evidence-based fashion. Since the resolution by the World Health Assembly (WHA 67.9 2014), which aims to improve the healthcare and inclusion of people living with psoriasis, the Global Burden of Disease (GBD) initiative has increased its attention to the global epidemiology of the burden imposed by psoriasis, and the present study attempts to quantify it.

METHODS

Overview of the Methodology

This study is part of the GBD 2019 (16), which, to the best of our knowledge, is the most comprehensive, methodologically robust report to date, which systematically estimates the spatial levels and temporal trends of the global burden caused by 369 diseases and injuries, as well as by 87 risk factors, in the period from 1990 to 2019. Seven super-regions, 21 regions, and 204 countries and territories were involved in the GBD 2019. The GBD 2019 adopts a 4-level hierarchical framework to classify and list causes as aggregate groupings. While level 1 causes include non-communicable disorders, injuries, and a category combining infectious, maternal, neonatal, and nutritional diseases/impairments, level 2 lists 22 diseases and injuries such as respiratory infections, cardiovascular disorders, and transport injuries. Level 3 and level 4 causes include specific causes, which differ based on the amount of details provided. For instance, psoriasis is a level 3 cause. Detailed GBD methodology is published elsewhere (16, 17).

Briefly, data on the disease burden attributable to psoriasis were extracted through a result tool on the website of the Institute for Health Metrics and Evaluation (IHME), University of Washington, Seattle, Washington, USA [http://ghdx.healthdata.org/gbd-results-tool]. The original data sources used for the estimations of the burden imposed by psoriasis can be found on the GBD 2019 Data Input Sources Tool website [http://ghdx.healthdata.org/gbd-2019/data-input-sources].
Since no identifiable data were used in the GBD 2019, a waiver of informed consent was in-depth reviewed and approved by the University of Washington Institutional Review Board (IRB).

Definition

A brief overview specific to the psoriasis estimation strategy is presented in this study. Psoriasis was defined as an autoimmune disorder clinically characterized by areas of raised, red skin with silvery scales, which may be itchy. The pathogenesis and the precise mechanisms underlying the disease are complex and multi-factorial and yet to be fully elucidated. They include the immune-mediated activation of inflammatory pathways and

cascades, resulting in the abnormal growth and behavior of certain types of skin cells. The case definition of psoriasis is based on the International Classification of Diseases (ICD)-10 codes, L40 and L41.

Data Sources

The GBD 2019 has pooled together several input data obtained from four main sources, which include: (i) available scholarly literature; (ii) various large, nation-wide epidemiological surveys; (iii) claims data obtained from the United States, Taiwan, Poland, and Russia; and (iv) outpatient/primary care data from Norway.

Concerning the former data source, in the GBD 2010 study, a systematic review of the literature using an *ad hoc* devised search strategy had been carried out by the authors and collaborators of GBD 2010, using two major scholarly electronic databases (namely, PubMed/MEDLINE and Google Scholar) to retrieve and collect all relevant epidemiological data related to psoriasis (18, 19). This search was re-run and updated in the subsequent GBD 2013 and 2016 studies to capture all eligible studies published in the *interim* period (from 2012 to 2014 and from 2014 to 2016) (20, 21). Investigations were retained and included if (i) incidence or prevalence data of psoriasis were provided; (ii) samples representative of the general population (for instance, in order to avoid selection biases, subjects enrolled into experimental arms of randomized clinical trials or recruited in dermatological clinics were not considered) were utilized; (iii) large samples (i.e., sample size >100 participants) were utilized; and (iv) judged of high-quality in terms of methodology and study design.

Several epidemiological surveys were included: (i) the Medical Expenditure Panel Survey (MEPS) conducted in the United States between 2000 and 2009; (ii) the Australian National Health Survey (ANHS) carried out in several subsequent waves (from 1995 to 1996, in 2001, from 2004 to 2005, and from 2007 to 2008); and (iii) the USA National Health Nutrition Examination Survey (NHANES) conducted in 2002 and 2005.

Claims data obtained from the United States (until 2015–2016) and Taiwan, as well as from Poland (2015–2017) and Russia (2010–2017) were utilized, linking claims for multiple inpatients and/or outpatient encounters to single individuals. These were extracted as prevalent cases if having one or more inpatient/outpatient diagnosis encounters with a psoriasis-related ICD code. The Norwegian outpatient/primary care database had diagnoses linked to individuals, which were as such extracted as prevalent cases.

In summary, 8 sources were utilized for calculating psoriasis incidence (from four contributing countries) and 123 sources for computing psoriasis prevalence (from 31 contributing countries), whereas 15 additional sources (from one contributing country) were used for quantitatively assessing the proportion of psoriasis cases and computing the prevalence rate. Overall, 132 unique data sources were employed in the present investigation (from 31 contributing countries). The detailed data sources used to estimate and compute the burden of psoriasis in the different countries can be found by accessing the GBD 2019 Data Input Sources Tool at the following link: http://ghdx.healthdata.org/gbd-2019/data-input-sources5.

Data Inclusion and Exclusion

According to the GBD methodology, outpatient data from healthcare settings based in the USA and Sweden were potentially eligible. However, after a thorough assessment, they could not be retained in the present investigation due to violations of well-consolidated regional patterns and age-related distribution trends. These violations could not be observed for other data sources from other countries as well, such as Norway.

Retained data were subsequently re-evaluated in terms of the presence of outliers (i.e., high values in young age groups), the inclusion of which would have resulted in a poor model fit or significant distortion/over-estimation of sub-national pseudo-random effects. Moreover, data found to be incoherent when compared to regional, super-regional, and global rate trends were excluded. None of the latter violations could be detected when data quality assessment was performed.

Statistical Analysis

Several health metrics indicators were computed, including prevalence, incidence, and disability-related estimates. More in detail, incidence and prevalence data related to diagnoses ascertained as psoriasis cases and extracted from the previously described data sources (administrative databases, physical examination-based studies) were used as input and entered into Disease Modeling—Meta-regression (DisMod-MR) 2.1, a Bayesian meta-regression tool, to estimate epidemiological metrics by age [23 age groups: (i) early neonatal, (ii) late neonatal, (iii) post-neonatal, (iv) 1–4, (v) 5–9, (vi) 10–14, (vii) 15–19, (viii) 20–24, (ix) 25–29, (x) 30–34, (xi) 35–39, (xii) 40–44, (xiii) 45–49, (xiv) 50–54, (xv) 55–59, (xvi) 60–64, (xvii) 65–69, (xviii) 70–74, (xix) 75–79, (xx) 8–84, (xxi) 8–89, (xxii) 90–94, and (xxiii) 95+ years], sex (male, female, and male/female combined), year (from 1990 to 2019), and geography (in terms of super-regions, regions, countries, and territories).

Instead of DisMod-MR, another biostatistical approach termed as Meta-Regression—Bayesian Regularised Trimmed (MR-BRT) was utilized to process the USA Marketscan data, along with rheumatoid arthritis diagnosis extracted from administrative data, adjusting them toward the level of other prevalence datapoints, which were deemed to be more representative of the general population. Data related to rheumatoid arthritis were also extracted since the differential diagnosis of psoriatic disease includes rheumatoid arthritis.

Concerning modeling strategy, psoriasis remission and duration ranges were set at 0.05–0.15, and 6.6–20 years, respectively, based on the current knowledge of psoriasis-related epidemiology, the consensus of expert opinions, the existing scientific literature, and previously published GBD studies. Excess mortality due to psoriasis was measured in years of life lost and assumed to be zero. Data collated and compiled generated a database large enough to ensure the possibility of utilizing relatively short time spans (10-year windows) to compute the goodness-of-fit of the datapoints.

Study-level covariates (including the main features of the populations under study, such as age or gender) were utilized in order to mark data extracted from self-report, outpatient/primary care, and claims data. From the MR-BRT

cross-walk adjustment analysis, setting the gamma parameter at 0.63, the beta coefficient (logit) for studies without physical examination was computed at −0.12 (ranging from −1.36 to 1.12), for studies utilizing the USA Marketscan 2000 data at −1.23 (ranging from −2.50 to −0.01), for studies employing the USA Marketscan 2010–2016 data at −0.82 (−2.06 to 0.43), and for studies with rheumatoid arthritis (RA) diagnosis obtained from administrative data at −0.87 (ranging from −2.12 to 0.37). The corresponding related adjustment factors yielded 0.47, 0.22, 0.31, and 0.29, respectively.

Socio-demographic index (SDI) and the absolute value of average latitude served as location-level (country-level) covariates to inform the estimation of the variables for countries and territories with the dearth of data. Exponentiated beta values (which can be understood as odds ratios, ORs) were computed at 0.19 (ranging from 0.17 to 0.20) and 1.01 (ranging from 1.01 to 1.01) for SDI and the absolute value of average latitude, respectively.

Prevalence estimates were multiplied by a multiplier known as disability weight (DW), computed from population-wide epidemiological surveys and an open-access web-based study, to yield years lived with disability (YLDs) and disability-adjusted life years (DALYs). The latter indicator combines in one measure the time lived with disability and the time lost due to premature mortality. A severity split analysis with DWs was conducted, according to the type and extent of *sequelae* (assessed as functional consequences and symptoms of the disease stage) (22). In other words, as done in previous GBD studies, different DWs for psoriasis were assigned based on its degree of disfigurement with itch/pain (levels of severity 1, 2, and 3) (23).

In the case of mild psoriasis, the subject reports a slight, even though visible physical deformity, which can be sore and/or itchy, besides causing psychological discomfort and worries. In this case, DW is 0.027 (ranging from 0.015 to 0.042). In the case of severe psoriasis, the individual has an obvious, very painful, itchy physical deformity, which causes psychological discomfort, worries, poor sleep quality, avoidance of social contacts, and suicidal thoughts. In this case, DW is 0.576 (ranging from 0.401 to 0.731). The intermediate case of moderate psoriasis is characterized by impaired sleep and concentration issues. In this case, DW is 0.188 (ranging from 0.124 to 0.267).

Measures of burden at the global, regional, and national levels were generated and estimated, both for epidemiological (incidence and prevalence) and disability (YLDs and DALYs) indicators due to psoriatic disease. All measures were reported as absolute (counts) and relative (percentages) numbers, both as crude and age-adjusted rates per 100,000 persons, where the procedure of age-standardization was applied based on the WHO world population age structure. All estimates were reported with their 95% uncertainty intervals (95% UI). These intervals were estimated by taking 1,000 samples from the posterior distribution of each quantity and using the 25th- and 97.5th-ordered draws of the uncertainty distribution. UIs are different from "classical" CIs, in enabling to capture and model uncertainty from multiple steps (such as model estimating, and parameter specifying steps), incorporating several, and also highly heterogeneous data sources. This is a considerable methodological advancement that ensures estimate robustness and reliability, with respect to "conventional" techniques that rely on sampling error alone.

Epidemiological and disability indicator estimates are also presented stratified according to the location/country level. Within the GBD methodological framework, countries are classified based on an objective measurement of their developmental status, namely, the SDI. This is a composite metric, which combines and summarizes various variables, including average income, educational attainment, and total fertility rate (TFR) under 25 years of age. Based on this computation, SDI is calculated and assigned to each country (24). SDI is scaled from zero, which represents the lowest income, educational attainment, and the highest TFR possible, to one, which, on the contrary, represents the highest income, educational achievement, and the lowest TFR possible. The relationship between epidemiological and disability rates and SDI status (categorized as high, high-middle, middle, low-middle, and low SDI countries) was conducted and is presented here.

Our present study reports findings in compliance with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement (25).

RESULTS

Incidence of Psoriasis in 2019 and Its Spatio-Temporal Trend

Worldwide, there were 4,622,594 (95% UI 4,458,904–4,780,771) incident cases of psoriasis in 2019. The age-standardized incidence rate in 2019 was 57.8 (95% UI 55.8–59.7) per 100,000 people. With respect to 1990, this corresponded to a decrease by 20.0% (95% UI −20.2 to −19.8). By sex, the age-standardized incidence rate was similar between men [57.8 (95% UI 55.8–59.8) per 100,000 people] and females [57.8 (95% UI 55.8–59.7) per 100,000 people]. With respect to 1990, this corresponded to a decrease by 19.5% (95% UI −19.8 to −19.2) and 20.4% (95% UI −20.7 to −20.2), respectively. **Figure 1** and **Table 1** show the age-specific numbers and rates of incident psoriasis cases at the global level and stratified by sex and GBD region in 2019. As it can be seen, the age-standardized incidence rate per 100,000 persons was found to vary widely across geographic locations. Regionally, high-income countries and territories had the highest age-standardized incidence rate of psoriasis [112.6 (95% UI 108.9–116.1)], followed by high-middle SDI countries [69.4 (95% UI 67.1–71.9)], while low SDI countries reported the lowest rate [38.1 (95% UI 36.8–39.5)]. Low-middle SDI countries [(45.1 (95% UI 43.4–46.6)] and middle-SDI countries [41.7 (95% UI 40.2–43.1)] reported a similar burden. Middle SDI countries documented the highest change in the age-standardized incidence rate in 2019 with respect to 1990, with a decrease by 21.8% (95% UI −22.1 to −21.4), whereas high SDI countries reported the lowest change with a decrease by 10.2% (95% UI −10.6 to −9.7). In terms of GBD regions, the age-standardized incidence rate was highest in Western Europe [204.5 (95% UI 197.6–211.4)], followed by Australasia [145.4

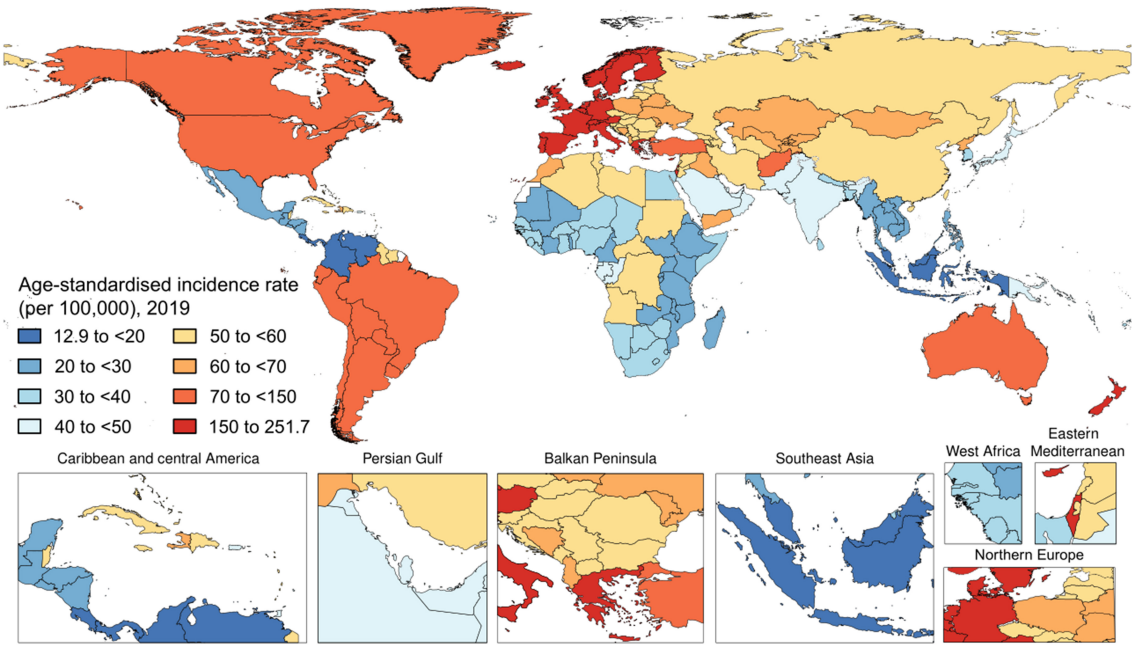

FIGURE 1 | The national age-standardized incidence rate of psoriasis (per 100,000) in 2019.

(95% UI 139.6–151.4)] and high-income North America [92.7 (95% UI 89.7–95.5)], whereas it was lowest in Southeast Asia [20.1 (95% UI 19.3–20.8)], followed by central Latin America [20.7 (95% UI 19.9–21.5)] and Eastern Sub-Saharan Africa [25.1 (95% UI 24.2–26.1)]. The GBD region which reported the highest decrease in the age-standardized incidence rate was North Africa and the Middle East, with a decrease by 23.1% (95% UI −23.7 to −22.5) in 2019 with respect to 1990. The lowest change was documented in the high-income Asia Pacific, with a decrease of 3.4% (95% UI −4.0 to −2.7). At the national level, the country with the highest rate was France [251.7 (95% UI 242.5–261.0)], whereas the lowest rate was reported in Indonesia [12.9 (95% UI 12.4–13.4)]. For further details, the reader can refer to **Supplementary Table 1**.

Prevalence of Psoriasis in 2019 and Its Spatio-Temporal Trend

Worldwide, there were 40,805,386 (95% UI 39,421,384–42,076,746) prevalent cases of psoriasis in 2019 (**Figure 2**). The age-standardized prevalence rate in 2019 was 503.6 (95% UI 486.9–519.2) per 100,000 people. With respect to 1990, this corresponded to a decrease of 23.7% (95% UI −24.0 to −23.5). By sex, the age-standardized prevalence rate was similar between men [510.7 (95% UI 493.4–526.4) per 100,000 people] and women [497.5 (95% UI 481.1–513.1) per 100,000 people]. With respect to 1990, this corresponded to a decrease by 22.9% (95% UI −23.3 to −22.6) and by 24.4% (95% UI −24.6 to −24.1), respectively. **Table 1** shows the age-specific numbers and rates of prevalent psoriasis cases at the global level and stratified by sex and GBD region in 2019. As it can be seen, the age-standardized prevalence rate per 100,000 persons was found to vary widely across geographic locations. Regionally, high-income countries and territories had the highest age-standardized prevalence rate of psoriasis [1,072.7 (95% UI 1,038.7–1,106.0)], followed by high-middle SDI countries [589.9 (95% UI 569.2–608.5)], while low SDI countries reported the lowest rate [300.8 (95% UI 290.5–311.1)]. Low-middle SDI countries [352.1 (95% UI 340.3–363.7)] and middle SDI countries [338.6 (95% UI 327.5–348.9)] reported a similar epidemiological burden. The most important temporal changes occurred in high-middle SDI countries [−21.1% (95% UI −21.4 to −20.7)] and middle SDI countries [−20.6% (95% UI −21.0 to −20.2)], whereas the lowest change was documented in low SDI countries [−11.1% (95% UI −11.5 to −10.6)]. In terms of GBD regions, the age-standardized prevalence rate was highest in Western Europe [1,884.1 (95% UI 1,817.4–1,948.3)], followed by Australasia [95% UI 1,506.1 (1,448.9–1,560.8)] and high-income North America [1,081.6 (95% UI 1,048.9–1,115.4)], whereas they were lowest in Southeast Asia [128.8 (95% UI 124.5–133.2)], followed by central Latin America [132.0 (95% UI 127.7–136.5)] and Eastern Sub-Saharan Africa [166.8 (95% UI 160.8–172.9)]. The GBD region which reported the highest decrease in the age-standardized prevalence rate was North Africa and the Middle East with a decrease of 26.9% (95% UI −27.5 to −26.2) in 2019 with respect to 1990. The lowest change was documented in the high-income Asia Pacific, with a decrease of 4.3% (95% UI −5.0 to −3.6). At the national level, the country with the highest rate was France [2,503.8 (2,395.4 to 2,608.6)], whereas the lowest rate was reported in Indonesia [79.8 (95% UI 76.9–82.7)]. For further details, the reader can refer to **Supplementary Table 2**.

TABLE 1 | Incidence, prevalence, and YLDs of psoriasis in 2019 and percentage change of age-standardized rates, by sex and GBD region.

	Incidence			Prevalence			YLDs		
	Number	Age-standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019	Number	Age-standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019	Number	Age-standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019
Global	4,622,594 (4,458,904 to 4,780,771)	57.8 (55.8 to 59.7)	−20.0% (−20.2 to −19.8)	40,805,386 (39,421,384 to 42,076,746)	503.6 (486.9 to 519.2)	−23.7% (−24.0 to −23.5)	3,505,736 (2,504,956 to 4,638,757)	43.3 (30.9 to 57.4)	−23.6% (−24.2 to −23.0)
Sex									
Male	2,315,841 (2,232,986 to 2,395,283)	57.8 (55.8 to 59.8)	−19.5% (−19.8 to −19.2)	20,448,885 (19,749,817 to 21,083,370)	510.7 (493.4 to 526.4)	−22.9% (−23.3 to −22.6)	1,772,054 (1,261,969 to 2,355,815)	44.2 (31.5 to 58.7)	−22.8% (−23.7 to −22.0)
Female	2,306,753 (2,224,308 to 2,384,894)	57.8 (55.8 to 59.7)	−20.4% (−20.7 to −20.2)	20,356,501 (19,672,490 to 20,990,702)	497.5 (481.1 to 513.1)	−24.4% (−24.6 to −24.1)	1,733,683 (1,241,898 to 2,282,839)	42.5 (30.4 to 56.1)	−24.2% (−25.1 to −23.4)
GBD region									
Central Sub-Saharan Africa	61,984 (59,320 to 64,656)	51.6 (49.4 to 53.8)	−16.5% (−17.8 to −15.0)	445,748 (427,754 to 462,996)	412.7 (397.2 to 427.9)	−19.1% (−20.1 to −18.0)	39,139 (27,548 to 52,169)	35.6 (25.0 to 47.1)	−18.2% (−23.9 to −12.4)
Eastern Sub-Saharan Africa	89,695 (86,383 to 93,561)	25.1 (24.2 to 26.1)	−9.8% (−10.3 to −9.2)	551,213 (530,511 to 573,329)	166.8 (160.8 to 172.9)	−9.4% (−10.0 to −8.9)	48,807 (34,514 to 65,163)	14.5 (10.3 to 19.2)	−8.8% (−12.7 to −5.2)
Southern Sub-Saharan Africa	25,357 (24,396 to 26,331)	32.9 (31.7 to 34.1)	−10.6% (−11.3 to −10.0)	168,145 (162,227 to 174,017)	223.0 (215.2 to 230.2)	−10.5% (−11.0 to −9.8)	14,553 (10,384 to 19,199)	19.2 (13.7 to 25.3)	−11.0% (−15.2 to −6.6)
Western Sub-Saharan Africa	131,825 (127,072 to 137,224)	32.5 (31.3 to 33.6)	−20.2% (−20.5 to −19.8)	840,876 (810,132 to 871,926)	225.2 (217.3 to 232.9)	−23.1% (−23.5 to −22.7)	74,188 (52,193 to 98,677)	19.5 (13.9 to 25.9)	−22.7% (−24.9 to −20.7)
Andean Latin America	52,103 (49,796 to 54,275)	82.4 (78.8 to 85.8)	−13.1% (−14.3 to −11.9)	444,522 (427,695 to 461,805)	712.9 (685.9 to 739.6)	−16.3% (−17.3 to −15.2)	38,808 (27,362 to 51,290)	62.1 (44.0 to 82.0)	−16.2% (−20.2 to −11.9)
Tropical Latin America	202,572 (195,312 to 209,349)	87.1 (84.1 to 90.0)	−5.7% (−6.2 to −5.1)	1,830,253 (1,765,446 to 1,893,664)	767.2 (741.1 to 792.9)	−5.2% (−5.7 to −4.6)	157,656 (112,010 to 207,987)	66.2 (46.9 to 87.6)	−4.6% (−6.9 to −2.5)
Central Latin America	52,370 (50,378 to 54,362)	20.7 (19.9 to 21.5)	−12.2% (−12.7 to −11.7)	334,104 (322,899 to 345,848)	132.0 (127.7 to 136.5)	−12.3% (−12.8 to −11.8)	29,285 (20,556 to 39,034)	11.6 (8.1 to 15.4)	−11.9% (−15.4 to −8.3)
Southern Latin America	70,211 (67,264 to 73,298)	102.1 (97.9 to 106.3)	−7.3% (−8.8 to −5.7)	650,187 (624,126 to 674,258)	898.7 (863.3 to 933.3)	−12.9% (−14.1 to −11.7)	56,128 (39,341 to 74,462)	78.0 (54.5 to 103.2)	−12.9% (−17.3 to −8.1)
Caribbean	27,467 (26,394 to 28,614)	56.9 (54.7 to 59.2)	−7.1% (−8.1 to −6.1)	202,492 (195,171 to 209,683)	413.1 (398.4 to 427.7)	−7.5% (−8.3 to −6.6)	17,529 (12,493 to 23,481)	35.8 (25.5 to 47.9)	−7.6% (−12.2 to −2.9)
Central Europe	76,996 (74,396 to 79,469)	60.3 (58.5 to 62.2)	−15.5% (−16.3 to −14.6)	624,819 (606,034 to 641,226)	440.8 (428.2 to 452.1)	−18.1% (−19.0 to −17.2)	53,356 (38,034 to 70,323)	38.3 (27.0 to 50.8)	−17.8% (−20.2 to −15.5)
Eastern Europe	139,976 (134,745 to 144,910)	59.5 (57.6 to 61.5)	−11.3% (−11.9 to −10.6)	1,072,655 (1,036,778 to 1,105,301)	423.7 (410.5 to 436.8)	−13.0% (−13.7 to −12.2)	91,625 (64,980 to 120,358)	36.7 (25.8 to 48.4)	−12.5% (−15.0 to −10.2)

(Continued)

TABLE 1 | Continued

	Incidence			Prevalence			YLDs		
	Number	Age-Standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019	Number	Age-Standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019	Number	Age-Standardised rate (per 100 000 people)	Percentage change in age-standardised rates, 1990–2019
North Africa and Middle East	336,787 (324,072 to 349,591)	55.5 (53.5 to 57.5)	−23.1% (−23.7 to −22.5)	2,426,320 (2,342,733 to 2,509,856)	414.3 (400.3 to 427.8)	−26.9% (−27.5 to −26.2)	211,107 (149,579 to 279,840)	35.8 (25.5 to 47.3)	−26.9% (−29.0 to −24.6)
Central Asia	58,976 (56,469 to 61,360)	62.2 (59.7 to 64.7)	−16.0% (−16.9 to −15.0)	420,455 (404,188 to 436,205)	454.9 (437.6 to 471.2)	−19.9% (−20.6 to −19.2)	36,746 (25,998 to 49,012)	39.6 (27.9 to 52.8)	−19.8% (−23.2 to −16.3)
South Asia	792,848 (765,638 to 821,309)	44.4 (42.9 to 46.0)	−8.2% (−8.6 to −7.8)	5,873,201 (5,668,229 to 6,075,556)	334.5 (322.9 to 345.6)	−5.1% (−5.6 to −4.7)	507,805 (359,434 to 669,841)	28.7 (20.4 to 37.8)	−4.6% (−6.8 to −2.1)
Southeast Asia	139,036 (133,404 to 144,184)	20.1 (19.3 to 20.8)	−12.9% (−13.4 to −12.4)	887,599 (856,929 to 918,713)	128.8 (124.5 to 133.2)	−14.3% (−14.8 to −13.7)	77,728 (55,264 to 104,730)	11.2 (8.0 to 15.2)	−13.8% (−17.2 to −10.2)
East Asia	925,967 (891,325 to 958,216)	54.1 (52.2 to 55.9)	−20.8% (−21.3 to −20.4)	7,948,327 (7,669,027 to 8,215,035)	436.6 (422.0 to 450.1)	−24.7% (−25.1 to −24.2)	688,337 (490,650 to 909,286)	38.1 (27.1 to 50.2)	−24.4% (−26.0 to −22.8)
Oceania	4,694 (4,512 to 4,889)	39.2 (37.6 to 40.8)	−9.1% (−10.5 to −7.7)	31,161 (29,970 to 32,394)	278.0 (267.9 to 288.3)	−9.2% (−10.5 to −7.8)	2,711 (1,891 to 3,664)	23.8 (16.7 to 31.9)	−9.3% (−16.9 to −0.7)
High-Income Asia Pacific	83,991 (80,923 to 86,862)	40.0 (38.5 to 41.4)	−3.4% (−4.0 to −2.7)	613,404 (591,525 to 633,631)	262.2 (253.4 to 270.8)	−4.3% (−5.0 to −3.6)	52,711 (37,862 to 69,195)	23.0 (16.4 to 30.7)	−4.1% (−8.4 to 0.1)
High-Income North America	359,271 (347,584 to 370,502)	92.7 (89.7 to 95.5)	−11.8% (−12.5 to −11.0)	4,693,639 (4,553,019 to 4,837,451)	1,081.6 (1,048.9 to 1,115.4)	−14.9% (−15.8 to −14.0)	392,467 (282,948 to 516,020)	92.0 (66.2 to 121.5)	−15.3% (−16.8 to −13.7)
Western Europe	946,916 (913,064 to 979530)	204.5 (197.6 to 211.4)	−5.7% (−6.2 to −5.2)	10,236,919 (9,862,029 to 10,589,120)	1,884.1 (1,817.4 to 1,948.3)	−9.4% (−10.0 to −8.9)	871,673 (623,279 to 1,153,354)	163.1 (115.8 to 216.7)	−9.4% (−10.7 to −8.1)
Australasia	43,553 (41,826 to 45,339)	145.4 (139.6 to 151.4)	−7.9% (−9.5 to −6.3)	509,347 (490,055 to 528,245)	1,506.1 (1,448.9 to 1,560.8)	−12.3% (−13.7 to −10.9)	43,378 (30,992 to 57,275)	129.9 (92.1 to 171.1)	−12.3% (−16.6 to −8.0)

Data in parentheses are 95% uncertainty intervals (UI). GBD, global burden of disease, injuries, and risk factors study; YLDs, years lived with disability.

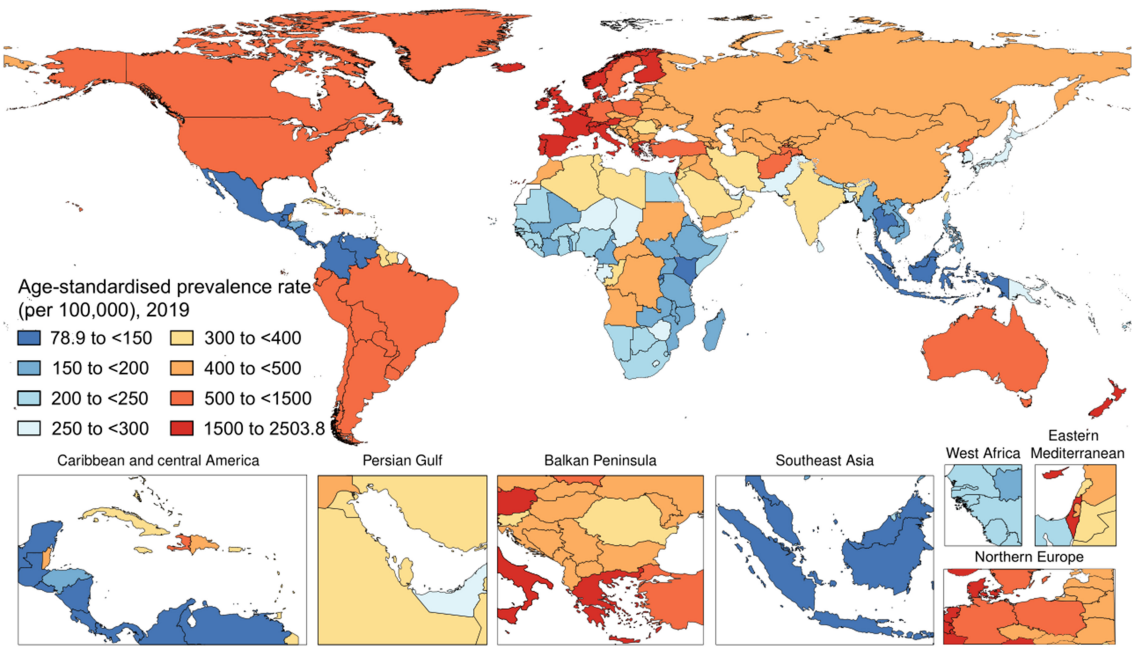

FIGURE 2 | The national age-standardized prevalence rate of psoriasis (per 100,000) in 2019.

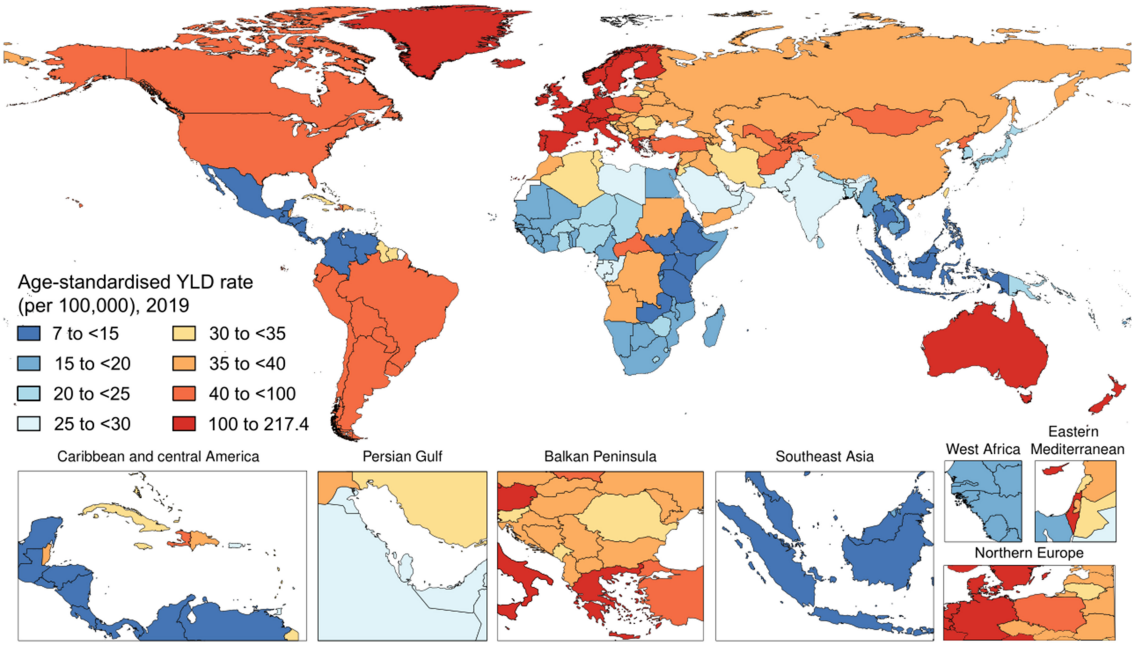

FIGURE 3 | National age-standardized years lived with disability (YLDs) rate of psoriasis (per 100,000) in 2019.

YLD of Psoriasis in 2019 and Its Spatio-Temporal Trend

Worldwide, psoriasis generated 3,505,736 (95% UI 2,504,956–4,638,757) YLD cases of psoriasis in 2019. The age-standardized YLD rate in 2019 was 43.3 (95% UI 30.9–57.4) per 100,000 people (**Figure 3**). With respect to 1990, this corresponded to a decrease by 23.6% (95% UI −24.2 to −23.0). By sex, the age-standardized YLD rate was similar between men [44.2 (95% UI 31.5–58.7) per 100,000 people] and women [42.5 (95% UI 30.4–56.1) per 100,000 people]. With respect to 1990, this corresponded to a

decrease by 22.8% (95% UI −23.7 to −22.0) and by 24.2% (95% UI −25.1 to −23.4), respectively. **Table 1** shows the age-specific numbers and rates of YLD psoriasis cases at the global level and stratified by sex and GBD region in 2019. As it can be seen, the age-standardized YLD rate per 100,000 persons was found to vary widely across geographic locations. Regionally, high-middle SDI countries [51.1 (95% UI 36.5–67.7)] and high SDI countries [92.3 (95% UI 65.6–122.2)] reported the highest age-standardized YLD rates, whereas low SDI countries [25.9 (95% UI 18.2–34.0)], low-middle SDI countries [30.3 (95% UI 21.6–40.2)], and middle SDI countries [29.4 (95% UI 20.8–38.8)] reported comparable rates for both sexes combined and also when stratifying according to gender, as pictorially shown in **Supplementary Figure 1**. The most important temporal changes occurred in high-middle SDI countries [−20.8% (95% UI −21.9 to −19.6)] and middle SDI countries [-20.5% (95% UI −21.9 to −19.1)], whereas the lowest change was documented in low SDI countries [-10.6% (95% UI −12.9 to −8.2)]. In terms of GBD regions, the age-standardized YLD rate was highest in Western Europe [163.1 (95% UI 115.8–216.7)], followed by Australasia [129.9 (95% UI 92.1–171.1)] and high-income North America [92.0 (95% UI 66.2–121.5)], whereas it was lowest in Southeast Asia [11.2 (95% UI 8.0–15.2)], followed by central Latin America [11.6 (95% UI 8.1–15.4)] and Eastern Sub-Saharan Africa [14.5 (95% UI 10.3–19.2)]. The GBD region which reported the highest decrease in the age-standardized prevalence rate was North Africa and the Middle East with a decrease of 26.9% (95% UI −29.0 to −24.6) in 2019 with respect to 1990. The lowest change was documented in the high-income Asia Pacific, with a decrease by −4.1% (95% UI −8.4 to 0.1). For further details, the reader can refer to **Supplementary Table 3**. Furthermore, the age-standardized YLD rate per 100,000 persons was found to gradually increase in the groups from 1–4 to 60–64 years, reaching its plateau in the 65–69 years group, and decreasing afterward, as pictorially shown in **Supplementary Figures 2–4**. In terms of YLDs, among level 3 causes, psoriasis was ranked as the 49th cause for both sexes combined, while it was ranked 50th and 52nd in 2010 and 2019, respectively.

DISCUSSION

The most recent iteration of the global disease burden estimation, GBD 2019, reveals that psoriasis burden is greatest in the age groups of 60–64 and 65–69 years, with relatively similar burden among males and females throughout all age groups. The high-income GBD super-region, specifically North America, Western Europe, Australasia, and Southern Latin America, shared the greatest incidence, prevalence, and DALY rates from psoriasis compared to the other world regions. Congruently, high SDI countries shared a greater psoriasis-registered burden compared to low or middle SDI countries. Our results indicate that the burden of psoriasis has varied little over the past 29 years. Though marginally all <0.5% increased, the greatest percentage change in DALY rate from 1990 to 2019 was found in North Africa and the Middle East, followed by East Asia, Southeast Asia, and high-income North America. Given the various newly identified monogenic factors such as IL36RN and AP1S3 associated with significantly increased risk for psoriasis, perhaps the higher rate of consanguinity observed in the Middle East puts this population at greater risk for the development of psoriasis (26, 27).

Broad-scale genetic susceptibilities due to ethnicities and ancestries could also account for the difference in incidence and prevalence across various populations, particularly when considering regions of similar SDI that should have equal access to necessary diagnostic and treatment modalities (28). In fact, in the highest SDI regions, the incidence of psoriatic disease and associated YLDs was more than two times higher in central Europe than in the high-income Asia Pacific.

Our study adds to and complements the existing literature. Utilizing data from the GBD 2017, AlQassimi et al. (29) found that in 2017, the age-standardized prevalence psoriasis rate globally was 811 per 100,000 population (around 0.84% of the world population, ∼64.6 million subjects). The incidence rate increased from 92 to 99 per 100,000 in 1990–2017, with the highest and the lowest rates being reported in North America and Western Europe, and in Asia and Western Pacific regions, respectively. In terms of age distribution, a peak in the incidence was noted around 55–60 years, with women being slightly more affected compared to men. Another study (30) utilized data from the GBD 2017 and came to similar conclusions. Mehrmal et al. (30) were able to find positive linear relationships between psoriasis prevalence and several comorbidities, including mental and cardiovascular disorder, stroke, metabolic impairment and diabetes, malignancies (non-Hodgkin and Hodgkin lymphoma, and non-melanoma skin cancers), and inflammatory bowel diseases, with the lowest and the highest associations being reported for stroke and non-Hodgkin lymphoma, respectively. Parisi et al. from the "Global Psoriasis Atlas" (31) deployed Bayesian inference, and the Hamiltonian Markov chain Monte Carlo method, to inform and enrich a systematic review of the literature on the global burden of psoriasis, and found that about 81% of the countries in the world lacked detailed information concerning psoriasis criteria. In adults, authors estimated an incidence rate varying from 30.3 to 321.0 per 100,000 person years in Taiwan and Italy, respectively. The prevalence of psoriasis was computed to range from 0.14% in East Asia to 1.10–1.50% in high-income southern Latin and North America, 1.83–92% in central and western Europe, and 1.99% in Australasia.

To the best of our knowledge, no study exists relying on data from the GBD 2019 study. Only two studies (32, 33) have recently reported and analyzed such data, but only partly, with one focusing only on China (32) and the other (33) investigating high-level changes in the GBD imposed by psoriasis. More in detail, utilizing an innovative decomposition-based modeling method, Xu et al. (33) have identified four major demographic and epidemiological patterns explaining the spatio-temporal heterogeneity of the global burden of psoriasis, which include (i) a substantial increase in population growth (observable in regions such as North Africa and the Middle East, Western, Eastern, and Central Sub-Saharan Africa, Andean, and Central Latin America, South Asia, and Oceania); (ii) a moderate

increase in population growth (like in Western Europe, and high-income North America, Caribbean, Tropical, and Southern Latin America, Southern Sub-Saharan Africa, Southeast Asia, and Australasia); (iii) increase in population aging (observable in the high-income Asia Pacific); and (iv) combined effect of the increase in population growth and aging (as in Central, and Eastern Europe, Central, and East Asia).

There are limitations of this study, which will be briefly discussed. Psoriasis is not solely a skin disease. Approximately 30% of psoriatic patients develop psoriatic arthritis, which can be debilitating and both physically and emotionally devastating (34). Psoriatic arthritis burden is not assessed in GBD psoriasis estimates. In addition, GBD does not address the significant and potentially deadly comorbidities associated with psoriasis, including cardiovascular disease and metabolic syndrome (34). While the DW does attempt to capture worry, trouble sleeping, difficulty in concentrating, and suicidal ideation due to disfigurement and itch/pain from skin diseases, the psychological sequelae from psoriasis may be more severe than from other skin diseases and could be disproportionate to body surface area involvement (35). GBD estimation methods are dependent on the availability of data. Prevalence data sources informing psoriasis estimation represent 7 of 7 GBD super-regions, but only a part of GBD regions and countries. Geographic differences in psoriasis burden could be at least partly due to ascertainment bias in higher SDI countries. Conversely, future estimation of psoriasis burden must address the lack of data from low SDI countries, which is related to access to healthcare, diagnostic rate, and dependence on national and regional registers.

The GBD-based estimations allow for objective data to inform multiple levels of public policy. Since 2015, GBD has sought to measure progress toward sustainable development goals, which were set forth by the United National General Assembly to ensure healthy well-being for the current and future populations at large (36). Just as importantly, many countries and regions around the world have created partnerships with GBD in order to enhance local data collection systems, strengthen subnational collaborations, and ultimately, orient national healthcare strategies.

The therapeutic landscape for psoriasis has been revolutionized by biologic therapies over the most recent decade by increasing disease-free or disease-minimal periods (37). These therapies are postulated to alter the epidemiological landscape for psoriasis burden, though this has not been captured in our study. The global psoriasis treatment market is projected to generate $10.68 billion by 2022 (38). As molecular pathways of psoriasis immunopathogenesis are elucidated, a mechanistic approach to therapy has revolutionized medicine. As of the writing of this study, the list of commercially available biologic agents for psoriasis is constantly growing, including, but not limited to, inhibitors of tumor necrosis factor (TNF), interleukin (IL)-17 receptor, IL-17, IL-12/23, IL-23, phosphodiesterase, and Janus kinases. Clinical studies to assess treatment efficacy have identified tools such as the Psoriasis Area and Severity Index (PASI), with increasing benchmark endpoints of PASI 50, PASI 75, and PASI 90 (39, 40). This individual clinical approach must be balanced with a population-level view.

Concerning the strengths of the present study on a global scale, GBD 2019 assembles the most reliable epidemiological data available to estimate disease burden and, more specifically, the burden imposed by psoriasis across countries. In addition, GBD estimation is internally consistent, eliminating biases from external estimation strategies (41). The GBD process is repeated for each data iteration as new data sources are identified, and further refinements are made to analytic approaches. The fluid, high-quality, and transparent nature of GBD has transformed the epidemiological landscape for psoriasis. With future iterations, GBD strives to estimate psoriasis comorbidities including autoimmune, cardiovascular, metabolic, cutaneous, and psychiatric conditions. As more data sources become available on the local burden of disease, more precise estimates are generated at local, national, regional, super-regional, and global levels. Overall, the burden from psoriasis remains substantial, with little change over time, despite significant therapeutic advances.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Washington Institutional Review Board (IRB). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GD, CK, DW, and GA: substantial contributions to the conception or design of the work. CK, NB, GA, and RD: substantial contributions to the acquisition and substantial contributions to analysis or interpretation of data. GD, NB, and CK: drafting the work. GD, NB, CK, DW, GA, DM, CG, RD, AG, PW, CL, L-ST, KC, and MN: revising the work critically for important intellectual content and provide approval for publication of the content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.743180/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Future of Precision Prevention for Advanced Melanoma

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Precision prevention of advanced melanoma is fast becoming a realistic prospect, with personalized, holistic risk stratification allowing patients to be directed to an appropriate level of surveillance, ranging from skin self-examinations to regular total body photography with sequential digital dermoscopic imaging. This approach aims to address both underdiagnosis (a missed or delayed melanoma diagnosis) and overdiagnosis (the diagnosis and treatment of indolent lesions that would not have caused a problem). Holistic risk stratification considers several types of melanoma risk factors: clinical phenotype, comprehensive imaging-based phenotype, familial and polygenic risks. Artificial intelligence computer-aided diagnostics combines these risk factors to produce a personalized risk score, and can also assist in assessing the digital and molecular markers of individual lesions. However, to ensure uptake and efficient use of AI systems, researchers will need to carefully consider how best to incorporate privacy and standardization requirements, and above all address consumer trust concerns.

Keywords: melanoma, prevention, artificial intelligence, genomics, risk stratification

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INTRODUCTION

Clinician-led skin examinations with dermoscopy are the mainstay of melanoma detection, with unaided ("naked-eye") examinations alone now considered insufficient (1). Dermoscopy requires some training to use effectively, but significantly improves the specificity of diagnosis (2). Increasingly, high-risk patients are managed with total body photography and sequential digital dermoscopic imaging, (3) allowing clinicians to monitor for changes in melanocytic naevi (moles) over time; this is particularly useful for patients with many atypical naevi (commonly called dysplastic naevi) (4). Clinician-led screening of high-risk patients is associated with earlier detection and a better prognosis, but imprecise diagnosis continues to have a major impact on patients and the health system (5).

Underdiagnosis, a missed or delayed melanoma diagnosis, leading to untreated or improperly treated disease, is a familiar problem to clinicians. This is particularly undesirable in melanoma, where a correct early diagnosis often allows successful treatment with a simple excision, while advanced melanoma treatment is expensive and associated with a poorer prognosis and undesirable side effects of treatment (6, 7). Medico-legal fears also incline clinicians to excise rather than monitor a suspicious lesion and patients often express a preference for an early excision (5, 8).

Overdiagnosis is a less well-known but increasingly recognized problem, defined as detecting true cancers that are so slow-growing (indolent) that they would not cause a problem in the patient's lifetime (9). Overdiagnosis is a common observation in many cancers such as thyroid cancer and breast cancer (9) and, remarkably, it is estimated that up to 58% of melanomas in Australia are overdiagnosed (10). These indolent cancers are currently indistinguishable from melanomas with invasive potential, so they are typically also excised for patient and clinician peace of mind. These potentially avoidable excisions add an extra burden to the health care system and increase a patient's risk of scarring, infection, and other adverse events (5). In addition, the diagnosis of melanoma, even *in-situ* melanoma, can incur psychological distress (11). The same techniques that enable early detection of thin but potentially invasive melanomas also appear to increase detection of indolent melanomas. It is critical that we learn to distinguish melanoma interventions that actually benefit patients long-term from those that promote overdiagnosis (12), and to differentiate between slow-growing and potentially invasive melanomas (13).

Precision prevention of advanced melanoma has been proposed to address these problems. It consists of first stratifying patients into an appropriate level of surveillance with personalized risk scores, which combine demographic, phenotypic and genetic risk factors, and then customizing their screening requirements accordingly. By using a low-intensity surveillance regimen for people identified to be at low-risk, the likelihood of overdiagnosis is decreased. Low-risk surveillance may consist of education to promote self-skin examination, thereby bringing new or changing lesions to primary care providers. In contrast, high and ultra-high risk patients (those who have multiple risk factors or have already had one or more melanomas, respectively) could potentially benefit from more intensive surveillance by clinicians using total body imaging and sequential digital dermoscopy that can detect early changes of emerging melanomas, especially in patients with multiple and/or atypical naevi, where a diagnosis without photographic documentation may be difficult. For these patients, it may also soon become possible to use a combination of molecular and digital biomarkers, collected through non-invasive or minimally-invasive techniques, to assess individual lesions for their likelihood to be a true melanoma or an aggressive melanoma.

RISK STRATIFICATION

Several types of risk can be assessed to approximate a patient's risk of developing melanoma: clinical phenotype, comprehensive imaging phenotype of sub-clinical factors ("deep image-based phenotype"), familial and polygenic risks. For best results, however, these assessments can be combined to produce a more nuanced, personalized holistic risk score (**Figure 1**). Clinical risk comprises readily-observable data such as age, sex, pigmentation traits of hair, eye and skin color, number of naevi, personal and family melanoma history. This kind of data is commonly used by clinicians in *ad-hoc* assessments of melanoma risk. However, deep image-based phenotyping, polygenic and familial genetic risk are newer approaches that are slowly being integrated in clinical use. In addition, the particular risk profile of each patient may direct clinicians to be on the lookout for particular types of melanoma, such as lentigo maligna melanoma in older patients with severe chronic UV damage, many solar lentigines and a history of basal or squamous cell carcinomas (14), or amelanotic lesions in patients with mutations in the albinism pathway (15).

Clinical Phenotype

Clinical phenotype, already used in an *ad-hoc* way by many clinicians to assess patients' melanoma risk, is an important inclusion in a holistic risk score. Age, sex, pigmentation traits of hair, eye and skin color, and number of large naevi are well-known melanoma risk markers. Non-melanoma skin cancers, as well as multi-cancer syndromes such as Li-Fraumeni syndrome (16) further add to risk estimates. Finally, prior and ongoing medical treatment, such as immunosuppressive treatment or PUVA, while relatively rare compared to other clinical phenotype markers, may also be included, although their link with basal and squamous cell carcinomas are much stronger than melanoma (17, 18).

Deep Image-Based Phenotype

Deep image-based phenotyping is the concept of creating an automated and objective assessment of phenotypic melanoma risk factors directly from total body imaging. Such measures include constitutional and facultative skin color, naevus phenotype, freckling phenotype and UV damage phenotype; these sub-clinical factors are known melanoma risk indicators (19).

It is well known that those with fairer skin tones are at higher risk of developing melanoma; however in those with darker skin tones, melanoma is often diagnosed later and has higher rates of mortality (20). While skin color is a continuous measure, it is often categorized for ease of assessment. The Fitzpatrick skin type is commonly used and is calculated based on pigmentation traits and self-report of the skin's reaction to the sun. While easy to calculate, it relies on the subjective assessment of the individual and/or healthcare provider and is a poorer proxy in those with darker skin tones (21). The individual topography angle (ITA) maps color onto a 2-dimentional space using the CIE L*a*b*, with gold standard measures achieved using a spectrophotometer or colorimeter. However, such measures can also be extracted directly from digital images, (22). eliminating the need for specialist equipment and removing subjectivity.

A high total body naevus count has long been known to be a strong melanoma risk factor. A lack of adoption of a standard protocol for counting naevi has resulted in little consistency across studies, with variations in who counts them (clinicians, researchers) and the size counted (>2 mm, >3 mm, >5 mm) (23, 24). In addition naevus counts are time-consuming and therefore studies often rely on self-report, which tends to have low agreement with experts, and can lead to misclassification of risk (25). As part of the deep image-based phenotype, automated objective naevus counts can be obtained using convolutional neural networks applied to 3D total body photography (26).

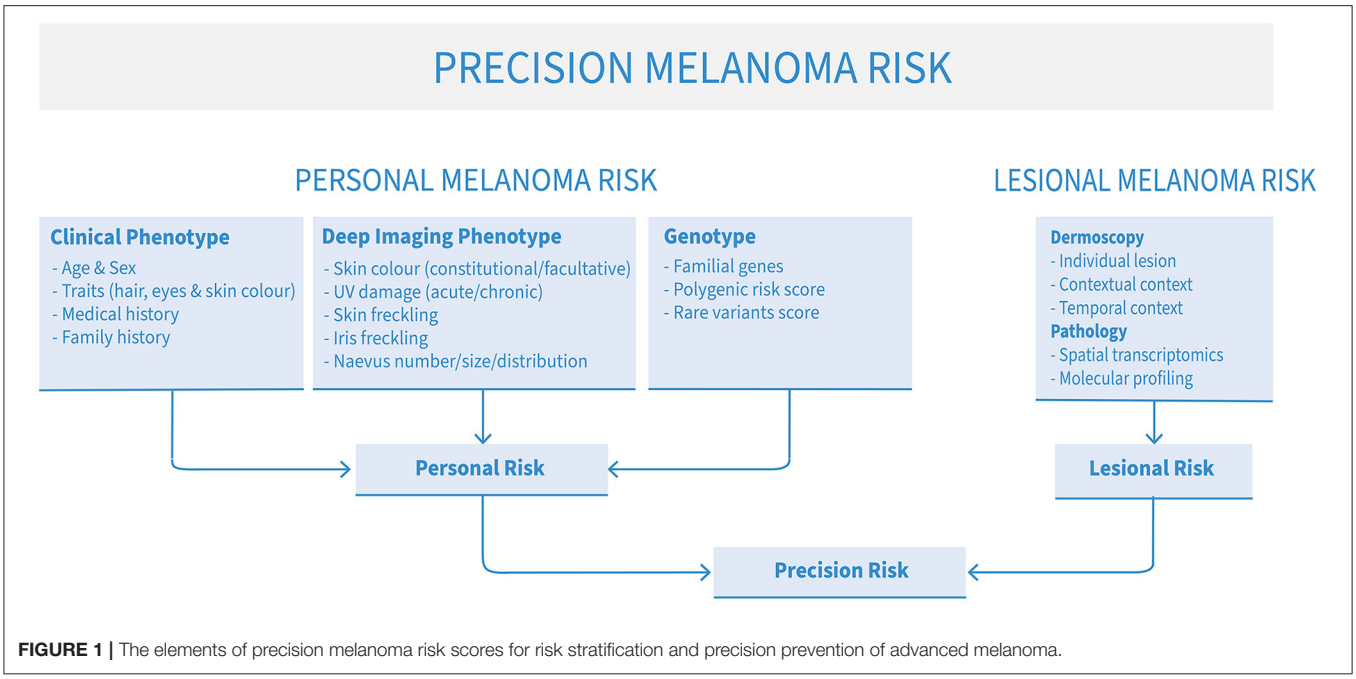

FIGURE 1 | The elements of precision melanoma risk scores for risk stratification and precision prevention of advanced melanoma.

UV exposure is the primary environmental risk factor, but quantifying an individual's chronic exposure level has been difficult, largely relying on self-report as to time in the sun and protective strategies used. We have shown that photo-numeric scales can be accurately used to grade sun damage across all body sites (27), and we are currently automating this process with convolutional neural networks. Freckling is also a well-known risk factor, (28). indicating UV exposure interacting with defects in pigmentation genes such as *MC1R*. Similar to the methods applied to assess UV damage, an automated measure of freckling density is also being developed by our group.

Familial Melanoma Genetics and Polygenic Risk Scores

Twin studies have estimated melanoma heritability to be 55% (29), and first-degree relatives of an affected individual have a two-fold increased risk of developing melanoma in their lifetime (30). Approximately 10% of melanoma is familial, but only 20% of melanoma-prone families will carry a mutation in a known melanoma gene (31). In 90% of positive cases, the mutation occurs in *CDKN2A*, with mutations being more rarely identified in *CDK4, BAP1, BRCA1, BRCA2, MITF, PTEN, TERT, POT1, POLE, TERF2IP, ACD, RB1* and *TP53*. (16, 31–34). Individuals with mutations in *CDKN2A* have a 52% average lifetime risk of developing melanoma, with an increased risk of developing multiple melanomas, and a higher probability of being diagnosed at an earlier age (35) *CDKN2A* mutation carriers' lifetime melanoma risk is further increased if they also carry common red hair color variants in *MC1R* (36). Recent systematic reviews have found that *CDKN2A* testing is associated with minimal, if any distress (37) and some positive impacts on primary and secondary preventative behaviors (38).

Though melanoma risks are significant in familial melanoma cases, they account for a relatively small portion of individuals diagnosed with melanoma annually. A meta-analysis of genome-wide association studies comparing hundreds of thousands of individuals with and without a personal history of melanoma has found 68 single nucleotide polymorphisms (SNPs) in 54 locations across the genome implicated in melanoma risk (39). Each of these SNPs is associated with an individual risk ratio or odds ratio. These weighted risks can be summed to generate a single, cumulative disease-specific polygenic risk score (PRS). These have been created for multiple cancers, cardiovascular disease and mental illnesses with the goals of population risk stratification, risk refinement in high-risk families and informing clinical management (40). Early studies in diverse disease groups show that communication of this risk information is not associated with undue psychological sequelae or adverse health behaviors (41). In keeping with familial melanoma testing, initial studies communicating melanoma PRS in the general population show no impact on psychological distress and a positive improvement in some primary preventative behaviors (42).

INDIVIDUAL LESION ASSESSMENT

Digital Markers

Since the seminal paper was published on the topic (43), Convolutional Neural Networks (CNNs) have been applied to individual dermoscopic lesion images, with research showing that automated algorithms can, in most cases, classify lesions with higher accuracy than dermatologists (44). Human-computer collaboration has been shown to further improve accuracy (45). Several commercial software offer dermoscopic lesion classification and also provide a malignancy risk score. Automated algorithms are now being extended to closer

represent the clinical environment, incorporating within-patient context by providing the algorithm multiple images per timepoint (46). It is now possible for automated algorithms to incorporate longitudinal series of dermoscopic images, with initial results indicating the algorithm is able to detect melanoma earlier than clinicians while still avoiding overdiagnosis (47). Additionally, such techniques are being applied to clinical images to identify suspicious naevi (48). Image processing methods are also being used by software such as Canfield Scientific Inc (Parsippany, NJ, USA) VAM module, which can identify individual lesions from 3D total body photography, and provide lesion metrics such as diameter, hue and asymmetry (26). Additionally, through image processing and markerless tracking technology, lesions can be tracked over time to monitor changes in color, size and shape.

Spatial Transcriptomics and Molecular Profiling

Techniques for molecular analysis of DNA and RNA have rapidly evolved in the past few years, leading to efforts to develop a refined and integrated molecular signature that could reliably detect melanoma using a minimally-invasive technique, such as a micro-biopsy or tape-stripping device (49). This aims to allow analysis of suspicious melanocytic lesions without requiring a full sized biopsy, particularly useful for patients with high numbers of atypical lesions that meet the criteria for excision. Each specimen would be analyzed for precise hallmarks of melanoma, and the lesion would only be excised if a positive signal was identified.

Current testing for *BRAF*, *NRAS*, *HRAS* and *cKIT* mutation have been recognized as useful clinical markers for advanced melanoma therapy decision-making, but the prevalence of these mutations in benign melanocytic lesions makes them impractical for early detection purposes (50). Gene expression profiling (GEP), using a panel of genes known to be differentially expressed between benign and malignant melanocytic lesions, may become a useful technique here; however commercially available GEP panels require further evaluation against standard-of-care clinicopathologic risk markers to verify that they add value over the current clinical, genetic and phenotypic risk profile (51).

With the advances of deep sequencing technologies, it is now routine to survey the whole genome and transcriptome from a fresh tissue biopsy. These powerful tools have fast tacked the discovery of drug targets for cancer treatment (52), tumor mutational load for prediction of immunotherapy outcome (53), and importantly the discovery of novel and interacting signaling pathways to greater understand cancer progression (54).

While previously these analyses were conducted on all cells present in the tissue ("bulk" sequencing analysis), single-cell technologies are now available which permit discrete molecular profiling of each cell type present in the tissue biopsy (55). These tools combined with the deep sequencing technologies have enabled precise gene expression analysis, thus allowing cell-type (or cell state, e.g., malignant) specific profiles to be discovered to empower progression biomarker discovery (56).

Spatial profiling, including spatial transcriptomics, is another emerging technology which will revolutionize our understanding of lesion heterogeneity. These technologies allow for the analysis of whole transcriptomes, spatially resolved to defined regions of interest within histopathology tissue sections, allowing a comparison of histopathologically-identifiable melanoma structures and their molecular profiles (57, 58).

These cutting-edge tools currently determine the complete molecular profile of the whole tissue from a complete excision or punch biopsy. Their integration into microbiopsy, tape-stripping or other minimally-invasive devices will be critical for delivering individual lesion molecular assessment to the clinic.

CONSIDERATIONS FOR IMPLEMENTATION

Consumer Trust in AI Computer-Aided Diagnostics

Central to the acceptance and use of technology-aided diagnostics is consumer and clinician trust. Technology-aided diagnostics and teledermoscopy services bring many benefits for consumers, such as convenience, reduced travel time, fewer unnecessary referral for benign lesions, potential costs savings, (59). and improved triage and management (60, 61), but barriers to consumer trust and uptake include privacy and confidentiality concerns, diagnostic confidence, and concerns around inadequate patient-clinician interaction (61, 62). When skin self-examination is conducted using teledermoscopy, additional barriers include technological difficulties and the challenge of conducting whole body skin self-examination. A recent study of teledermoscopy consumers revealed modest trust levels and decreased acceptance following experience with using the technology, but also a willingness to use it again in future (63).

Trust issues are likely to be exacerbated with the inclusion of artificial intelligence (AI) in diagnostics, despite its potential ability to increase diagnostic accuracy (45), due to the black-box nature of many AI algorithims, which do not explicitly show users how the algorithm came to its conclusion. A recent representative study of over 6,000 people across five western countries indicates only 37% of people are willing to trust AI-enabled health diagnostic services (64). The exact way AI technology should be used to support the early diagnosis of melanoma is also not yet clear, with some proposing that AI should triage lesions so that the workload of clinicians would be reduced, while others propose AI should provide a second opinion so that clinicians could reassess lesions where the AI diagnosis differs from their own (45, 65).

Standardization

Another barrier to technological uptake in the clinic, particularly AI uptake, is lack of standardization (66). Digital Image Communication in Medicine (DICOM) is the standard in medical imaging (67). DICOM provides a standardized way to encode and store medical images and

their associated metadata, but more importantly DICOM is an interoperability standard that facilitates the sharing of medical images and associated data both within and between organizations.

The first version of DICOM was published in 1985. It has been evolving in some medical image-producing specialities (e.g., radiology and cardiology) since then and now enjoys ubiquitous use (68). However, it was not until 2020 that the first dermatology-specific extension to the DICOM standard was published (69). Until recently, (68). dermatology imaging largely consisted of clinical images acquired on commercial, off-the-shelf cameras and smart devices. The need for standardization and the adoption of DICOM for dermatology has been driven by a number of factors including the clinical use of advanced imaging modalities (e.g., total body photography, confocal microscopy), the use of sequential dermoscopic imaging, teledermatology, and the potential of AI.

The adoption of standards for dermatology imaging can improve AI workflows by encoding derived objects (e.g., secondary images, visual explainability maps, AI algorithm output) and the efficient curation of multi-institutional datasets for machine learning training, testing, and validation (70). The use of DICOM for the management of dermatological images will not guarantee effective clinical translation of AI in dermatology but may address important technological and implementation challenges (70).

Privacy

Addressing privacy in dermatology imaging is a further very relevant implementation consideration. The use of dermatological imaging and AI in dermatology is currently impeded by lack of guidance for clinicians and researchers on the acceptable use of the images. Further, patients may not fully understand the possible privacy consequences of interacting with these technologies. There are dermatology-specific issues such as nudity in total body photography and difficulty in de-identifying data for secondary use due to the patient being visually identifiable that are not addressed in existing health privacy frameworks (68).

CONCLUSION

Precision prevention of advanced melanoma is fast becoming a realistic prospect, with remaining obstacles well-defined and under investigation by many researchers. A major challenge is promoting consumer trust in these emerging technologies, along with prioritizing privacy and standardizing image collection to allow AI algorithms to work effectively. However, if we are able to meet these challenges, risk stratification, using clinical and subclinical, deep image-based phenotype, familial and polygenic risk factors, combined with increasingly sophisticated assessment of digital and molecular markers, promises to continue to improve early melanoma detection and surveillance for those at ultra-high risk while minimizing overdiagnosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HS and KL contributed to conception of the paper. KL wrote the first draft of the manuscript. BB-S, AM-L, LC, MJ, NG, MS, TY, and HS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association Between Atopic Dermatitis, Asthma, and Serum Lipids: A UK Biobank Based Observational Study and Mendelian Randomization Analysis

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Background: Both atopic diseases and dysregulation of serum lipids (SLs) add to significant health burden, but evidences about their association are inconsistent.

Objective: This work is to evaluate the association between asthma/atopic dermatitis (AD) and SLs and investigate the potential causal relationship.

Methods: A large-scale cross-sectional study based on the UK Biobank (UKB) and then examined the casual relationships between SLs with asthma/AD based on a Mendelian randomization (MR) analysis.

Results: A total of 502,505 participants were included in analysis. After full adjustment, AD was associated with lower TG ($\beta = -0.006$; 95%CI, −0.010 to −0.002; $P = 0.006$), lower LDL ($\beta = -0.004$; 95%CI, −0.006 to −0.002, $P < 0.001$), and lower TC ($\beta = -0.004$; 95%CI, −0.005 to −0.002; $P < 0.001$) but insignificantly correlated to HDL ($P = 0.794$). Asthma was also inversely correlated to TG ($\beta = -0.005$; 95%CI, $= -0.007$ to −0.003; < 0.001), LDL ($\beta = -0.003$; 95%CI, −0.004 to −0.002; $P < 0.001$), and TC ($\beta = -0.002$; 95%CI, −0.003 to −0.002; $P < 0.001$), but was positively correlated to HDL ($\beta = 0.004$; 95%CI, 0.003 to 0.005; $P < 0.001$), respectively. In subsequent MR analysis, both allergic diseases and asthma showed a protective effect on TC. Allergic diseases, asthma, and AD all showed a negative effect on LDL.

Conclusion: Collectively, we identify a protective causal effect of allergic diseases on serum lipids, as well as a potentially positive association of HDL with asthma. Owing to the largest sample size and the application of IVs in causal inference, this study will provide a robust evidence for the management of asthma and AD and the prevention of dyslipidemia.

Keywords: asthma, atopic dermatitis, serum lipids, UK biobank, Mendelian randomization

INTRODUCTION

Atopic diseases, including atopic dermatitis (AD), asthma and allergic rhinitis remain a great challenge worldwide. Allergic diseases affect ∼10–30% population in developed countries and their global prevalence is still increasing (1, 2). Worse yet, the constant impact of atopic diseases often contributes to the onset of other comorbidities (3–5). To investigate the relationships between allergic diseases and their comorbidities are vital, since it may guide the treatment and management. Also, in some cases, observations on the atopic diseases and their comorbidities can lead to novel findings of the pathophysiology (4).

Serum lipids (SLs), including cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL), serve as an essential part of the energy supply of the whole body. On the other hand, the alteration of their concentration can lead to chronic vascular inflammation (6). Epidemiologically, unfavorable concentrations of SLs have been well clarified as a major risk factor for cardiovascular diseases (CVD), a leading cause of death worldwide. According to a previous estimation, over 50% global incidence of coronary artery disease (CAD) could be attributable to the dysregulation of SLs (7). More importantly, the association between dysregulated SLs and chronic diseases, such as psoriasis, psoriatic arthritis, diabetes, systemic lupus erythematosus, has been clarified apart from CVD (8–11). However, the association between atopic diseases and SLs remains greatly controversial. A meta-analysis of ten observational studies in 2017 suggested that the association between SLs and asthma was significant, but the effect varied from childhood to adulthood (12). On the other hand, a recent cohort study suggested that SLs might be associated with the diagnosis of asthma but not with its severity (13). More recently, an analysis of the cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) in the U.S. revealed an insignificant association between SLs and asthma in children and adolescents (14). As for AD, only a few studies reported the potential association (15, 16). More evidences are needed to validate the casual relationship between atopic diseases and SLs and the underlying mechanisms.

Considering that previous inconsistent findings may be due to the sample size, age of the participants, and their incapability for causal inference, we herein conducted a large-scale cross-sectional study based on the UK Biobank (UKB) and then examined the casual relationships between SLs with asthma and AD based on a Mendelian randomization (MR) analysis.

METHODS

Study Design and Participants

UKB is a large population-based study with over 500,000 participants, recruited during 2006 and 2010 from across England, Scotland, and Wales. The volunteers were aged between 40 and 70 at the time of recruitment, and provided data from touchscreen questionnaires, physical measurements, genotyping, and longitudinal follow-up, with further data continuing to be added (17). Because the SLs data was collected from all participants at baseline but was not repeatedly measured for most subjects during the follow-up period, we conducted a cross-sectional study rather than a longitudinal cohort study.

Measurements and Definitions

Sociodemographic information, including age, sex, ethnicity, education, smoking status, alcohol consumption, household income, was obtained *via* face-to-face interviews or self-administered touchscreen questionnaires conducted at the baseline assessment center. Body height and weight were measured by research nurses, and body mass index (BMI) was then calculated. For asthma and AD, we used a variable that incorporated both self-reported history and medical diagnosis from inpatient or primary health care records.

Blood collection procedures are described in detail elsewhere and information on assay performance can be found on the UK Biobank website (18). SLs measured included total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG). Other biomarkers including fasting blood glucose (FBG), HbA1c, testosterone, and sex hormone-binding globulin (SHBG) were included as potential confounders. For the history of taking lipid-controlling agents (LCAs), we extracted related information based on the treatment/medication quires via verbal interview. Data fields of UKB used in this study were listed in **Supplementary Table 1**.

Observational Study

We performed a cross-sectional analysis to test the association SLs of asthma/AD with SLs. First, concentrations of four SLs including TC, TG, LDL, and HDL were processed via testosterone logarithmic transformations owing to skewed distributions. Next, multivariable linear regression models were performed to estimate the associations of asthma/AD with different SLs. Based on previous studies about risks factors of SLs concentration (6, 19–21), we set the following models with adjustments for potential confounders: model 1 only included asthma and AD; model 2 further included age, sex, race, BMI, smoking status, alcohol intake, and household income in addition to model 1; and model 3 further included laboratory parameters including FBG, HbA1c, testosterone, and SHBG in addition to model 2. Since 4 parameters of SLs were involved, a P-value $< (0.05/4)$ was considered statistically significant.

Mendelian Randomization Analysis

We conducted a two-sample MR analysis based on a previous method (22). We used published summary statistic datasets from GWAS studies available on OpenGWAS database API (https://gwas.mrcieu.ac.uk/) (23), and only data from participants of European ancestry was included for the current analysis., we chose two datasets from the latest GWAS studies for TC, LDL, and HDL, and one dataset for TG. We chose one dataset for atopic diseases (including asthma, atopic dermatitis and hay fever), one for asthma, one for asthma with childhood/adulthood onset, and one for AD. Detailed information about the datasets we used is listed in **Supplementary Table 2**. Inverse-variance weighted (IVW) two-sample MR was performed using the R package "TwoSampleMR", following the guidelines provided by the developers (https://mrcieu.github.io/TwoSampleMR), and in-house developed R scripts. Single nucleotide polymorphisms

(SNPs) as instrumental variables (IVs) were carefully selected for association ($P < 5 \times 10^{-8}$) and processed for linkage disequilibrium (LD) removal ($r^2 > 0.05$) via the clump data function in this package. The IVs used in this study were listed in **Supplementary Table 3**. Moreover, to test if this association was bi-directional, a reverse MR analysis, where the exposure and outcome were exchanged, was also conducted.

RESULTS

Observational Study Based on UKB

A total of 502,505 participants were included in analysis. The sociodemographic information and related laboratory information are shown in **Table 1**. Generally, the mean age was 56.5 years, 52.7% were females, and 81.5% were Caucasian. Among the total participants, 13,822 participants were categorized as the AD group and 67,896 as the asthma group, with 3,071 participants overlapped in both groups. Most variables were significantly associated with AD/asthma ($P < 0.05$).

First, we examined the association between SLs and asthma/AD by model 1 and found that serum concentrations of TC, TG and LDL were significantly associated with asthma and AD ($P < 0.00125$) (**Table 2**). In model 3 with full adjustment, AD was associated with lower TG ($\beta = -0.006$; 95%CI, -0.010 to -0.002; $P = 0.006$), lower LDL ($\beta = -0.004$; 95%CI, -0.006 to -0.002, $P < 0.001$), and lower TC ($\beta = -0.004$; 95%CI, -0.005 to -0.002; $P < 0.001$) but insignificantly correlated to HDL ($P = 0.794$) (**Table 2**). Asthma was also inversely correlated to TG ($\beta = -0.005$; 95%CI, $= -0.007$ to -0.003; $P < 0.001$), LDL ($\beta = -0.003$; 95%CI, -0.004 to -0.002; $P < 0.001$), and TC ($\beta = -0.002$; 95%CI, -0.003 to -0.002; $P < 0.001$), but was positively correlated to HDL ($\beta = 0.004$; 95%CI, 0.003–0.005; $P < 0.001$), respectively (**Table 2**).

In sensitivity analysis, we checked whether the association was modified by the administration of LCAs or genetic background. We extracted the participants without a history of taking LCAs and those of Caucasian origin, respectively (**Table 1**). The associations SLs retained significant with minor alterations in effect size among those reporting no history of taking LCAs (**Table 2**).

Mendelian Randomization

In order to illustrate the potential causal relationship, we further conducted two-sample MR analyses. After removal of LD and harmonization, different numbers of IVs were included in the final analysis (**Figure 1**). Despite that the associations were not statistically significant in some datasets, both allergic diseases and asthma showed a protective effect on TC. In contrast, the association of TG with atopic diseases was not significant ($P > 0.05$). Allergic diseases, asthma, and AD all showed a negative effect on LDL. The effect on HDL, however, exhibited a high inconsistency among different outcomes.

To test the horizontal pleiotropy of our analysis, we conducted the MR-Egger regression of each MR pair, and the results indicated no significant pleiotropy (**Supplementary Tables 4**–**7**). Besides, to reveal whether SLs could have a causal effect of asthma/AD, the reverse MR analysis was also performed, and no significance was found (**Supplementary Tables 4**–**7**).

DISCUSSION

To our knowledge, this study was based on the largest sample size and the first MR analysis to describe the relationships between SLs and asthma/AD. We found that both asthma/AD were negatively associated with TC, TG, and LDL. Subsequent MR analysis revealed a genetical casual effect of asthma on TC and LDL.

So far, both atopic diseases and SLs dysregulation have raised public concern. Evidences about their association, however, are highly heterogenous. A meta-analysis in 2017 suggested that HDL was significantly lower in asthmatic children and LDL was significantly higher in asthmatic adults (12). But the evidences included in this meta-analysis seemed highly heterogenous. Even based on the same data resource, results can be inconsistent. For instance, Fessler et al. and Lu et al. investigated the association between SLs and asthma using data from NHANES from 2005 to 2006 and from 1999 to 2012, respectively (14, 24). The former study revealed that TC and non-HDL-C are inversely correlated to asthma. The latter, however, claimed that there was no significant association between SLs and asthma, suggesting a need for expanded study. Besides, atopic diseases usually occur early during childhood, while the dysregulation of SLs are often observed in middle aged or even later. Majority of previous studies were based on younger populations such as children or adolescence, which are not considered to be representative for dyslipidemia research. In this study, we identified a negative association between TC/LDL and asthma/AD using a mid-aged population. The result was inconsistent with the previous studies, and we suspected that this was resulted from the differences in the age of participants and sample size (12–14).

Concerning the casual relationships between SLs and atopic diseases, most evidences were from cross-sectional studies and cannot indicate a causal relationship. Due to the beneficial role of calorie-restriction on atopic diseases, more attention was paid on investigating whether SLs dysregulation can contribute to the onset of atopic diseases (12, 16, 25–27), which may leave a bias on investigating the casual relationships between SLs and atopic diseases. Therefore, we explored the causal relationships through MR analyses, which showed consistent results with the observational study, supporting the protective effect of asthma/AD on lowering TC/LDL. The reverse MR further indicated that the casual effect of asthma/AD on SLs was unidirectional, indicating a non-existence of casual effect for SLs on allergic diseases. Taken together, our findings challenged the previous concepts that atopic diseases might contribute to dyslipidemia and on the contrary, proposed that atopic diseases might be intrinsically protective for dyslipidemia.

Our study also shed light on basic research. Inspired by the findings from MR analysis, we suspected that the lowering of SLs concentration might attributed to the genetic background of allergic population. Variations in human leukocyte antigen region (HLA) have been well-clarified to be associated with

TABLE 1 | Characteristics of participants by atopic dermatitis and asthma.

Characteristics	Total (*N* = 5,02,505)	AD		*P*	Asthma		*P*
		No (*N* = 4,88,683)	Yes (*N* = 13,822)		No (*N* = 4,34,609)	Yes (*N* = 67,896)	
Age (years), mean ± SD	56.53 ± 8.095	56.53 ± 8.097	56.53 ± 8.096	0.359	56.59 ± 8.069	56.16 ± 8.249	0.000
Female, *n* (%)	2,64,796 (52.7)	2,57,020 (52.6)	7,776 (56.3)	0.000	2,26,999 (52.2)	37,797 (55.7)	0.000
Body mass index (kg/m^2), mean ± SD	27.43 ± 4.803	27.43 ± 4.799	27.56 ± 4.935	0.024	27.40 ± 4.690	28.29 ± 5.392	0.000
Caucasian, *n* (%)	4,09,615 (81.5)	3,98,237 (81.5)	11,378 (82.3)	0.014	3,54,487 (81.6)	55,128 (81.2)	0.021
Smoking, *n* (%)							
Never	2,73,522 (54.43)	2,66,204 (53.1)	7,318 (1.5)	0.004	2,37,327 (47.3)	36,195 (7.2)	0.000
Previous	173,056 (34.44)	168,083 (33.5)	4,973 (1.0)		148,859 (29.7)	24,197 (4.8)	
Current	52,978 (10.5)	51,530 (10.3)	1,448 (0.3)		45,903 (9.2)	7,075 (1.4)	
Alcohol, *n* (%)							
Never	22,385 (4.5)	21,760 (4.3)	625 (0.1)	0.125	19,013 (3.8)	3,372 (0.7)	0.000
Previous	18,104 (3.6)	17,569 (3.5)	535 (0.1)		14,892 (3.0)	3,212 (0.6)	
Current	460,362 (91.6)	447,743 (89.3)	12,619 (2.5)		399,270 (79.6)	61,092 (12.2)	
Household income, *n* (%)							
< 18,000	97,198 (19.3)	94,323 (19.0)	2,875 (0.6)	0.000	82,406 (16.6)	14,792 (3.0)	0.000
18,000–30,999	1,08,177 (21.5)	1,05,166 (21.2)	3,011 (0.6)		94,158 (19.0)	14,019 (2.8)	
31,000–51,999	1,10,772 (22.0)	1,07,786 (21.7)	2,986 (0.6)		96,585 (19.5)	14,187 (2.9)	
52,000–100,000	86,266 (17.2)	84,006 (16.9)	2,260 (0.5)		75,061 (15.1)	11,205 (2.3)	
>100,000	22,929 (4.6)	22,406 (4.5)	523 (0.1)		19,974 (4.0)	2,955 (0.6)	
FBG (mmol/L), mean ± SD	5.12 ± 1.243	5.13 ± 1.244	5.11 ± 1.239	0.220	5.12 ± 1.226	5.16 ± 1.352	0.849
HbA1c (mmol/mol), mean ± SD	36.13 ± 6.776	36.13 ± 6.784	36.10 ± 6.493	0.353	36.06 ± 6.696	36.60 ± 7.250	0.000
Testosterone (nmol/L), mean ± SD	6.56 ± 6.054	6.57 ± 6.056	6.18 ± 5.984	0.000	6.59 ± 6.065	6.31 ± 5.976	0.000
SHBG (nmol/L), mean ± SD	51.63 ± 27.781	51.60 ± 27.752	52.81 ± 28.789	0.000	51.80 ± 27.711	50.53 ± 28.200	0.000

TABLE 2 | Associations of atopic dermatitis and asthma with serum lipids.

Lipids	Model	Disease	Total		Lipid-controlling drug excluded		Caucasian only	
			β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
TC	Model 1	AD	−0.003 (−0.004 to −0.001)	1.33E-03	−0.002 (−0.004 to −0.001)	5.00E-03	−0.003 (−0.004 to −0.001)	1.94E-03
		Asthma	−0.002 (−0.003 to −0.002)	0.00E+00	−0.002 (−0.002 to −0.001)	1.41E-05	−0.002 (0.003 to −0.001)	5.77E-07
	Model 2	AD	−0.004 (−0.005 to −0.002)	0.00E+00	−0.003 (−0.005 to −0.002)	3.39E-05	−0.003 (−0.005 to −0.002)	4.44E-05
		Asthma	−0.002 (−0.003 to −0.001)	8.01E-08	−0.002 (−0.002 to −0.001)	2.71E-06	−0.002 (−0.003 to−0.001)	6.55E-06
	Model 3	AD	−0.004 (−0.005 to −0.002)	5.29E-05	−0.003 (−0.005 to −0.001)	1.00E-03	−0.004 (−0.006 to −0.002)	6.34E-05
		Asthma	−0.002 (−0.003 to −0.002)	7.98E-05	−0.002 (−0.003 to −0.001)	0.00E+00	−0.002 (−0.002 to −0.001)	1.38E-03
TG	Model 1	AD	−0.006 (−0.010 to −0.003)	1.00E-03	−0.005 (−0.010 to −0.001)	1.37E-02	−0.008 (−0.013 to −0.004)	1.46E-04
		Asthma	0.007 (0.006 to 0.009)	7.08E-15	0.007 (0.005 to 0.009)	1.17E-10	0.007 (0.005 to 0.009)	5.81E-11
	Model 2	AD	−0.005 (−0.009 to −0.002)	4.00E-03	−0.004 (−0.008 to −0.000)	3.00E-02	−0.007 (−0.011 to −0.003)	3.30E-04
		Asthma	−0.003 (−0.005 to −0.002)	0.00E+00	−0.003 (−0.005 to −0.001)	2.84E-03	−0.004 (−0.006 to −0.002)	3.38E-05
	Model 3	AD	−0.006 (−0.010 to −0.002)	6.00E-03	−0.004 (−0.009 to −0.000)	5.37E-02	−0.006 (−0.011 to −0.002)	4.25E-03
		Asthma	−0.005 (−0.007 to −0.003)	1.25E-07	−0.005 (−0.008 to −0.003)	8.38E-07	−0.006 (−0.008 to −0.004)	1.02E-07
LDL	Model 1	AD	−0.004 (−0.006 to −0.002)	0.00E+00	−0.003 (−0.005 to −0.001)	6.49E-04	−0.004 (−0.006 to −0.002)	5.71E-04
		Asthma	−0.004 (−0.004 to −0.003)	5.37E-14	−0.002 (−0.003 to −0.001)	4.83E-06	−0.003 (−0.004 to −0.002)	2.41E-10
	Model 2	AD	−0.004 (−0.006 to −0.002)	1.23E-05	−0.004 (−0.006 to −0.002)	4.23E-05	−0.004 (−0.006 to −0.002)	9.57E-05
		Asthma	−0.004 (−0.004 to −0.003)	2.00E-16	−0.003 (−0.004 to −0.002)	1.48E-12	−0.004 (−0.005 to −0.003)	5.75E-14
	Model 3	AD	−0.004 (−0.006 to −0.002)	0.00E+00	−0.004 (−0.006 to −0.001)	1.00E-03	−0.004 (−0.007 to −0.002)	2.31E-04
		Asthma	−0.003 (−0.004 to −0.002)	6.10E-10	−0.003 (−0.004 to −0.002)	8.86E-11	−0.003 (−0.004 to −0.002)	2.29E-07
HDL	Model 1	AD	0.003 (0.001 to 0.005)	8.00E-03	0.003 (0.001 to 0.005)	1.41E-02	0.003 (0.000 to 0.005)	2.35E-02
		Asthma	−0.001 (−0.002 to −0.000)	3.90E-02	−0.002 (−0.003 to −0.001)	5.69E-04	−0.001 (−0.002 to 0.000)	1.10E-01
	Model 2	AD	0.000 (−0.001 to 0.002)	5.82E-01	0.000 (−0.001 to 0.002)	7.42E-01	0.001 (−0.001 to 0.003)	4.82E-01
		Asthma	0.004 (0.003 to 0.005)	2.00E-16	0.003 (0.002 to 0.004)	6.54E-12	0.004 (0.003 to 0.005)	2.00E-16
	Model 3	AD	0.0002 (−0.002 to 0.002)	7.94E-01	0.000 (−0.002 to 0.002)	9.90E-01	0.000 (−0.002 to 0.002)	7.51E-01
		Asthma	0.004 (0.003 to 0.005)	2.00E-16	0.003 (0.002 to 0.004)	9.90E-09	0.004 (0.003 to 0.005)	8.68E-16

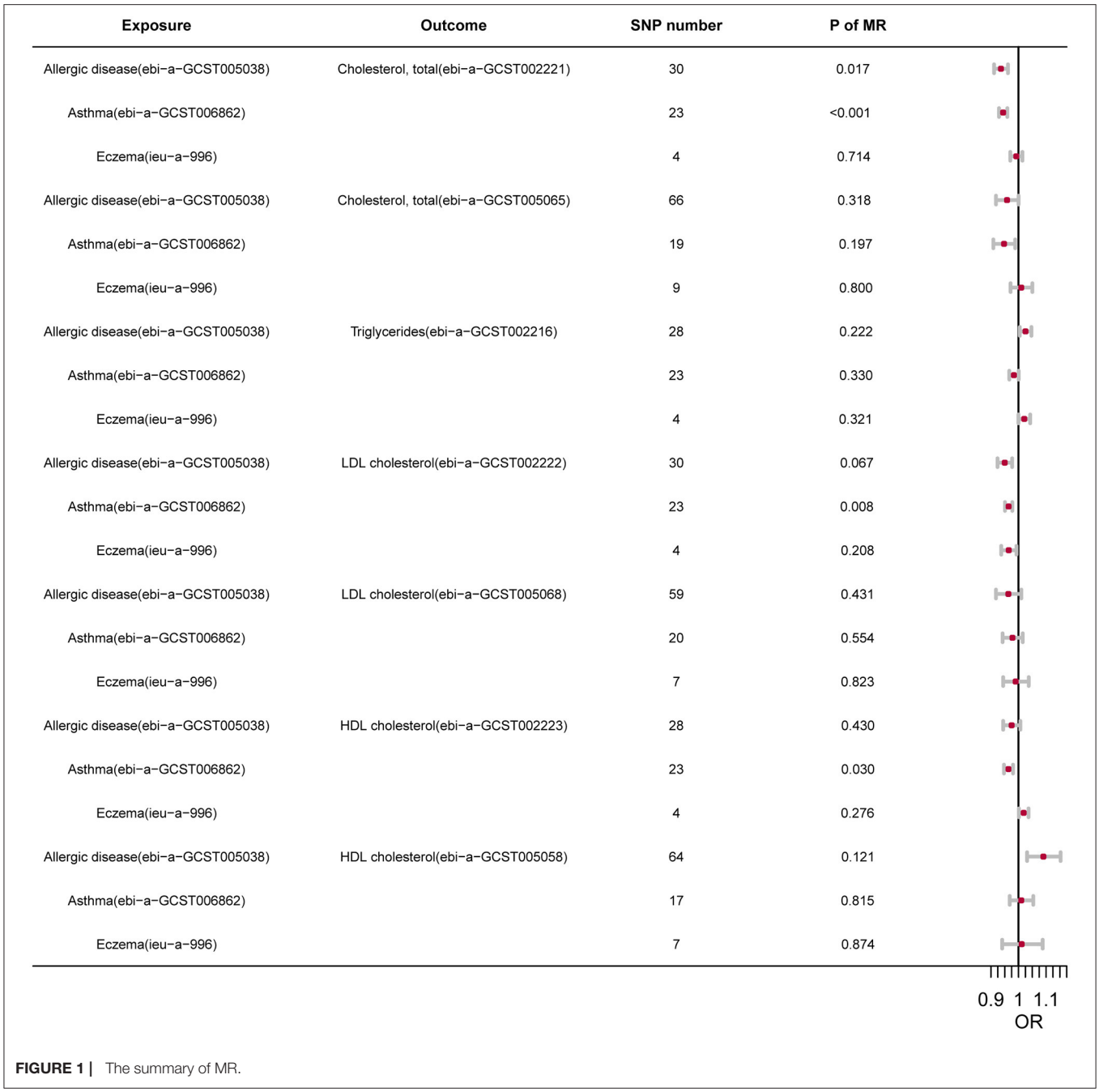

FIGURE 1 | The summary of MR.

allergic diseases by numerous GWAS studies (28). One small-scaled study proposed an inverse correlation between HLA-DR expression and serum triglycerides concentrations (29). Results from another observational study indicated that variation in HLA-DQB1 were positively associated with lipid homeostasis and human longevity (30). Unfortunately, these studies merely revealed the association but did not provided further functional evidence, and future effort should be taken on the mechanical role of allergy-associated variation in dyslipidemia and CVD. On the other hand, allergic diseases are often featured or by an enhancement of Th2 cell-mediated responses. As the major and direct consequence of dyslipidemia, atherosclerosis can be attenuated by Th2-associated cytokines, such as IL-5 and IL-13, according to previous studies (31). Although the debate remains, studies also suggested that a higher proportion of Th2 cells among peripheral blood lymphocytes is positively correlated with lower subclinical atherosclerosis burden, and IL-4, another critical cytokine related to allergy, also inversely correlates with clinical atherosclerosis (31–33). Whether the protective role of Th2-associated cytokines is mediated by lipid metabolism, remain to be explored in the future.

Collectively, we identify a protective causal effect of allergic diseases on serum lipids. Owing to the largest sample size and the application of IVs in causal inference, this study will provide a robust evidence for the management of asthma and AD and the prevention of dyslipidemia.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found in the article/supplementary material. Further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was based on UKB (Application No.55257), and all individuals in this cohort provided written informed consent. North West Multi-Centre Research Ethics Committee approved the UK Biobank ethical application. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZT drafted the manuscript. MS and ZT analyzed the data. MS and YX designed the study. MS, HL, and XC obtained the funding. All authors participated in the design, data collection, critically revised the manuscript, and gave final approval to the version submitted for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.810092/full#supplementary-material

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CASE REPORT
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Case Report: Chemotherapy-Associated Systemic Sclerosis: Is DNA Damage to Blame?

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Systemic sclerosis, also known as scleroderma, is an autoimmune disease characterized by cutaneous and visceral fibrosis, immune dysregulation, and vasculopathy. Generally, the degree of skin fibrosis is associated with an increased likelihood of visceral organ involvement. Its pathogenesis is poorly understood; however, it is clear that changes in both the innate and adaptive immune responses are associated with fibroblast dysfunction and vascular damage. Further, DNA damage has been postulated as one of the triggering factors in systemic sclerosis, although the association of DNA damage with the progression of this disease is more poorly established. Recently, abnormal DNA damage response repair pathways have also been identified in patients with systemic sclerosis, suggesting that cells from patients with this disease may be more susceptible to DNA damaging agents. Chemotherapeutic drugs and other DNA damaging agents have been associated with the development of systemic sclerosis, as these agents may provide additional "hits" that promote abnormal DNA damage responses and subsequent inflammatory changes. Herein, we present the case of a 39-year-old female who developed scleroderma after the treatment of her breast cancer with chemotherapeutic agents. Her scleroderma was subsequently successfully treated with autologous hematopoietic stem cell transplantation. We also completed a literature review for previously published cases of chemotherapy associated with systemic sclerosis and highlighted a role of DNA damage in promoting the disease. Our case is the first case of chemotherapy associated with systemic sclerosis treated with hematopoietic stem cell transplantation.

Keywords: scleroderma, systemic sclerosis, chemotherapy, DNA damage, hematopoietic cell transplantation

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INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is an autoimmune disease characterized by cutaneous and visceral fibrosis, immune dysregulation, and vasculopathy (1). Early in the disease (<3 years from its onset), patients may develop skin fibrosis that is not extensive, although some patients may also develop rapidly progressive skin fibrosis [or early diffuse SSc (edSSc) (2–4)], which is characterized by skin thickening extending beyond the elbows, and often the trunk over a short disease duration. Generally, the degree of skin fibrosis is associated with an increased likelihood of visceral organ involvement and mortality (5).

The pathogenesis of SSc is poorly understood, although it is clear that changes in both the innate and adaptive immune responses are associated with fibroblast dysfunction and vascular damage (6). DNA damage, promoted by reactive oxygen species (ROS), has also been postulated as one of the triggering factors in SSc (7–10), although, the association of DNA damage with the progression of SSc is poorly established. Recently, abnormal DNA damage response repair (DDR/R) pathways have been identified in patients with SSc, suggesting that cells from patients with SSc may be more susceptible to DNA damaging agents (11, 12) (**Figure 1**).

Chemotherapy functions to avoid malignant invasion and metastasis by inhibiting cell proliferation and tumor growth using traditional agents aimed at inhibiting DNA, RNA, or protein synthesis (13). This process is what leads to their cytotoxic effects and subsequent adverse reactions. Chemotherapeutic drugs, including, but not limited to, alkylating agents, antimetabolites, mitotic inhibitors, and anthracyclines, have been associated with the development of scleroderma, with the taxane group of medications, in particular, being highly associated with this disease (14–16). Thus, these agents may provide the additional cellular "hit" that promotes abnormal DNA damage responses and downstream inflammatory signals that promote characteristic fibroblast and immune cell abnormalities described in SSc (**Figure 1**) (1).

Here, we present a case of chemotherapy-associated scleroderma that was subsequently successfully treated with autologous hematopoietic stem cell transplantation (HSCT). As part of our description, we have completed a brief review of the literature for previously published cases of chemotherapy associated with the development of skin fibrosis, and we describe the role of DNA damage in the pathogenesis of SSc. To the best of our knowledge, this is the first case of edSSc associated with chemotherapy and this is the first demonstration of subsequent treatment using HSCT.

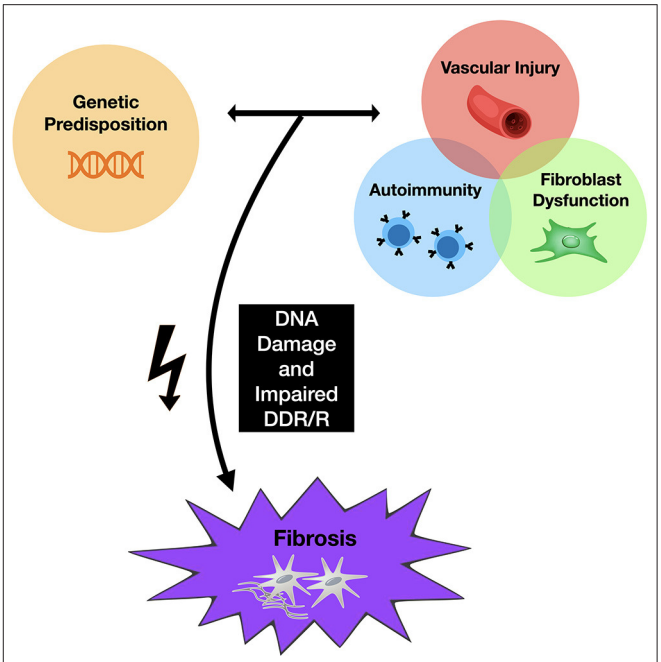

FIGURE 1 | Proposed mechanism of skin fibrosis associated with chemotherapy. Genetic predisposition to SSc, along with changes in both the innate and adaptive immune responses, promote fibroblast dysfunction and vascular damage, leading to fibrosis. Abnormal DNA damage response repair pathways have also been identified in patients with SSc, suggesting that cells from patients with SSc may be more susceptible to DNA damaging agents. Chemotherapeutic agents may provide the additional cellular "hit" that promotes abnormal DNA damage responses and subsequent inflammatory changes.

CASE REPORT

A 39-year-old Caucasian female was diagnosed with biopsy-proven grade III invasive ductal carcinoma cancer of the right breast, and subsequently underwent a right mastectomy. Then, she was treated with three cycles of 5-fluorouracil, epirubicin, cyclophosphamide, and docetaxel chemotherapy. She received 45 Gy of radiation therapy to the affected areas, which was complicated by mild lymphedema.

During her last two cycles of chemotherapy, the patient complained of swollen or "puffy" fingers bilaterally, resembling dactylitis, leaving her unable to fully extend her fingers. This was associated with bilateral leg and foot swelling. One month later, she presented with symptoms of numbness and poor perfusion in the areas distal to the metacarpophalangeal joints on both hands that appeared to have a biphasic nature (ischemic and erythema phase) that was highly suggestive of Raynaud's phenomenon. There was no cyanotic phase affecting her fingers at the time. The patient's symptoms were most notably precipitated in the shower and by cold temperatures. Additionally, tightness of her mouth, neck and face were noted. She was unable to abduct her arms above her head. Furthermore, she developed gastroesophageal reflux not associated with symptoms of dysphagia or looser, more frequent bowel movements. Notably, the patient developed progressive skin fibrosis (starting from her hands and moving to her trunk) associated with profound skin itchiness which led to impairment and difficulties with her activities of daily living.

Her clinical examination revealed skin tightness in the bilateral upper extremities extending to the elbows. Some patches of skin were associated with calcinosis cutis. She had no digital ulcers, but her hands had evidence of sclerodactyly with reduced extension compatible with a positive prayer sign (**Figure 2**). Investigations were in keeping with SSc, as suggested by anti-RNA polymerase III antibodies [RP11 and RP155, performed by a reference laboratory Mitogen Laboratories (MitogenDx, Calgary, AB, Canada)]. Other SSc-specific autoantibodies (e.g., anti-Scl70, anti-fibrillarin, anti-Th/T0, and anti-centromere) were absent. Echocardiogram, CT of the chest, abdomen and pelvis were also normal (specifically there was no evidence of breast cancer recurrence) except for mild lung fibrosis only in the breast radiation field and severe hepatic steatosis. Forced vital capacity (FVC) was 63%, likely due to chest wall fibrosis. Gastroscopy did not reveal the presence of esophagitis or strictures. Esophageal manometry revealed hypomotility (40% swallows failed and

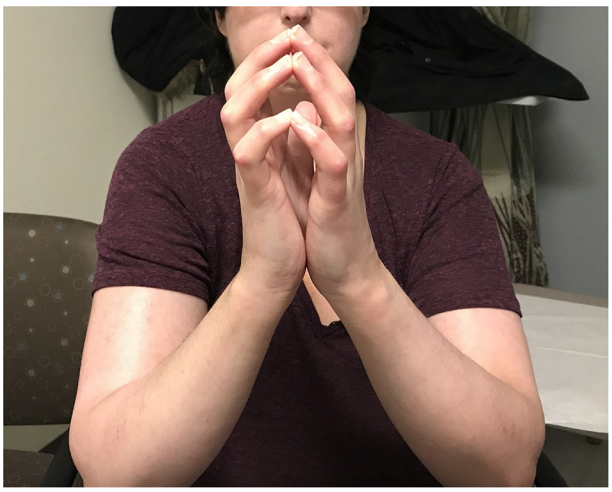

FIGURE 2 | On exam, the patient had no digital ulcers, but her hands were fixed in flexion, with sclerodactyly and a positive "prayer sign". There is also evidence of skin tightness in the bilateral upper extremities extending to the elbows.

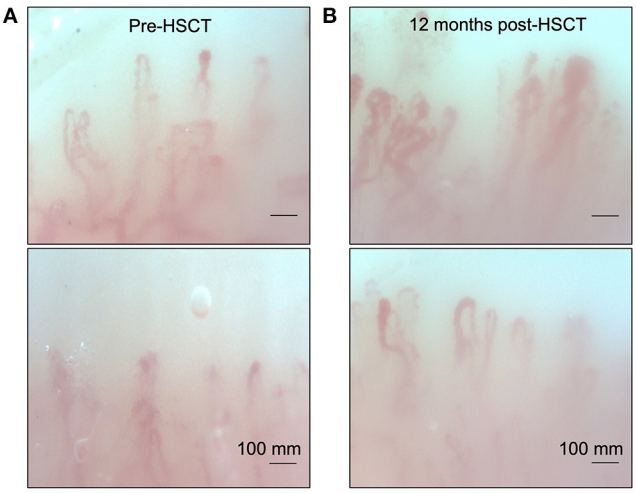

FIGURE 3 | Nailfold video capillaroscopy for our patient showing a late pattern described in SSc. **(A)** Note the capillary disorganization and decreased capillary density present before autologous hematopoietic stem cell transplantation. **(B)** Repeat nailfold video capillaroscopy examination 12 months post HSCT. Note the increased capillary density and improved organization after transplant.

20% swallows were weak). Nailfold video capillaroscopy showed decreased capillaries in most digits [mean capillary density 4.2 capillaries per mm, **Figure 3A**—pattern described as a "late capillary SSc pattern" (17)]. Her pre-HSCT modified Rodnan skin score (mRSS) was 31/51.

She was started on mycophenolate mofetil (MMF) 1,000 mg PO b.i.d. for immunosuppression, with good drug tolerance. Antihistamines and low-dose prednisone, at 5 mg PO daily, were also initiated as the patient's pruritus was significantly affecting her quality of life. After 14 months from symptom onset, she was referred for evaluation of autologous HSCT therapy. It was felt that although her presentation was atypical, her likelihood of survival with conventional therapy was reduced compared to HSCT with an estimated 5-year survival of 85% with stem cell transplant vs. 50–75% with conventional immunosuppressive therapy. Her quality of life was expected to be superior after stem cell transplant. The patient underwent autologous hematopoietic cell transplantation (HSCT) (18) ∼18 months after her initial symptoms of skin thickening. Her course was complicated by a catheter-induced left internal jugular vein thrombosis associated with heparin-induced thrombocytopenia and thrombosis (HITT). She was started on fondaparinux for this complication. By 8 days post-transplant, she had become neutropenic but was initiated on granulocyte colony stimulating factor (G-CSF) and subsequently recovered her cell counts with no further complication. After about 6 months post-transplant, the patient still endorsed some shortness of breath on exertion but overall was feeling less fatigued. FVC at 1 year post-transplant was 67% predicted. She noticed some improvement in her skin tightening but still had flexion contractures at several joints. She also described ongoing Raynaud's symptoms, but minimal digital ulcerations. She had ongoing gastroesophageal reflux that had not improved post-transplant. At ∼18 months post-transplant, her mRSS has markedly improved (15/51). Post-transplant nailfold capillaroscopy showed improvement with capillary density at 5.8 capillaries/mm with mild apical enlargement (∼32 microns in 30% of capillaries), minimal giant capillaries and microhemorrhages (**Figure 3B**). She continues to be followed as an outpatient and continues to exhibit subjective clinical improvement.

DISCUSSION

Chemotherapy-associated skin fibrosis has been previously described in the literature, with cutaneous fibrosis being one of the most common symptoms, and taxane chemotherapeutic agents being the primary offender (5, 16, 19–23). The earliest cases describing chemotherapy associated skin fibrosis were published by Battafarano et al. in 1995, describing three patients who developed diffuse lower extremity edema and subsequent scleroderma-like changes after receiving multiple cycles of docetaxel therapy for various malignancies (16). Rheumatoid factor, antinuclear antibodies, anticentromere, and topoisomerase antibodies were not present in any patient, and the discontinuation of docetaxel correlated with resolution of edema and softening of the skin.

The occurrence of edSSc associated with chemotherapeutic agents manifesting as severe skin fibrosis, the presence of specific autoantibodies, and vasculopathy is rare. Indeed, to the best of our knowledge, our case is the first case of edSSc (3, 4) in this setting. Case reports of SSc or scleroderma-like changes occurring after treatment with various other chemotherapeutic drugs, such as bleomycin (24–26),

gemcitabine (27–29), and pemetrexed (30–32), have also been published, however, none of these cases had associated vasculopathy and SSc-specific autoantibodies. Moreover, our case was successfully treated with HSCT, which further underpins the utility of HSCT in the management of rapidly progressive SSc.

The mechanisms by which various chemotherapeutic agents induce specific scleroderma-like skin changes remain unclear. However, a driver associated with skin and visceral organ fibrosis may be DNA damage (4, 11, 33, 34). DNA damage signals are associated with dysregulated type I interferon activation (35) and downstream interleukin 6 (IL-6) release (36), which are known to be associated with fibrotic mechanisms in SSc. Clearly, not all patients receiving chemotherapeutic agents will develop SSc. Rather, DNA damaging agents may trigger vasculopathy and fibrosis in patients with inherent susceptibilities to SSc via a "multiple hit" mechanism (as summarized in **Figure 1**). This observation is not unique to chemotherapeutic agents or radiation, as other DNA damaging agents such as silica and organic solvents have been linked with SSc (37–39). Some of these risks may be present in genetic factors (40, 41) which are shared in other autoimmune diseases (42–46).

In this schema, DNA damage signals from ROS (or chemotherapeutic agents) may promote a dysregulated fibroblast phenotype characterized by increased migration and invasion. These activated fibroblasts, in turn, may promote vascular dysfunction via aberrant endothelial cell interactions (47). Similarly, aberrant DDR/R mechanisms in mesenchymal cells may promote inflammatory changes present in SSc (such as M2 macrophage polarization) (48). Indeed, taxane-based chemotherapies can result in increased levels of circulating inflammatory cytokines, such as IL-6, which are thought to be important drivers of SSc (49). DNA damage signals may also be associated with increased type I interferon production in circulating leukocytes as recently suggested by Vlachogiannis et al. particularly in patients with more progressive SSc (11). Thus, chemotherapeutic agents may potentiate fibrosis via these mechanisms in certain individuals.

Use of HSCT in Chemotherapy Associated SSc

HSCT has been used in the treatment of autoimmune diseases unresponsive to conventional immunosuppressive therapies for decades (50). Briefly, the procedure includes chemotherapy, with or without total body irradiation, followed by the infusion of autologous (patient's own) or allogeneic (donor) stem cells intravenously to re-establish hematopoietic function in patients whose bone marrow or immune system has been damaged. These stem cells typically come from the bone marrow, peripheral blood, or umbilical cord blood (51). The mechanisms by which HSCT in SSc are unclear—although it may re-institute immune homeostasis via multiple mechanisms (52)—which perhaps may include improved inflammatory responses to DNA damage (53). In idiopathic SSc, HSCT has been shown to promote a significant improvement in skin fibrosis and mortality, in addition to a reduction of disease associated disability (54). Furthermore, HSCT improves SSc-associated vasculopathy as suggested by improved nailfold capillary loss (55). While our patient still had endorsed some shortness of breath on exertion and fatigue at $\geq$1 year post-transplant, these improved compared to pre-transplant. She had noticed some improvement in her skin tightening, and had decreased digital ulcerations, although her Raynaud's symptoms persisted. She, unfortunately, still had ongoing dysphagia and gastroesophageal reflux that had not improved post-transplant. Ultimately, our patient's response to HSCT was promising and brought forth the need to study the mechanism of HSCT in non-idiopathic SSc.

Cancer, Chemotherapy and SSc in Our Patient

There has been some association of an increased risk of developing breast cancer in patients with pre-existing scleroderma (56). Cancers in SSc have been considered to stem from underlying immune dysregulation and impaired cancer immunosurveillance. In the case of our patient, symptoms began after her cancer diagnosis, there was no evidence of detectable recurrence of breast cancer, and the SSc symptoms started in the last two cycles of chemotherapy. Together, it would be less likely that her diagnosis of SSc was solely based on the underlying malignancy, although it likely contributed to it. We have also considered a paraneoplastic picture for her disease, whereby the cancer itself induced her cutaneous changes (57). However, given the timing and onset of her SSc far after her cancer diagnosis, and its onset in conjunction with her chemotherapy, paraneoplastic SSc is less likely. With all factors considered, we suspect that our patient was exposed to "multiple hits": namely, previous history of neoplastic disease (suggesting inherently poor DDR/R mechanisms and abnormal immunosurveillance), an underlying, but poorly defined, genetic/epigenetic susceptibility for developing SSc, and finally, chemotherapeutic agents inducing DNA damage, which culminated in her development of edSSc (58).

CONCLUSION

In summary, we present a case of a 39-year-old Caucasian female with chemotherapy associated edSSc, which subsequently responded to autologous HSCT. We propose that in certain individuals, particularly those with abnormal DNA repair mechanisms, such as our patient, chemotherapeutic agents may promote DNA damage signals which in turn potentiate skin fibrosis, vasculopathy, and autoimmunity. Because of the severity of her disease and how rapidly she functionally declined, she was referred for autologous HSCT, a procedure aiming to restore normal immune and mesenchymal functions resulting in a dramatic improvement. Thus, our patient reinforces the notion that HSCT may

provide additional non-immunological benefits that have been previously proposed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Population-Based Study Detailing Cutaneous Melanoma Incidence and Mortality Trends in Canada

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Background: Cutaneous melanoma (CM) is one of the most fatal types of skin cancer. Alarmingly, increases in incidence and mortality were noted globally for this malignancy, despite increase in understanding of melanoma pathogenesis and enhanced prevention efforts.

Methods: Data was extracted for CM patients for provinces and territories (except Quebec) using two independent, population-based registries. Analysis was performed using both clinical and pathological characteristics: tumor morphologic classification, age, sex, anatomic site affected and place of residence. Mortality trends were assessed over a 7-year period. Results were compared to prior findings for 1992–2010.

Results: During 2011–2017 39,610 patients were diagnosed with CM, with 5,890 reported deaths. National crude CM incidence was 20.75 (age-standardized incidence: 14.12) cases per 100,000 individuals per year. Females accounted for 45.8% of cases and 37.1% of deaths. While CM incidence rates continue to increase in both sexes, since 2013 the CM mortality is declining. We observed important differences across the provinces/territories, where Nova Scotia, Prince Edward Island, southern Ontario/British Columbia and certain coastal communities of New Brunswick demonstrated higher CM incidence and mortality rates. The observed incidence and mortality trends for 2011–2017 validate and extend earlier observations from 1992 to 2010 for CM.

Conclusion: This population-based study highlights that while melanoma's incidence is increasing in Canada, mortality rates are for the first time decreasing since 2013. We detail regional distribution of this cancer highlighting communities in southern/coastal areas, as being most at risk as well as the latest trends of melanoma incidence by age,

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sex and anatomic site. In males, melanoma is more common on the head/trunk, while in females on the extremities. Notably, Acral Lentiginous Melanoma was the only CM subtype that was more common in females, which primarily affects hands and feet.

Keywords: cutaneous melanoma, acral lentiginous melanoma, incidence, mortality, Canada, risk factors, epidemiology

INTRODUCTION

Cutaneous melanoma (CM) causes more deaths than any other skin cancer (1), accounting for ∼1.9 and 1.2% of all cancer deaths in males and females, respectively, in Canada (2). Globally, there were ∼290,000 new cases of CM in 2018 (3). Countries with the highest incidence rate per capita include Australia, New Zealand, Norway, Denmark, Netherlands, Sweden and Germany (3). Overall, there was a 44% increase in the incidence rate of CM between 2008 and 2018, with a corresponding surge of 32% in mortality (3). In recent decades, the incidence of CM has been on the rise in fair-skinned individuals in Europe, North America and other parts of the world (4). The incidence rate was further linked to the ongoing climate crisis, as depletion in ozone layer was correlated with subsequent increase in CM incidence (3).

The relationship between ultraviolet (UV) radiation exposure and the risk of developing a skin cancer has been well-established for decades. While solar/artificial UV exposure plays a critical role in the development of melanoma, keratinocyte carcinoma and Merkel cell carcinoma, many host/other exposure factors (Fitzpatrick skin phototype, individual's number of melanocytic nevi, personal/family history of melanoma and other skin cancers, previous therapy with psoralen UVA or broad band UV therapy, history of sunburns, residing closer to the equator or at higher elevation, immunosuppression, other genetic factors/mutations) interplay with the environment to determine the ultimate risk for this deadly disease (5, 6). Despite extensive knowledge on the detrimental impact of UV radiation on skin photoaging, skin cancer development and direct/indirect causation of other common cutaneous diseases [e.g., melasma, rosacea (7–9)], many still fail to exercise sun protection and sun avoidance.

Our group has previously studied the epidemiologic trends of CM in Canada (10–12). In the present study we provide an updated detailed analysis of national CM incidence and mortality trends during 2011–2017 period and compare these findings to the 1992–2010 trends (12).

MATERIALS AND METHODS

This study was conducted in accordance with the QICSS-RDC-668035 and 13-SSH-MCG-3749-S001 protocols approved by the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Quebec Inter-University Centre for Social Statistics (QICSS), respectively. In addition, in accordance with the institutional policy, this study received an exemption from the McGill University Research Ethics Board review. We examined the data on the incidence and mortality of CM using two distinct population-based cancer databases: the Canadian Cancer Registry (CCR) and Canadian Vital Statistics (CVS) for the period of 2011–2017 using the International Classification of Diseases for Oncology ICD-O-3 and ICD-10 codes for all subtypes of CM (**Supplementary Table 1**), as previously reported (10–33). Only invasive melanoma was included in the analysis (i.e., melanoma *in-situ* and lentigo maligna cases were not included). We conducted analyses of the complete data on all CM patients across Canada, with the exception of Quebec, between 2011 and 2017. All crude rates are presented per 100,000 individuals per year. Where indicated in this study, 95% confidence intervals were calculated based on the exact Poisson distribution (10). *P*-values were calculated with the Chi-square goodness of fit test and that $p < 0.05$ were considered statistically significant. Incidence and mortality rates were plotted using linear regression models using GraphPad software to assess trends over time (10). Age-standardized incidence (ASIR) and age-standardized mortality (ASMR) rates for Canada were calculated using the WHO 2000–2025 standard population (10, 34), while in Canadian jurisdictions incidence/mortality was standardized based on Canadian national average, as previously described (10, 11, 16). Geographic maps of Canada divided by FSA codes indicating the residence of patients with CM documented by the CCR or CVS databases were generated using geographic information systems software (ArcMap 10.4; Environmental Systems Research Institute, Redlands, Calif) (10, 22, 23).

RESULTS

Incidence Trends of CM

Analysis of invasive CM incidence revealed that there were 39,610 cases diagnosed in Canada (excluding Quebec) during the 2011–2017 period (**Table 1A**). Quebec was excluded since Le Régistre Québécois du Cancer (LRQC) has not released the data past 2010.

The average crude incidence rate for CM during 2011–2017 was 20.75 cases per 100,000 individuals per year (95% CI: 20.54–20.95). When compared to the world population (WHO 2000–2025 standard population), the ASIR was 14.12 cases per 100,000 individuals per year (95% CI: 14.10–14.14). For comparison, the 1992–2010 Canadian crude incidence rate was 12.29 and ASIR was 9.63 cases per 100,000 individuals per year. Linear regression analysis of annual incidence highlighted an increasing trend in invasive CM rates across the country, with an annual increase of 0.59 cases per 100,000 individuals ($R^2 = 0.90$; $p = 0.0011$) (**Figure 1**). With regards to CM subtypes, the rates of incidence for skin malignant melanoma (not otherwise specified), nodular melanoma, malignant melanoma (regressing) and superficial spreading melanoma increased in 2011–2017, when compared

TABLE 1 | Clinical characteristics of CM patients in Canada during 2011–2017: (A) analysis by sex and melanoma subtype (B) analysis by age, sex and anatomic site for all CM subtypes.

A.

CMM Subtypes	ICD-O-3 code	# of patients*	% of total	Male (%)	Female (%)	Mean age ± SD	*P*-value
Malignant melanoma, NOS	8720	16,480	41.6	54.3	45.7	62.97 ± 17.42	<0.001
Superficial spreading melanoma	8743	14,375	36.3	51.1	48.9	60.00 ± 15.46	0.007
Nodular melanoma	8721	4,390	11.1	59.9	40.1	68.03 ± 15.56	<0.001
Lentigo maligna melanoma	8742	3,055	7.7	60.2	39.8	72.12 ± 11.99	<0.001
Acral Lentiginous melanoma	8744	510	1.3	43.1	56.9	66.07 ± 15.10	0.002
Desmoplastic melanoma	8745	390	1.0	60.3	39.7	70.14 ± 14.13	<0.001
Amelanotic melanoma	8730	85	0.2	52.9	47.1	68.14 ± 16.16	0.59
Malignant melanoma, regressing	8723	195	0.5	64.1	35.9	64.07 ± 14.51	<0.001
Malignant melanoma in junctional nevus	8740	35	0.1	57.1	42.9	61.14 ± 15.38	0.40
Malignant melanoma in a giant nevus	8761	80	0.2	56.3	43.8	51.76 ± 17.48	0.26
Balloon cell melanoma	8722	<10	0.03	N/A	N/A	67.25 ± 15.00	-
Mucosal lentiginous melanoma	8746	<5	0.01	N/A	N/A	66.80 ± 8.38	-
Overall	-	39,610	100	54.2	45.8	63.26 ± 16.48	<0.001

B.

		Males		Females		Both sexes	
		#*	%	#*	%	#*	%
Age (years)	0–19	35	0.2	70	0.4	105	0.3
	20–39	1,145	5.	2,045	11.3	3,185	8.0
	40–59	5,735	26.7	6,230	34.3	11,970	30.2
	60–79	10,740	50.0	7,105	39.2	17,845	45.1
	≥80	3,820	17.8	2,685	14.8	6,510	16.4
Anatomic site of melanoma	Skin of lip	25	0.1	30	0.2	55	0.1
	Eyelid	65	0.3	65	0.4	130	0.3
	External ear	795	3.7	195	1.1	990	2.5
	Skin of other parts of face	2,210	10.3	1,500	8.3	3,710	9.4
	Skin of scalp and neck	1,985	9.2	655	3.6	2,640	6.7
	Skin of trunk	8,435	39.3	4,060	22.4	12,500	31.6
	Skin of upper limb and shoulder	4,745	22.1	5,290	29.2	10,035	25.3
	Skin of lower limb and hip	2,155	10.0	5,705	31.5	7,865	19.9
	Overlapping lesion of skin	90	0.4	40	0.2	135	0.3
	Skin, NOS	965	4.5	590	3.4	1,555	3.9
	Total	21,470	100	18,130	100	39,615	100.00

**Rounded to the nearest 5.*

to 1992–2010. In contrast, incidence rates for lentigo maligna melanoma and acral lentiginous melanoma decreased in recent years (**Figure 2**) (10).

Incidence of other CM subtypes is detailed in **Table 1A** and **Figure 2**. Notably, the only subtype that was more common in females was the acral lentiginous melanoma (56.9 vs. 43.1% of cases; $p = 0.002$), which primarily affects hands and feet. The same trend was observed in our 1992–2010 analysis (10).

Analysis of CM Incidence by Age and Sex

The mean age at diagnosis increased from 58.5 ± 21.6 years during 1992–2010 (10) to 63.3 ± 16.5 years in 2011–2017 years [65.3 ± 14.6 years for males, 60.8 ± 18.2 years for females (**Tables 1A,B**) provide data for 2011–2017 years, prior data is presented in (10)]. Notably, there was an increase in the number of patients diagnosed with CM >60 years of age, increasing from 48.7% in 1992–2010 to 61.5% in 2011–2017 (**Table 1B**), compared to 54.0% of males and 42.9% of females being >60, when receiving a diagnosis of melanoma during 1992–2010 (10). The majority of CM subtypes were diagnosed in the 60–79 years of age bracket (**Tables 1A,B**). Based on 1992–2010 data, most subtypes were diagnosed in their late 50's and early 60's with the exception of patients with desmoplastic melanoma and lentigo maligna melanoma, where average age at diagnosis was 70.1 and 72.1 years, respectively. The diagnosis age for these two subtypes remained unchanged for 1992–2010 and 2011–2017 years (10).

With regards to the analysis by sex, we continued to observe a higher incidence in males than in females (54.2 *vs.* 45.8%),

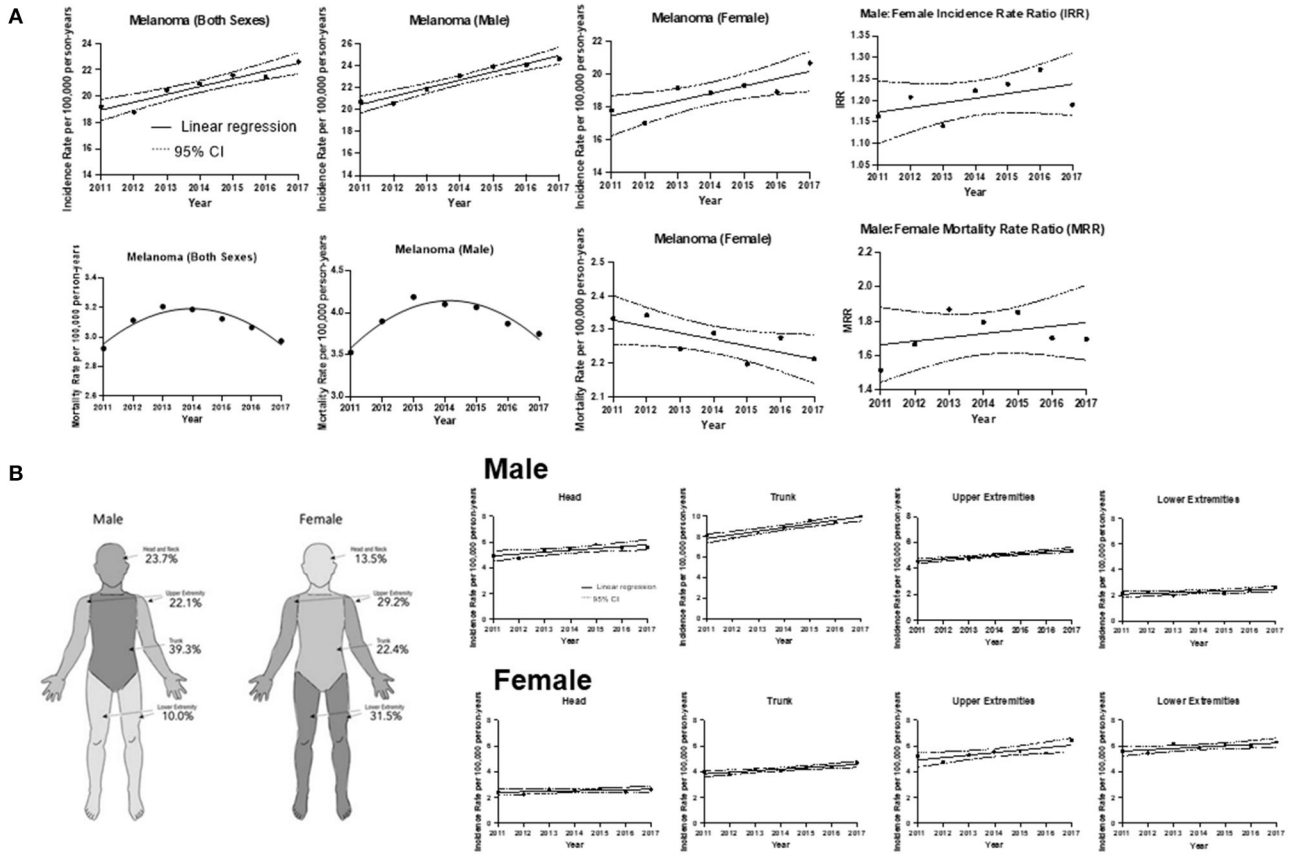

FIGURE 1 | CM incidence and mortality trends. **(A)** Incidence and mortality rates for all cases during 2011–2017 with the line of best fit, and linear regression analysis by sex. The average incidence rate of CM in Canada for both sexes from 2011 to 2017 was 20.75 cases per 100,000 individuals per year. $[R^2] = 0.902$; $p = 0.0011$. The slope of the line = 0.594 ± 0.0878 cases per 100,000 individuals per year. Incidence of CM for male sex average rate was 22.70. $[R^2] = 0.942$; $p = 0.0003$. The slope of the line = 0.741 ± 0.0822. Incidence of CM for female sex average rate was 18.84, $[R^2] = 0.701$; $p = 0.0188$. The slope of the line = 0.449 ± 0.131. Mortality of CM for both sexes ($Y = -231611 + 230.0X - 0.0571X^2$). The average mortality rate in Canada was 3.09 cases per 100,000 individuals per year (95% CI: 3.00–3.16). Mortality of CM for male sex ($Y = -108970 + 108.2X - 0.0269X^2$). Mortality of CM for female sex, $[R^2] = 0.549$; $p = 0.0568$. The slope of the line = −0.0193 ± 0.00784. Male to Female Incidence Rate Ratio (IRR). Linear regression analysis of CM incidence rate over time. Coefficient of determination $[R^2] = 0.28$; $p = 0.22$; CI and the slope of the line = 0.011 ± 0.0078. Line of best fit indicates an average IRR of 1:20:1. Male to Female Mortality Rate Ratio (MRR). $[R^2] = 0.14$; $p = 0.4018$ and the slope of the line = 0.022 ± 0.024. Line of best fit indicates an average MRR of 1.73:1. **(B)** Trends of CM incidence by anatomic site (head, upper extremities, trunk and lower extremities) over time for males and females. Right panel: Schematic diagram highlighting that the trunk was the most frequent site of CM for male patients, whereas the lower extremities were the most common among female patients. Left panel: Males: head, $[R^2] = 0.677$, $p = 0.023$ and the slope of the line = 0.14 cases per 100,000 individuals per year; trunk, $[R^2] = 0.917$; $p = 0.0007$ and the slope of the line = 0.36. For upper extremities, $[R^2] = 0.911$; $p = 0.0008$ and the slope of the line = 0.146; lower extremities, $[R^2] = 0.518$; $p = 0.0682$ and the slope of the line = 0.0639. Females: head, $[R^2] = 0.288$; $p = 0.2413$ and the slope of the line = 0.0393; trunk, $[R^2] = 0.817$; $p = 0.0052$ and the slope of the line = 0.123; upper extremities, $[R^2] = 0.666$; $p = 0.0251$ and the slope of the line = 0.192; lower extremities, $[R^2] = 0.582$; $p = 0.0460$ and the slope of the line = 0.106.

and this trend remained consistent throughout the majority of CM subtypes (**Table 1A**). **Figure 1A** depicts the male-to-female incidence rate ratios (IRR) for 2011 to 2017. The mean IRR for this period was 1.20, signifying an ever-increasing male to female ratio. This is consistent with previously noted trends (IRR of 1.12 for 1992–2010) (10). While the overall incidence was higher in males than in females, young (0–39 years) and middle-aged (40–59) females had a higher incidence rate than their male counterparts.

Analysis of CM by Anatomic Site

Analysis of CM by anatomic location revealed similar trends to those observed in 1992–2010 (10). The majority (63.0%) of CM in males developed on the head, neck and trunk, while in females, upper and lower extremities accounted >60% of cases. Overall, there was an increase in incidence rates in all anatomic sites in both sexes, with the trunk and upper extremities exhibiting the most significant increase in incidence (**Figure 1B**). The annual rate of increase of CM incidence (using the line of best fit) on the trunk in males was 0.36 cases per 100,000 individuals, while it was 0.19 cases per 100,000 individuals for the upper extremities of females (**Figure 1B**). We observed a substantial increase in incidence of CM on the trunk in males (0.14 cases per 100,000 individuals per year during 1992–2010 and 0.36 during 2011–2017) on the trunk in females (0.062 during 1992–2010 and 0.123 during 2011–2017) and on

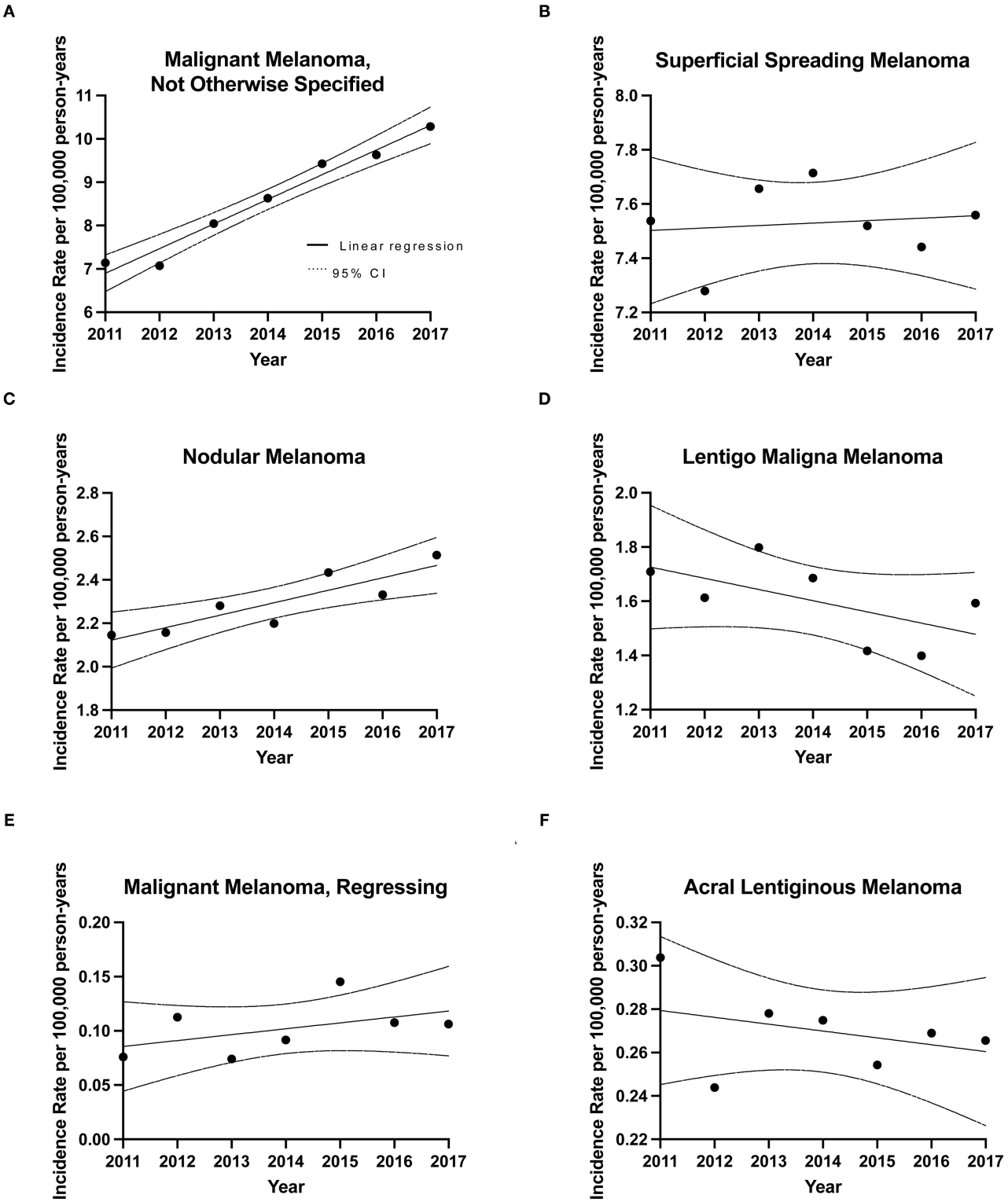

FIGURE 2 | Incidence rates for CM subtypes during 2011–2017. Linear regression analysis of CM subtype incidence rates over time along with CIs. **(A)** Malignant Melanoma, Not Otherwise Specified (NOS) (MM, NOS), slope= 0.569 ± 0.0457, $[R^2] = 0.969$; $p < 0.0001$, **(B)** Superficial Spreading Melanoma (SSM), slope= 0.00905 ± 0.0292, $[R^2] = 0.0188$; $p = 0.7692$, **(C)** Nodular melanoma (NM), slope = 0.0574 ± 0.0139, $[R^2] = 0.773$; $p = 0.0091$, **(D)** lentigo maligna melanoma (LM), slope= −0.0413 ± 0.0246, $[R^2] = 0.360$; $p = 0.1541$, **(E)** Acral lentiginous melanoma (ALM), slope = −0.00315 ± 0.00369, $[R^2] = 0.128$; $p = 0.4312$, **(F)** Malignant Melanoma, Regressing (MMR), slope = 0.00543 ± 0.00445, $[R^2] = 0.229$; $p = 0.2768$.

upper extremities in females (0.086 during 1992–2010 and 0.192 during 2011–2017).

Geographic Distribution of CM

When analyzing CM rates by province, we discovered that maritime provinces of Prince Edward Island (crude incidence rate of 33.86 cases per 100,000 individuals per year), Nova Scotia (30.77) had notably high incidence rates [**Tables 2A,B**; crude and age-standardized rates (ASIR) provided]. CM crude incidence rates in New Brunswick (22.55), Ontario (22.47) and British Columbia (20.89) were higher, but comparable to the national average of 20.75 cases per 100,000 individuals per year. Newfoundland and Labrador, territories and the prairie provinces had lower rates than the Canadian average. Adjusting for age further confirmed these findings (**Table 2**). Nova Scotia and Prince Edward Island demonstrated the highest incidence rates in the country based on our 1992–2010 results (10). Notably, all provinces demonstrated an appreciable increase in melanoma incidence in recent years.

We further analyzed CM incidence rates by postal code [forward sortation area (FSA); the first 3 entries in the postal code – e.g., H4A]. This analysis highlighted that postal codes/FSAs located in the southern regions of Canada, especially in the proximity of warmer waters (southern and coastal British Columbia, southern Ontario, Nova Scotia, Prince Edward Island and New Brunswick communities) as well as certain regions located near well-known vacation areas (e.g., postal codes near Banff National Park, AB) had higher rates of CM (**Figure 3** and **Supplementary Tables 2, 3**). Outside of these high-risk areas select locations in city centers (A1E postal code in St. John's, NL; R2G, R3F and R3P postal codes in Winnipeg, MB; T2V and T2L postal codes in Calgary, AB) were also noted to have higher CM incidence (**Figure 3** and **Supplementary Tables 2, 3**).

Analysis of CM Mortality Across Canada

The CVS database enabled us to examine deaths caused by CM (**Table 2C**). Mortality trends were reflective of the detailed above incidence trends, whereby there were more deaths due to CM in males than in females (62.9 *vs.* 37.1%; $p < 0.001$) and differences were observed by region. Notably, melanoma mortality in both sexes since 2013 has been decreasing in Canada (**Figure 1A**). Analysis by age group found that deaths peaked in the 70–80's age group (**Table 2C**).

DISCUSSION

Using the CCR and CVS databases, this paper provides a detailed description of the epidemiologic trends of CM in Canada between 2011 and 2017 highlighting variation by age, sex, anatomic site involved as well as striking geographic differences. While CM is increasing in Canada at an alarming rate, based on the mapping analysis, it is evident that southern regions of Ontario, British Columbia, and maritime provinces, especially, when surrounded by warmer waters, had significantly higher incidence rates. These results also correlate well with our and other previous reports highlighting variation in population by province/territory by Fitzpatrick skin phototype in Canada (12, 35). Specifically, the provinces of high CM incidence (NS and PEI) had the highest percentage of individuals with a British Isles background, which includes people of Cornish, English, Irish, Manx, Scottish and Welsh descent, who are known to have a predominance of Fitzpatrick skin types I-II (12, 35).

Notably, previous reports comparing coastal *vs.* inland areas documented that there was a greater incidence of CM cases along the coast, with an IRR of 1.23 after adjusting for socioeconomic status, UV index and latitude (36). Our mapping results visually underscore these findings in Canada, while providing specific details on the communities at risk. Hence, CM incidence in high-risk population (e.g., Fitzpatrick phototype I-III skin) greatly depends on climate/geography, which impacts human behavior, clothing styles and sun protection practices leading to higher or lower melanoma rates. Our findings are also in-line with the recently reported melanoma analysis on NL highlighting similar trends (35).

Our study highlights that CM incidence rates continue to increase in both sexes, while CM mortality is declining since 2013 likely due to the emergence of effective targeted and immunotherapy treatments (37). The overall incidence rate of CM in Canada was 20.75 cases per 100,000 individuals per year (22.70 in males and 18.84 in females) and the ASIR per 100,000 in Canada was 14.12 cases per 100,000 individuals per year. In 2017, the United States' Surveillance, Epidemiology, and End Results Program (SEER) database found the ASIR of melanoma to be 30.1 cases per 100,000 males, and 18.5 cases per 100,000 females across all ethnicities (38). When observing the United States ASIR trends for 2000–2018, a steady increase in incidence in both sexes was noted, similar to the evolution of CM in Canada, although the rate of change for males was more pronounced. Considering the north-to-south gradient that has been previously established (10), it is expected that the United States, with a great majority of its population living in warmer, sunnier climates has higher rates of CM than Canada. Furthermore, as expected, warmer countries with substantial population comprised of fair skin individuals have even higher rates of CM. The 2012 CM ASIRs for New Zealand and Australia were 35.8 and 34.9 cases per 100,000 individuals per year, respectively (39).

Ultraviolet radiation is the primary risk factor for CM, with sunlight acting as the main source for UV rays, along with artificial sources, such as tanning beds, booths or sun lamps (40–45). We noted an increase in incidence in all anatomic sites, with the male trunk and female extremities showing the most significant increases in incidence. Notably, out of all CM subtypes studied, acral lentiginous melanoma was the only one demonstrating a female predominance (56.9 *vs.* 43.1% in males) and was previously hypothesized to have been associated with increased exposure to UV nail lamps (at times in individuals taking a photosensitizing medication) (46–48). Considering this, in addition to targeting high risk geographic areas, it is of utmost importance to tailor recommendations for each sex/gender differently. According to the American Cancer Society, melanoma of the trunk and legs have the highest

TABLE 2 | Distribution of CM patient (A) incidence and B) mortality in Canadian provinces and territories. Incidence rate is per 100,000 individuals per year. (C) Clinical characteristics (anatomic site involved, sex and age) of CM in deceased individuals during 2011–2017.

A.

Province	Cases*	Population‡	Crude Incidence	Lower CI (95%)	Upper CI (95%)	Age-standardized incidence	Variance Rate, Poisson	Lower CI (95%)	Upper CI (95%)
Nova Scotia§	2,030	942,000	30.77	29.45	32.14	27.66	0.38	26.45	28.87
Prince Edward Island§	345	146,000	33.86	30.38	37.63	30.94	2.80	27.66	34.22
British Columbia±	11,830	4,709,000	20.89	20.39	21.38	19.78	0.057	19.31	20.25
New Brunswick§	1,200	760,000	22.55	21.20	23.77	19.99	0.34	18.85	21.13
Ontario§	21,445	13,634,000	22.47	22.17	22.77	22.24	0.023	21.95	22.54
Alberta#	4,385	4,045,000	15.49	15.03	15.95	17.91	0.074	17.38	18.44
Saskatchewan#	1,125	1,110,000	14.49	13.64	15.35	15.14	0.20	14.25	16.03
Manitoba#	1,460	1,281,000	16.28	15.45	17.14	16.99	0.20	16.12	17.86
Newfoundland and Labrador#	690	528,000	18.69	17.19	19.99	16.63	0.41	15.37	17.88
Northern Territories#	50	117,000	6.09	4.52	9.03	7.93	1.33	5.67	10.19
Canada (excluding Quebec)	39,615	27,272,000	20.75	20.54	20.95	N/A&	N/A&	N/A&	N/A&
B.									
Nova Scotia§	280	942,000	4.24	3.76	4.77	3.80	0.052	3.35	4.25
Prince Edward Island§	50	146,000	4.91	3.64	6.47	4.51	0.411	3.26	5.77
British Columbia#	940	4,709,000	2.85	2.67	3.04	2.69	0.0077	2.52	2.87
New Brunswick±	165	760,000	3.10	2.65	3.61	2.76	0.047	2.33	3.18
Ontario§	3,360	13,634,000	3.52	3.40	3.64	3.48	0.0036	3.36	3.60
Alberta#	585	4,045,000	2.07	1.90	2.24	2.46	0.011	2.26	2.66
Saskatchewan#	190	1,110,000	2.45	2.11	2.82	2.48	0.033	2.13	2.83
Manitoba#	215	1,281,000	2.40	2.09	2.74	2.43	0.028	2.11	2.76
Newfoundland and Labrador#	95	528,000	2.57	2.08	3.15	2.38	0.061	1.89	2.86
Canada (excluding Quebec)	5,880	27,272,000	3.08	3.00	3.16	N/A&	N/A&	N/A&	N/A&

C.

CM Mortality Trends		Number of patients*	% of reported case
Anatomical site	Lip + eyelid, including canthus	N/A	N/A
	Ear and external auricular canal	30	0.5
	Other and unspecified parts of face	90	1.5
	Scalp and neck	95	1.6
	Trunk	230	3.9
	Upper limb, including shoulder	115	2.0
	Lower limb, including hip	165	2.8
	Skin, unspecified	5,155	87.7
	Total	5,880	100
Sex	Male*	3,705	62.9
	Female*	2,185	37.1
Age (Both sexes)	0–19	N/A	N/A
	20–39	210	3.6
	40–59	1,240	21.1
	60–79	2,715	46.1
	80+	1,720	29.2
Age (Males)	0–19	N/A	N/A
	20–39	120	3.2
	40–59	755	20.4
	60–79	1,805	48.7
	80+	1,030	27.8
Age (Females)	0–19	N/A	N/A
	20–39	100	4.6
	40–59	480	22.1
	60–79	905	41.6
	80+	690	31.7

Case counts are rounded to the nearest 5.

‡*All population numbers are rounded to the nearest thousand.*

* $p < 0.01$.

§*Statistically significant higher rates than the national average.*

#*Statistically significant lower rates than the national average.*

±*Statistically not significant rates.*

&*The rates are adjusted to the Canadian average and, hence, the national rates remain unchanged.*

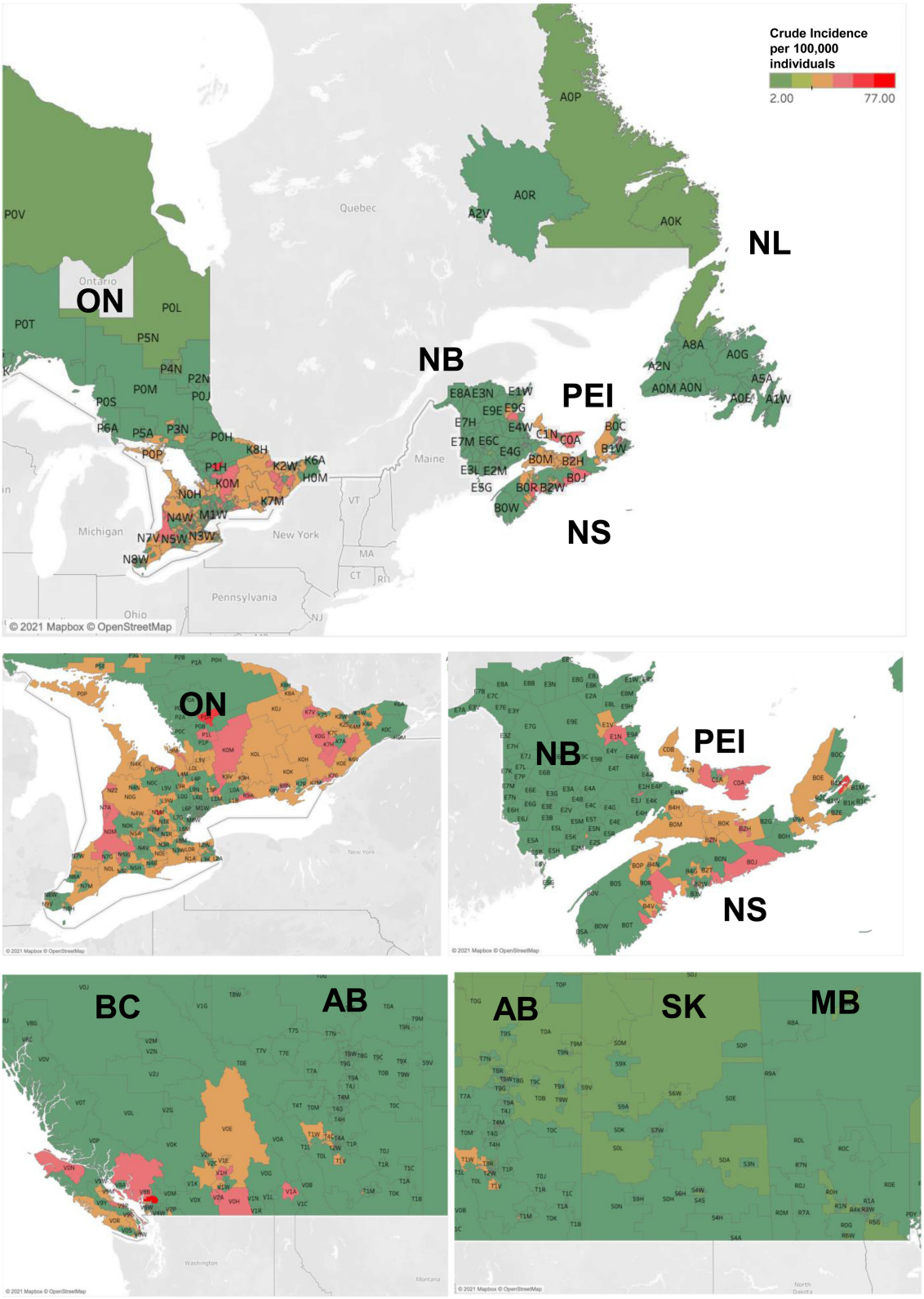

FIGURE 3 | Incidence and mortality rates of CM in Canadian provinces and territories during 2011–2017. Geographic maps illustrating incidence rates of CM (per 100,000 individuals per year) by Forward Sortation Area (FSA) postal code. NL- Newfoundland and Labrador; NS-Nova Scotia, NB-New Brunswick; PEI- Prince Edward Island; QC-Quebec; ON-Ontario; MB-Manitoba, SK-Saskatchewan; AB-Alberta; BC-British Columbia.

association to frequent sunburns, when compared to other sites (49). For this reason, public education campaigns targeting to protect high-risk anatomic sites in different sexes/genders are essential in preventing CM.

CM represents a significant patient and economic burden. Not only is it among the most common cancers found in adolescent and young adult populations, but it is also one of the leading skin cancers in terms of average years of life lost due to a disease (50). On average, an individual dying from melanoma loses 20.4 years of potential life (51). In 2015, melanoma was responsible for almost 1.6 million disease-adjusted life years (DALY) globally, which, when age-standardized, gave a rate of 23 DALYs per 100,000 individuals (52). The total estimated cost to the Canadian healthcare system of skin cancer in 2004 was $532 million, almost 85% of which was attributable to costs related to melanoma treatment (53). Projections concluded that by 2030's in Canada, the financial burden of skin cancer would rise to $1 billion annually, with melanoma consuming the greatest majority of these resources (53).

CONCLUSIONS

Effective programs to help decrease UV radiation exposure have been conducted. For instance, in Australia, a country with one of the highest incidence of CM in the world (54), due to effective public health campaigns, the proportion of adolescents/young adults who reported preferring having a tan decreased from 60% in 2003 to 38% in 2019 (55–57). Development of an effective campaign requires detailed knowledge of the population at risk, awareness levels, potential specific risk factors contributing to melanoma incidence and barriers to sun protection practices. This study represents an important step toward refinement of melanoma/skin cancer campaigns in Canada and provides important epidemiologic data for this vast and multicultural region of the world.

LIMITATIONS

Due to the nature of large, population-based studies, this retrospective analysis had several limitations including missing data and a risk of misclassification of patients (58). An important limitation was unavailability of data for Quebec during this period. Finally, this study could not explore confounding factors that influence melanoma incidence and mortality, including but not limited to ethnicity, clinical staging or Breslow thickness and patient socioeconomic status because this data was not available.

It is important to highlight that as Canada's healthcare system is a single-tier (payer), funded and operated by the provincial governments, the data is collected with consistency, where each provincial and territorial cancer registry identifies tumors in its population by combining information from multiple sources (cancer clinic files, radiotherapy and hematology reports, records from in-patient hospital stays, out-patient clinics, pathology and other laboratory/autopsy reports, radiology/screening program reports, medical billing and hospital discharge administrative databases). The CCR performs multiple processes to ensure accuracy including an internal record linkage to identify possible duplicate records.

Several studies investigated the detection rates/accuracy of diagnostic data in the largest provincial branch of the CCR: the Ontario Cancer Registry which collects data from the most populous province. In fact, a case ascertainment of ∼99%, a detection rate (detecting and accurately assigning index tumor site) of 81.4–96%, and a confirmation rate (correctly assigning tumor site) of 90.9% were documents by several studies (59–61), which confirms the high quality of data and detection rates in the examined registries.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SC and FG collected data, plotted and analyzed data, plotted the figures, and wrote the initial draft of the manuscript. ML and AA collected data. FL, IM, JC, AM, WM, JC, TS, EN, and RG analyzed data, prepared tables and figures, and co-wrote the manuscript. HN and ER performed statistical analyses. DS collected data, performed statistical analyses, and wrote the article. IL collected data, obtained funding, designed and supervised the study, and wrote the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.830254/full#supplementary-material

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REVIEW
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Unmet Medical Needs in Chronic, Non-communicable Inflammatory Skin Diseases

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An estimated 20–25% of the population is affected by chronic, non-communicable inflammatory skin diseases. Chronic skin inflammation has many causes. Among the most frequent chronic inflammatory skin diseases are atopic dermatitis, psoriasis, urticaria, lichen planus, and hidradenitis suppurativa, driven by a complex interplay of genetics and environmental factors. Autoimmunity is another important cause of chronic skin inflammation. The autoimmune response may be mainly T cell driven, such as in alopecia areata or vitiligo, or B cell driven in chronic spontaneous urticaria, pemphigus and pemphigoid diseases. Rare causes of chronic skin inflammation are autoinflammatory diseases, or rheumatic diseases, such as cutaneous lupus erythematosus or dermatomyositis. Whilst we have seen a significant improvement in diagnosis and treatment, several challenges remain. Especially for rarer causes of chronic skin inflammation, early diagnosis is often missed because of low awareness and lack of diagnostics. Systemic immunosuppression is the treatment of choice for almost all of these diseases. Adverse events due to immunosuppression, insufficient therapeutic responses and relapses remain a challenge. For atopic dermatitis and psoriasis, a broad spectrum of innovative treatments has been developed. However, treatment

responses cannot be predicted so far. Hence, development of (bio)markers allowing selection of specific medications for individual patients is needed. Given the encouraging developments during the past years, we envision that many of these challenges in the diagnosis and treatment of chronic inflammatory skin diseases will be thoroughly addressed in the future.

Keywords: medical need, skin, inflammation, atopic dermatitis, psoriasis, alopecia areata, chronic spontaneous urticaria, hidradenitis suppurativa

CHRONIC, NON-COMMUNICABLE INFLAMMATORY SKIN DISEASES

Chronic, non-communicable skin inflammation can be caused by many different diseases. Herein, we categorized these into (i) chronic inflammatory diseases (atopic dermatitis, psoriasis, lichen planus, chronic prurigo, and hidradenitis suppurativa), (ii) autoimmune diseases (alopecia areata, vitiligo, chronic spontaneous urticaria, pemphigus, bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquisita), (iii) autoinflammatory diseases (cryopyrin-associated periodic syndrome and Schnitzler's syndrome), and (iv) rheumatic diseases (cutaneous lupus erythematosus, dermatomyositis, and systemic sclerosis). This categorization is based on the main driving pathomechanism(s) of each disease. However, a clear classification of the pathologic driver is challenging as in lichen planus and psoriasis autoreactive T- and B- cells potentially contribute to disease pathogenesis (1, 2). This classification is also expected to change over time, as it will need to adopt and consider new data on disease pathogenesis. Alternatively, to the here used classification, chronic inflammatory skin diseases may be categorized based on key driving molecules. For example, Janus kinases (JAK) in atopic dermatitis, alopecia areata, vitiligo, and cutaneous lupus erythematosus. Furthermore, as detailed below, for many chronic skin inflammatory diseases the clinical presentation varies greatly even within the same disease, as with psoriasis or bullous pemphigoid (3, 4). With the emerge of multidimensional datasets, it has been proposed to classify inflammatory skin diseases based on molecular patterns (5). The increasing understanding of (molecular) disease pathogenesis and availability of appropriate biomarkers for their identification, we expect a more complex, but more tailored categorization of molecular disease pathogenesis is leading to the emergence of potential biomarkers, and a more categorization of chronic, non-communicable skin inflammatory diseases. These diseases are a major medical burden because of their high and, in many cases, increasing prevalence (**Table 1**), diagnostic challenges, lack of curative treatments, co-morbidity, as well as significant economic impact. We here selected 17 chronic, non-communicable skin inflammatory diseases that collectively affect 15–20% of the population (**Table 1**). For each disease, the current diagnostic and therapeutic challenges are outlined. Furthermore, a perspective is given on how these challenges may be met in the future.

CHRONIC INFLAMMATORY SKIN DISEASES

Atopic Dermatitis

Atopic Dermatitis (AD) or atopic eczema is a common, chronic, relapsing inflammatory disease, affecting up to 30% of the pediatric population and 2–10% of adults (36). While most commonly symptoms start in the first 5 years of life, it is now recognized that onset can occur at any age. There can be a significant effect on patient's quality of life and sleep due to itch and pain (37). There are also significant effects on patients' mental health with higher incidence of depression and suicide (38). The high burden of disease can interfere with work productivity, not only from the baseline disease but particularly from flares (39). Patient also have many out-of-pocket costs, including cleaning products, clothing, moisturizers, and other expenses (40). In AD, there is an interplay between barrier dysfunction, immune dysregulation, and the microbiome (41). Both genetics and environmental factors play a role in the pathogenesis (42). In AD, the stratum corneum, composed of the terminally differentiated enucleated keratinocytes called corneocytes, is often compromised. Among European Caucasians, filaggrin mutations are associated with early-onset and severe AD (43). Filaggrin is broken down into compounds that constitute natural moisturizing factor which is important for appropriate hydration, desquamation, plasticity, acidity, and the commensal microbiome (44, 45). Patients with AD have a higher burden of Staphylococcus aureus which contributes to the inflammation (46). As allergens penetrate the defective skin barrier in AD, pro-inflammatory cytokines are released. While a type 2 immune response with elevated levels of IL-4 and IL-13 predominate in the acute phase, chronically, a mixed response of Th1, Th17, and Th22 immune cells is observed (47). IL-31 is particularly implicated in pruritus (48).

Diagnosis

AD is usually diagnosed based on clinical experience (**Figure 1A**). There are diagnostic criteria, but no simple test for definitive diagnosis (49). When patients manifest in atypical locations, develop lesions later in life, have uncommon morphologies or other overlying skin diseases the diagnosis can be challenging. AD is heterogenous and can show racial variation (50). Asians may manifest with well-demarcated lesions and skin of color patients may have increased xerosis, follicular eczema, and post-inflammatory pigmentation changes (51).

TABLE 1 | Epidemiology of selected chronic inflammatory skin diseases.

Disease	Prevalence rate	Sex distribution	Ethnic/geographic predisposition	Notable trends	References
Atopic dermatitis	10–30% in children and 2–10% in adults	Almost equal sex distribution	Higher in high-income countries	Two- to three-fold increase over the past several decades	(6–8)
Psoriasis	2–3%	Equally prevalent in both sexes	Most common in populations of northern Europe and least common in eastern Asia	An apparent upward trend is observed in several countries	(9–11)
Prurigo nodularis	0.1%	Higher among females	None	Increasing incidence over time	(12, 13)
Lichen planus	0.2–1.3%	Equally prevalent in both sexes	CLP: equally prevalent in both sexes MLP: more frequent in the female population LPP: more frequent in the female population	NA	(14, 15)
Hidradenitis suppurativa	0.1–1.3%	Overall almost equal distribution, but varies between races	Higher in African Americans	NA	(16–18)
Alopecia areata	2%	Slightly higher among females	Higher in African American and Hispanics	The incidence is increasing over time	(19)
Vitiligo	0.2–1.8%	Higher among females	Higher prevalence in African nations	Constant or decreasing frequency in the past decades	(20)
Chronic spontaneous urticaria	0.1–1.4%	Slightly higher among females	Higher prevalence in Asian nations	Increasing incidence over time	(21)
Pemphigus	Orphan	Higher among females	Higher in Ashkenazi Jewish and Mediterranean population	Inconsistent findings	(22, 23)
Bullous pemphigoid	Orphan	Higher among females	None	1.9- to 4.3-fold rise over the past two decades	(24)
Mucous membrane pemphigoid	Orphan	Higher among females	None	NA	(23)
Epidermolysis bullosa acquisita	Orphan	Equally prevalent in both sexes	HLA-DR2 and HLA-DRB1*15:03-associated susceptibility among Africans	NA	(23, 25, 26)
Cryopyrin-Associated periodic syndrome	Orphan	Equally prevalent in both sexes	None	NA	(27, 28)
Schnitzler's syndrome	Orphan	Higher among males	None	NA	(29, 30)
Cutaneous lupus erythematosus	Orphan	Higher among females	Higher in Māori/Pacific population	NA	(31, 32)
Dermatomyositis	Orphan	Higher among females	Higher among Africans and Hispanics	Increasing incidence over time	(33, 34)
Systemic sclerosis	Orphan	Higher among females	Higher among Africans and Hispanics	Increasing incidence over time	(34, 35)

Orphan, Disease prevalence 5/10,000 or less; NA, not applicable.

Allergic contact dermatitis may overly AD, so patch testing should be considered in those with recalcitrant atopic dermatitis. AD is notably associated with other atopic disorders such as asthma, allergic rhinitis, and food allergies. There also has been an association with obesity, malignancy, and cardiovascular disease (52–54). For a precision medicine approach, validated and reliable biomarkers are needed to individually tailor treatment (55).

Treatment

Treatment is mainly aimed at restoring the skin barrier and modulating the abnormal immune response. Education on skin hygiene strategies is important for all patients, ideally with written action plans. There is uncertainty as to ideal bathing recommendations as it may improve skin hydration and provide some symptom relief while use of detergents may have a dehydrating effect. Emollients are a cornerstone of treatment

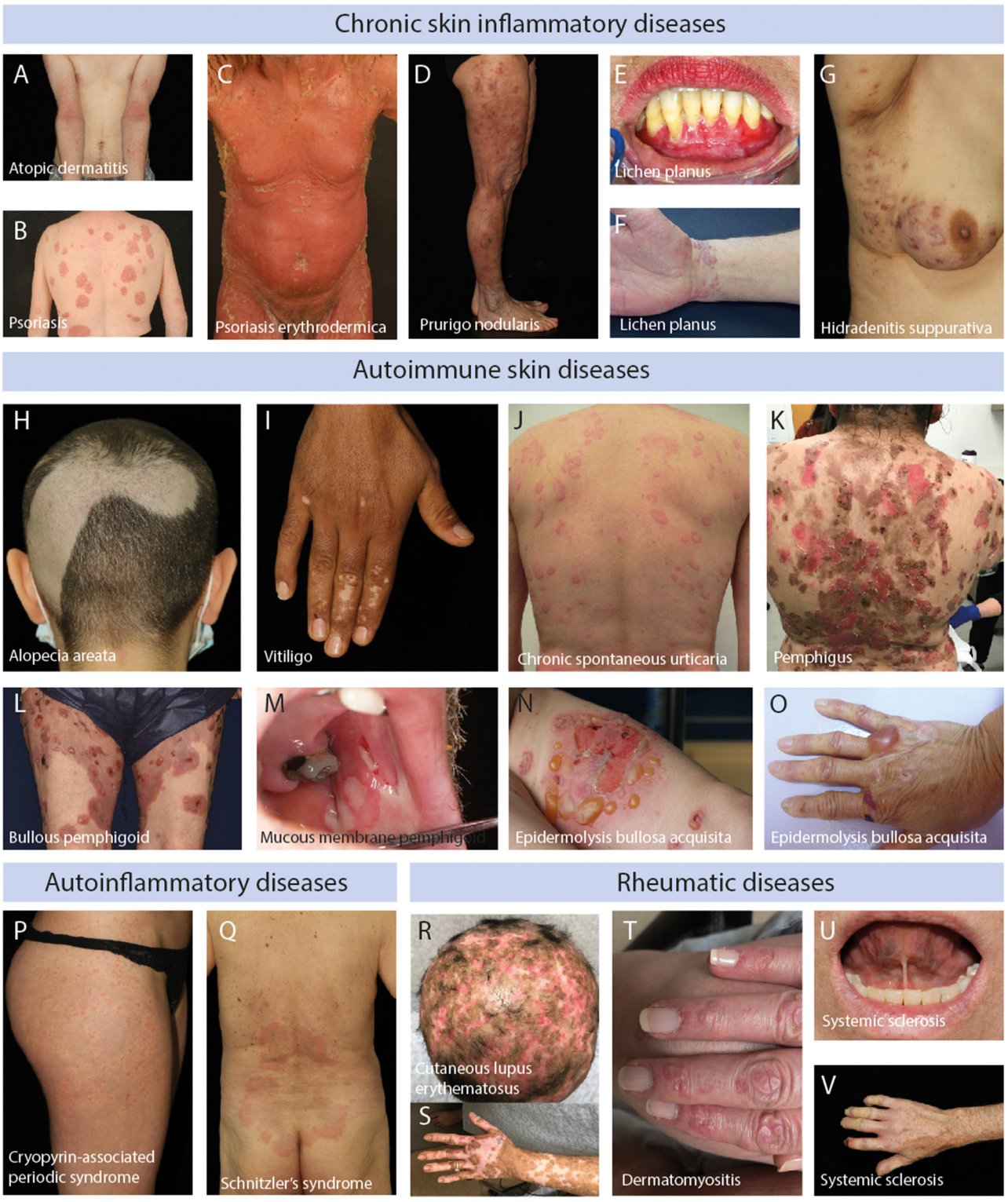

FIGURE 1 | Clinical images of patients with chronic skin inflammatory diseases. **(A)** Blurry erythema and lichenification at the inside the bend of the elbows and arms of a patient with atopic dermatitis. **(B)** Sharply demarked, scaling, erythematous plaques at the back of a patient with psoriasis vulgaris. **(C)** Generalized erythema and scaling in a patient with psoriasis. **(D)** Erythematous nodules, partially excoriated, in a patient with prurigo nodularis. **(E)** Erosions of the lower gums in a patient with mucosal lichen planus. **(F)** Polygonal, scaling, reddish-violet plaques at the wrist of a patient with cutaneous lichen planus. **(G)** Scaring, nodules and pustules located at the sub-axillary region of a patient with hidradenitis suppurativa. **(H)** Sharply demarked hair loss at the back of the head in a patient with alopecia areata.

(Continued)

FIGURE 1 | (I) Sharpley demarked white maculae at the hands of a patient with vitiligo. **(J)** Wheals at the back of a patient with chronic spontaneous urticaria. **(K)** Brown macules and erosions at the back of a patient with muco-cutaneous pemphigus vulgaris. **(L)** Tense blisters on erythematous skin on the legs of a patient with bullous pemphigoid. **(M)** Oral erosions in a patient with mucous membrane pemphigoid. **(N)** Tense blisters on erythema on the arm of a patient with inflammatory/non-mechano-bullous epidermolysis bullosa acquisita. **(O)** Tense blister and scaring on the hand of a patient with predominant mechano-bullous epidermolysis bullosa acquisita. **(P)** Wheals at the leg of a patient with cryopyrin-associated periodic syndrome. **(Q)** Urticarial exanthema at the lower back of a patient with Schnitzler's syndrome. **(R)** Alopecia and erythema at the head of a patient with cutaneous lupus erythematosus. **(S)** Erythema and depigmentation at the arm of a patient with cutaneous lupus erythematosus. **(T)** Gottron papules in a patient with dermatomyositis. **(U)** Shortening of the sublingual frenulum in a patient with systemic sclerosis. **(V)** Raynaud's phenomenon (anemic color of the fingers) and necrosis of the index finger in a patient with systemic sclerosis.

and can lead to a decrease in the amount of prescription topical agents needed to treat AD (56). However, it is not known the optimal amount or frequency of emollient application. Additionally, there are some moisturizers that may irritate the skin of individual patients. Besides emollients, topical agents including corticosteroids are first-line therapy. Non-steroidal options such as topical calcineurin inhibitors (TCIs) are useful for areas of sensitive skin such as face, neck, and genitals. Calcineurin inhibitors can also be used as maintenance twice a week to reduce the frequency and severity of flares (57). While there was initial concern regarding the use of TCIs and the risk of malignancy, post-marketing research has been reassuring as to the safety of these treatments (58). In patients who fail topical treatment, phototherapy, oral immunosuppressants, and targeted biologics are indicated. In particular, the anti-IL4 receptor alpha inhibitor dupilumab has changed the way we treat AD in both pediatric and adult patient. While sedating antihistamines for short-term use can assist with sleep disturbance caused by pruritus, there is a lack of evidence to support the use of non-sedating and sedating antihistamines for generalized, extended use. Due to cumulative side effects, oral corticosteroids should be avoided in the long-term and in children. There are many exciting new mechanisms of action in development (or very recently approved) to treat atopic dermatitis including aryl hydrocarbon receptor agonists, commensal bacteria, JAK inhibitors (JAKi), and new biologics that target IL-13, IL-31, IL-33, and OX-40 (59, 60).

Perspectives

Atopic dermatitis is one of the most common inflammatory skin disorders and there are still multiple unmet needs and educational gaps. Instructing patients and caregivers regarding skin hygiene with liberal use of emollients is essential for all. Additionally reassuring fears of corticosteroids is an important task of providers. There is no generally accepted goal of treatment, so currently plans are individualized for patients with a need for biomarkers and research into personalized medicine. Adherence to therapy remains a long-term challenge as care of atopic dermatitis can be quite time consuming and costly. There are an increasing number of therapeutic options that are being developed due to our improved understanding about the pathogenesis of AD and with it, improved hope at helping more patients who suffer from atopic dermatitis.

Psoriasis

Over the past three decades, psoriasis has become a model disease for the study of chronic inflammatory diseases. Several new drugs have been and are being developed first for psoriasis and then extended to other indications (61). Central to our current understanding of the pathogenesis of psoriasis is a close interaction between components of the innate and adaptive immune systems (62, 63). For example, the former branch is represented by macrophages, neutrophilic granulocytes, and (plasmacytoid) dendritic cells; the latter by T lymphocytes, primarily Th17 cells. Communication between these immune cells is mediated by various cytokines including TNFα, IL-17, and IL-23 which have become targets of multiple biologic therapies (64, 65).

Diagnosis

Psoriasis is diagnosed based on history and clinical presentation—only rarely a biopsy is needed to confirm the diagnosis. Comorbidity, especially psoriatic arthritis should be excluded at diagnosis and during follow-up (62). However, psoriatic disease is not a uniform disease entity (**Figures 1B,C**). Although current drugs were developed and approved for the so-called chronic plaque psoriasis, we encounter psoriasis in the clinic as a spectrum ranging from acute exanthematous to chronic stable, from classically scaly and sharply demarcated plaques to highly inflammatory, pustular or erythrodermic forms, or from forms restricted to a few predilection sites to generalized or inverse forms. Specific underlying genetic patterns have now been identified for some of these manifestations; e.g., in *IL36RN* (3, 66). The involvement of other organ systems (comorbidity) and provoking factors in psoriasis as a systemic disease also influence the disease process. To account for the increased inflammation throughout the organism with (possible) systemic impairment of several other organ systems, we now tend to refer to it as psoriatic disease.

Treatment

There are well-defined guidelines for the treatment of psoriasis (67, 68). The following drugs are FDA or EMA approved for psoriasis and/or psoriatic arthritis: TNFα inhibitors etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab; IL-17a inhibitors secukinumab and ixekizumab; IL-17A and IL-17F dual inhibitor bimekizumab; IL-17 receptor A/C inhibitor brodalumab; IL-12 and IL-23 inhibitor, ustekinumab; and IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab (69–72). Very recent developments also include mirikizumab and netakimab (73). The development of specific therapeutics against essential cytokines in the IL-23/IL-17 axis is a good illustration of how basic and translational immunological research has led to the development of highly potent drugs that can effectively and safely treat most patients with at least moderate psoriasis.

These therapies have been and continue to be included in current guidelines (67, 68, 74, 75). In addition, small-molecule drugs have been and are being developed, such as apremilast against phosphodiesterase 4 (PDE4), deucravacitinib against tyrosine kinase 2 (Tyk2) and piclidenoson, a Gi protein-associated A3 adenosine receptor agonist (73). Compared to the era before biologics, the impact has been so great that it is fair to label these treatments revolutionary. Thus, we are now in a fairly comfortable position with regard to the treatment psoriatic disease: there are now numerous effective and well-tolerated preparations available and due to competitive pressure and the increasing availability of biosimilars, the price will (hopefully) come down in such a way that more and more patients can be treated with these systemic therapeutics. Still, there are still unmet medical needs for psoriasis that related to diagnostics and treatment. Specifically, in terms of personalized and precision medicine, however, there is definitely still a need for development here, since by no means do all of our patients meet the "standard" of chronic plaque psoriasis, which is usually considered in registration studies. On this basis, later extensions of indications are also conceivable for diseases that have similar pathogenetic features and for which, due to their relative rarity, large prospective clinical trials are usually not conducted (76). The categorization and characterization of inflammatory and autoimmunity patterns, which is already under development, may help in this regard (77). There is also not yet enough data on combination therapies for psoriasis (78). In particular, combinations of modern and conventional therapies could in some cases increase effectiveness and reduce costs. Similar considerations apply to individualized dosing regimens and terminations of therapies.

Perspectives

It is thus clear that the pathogenesis of psoriasis is complex. Increasingly, it is becoming clear that the overall pattern of inflammatory mediators and cells, which may well shift over the course of the "disease career," is ultimately responsible for the individual form of manifestation. Therefore, it is reasonable to strive for a more detailed understanding of these inflammatory patterns and the factors regulating them on a "holistic" level. Hence, the establishment and clinical validation of biomarkers and molecular genetic patterns could enable predictions of response or loss of efficacy of specific therapies in individual patients (79). If successful, patients could quickly and sustainably receive the most appropriate therapy for them and we would avoid unnecessary delays, side effects and costs. This is only beginning to happen and should improve over time (80). Regarding therapeutics, development is proceeding in two major directions: On the one hand, further mediators are being inhibited in a targeted manner and with more refined methods and reagents. The most recently approved example is an antibody that blocks the effects of both IL-17A and IL-17F (bimekizumab) (81). The clinical effectiveness of this approach is convincingly good. The development was prompted by scientific findings that although IL-17A, which was initially considered, has a much higher affinity at the receptor, that the homologous IL-17F isoform is present in much greater amounts in psoriatic skin. In addition, IL-17A and IL-17 F may also act as heterodimers at the receptor (82). Other interesting developments also include mediators that have been primarily attributed to more innate immune mechanisms that may factor more strongly in therapeutic considerations and developments. A good example of this is the development of IL-36 antagonists or blockade of other members of the IL-1 family (83), which are proving to be promising in pustular and highly inflammatory forms of psoriasis (84). Besides biologics, small-molecules which are orally available and able to penetrate cells are being pursued. They inhibit central signaling pathways in pathogenetically relevant cell types. Due to their small molecular size, these substances are in principle also suitable for topical application. In contrast to the older preparations such as methotrexate, retinoids, or fumaric acid esters, whose effects are quite broad and where mechanisms have not yet been completely clarified, the newer preparations have a more selective effect. Despite supposed selectivity, however, the effect is sometimes more pleiotropic and there are more off-target effects than with biologics. The first compound approved for the treatment of psoriasis in this group is the PDE4 inhibitor apremilast. In late stages of clinical development is the TYK2 inhibitor deucravacitinib, which in clinical trials offers quite convincing clinical effects with a good safety profile. The background for the latter development is the recognition that many mediators, for example type I interferons or IL-23, mediate their inflammatory signals via Janus kinases (JAK, to which TYK2 also belongs) (85, 86). Thus, by blocking these signaling molecules, an (indirect) inhibition of inflammatory mechanisms can be achieved.

To address most of these challenges, it is likely that proteogenomic approaches will have to be expanded, implemented and/or developed in conjunction with sophisticated immunological-functional studies. These will need to be supported by comprehensive "real world" data, for example from registry studies, to capture the full actual spectrum of psoriatic disease. Only in this way will it be possible to stratify the heterogeneous population of patients with psoriatic disease even more precisely in cross-section and to characterize it down to the level of the individual. It will also enable a more accurate longitudinal characterization of the disease over its lifelong course. The ultimate goal must be to find and apply the most effective, and at the same time best tolerated therapy for each individual patient at any point in their "disease career," sometimes in a quite variable manner (87).

Prurigo Nodularis

Prurigo nodularis (PN) belongs to the spectrum of chronic prurigo and it is the dominant phenotype for 70% of patients with chronic prurigo (13, 88, 89). Chronic prurigo is a persistent and burdensome neuroinflammatory dermatosis associated with severe itching, permanent scratching behavior and diverse comorbidities. Among the comorbidities, for example atopic predisposition, atopic dermatitis, bullous pemphigoid, lichen planus, chronic kidney disease, hepatobiliary diseases, diabetes mellitus, chronic iron deficiency, HIV, and solid tumors have been reported to be causally related to PN (90). However, the role

of these comorbidities as etiological factor in PN is still debated and needs additional studies. PN affects both sexes, all races and all ages with a preference for females above age of 60 years (90). Children may be affected, but this is very rare. Epidemiological studies are infrequent and report different prevalences depending on the method and population included (13, 91, 92). For example, Poland reported an estimated prevalence of 6.5/100,000, USA of 36.7 to 43.9/100,000 and Germany up to 100/100,000. However, all studies seem to argue for the fact that PN is not really a rare disease. Currently, neuroimmune mechanisms are considered the dominant mechanism underlying PN (93). In PN skin, different helper T cell phenotypes have been identified including Th1, Th2, Th17, and Th22 cells. Especially Th2 cytokines such as interleukin (IL)-4 and IL-31 are abundantly present in PN skin. Cutaneous sensory C- and Ad- nerve fibers express corresponding IL receptors. This enables a close neuroimmune communication with continuous stimulation of nerve fibers, their release of neuropeptides and induction of itch. Interestingly, IL31 has a prominent role not only enhancing the inflammation, but also leading to epidermal hyperplasia and fibrosis formation of the dermal collagen tissue. In addition to IL-31, also upregulated periostin might promote fibrosis formation by releasing IL31 from various immune cells (94, 95) from various immune cells. Fibrosis is a prominent feature in PN and distinguishes the disease histologically from atopic dermatitis. In addition, IL-4 plays a major role in fostering neuroimmune communication and neuronal hypersensitivity *via* the IL-4Rα/JAK pathway. Recent studies suggested that nerve fiber dysfunction and structural neuroanatomical changes are present in PN skin which are induced by scratching and maintained by inflammation (96, 97).

Diagnosis

The diagnosis of PN is made clinically (98). PN is characterized by symmetrically distributed nodules; papules, and plaques may occur (**Figure 1D**). The severity of PN can range from some single nodules to several hundreds. All lesions are itchy and subject to scratching, formation of excoriations and bleeding. Lesions are found mainly on the extensor surfaces of the extremities and trunk with a typical butterfly sign at the back (lack of lesions at the central back which can be explained by the patient's inability to scratch these skin areas). Palms, soles and the face are rarely affected. PN can be documented by a PN-specific, validated investigator global assessment (99). The validated investigator questionnaire Prurigo Activity and Severity Score (PAS) assesses several parameters of the disease such as type, number, and distribution of pruriginous lesions, proportion of PN lesions with excoriations and proportion of healed lesions (100). Itch intensity is monitored best with validated instruments such as the numerical rating scale (NRS) for example as it is also done in other types of pruritus (101). The health-related quality of life can be documented either by Dermatology Life Quality Index (DLQI) or the itch-specific ItchyQol (102).

Treatment

The first international guideline on diagnostic and therapy of PN recommends a laddered approach to treat PN (98). The first two steps comprise topical and intralesional corticosteroids, topical calcineurin inhibitors, capsaicin, systemic antihistamines and UV-phototherapy. In the third step, either neuronal therapies or immunosuppressants are advised such as gabapentinoids, antidepressants as well as cyclosporine and azathioprine. The clinical findings (inflamed vs. non-inflamed nodules) and quality of itch (itch with pain, burning and stinging) may guide to the right therapy.

Perspectives

Novel, effective, safe and approved therapies are urgently needed as patients are in general dissatisfied with the currently medical care (103). Currently, opioid modulators and investigational substances (dupilumab, nemolizumab) are recommended as off-label treatments in refractory cases (104, 105). For some of these substances, clinical trials are currently being conducted. For example, opioid modulators as well as IL4 and IL31 receptor antibodies are in current pharmaceutical development. IL31 signals through a heterodimeric receptor complex consisting of IL-31 receptor α (IL-31RA) and oncostatin M receptor β (OSMRβ). Novel substances target each of the two receptor components and are in phase II and phase III stage of development.

Lichen Planus

Lichen planus (LP) is a chronic immune-mediated disease which affects skin, mucosa and skin appendages. LP is the prototype of a lichenoid dermatosis which is characterized by a dense dermal T cellular and macrophage-rich infiltrate. LP is a common disease with an incidence in the general population is up to 1.27%. While LP is most common in the third and sixth decade, it may occur at any age. Mucosal LP (MLP) shows a prevalence of 0.89% and it is more commonly diagnosed in the female population. Involvement of the scalp is also more often reported in female patients, with a sex ratio close to 5:1. Clinically, we recognize three major subtypes of LP: cutaneous LP (CLP), MLP, and LP of the scalp, classically called lichen planopilaris (LPP) (14, 106, 107). CLP is classically characterized by violaceous, polygonal, slightly scaling and extremely pruriginous flat papules, which affect mostly the extremities (**Figures 1E,F**). Typically, CLP lesions show Wickham striae, whitish net-like lines that represent the clinical expression of the histologically seen epidermal hypergranulosis. Furthermore, several variants of CLP have been reported in the literature, including annular LP, atrophic LP, and LP verrucosus. A rare entity is represented by LP pemphigoides, which is clinically characterized by papules and blisters and serologically by the detection of IgG autoantibodies against BP180 and BP230 (108–110). MLP affects most frequently the oral mucosa. It has been more often described in female patients in the fourth decade (107). Clinically, MLP of the oral cavity is characterized by Wickham striae, erythematous macules, and, in some aggressive cases, by ulcerations (**Figure 1E**). A concomitant genital involvement has been reported in every second female patient affected by oral MLP (106). LP can involve other mucosal

sites, including ocular, laryngeal, and esophageal mucosa. In the last case, the presence of dysphagia or odynophagia has been frequently reported, in 80 and 30% of cases, respectively (111). LPP is clinically characterized by red papules or plaques and perifollicular erythema. The chronic inflammation leads to destruction of hair follicles and to development of scarring alopecia. Patients affected by LPP may experience itching, burning of the scalp, and hair fragility. LPP requires an intensive and long-lasting therapy because of the characteristic refractory course of the disease. A variety of drugs may trigger LP, including antibiotics (e.g., dapsone and tetracycline), antifungal, and antimalarial drugs. Therefore, a detailed pharmacologic history is mandatory. The typical histological feature of LP is a band-like lymphohistiocytic infiltrate at the dermal-epidermal junction and in the upper dermis. Furthermore, hypergranulosis, irregular hyperplasia of the rete ridges with a classical saw-toothed pattern, and basilar vacuolar degeneration have been typically reported. Apoptosis of epidermal keratinocytes leads to the development of Civatte bodies, described as rounded, homogenous, eosinophilic cellular deposits in the upper dermis that can be identified by PAS staining and direct immunofluorescence microscopy (112).

Diagnosis

The diagnosis should be performed according to the clinical and histopathological features. In addition, several differential diagnoses should be excluded, such as lichenoid drug eruptions, lichen planus pemphigoides, graft-vs. host disease, granuloma annulare, oral candidiasis, and oral leukoplakia (113). However, diagnosis is often delayed because of the highly variable clinical appearance and inconsistent histopathological findings in LP (114).

Treatment

At times, LP may pose a therapeutic challenge. Indeed, some clinical variants are characterized by a refractory course, especially LPP, ulcerative oral LP and genital LP (14, 109). In CLP topical steroid treatments usually in combination with UVB or PUVA phototherapy are recommended. In recalcitrant cases, oral prednisone or oral retinoids may be useful (115). Oral LP can be initially treated with topical potent corticosteroids (e.g., clobetasol propionate 0.05%). Intralesional injection of corticosteroids can be useful in ulcerative oral LP. In addition, an off-label therapy with topical application of pimecrolimus or tacrolimus can be used. In case of severe involvement of the oral mucosa, several systemic therapies have been tried, including systemic corticosteroids, azathioprine, methotrexate, and retinoids (115, 116). In LPP an early and rapid control of inflammation is of pivotal importance to prevent the development of scaring alopecia. Topically, potent corticosteroids can be used in moderate cases (115). Alternatively, treatment with topical calcineurin inhibitors or with topical JAKi (e.g., tofacitinib) have been shown to be effective (109, 117). In more aggressive cases, a concomitant treatment with systemic corticosteroids is recommended. Alternatively, hydroxychloroquine or methotrexate can be used as second-line treatment. In recalcitrant cases, mycophenolate mofetil or cyclosporine A can be used as off-label treatment (118).

Perspectives

Recently, the use of anti-IL-17, anti-IL-12/IL-23, and anti-IL-23 monoclonal antibodies was reported to lead to an improvement of oral ulcerations in extremely refractory cases (109). This off-label use of these therapeutics was based on the observation of a Th1/Th17-dominated cell response in the peripheral blood of LP patients (1). To address, if this pathway is amendable to pharmacological interventions, a total of five patients with lichen planus were treated in a compassionate use trial. Of these, three received secukinumab, one patient ustekinumab and one guselkumab. In all cases, marked improvement was documented within the 12-week observation period. Of note, the clinical improvement was accompanied by a strong reduction of the Th1 and Th17/Tc17 cellular mucosal infiltrate, suggesting that IL-17-producing T cells are central to disease pathogenesis (109) At this regard, an open label, parallel, randomized, multi- center, phase II trial to evaluate the efficacy, ssafety, and tolerability of guselkumab in patients with oral LP is now ongoing (EudraCT Number: 2021-000271-36). In addition, a phase II study to evaluate the efficacy, safety, and tolerability of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven clinical variants of LP is ongoing (EudraCT number 2019-003588-24). Furthermore, JAKi have emerged as promising therapeutic agents in LP (14, 117).

Hidradenitis Suppurativa

Patients with hidradenitis suppurativa (HS) suffer from chronic painful inflammatory skin lesions in intertriginous sites (119) (**Figure 1G**). The manifestation of the disease mostly occurs around the age of 25. The average prevalence rate of HS is 0.2–0.4%, with highest rates in the Caucasian (0.75%) and the African American populations (1.3%) (17). Both sexes are affected with similar frequencies (16, 18, 120). Besides skin alterations, HS patients commonly suffer from numerous systemic comorbidities such as metabolic syndrome, spondyloarthritis or spondyloarthropathy (SpA), mental depression, and inflammatory bowel disease (121–125). HS leads to profound impairment in the quality of life of affected people, which is much more pronounced than the impairment caused by other dermatoses (16, 126). Furthermore, HS is associated with patients' body image impairment and increased suicidal behaviors (127–129). Ischemic heart diseases as well as accidents and violence (incl. suicides) contribute to the massively shortened (∼15 years) life expectancy of patients with HS (130).

Diagnosis

The diagnosis of HS is based solely on the physical examination and medical history (119). HS is confirmed when the following criteria are met: (i) typical skin alterations such as inflammatory nodules, abscesses, inflamed and draining tunnels (sinus tracts or fistulas), and rope-like scarring, (ii) in typical localizations such as in axillary (armpits), inguinal (groin), gluteal, perianal, and submammary (women) areas of the body, and (iii) typical occurrence, i.e., persistent (at least 6 months) or recurrent (>2 skin lesions occurring or recurring within 6 months) (119). Surprisingly, diagnosis is frequently delayed, although

the diagnostic criteria are very clear (120). In Germany, the average duration between the manifestation of first symptoms and the HS diagnosis is 10 years (120). Importantly, the longer the delay of diagnosis, the more misdiagnoses, the greater the disease severity at diagnosis, and the higher the number of concomitant diseases (120). Various clinical scores are used to assess the severity of HS skin alterations. The International Hidradenitis Suppurativa Severity Score System (IHS4) is becoming increasingly important. It is a dynamic score based on the number of nodules, abscesses, and draining tunnels and allows dividing the severity of the disease into mild, moderate, severe (131). Patient-reported outcome measures, like DLQI, are also often used to assess the disease impact (132–134). Several blood biomarkers reflecting the activity of the immune system have been suggested, but none of them is currently used in everyday practice (135–137).

Treatment

Treatment options for HS lesions include pharmacological therapies (local and systemic) and surgical treatments (119). The choice of therapy depends on the type and severity of the skin lesions as well as the patient's expectations. Individual inflamed nodules can be treated with topical antiseptic or antibiotic ointments or creams. If there are several inflamed nodules or abscesses, local therapy is supplemented by systemic pharmacological treatment. Irreversible skin alterations such as tunnels and scars can be effectively treated by surgery. Therefore, it is highly important to prevent such alterations from occurring through timely and effective pharmacological therapy. A combination of clindamycin and rifampicin is commonly used for systemic treatment. However, surgical and conventional pharmacologic therapies of HS are not associated with long-lasting improvement of patients' quality of life (132). Furthermore, the anti-TNF-a antibody adalimumab is the only approved systemic treatment for HS so far (119). Thus, one of significant challenges in HS care is the lack of further systemic treatment options. This limitation is basically due to our limited understanding of the molecular and immunological processes underling the formation and persistence of skin alterations in HS (138). TNF-a, IL-1, 5-lipoxygenase and G-CSF are thought to have a role in HS pathogenesis, but the pathophysiology is not well-understood (139–142).

Perspectives

Due to the long delay in diagnosis, the enormous impairment of the quality of life caused by HS and the limited range of evidence-based therapies, patients with HS have an enormous unmet medical need. To change this situation, first and foremost the time interval between first symptoms and diagnosis must be significantly shortened. This is extremely important because of the progressive nature of the disease that over time leads to irreversible skin destruction. To this end, the patients must be pharmacologically treated as soon as the first symptoms appear. Training of doctors such as general physicians, dermatologists, surgeons, and gynecologists, as well as programs to raise/create the awareness of the disease within large parts of the society are needed. It is gratifying that many clinical trials with a focus on new systemic pharmacological treatment are currently being carried out. However, these are often without a well-founded scientific rationale and a better understanding of disease mechanisms is needed. Thus, we need extensive, well-founded translational research into the pathogenesis of the HS as the basis for the development of targeted systemic therapies for HS. A further aspect is a holistic view of the patient to include awareness of systemic inflammation evaluation, treatment of systemic comorbidities and pain, and psychological care for the patient. The last aspect is to motivate and support the patient in changing lifestyle factors that can contribute to the persistence of HS, such as smoking and obesity. Structured patient counseling that provides information about these associations, including referral to smoking cessation programs and weight loss might be helpful.

AUTOIMMUNE SKIN DISEASES

Alopecia Areata

Alopecia areata (AA) is an autoimmune skin disease that affects ∼2% of the worldwide population (19). In AA T cells attack the hair follicles causing an inflammatory, non-scarring, hair loss that is typically manifested in patches as a single or multiple well-demarcated areas. Patients with the patchy form of alopecia areata (AAP) commonly exhibit hair loss on the scalp but may also present hair loss in other hair-bearing areas of the body (**Figure 1H**). The disease course varies greatly between AA-affected individuals in terms of disease severity, duration, and prognosis. Hence, AA patients may present patchy, diffuse, confluent, or mosaic patterns of hair loss during a single episode, or recurrent disease episodes. Additionally, while, up to 75% of the AAP patients exhibit a spontaneous regrowth of hair within a few months (143), in up to 25% of all AAP patients, the disease progresses to its more severe form, and the hair loss extends to the entire scalp (alopecia totalis; AT) or body (alopecia universalis; AU) (144). In addition to hair loss, nail abnormalities, most commonly pitting and trachyonychia, are observed in patients with AA and are more prevalent in patients with AT and AU (145).

Diagnosis

The diagnosis of AA is typically made based on the patient's medical history and a clinical examination that determines the location and the extent of hair loss, and differentiates AA from other potential causes of hair loss, thereby providing a more accurate prognosis and identifying a favorable line of treatment (146). The clinical examination is often supported by a positive hair pull test at the periphery of the lesion, especially in patients with active disease. Additionally, the clinical diagnosis is frequently accompanied by trichoscopy examination that is used to examine the hair follicle, hair shaft, and the surrounding skin, and establish the phase of the disease (147). Dermatoscopic findings in AA may vary depending on the specific disease phase (146). In the acute phase of AA, exclamation point hairs that are located at the border of the plaque and broken hairs that are thicker proximal to the scalp are typically observed, while in the chronic stage of AA, dystrophic hairs, uniform black

dots, and yellow dots, are predominantly present. In cases with an unclear clinical presentation, clinical diagnosis is supported by a histological examination of a horizontally sectioned 4 mm scalp biopsy taken from an area of active hair loss (148). In the acute phase, a peribulbar infiltrate is observed that consists predominantly of CD4+/CD8+ T cells and Langerhans cells as well as eosinophils, mast cells, and plasma cells, in a typical "swarm of bees" pattern. In addition, pigment incontinence may also be present, due to the destruction of melanocytes in the apex of the dermal papilla. Other histological signs of AA characteristic of acute and the subacute phases include hair follicle miniaturization, a decreased anagen-to-telogen ratio, and a decreased terminal-to-vellus hair ratio (148).

Treatment

The first lines of therapy in most AA patients include corticosteroids and/or immunotherapy that is aimed at containing the inflammation and promote the recovery of dystrophic hair follicles. The type of treatment assigned is determined based on the age of the patient, and the extent and the severity of hair loss. The first line of therapy in AAP patients with active disease include intralesional (triamcinolone acetonide, triamcinolone hexacetonide, and hydrocortisone acetate) and topical corticosteroids (desoximetasone, betamethasone valerate, and clobetasol propionate), which show low solubility and promote maximum local anti-inflammatory actions with minimal systemic side effects (149). The adverse effects of topical and intralesional corticosteroids include folliculitis, reversible skin atrophy, telangiectasia, and hypopigmentation. In more severe cases, to contain rapidly progressing hair loss in AAP patients, systemic high-dose pulsed oral, or intravenous glucocorticoids (prednisolone) are recommended (150–152). However, one major drawback of this line of therapy includes recurrence of hair loss after therapy is discontinued (153). In AT, AU, and AAP patients with a chronic disease or in AAP patients with an active disease who fail to respond to topical or intralesional corticosteroids, topical application of contact allergens is recommended. In this line of therapy, potent contact allergens such as 1-chloro, 2, 4, dinitrobenzene (DNCB), diphenylcyclopropenone (DPCP), or squaric acid dibutyl ester (SADBE) are applied weekly onto the lesion to induce mild contact dermatitis, which *via* yet incompletely understood molecular mechanism, results in regrowth of hair (154, 155). Several side effects associated with this treatment include severe contact dermatitis, occipital or cervical lymphadenopathy, urticaria, dyschromia, and vitiligo (156, 157). Lastly, systemic glucocorticoids and systemic immunosuppressives (methotrexate, sulfasalazine, and azathioprine) can be used in patients with active AT and AU. Recently, a new class of small molecules known as JAKi were shown to be effective in AA. JAKi are especially effective in AA since they target a family of tyrosine kinases JAK1/2 and JAK1/3 that transduce cytokine-mediated signaling in T cells, which were shown to play a critical role in AA (158). Blockade of JAK1/3 and JAK 1/2 by the oral selective inhibitors, tofacitinib, and ruxolitinib, respectively, was shown to be effective in inducing regrowth of hair in AAP and AT/AU patients with active and chronic disease (159, 160). Although, no adverse side effects of these drugs were reported in AA patients, increased risk of infections and neoplasia were observed in rheumatoid arthritis patients treated with tofacitinib (161). Thus, future investigations into the potential side effects of prolonged treatment with JAKi, as well as examining the efficacy of topical JAKi formulations in AA, are required.

Perspectives

The heterogeneous clinical presentation, variability in the rate of spontaneous remission, and differences in disease prognosis still pose significant difficulties in assessing the efficacy of therapy in AA, making it challenging to generalize a certain line of treatment for different AA patients. Future, well-powered randomized placebo-controlled trials are required to systematically assess the efficacy of existing lines of therapy and facilitate the development of FDA-approved treatment options in AA. Large randomized placebo-controlled trials are underway for at least 3 JAKi in AA (Baracitinib, deuterated Ruxolitinib, and Ritlecitinib) with several others already approved for other inflammatory diseases (162, 163). Despite the significant improvements in our understanding of the pathophysiology of AA, future research is warranted to understand the contribution of environmental triggers to AA pathogenesis, since only a 55% concordance rate was observed in monozygotic twins, suggesting other factors contribute to disease onset (164).

Vitiligo

Vitiligo is an autoimmune depigmenting disorder of the skin. The depigmentation results from the loss of epidermal melanocytes. Clinically presenting with well-demarcated white patches on the body, vitiligo can be cosmetically very disabling and create a psychological burden (165, 166). There has been a great advance in understanding the pathological basis due to current research. JAK kinase signaling pathways and the cytokines involved in the Th1 pathway are the focus of the upcoming vitiligo treatments, followed by antioxidant and repigmenting agents (167).

Diagnosis

Vitiligo is usually diagnosed clinically (168). Occasionally skin biopsy may be recommended (169). A characteristic histological hallmark is the absence of melanocytes and epidermal pigment (**Figure 1I**). Screening to assess potential autoimmune diseases is recommended.

Treatment

Therapy of vitiligo is currently unsatisfactory. Topical treatments include corticosteroid and calcineurin inhibitors (170). Phototherapy, ranging from broadband, or narrowband UVB to psoralen plus UVA, may be another option (171). In severe or treatment-refractory cases systemic treatments include mini-pulses of oral steroids, methotrexate, cyclosporin or mycophenolate mofetil. Currently, there are several drugs available, alone or combination, aiming to arrest progression and induce repigmentation of the skin. The degrees of repigmentation vary (172). Of note, there is no approved treatment for vitiligo repigmentation and current off-label

therapies have limited efficacy. This emphasizes the need for better treatment options.

Perspectives

It is essential to increase awareness of the comorbidities associated with the disorder. The most common comorbid conditions of vitiligo are thyroid disease, diabetes mellitus, Addison's disease, pernicious anemia, rheumatoid arthritis, inflammatory bowel disease, ocular and audiological abnormalities, alopecia areata, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, scleroderma, psoriasis, and atopic dermatitis (173). Among emerging treatments that may meet the need for safe and effective vitiligo treatments, JAK inhibitors (topical and oral) are the most promising new class of drugs currently available and act best in conjunction with phototherapy (174–177). The result from the phase III TRuE-V clinical trial program (NCT04052425 and NCT04057573), evaluating the topical JAKi ruxolitinib (Opzelura^{TM} cream) showed a substantial repigmentation of vitiligo lesions. Hence, approval in the U.S. and Europe is expected in the upcoming months. Further treatment potential options like phosphodiesterase inhibitors (PDE4) or abatacept, a fully human fusion protein of CTLA-4 and the Fc portion of human IgG1 are sometimes used off-label. Considering the role of PD-1 ligand (PD-L1, a PD-1 agonist) and CTLA-4 in maintaining immune balance, targeting this pathway could be a therapeutic option. Furthermore, it was shown, that IL-15 acts *via* JAK STAT signaling pathways and has been recently implicated in oxidative stress mediated destruction of melanocyte. Thus, the future of vitiligo treatment may rely on the development of more specific drugs (167).

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is defined by the occurrence of itchy wheals, angioedema, or both for longer than 6 weeks (178). In most patients, CSU lasts for several years and then shows spontaneous remission. Because of the severe pruritus and the unpredictability of the occurrence of the signs and symptoms, most patients who are not adequately treated are severely affected in their quality of life (179). CSU is a mast cell-driven disease, and its signs and symptoms occur in response to the activation of skin mast cells and their subsequent release of histamine and other mediators. The exact underlying pathomechanisms of skin mast cell activation in CSU are not fully understood. Based on recent evidence, three subtypes of CSU have been described, type I autoimmunity (or "autoallergy"), type IIb autoimmunity ("classical autoimmunity"), and CSU due to unknown cause (180). In addition, other factors such as acute infections, certain drugs or stress modulate mast cell activation and drive exacerbations or worsening of CSU.

Diagnosis

In most patients, the diagnosis of CSU is straightforward, with spontaneously recurring itchy wheals, angioedema, or both, for longer than 6 weeks (**Figure 1J**). The current guideline on the definition, classification, diagnosis, and management of urticaria recommends a detailed patient history, physical examination (including pictures from patients) and a basic diagnostic workup consisting of a complete blood count with differential, CRP, IgG anti-TPO and total IgE (178). The questions and investigations are mainly aimed at ruling out rare differential diagnoses, for example urticaria vasculitis, autoinflammatory syndromes or bradykinin-mediated angioedema, assessing patients for underlying causes and modifying conditions, and identifying comorbid diseases and consequences of having CSU (180). Based on the answers to the respective questions, additional investigations such as histological examination of a skin biopsy or further laboratory analyses may be necessary. An important aspect of the diagnosis is the assessment of CSU activity, impact, and control. For this purpose, the urticaria activity score (UAS), the chronic urticaria quality of life questionnaire (CU-Q2oL) and the urticaria control test (UCT) should be used (178). In CSU patients with angioedema, the angioedema activity score (AAS), the angioedema quality of life questionnaire (AE-QoL), and the angioedema control test (AECT) should also be used (178).

Treatment

The goal of any treatment in CSU is the absence of signs and symptoms, complete disease control and a normal quality of life. To achieve this, an effective prophylactic treatment is required for all patients. The use of a 2nd generation H1-antihistamine is the recommended first-line treatment for CSU, first at standard dose and then, if needed, at up to 4-fold the standard dose (178). While 2nd generation antihistamines have proven to be a very safe long-term treatment, also at higher than standard doses (181), many patients with CSU do not achieve complete response. For those patients, the second step in the treatment algorithm is the addition of the monoclonal anti-IgE antibody omalizumab, which has been shown to be effective and safe in many H1-antihistamine refractory CSU patients (182). A significant proportion of CSU patients do not achieve complete control with omalizumab. Recent data indicate that patients with markers of type IIb autoimmune CSU, e.g., low total IgE and elevated levels of IgG anti-TPO, show slow and poor response to omalizumab treatment (180, 183). In patients who do not respond to omalizumab within 6 months of treatment (or earlier, if symptoms are unbearable), cyclosporin up to 5 mg/kg body weight is recommended in addition to antihistamines. Due to the poor safety profile, this is not possible in all patients and potential side effects should be rigorously monitored.

Perspectives

Better treatments are needed for CSU and several are currently under investigation (184), most of them mast cell-targeted (185, 186). These treatments aim to inhibit mast cell mediators, prevent mast cell activation (187), silence mast cells *via* inhibitory receptors, or deplete mast cells. One of the biggest challenges in treating CSU patients in the future will be to figure out which patients benefit best from which treatment. For example, fenebrutinib, an oral Bruton's tyrosine kinase inhibitor, has been shown to be most effective in type IIb autoimmune CSU (180). The identification of reliable and easy to analyze biomarker for response to treatment will thus be an important task for future research.

Pemphigus

Pemphigus refers to a group of rare autoimmune blistering diseases characterized by autoantibodies targeting desmosomal cadherins: most commonly desmoglein-1 (Dsg1) and desmoglein-3 (Dsg3). It presents with localized or widespread flaccid bullae which can rupture and progress to post-bullous erosions and crusts (**Figure 1K**). There are two major types: Pemphigus vulgaris (PV) and pemphigus foliaceus (PF). These subtypes are differentiated by oral and/or mucous membrane involvement in PV, which is absent in PF. The histological hallmark of pemphigus is acantholysis, caused by loss of adhesion between effected keratinocytes (188). Overall, pemphigus is associated with significant morbidity and mortality (22, 189).

Diagnosis

The diagnosis can be made by direct immunofluorescence (IF) microscopy of a perilesional skin biopsy, revealing deposition of IgG autoantibodies and/or C3 on the cell surface of keratinocytes (190). Detection of antibodies against Dsg1 or Dsg3 using ELISA, or use of indirect immunofluorescence microscopy against monkey esophagus allows serologic characterization (188). Significant delays in diagnosis are unfortunately common (191). Barriers to obtaining direct immunofluorescence microscopy serve as a roadblock in the diagnosis of pemphigus, particularly in the developing world (192). Immunohistochemical approaches, and even desmoglein ELISA have significant sensitivity limitations furthering diagnostic delays when direct immunofluorescent microscopy is not feasible (193). In the so far largest multicenter prospective study, anti-Dsg1/ Dsg3 serum antibodies were, however, detected in 329 (98.5%) of 333 pemphigus sera diagnosed by the clinical picture and direct IF microscopy using widely available assays.

Treatment

The first-line treatment for pemphigus is systemic corticosteroids, often used in conjunction with other immunosuppressive agents (194). More recently, evidence suggests the use of the anti-CD20 monoclonal antibody rituximab as an alternative first-line agent used alongside corticosteroids (195, 196). Additional therapies such as intravenous immunoglobulin (IVIg) and immunoadsorption can be used as adjuvant treatments, either in combination with first-line medications or when contraindications are present (194). However, despite the significant advances in the treatment of pemphigus in recent years, there are still numerous limitations in current therapies. To achieve clinical response during the acute phase of disease, high dose corticosteroids are generally required (197). While novel treatments such as rituximab may reduce cumulative steroid dosages, they do not work quickly. Furthermore, relapses are also frequently encountered (198).

Perspectives

Thus, there is a need for short-term agents that can minimize the need for high dose steroids. Once achieving complete remission, relapses remain common, though this can be decreased with more aggressive protocols utilizing additional rituximab infusions (199–201). An alternative approach, for example targeting autoantibody-induced tissue pathology have emerged (202, 203). In addition, attempts to incorporate precision medicine into the treatment of pemphigus are on the horizon (19). However, optimism must be tempered by the contributory role of non-desmoglein autoantibodies in pemphigus and aberrant cell signaling, which contribute toward the pathogenesis (204–206).

Bullous Pemphigoid

Bullous pemphigoid (BP) is one of the most common autoimmune blistering skin diseases, and it is characterized clinically by tense blisters with itchy urticarial erythema on the trunk and extremities (**Figure 1L**) (207). Mucosal surfaces can also be affected. It is most prevalent in the elderly (late 70s), but can appear in younger people (208). The molecules targeted by BP autoantibodies are the two hemidesmosomal proteins type XVII collagen (COL17, also called BP180) and BP230, and the former molecule has been recognized to be the major autoantigen. Triggering factors for BP include ultraviolet rays and other radiation, burns, trauma, and regulatory T-cell dysfunction (209–211). Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently gained attention as a cause of BP (212–214).

Diagnosis

BP is diagnosed based on the clinical, histological, and immunological findings (215, 216). In addition to the clinical features of tense blisters and urticarial erythema and the histological feature of subepidermal blistering, the detection of tissue binding and/or circulating autoantibodies against the dermal-epidermal junction (DEJ) is essential. Direct IF microscopy of perilesional skin is the most sensitive method for detecting autoantibodies in BP, with a linear IgG and/or C3 deposition at the DEJ. To detect circulating autoantibodies, indirect IF microscopy using cryosections of normal human skin or 1M NaCl-split human skin is useful. To confirm the target antigen of autoantibodies, an ELISA using recombinant BP180 NC16A is widely used. A full-length BP180 ELISA (217) and a BP230 ELISA are also useful. Diagnostic challenges are infrequently encountered in patients presenting with "classical" BP lesions, i.e., tense blisters on erythematous skin. By contrast, atypical clinical presentations, which occur in least 20% of all BP patients, diagnosis is often delayed by several months, if not years (4, 218, 219).

Treatment

In clinically localized or mild cases, superpotent topical corticosteroids (clobetasol propionate) are applied to lesions only or to the whole body except the face as a first choice (215, 216, 220). Low-dose oral corticosteroids, tetracycline (and nicotinamide) and dapsone are also used. In generalized or moderate/severe cases, oral corticosteroids (0.5–1.0 mg/kg/day) or superpotent topical corticosteroids are the mainstay treatment. If sufficient efficacy cannot be achieved, immunosuppressants (e.g.,

azathioprine, mizoribine, cyclophosphamide, cyclosporin, mycophenolate mofetil, methotrexate), steroid pulse therapy, plasma exchange/immunonoadsorption, or intravenous immunoglobulins should be added as appropriate (215, 216, 221, 222). A randomized controlled trial demonstrated the efficacy of doxycycline (200 mg/day) as an initial treatment for BP. Non-inferiority was shown in comparison with oral prednisolone (0.5 mg/kg/day), and the safety was significantly higher (223). Whilst all these treatments, especially those using topical or systemic corticosteroids, induce remission in over 90% of the patients within 4 weeks, relapses during tapering corticosteroids or after stopping treatment are frequent (220, 222, 224). This necessitates prolonged treatment with corticosteroids. In turn, this long-term use of oral corticosteroids frequently causes severe side effects, particularly in the elderly. In addition, although most BP cases are well-controlled by standard therapies, intractable and recurrent cases still exist. Therefore, new treatments that can suppress the disease activity and reduce or replace (oral) corticosteroids are much anticipated.

Perspectives

Based on the clinical and immunological characteristics, some molecules are considered as promising targets for BP therapies. As in pemphigus, the anti-CD20 antibody rituximab has been reported as effective against BP (225, 226). The pathogenicity of IgE autoantibodies has been described in many studies (227–229), and the efficacy of the anti-IgE antibody omalizumab against BP has been reported (227, 230, 231). Furthermore, the anti-IL-4 receptor alpha dupilumab has been reported as an alternative to prednisolone (232, 233). Several clinical trials targeting these molecules are under way, which may provide new treatment options for BP in the near future (234). Regarding the early diagnosis, continued education of healthcare providers, especially outside dermatology, is important to raise awareness for (atypical) BP (219), as well as forms of drug-induced BP (24). One important pillar in raising the awareness for BP and other rare skin blistering autoimmune diseases is the International Pemphigus & Pemphigoid Foundation (IPPF), the largest patient organization for those affected by pemphigus or pemphigoid.

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a subepithelial/subepidermal blistering autoimmune disease with predominant involvement of orifice-close mucosal surfaces and autoantibodies against proteins of the dermal-epidermal junction (**Figure 1M**) (235). The main target antigens are BP180 (type XVII collagen) and laminin 332 recognized in about 80 and 10–20% of patients, respectively. In <5% of MMP patients, type VII collagen is targeted and individual patients with reactivity against a6b4 integrin have been described (207, 236). The incidence of MMP has been estimated to 1.3 and 2.0/ million/year in France and Germany (237–239) and its prevalence was calculated to be 24.6 patients/million, i.e., about 2,000 patients in Germany in 2014 (23) MMP mainly occurs between the age of 60–80 years and is extremely rare in children and adolescents (240, 241). The oral cavity and conjunctivae are the most frequently affected mucosal surfaces followed by nasopharynx and genitalia, and more rarely, larynx, esophagus, and trachea. In about 30% of patients, additional skin lesions may occur (241). MMP is associated with a considerable morbidity including pain, difficulties in food intake and breathing as well as visual impairments that can lead to blindness (241). Further studies are needed to assemble more data about the incidence and prevalence of MMP in different geographical regions. So far, epidemiological studies have been mostly limited to central Europe. In the Schleswig-Holstein registry of autoimmune blistering diseases including all newly diagnosed patients in the most northern German province (www.sh-register-pemphigoid-pemphigus.de) we are prospectively mining the annual incidences of MMP since 2016.

Diagnosis

For the management of MMP the recent S3 guidelines of the European Academy of Dermatology and Venereology will be instrumental (241, 242). Diagnosis of MMP is based on the presence of predominant mucosal lesions and the detection of tissue-bound and/or circulating autoantibodies (242). Direct IF microscopy of a biopsy taken form perilesional tissue or unaffected oral mucosa is the diagnostic gold standard with a sensitivity of 60–90% (241–243). Like in all pemphigoid disorders, in MMP, it reveals linear deposits of IgG, IgA, and/or C3 at the subepithelial basement membrane zone (BMZ). Repeated biopsies for direct IF can increase the sensitivity from 70 to 95% (243, 244). Indirect IF microscopy on human salt-split skin is a convenient and sensitive screening assay for circulating autoantibodies against the subepithelial BMZ and allows the differentiation between IgG/IgA that binds to the roof of the artificial split, i.e., antibodies against BP180, BP230, and a6b4 integrin and IgG/IgA that labels the blister floor as seen with reactivity against laminin 332 and type VII collagen (245–247). Widely available antigen-specific test systems include ELISA and/or indirect IF applying the recombinant NC16A domain of BP180 NC16A, the NC1-domain of type VII collagen, a C-terminal stretch of BP230, and the laminin 332 heterotrimer (242, 248–252). In particular, detection of anti-laminin 332 antibodies is essential since-anti-laminin 332 MMP is associated with a malignancy in 25–30% of patients. After the initial observation of solid malignancies in 2 of 5 MMP patients with serum autoantibodies against laminin 332 by Leverkus et al. (253), Egan et al. reported malignancies in 10 of 35 patients (29%) (254). This important clinical association has then been corroborated by several other studies (249, 253–259). In contrast, using an in-house ELISA Bernard et al., did not recognize the association of anti-laminin 332 IgG and malignancies (260). Recently, in a large multicenter study, a 6.8-fold higher risk of malignancy has been calculated in anti-laminin 332 MMP patients compared to the general population (237). However, serological diagnosis is limited by relatively low autoantibody levels. In addition, no standardized assay is widely available for serum IgG against the BP180 ectodomain outside the NC16A domain, an immunodominant stretch in anti-BP180 MMP. Since IgA reactivity is frequently seen in MMP, the lack of widely available test systems for IgA reactivity against BP180, BP230, and type VII collagen is further limiting the diagnostic power.

Treatment

The European S3 guidelines recommend the first-line use of topical corticosteroids with or without dapsone, methotrexate or tetracyclines for mild and moderate MMP and for severe MMP, dapsone in combination with systemic cyclophosphamide with or without systemic corticosteroids (242). However, apart from two small phase IIa trials comparing dapsone with cyclophosphamide and prednisone with cyclophosphamide, respectively, in MMP patients with ocular disease, no randomized control trials have been performed in MMP (261). Hence, well-designed clinical trials are urgently needed to identify the best current available treatment options for MMP patients.

Perspectives

The highly standardized indirect IF test based on the expression of recombinant laminin 332 in a human cell line has become widely available (249). This assay will be instrumental for the in-depth analysis of the occurrence of malignancies in patients with anti-laminin 332 MMP, an association that has not yet been widely recognized in the community. In this sense, the recommendation of the S3 guidelines to assay for anti-laminin 332 reactivity in all patients with negative or dermal binding by indirect IF microscopy on salt-split skin will propel our knowledge. For the management of anti-BP180 MMP only the anti-BP180 NC16A IgG ELISA is widely available. Since in MMP the NC16A domain is not an immunodominant region and IgA reactivity is frequently found, assays for the detection of serum IgA and IgG against other parts of the BP180 ectodomain are urgently needed. Considerable progress is being awaited on our understanding of the disease mechanisms in MMP using a recently established mouse model of anti-laminin 332 MMP (262). In contrast to the previously reported model by Lazarova et al. this model depends on Fc receptor-mediated inflammatory pathways and C5aR1 (262, 263). The future use of the novel model to preclinically evaluate future therapeutic strategies has recently been supported by the observation that dapsone, first-line treatment in MMP, resulted in a significant reduction of oral and cutaneous lesions compared to vehicle-treated mice (264). Nonetheless, until a mouse model for anti-BP180 MMP, that represents the large majority of MMP cases, has been developed, it will remain unclear whether the anti-laminin 332 MMP model fully represents experimental MMP. In any case, the present anti-laminin 332 MMP mouse model opens the possibility to pre-clinically test anti-inflammatory agents and as such pave the way for randomized controlled trials in MMP.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is caused by autoantibodies targeting type VII collagen (COL7) which is a major component of anchoring fibrils (265, 266). Despite this singular key pathogenic principle, the clinical presentation of EBA is broad (**Figures 1N,O**). The disease may present as fragile skin with subsequent scaring, or as a widespread inflammatory disease with blistering and erosions. In addition to the skin and mucous membranes, internal organs may be affected (267). For example, strictures of the esophagus are relatively common (268). Thus, EBA imposes a high burden on the patients affected by this rare disease.

Diagnosis

EBA is confirmed if linear deposits of immunoglobulins and/or C3 are detected by direct immunofluorescence (IF) microscopy or perilesional skin biopsy and if an u-serrated pattern is seen in direct IF microscopy, or circulating COL7 autoantibodies are detected (247, 269). Due to the heterogeneous clinical presentation, EBA is often not considered as a differential. Thus, the challenge is to raise awareness for this rare disease because once considered as a differential, diagnosis can readily be obtained using direct IF microscopy and serology.

Treatment

There are no controlled clinical trials for EBA treatment which is thus based on expert recommendation. Unspecific immunosuppression is the mainstay of EBA treatment. Most commonly, systemic corticosteroids are used. In many cases additional immunosuppressants are added to systemic corticosteroids, most commonly azathioprine or cyclosporine are used (270). Overall, management of EBA is notoriously challenging—median time to remission is 9 months. In the same study, complete remissions were achieved in 45% of patients, with another 45% in partial remission and 10% with ongoing active disease−6 years after the initial diagnosis was made (271). Thus, treatments that induce remissions more reliably and faster are urgently needed to relieve the burden imposed by EBA.

Perspectives

In a metanalysis of over 1,000 EBA cases, use of the CD20 antibody rituximab or high dose intravenous immunoglobulin G (IVIG) were, compared to all other treatments, more often associated with the induction of remissions (270). These observations are a basis to establish protocols for clinical trials in EBA, evaluating the impact of either rituximab or IVIG. In addition, this also indicates that drugs targeting the B cells, such as the BTK inhibitor PRN1008, or compounds modulating the half-live of IgG, such as FcRn inhibitors, could be also effective in EBA (234). In addition, use of pre-clinical model systems has identified and validated a number of novel therapeutic targets in EBA (272–276). Based on these findings in pre-clinical EBA models, controlled clinical trials are currently performed—albeit in bullous pemphigoid patients (234).

AUTOINFLAMMATORY DISEASES

Cryopyrin-Associated Periodic Syndrome

Cryopyrin-associated periodic syndrome (CAPS) comprises a group of rare diseases that, despite certain clinical similarities, were previously considered separate disorders. These include Familial Cold Urticaria Syndrome (FCAS) which was first described in 1940 (277), Muckle-Wells Syndrome (MWS), and Chronic Infantile Neurologic Cutaneous and Articular or Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID). Its prevalence is about 1–2 per million inhabitants in Europe and the USA.These diseases are

characterized by an attack-like course with fever episodes lasting up to a few days and an enormous increase of inflammatory laboratory parameters, usually an accompanying urticaria-like exanthema, conjunctivitis, joint and muscle pain as well as hepatomegaly and splenomegaly (**Figure 1P**). In severe cases, cartilage growth leads to joint dysfunction. In MWS and NOMID/CINCA, central nervous involvement with mental retardation, epilepsy and hearing loss is found. The expression of the disease pattern varies from individual to individual. A long-term complication is the development of AA amyloidosis, which affects multiple organs, most prominently the heart and the kidney. As the cause for these diseases, heterozygous monogenetic deficiency in the NLRP3 (278), NLRP12 (279), PLCG2 (280), and NLRC4 (281) genes have been identified. However, a considerable number of cases are caused by mosaicism in the respective genes, such as in NLRP3 (282).

Diagnosis

The diagnosis is based on a careful history and observation of the clinical course, especially of the inflammatory parameters, as well as genetic testing, preferably requiring NGS panel diagnostics. It may be necessary to assess whether the disease can be influenced by corticosteroids, NSAIDs, and ultimately IL-1b inhibitors in an individual patient. The additional use of clinical scores, such as the EUROFEVER/PRINTO score (283), is helpful, although, given the rarity of the disease, a systematic approach is needed to differentiate it from other diseases. A special difficulty are cases where the disease is caused by somatic mosaicism or by a not yet identified unknown genetic defect. In such cases the diagnosis may not be made satisfyingly, leading to delay in efficient, but often expensive, treatment options. In addition to diagnosis, monitoring of disease activity is also of high importance. While ESR and CRP are routine diagnostics, the measurement of calprotectin levels or amyloid A in the serum, for example, are helpful but much less available. Another problem is the early diagnosis of AA amyloidosis and determination of its extent. Here, nuclear medicine methods such as a PET-CT scan with 18F-florbetaben have been described (284) but are also not yet routine.

Treatment

The IL-1β inhibitors anakinra and canakinumab are approved and available for the treatment of CAPS. However, other cytokines such as IL-18 have been described to be important in autoinflammatory diseases (285, 286). Hence, breakthrough attacks carried by IL-18 are not inhibited by current treatments. On the long run, secondary AA amyloidosis poses a challenge. Although it can be indirectly alleviated by inhibition of IL-1β signaling, targeted resolution of amyloid deposits is not possible to date (287).

Perspectives

Over the past 20 years, genetic defects have been identified for a variety of autoinflammatory diseases. Especially challenging are cases in which no classical germline mutation is present. In such cases, classical genetic methods reach their limits. The development of third generation sequencing methods such as nanopore sequencing with the simultaneous development of bioinformatics and advances in IT infrastructures could provide the solution for these cases as well (288). In addition to inhibition of secondary proinflammatory messengers such as IL-1β, inhibition of NLRP3 by small-molecule agents may also show promise (289, 290). To inhibit the action of IL-18, which is important in addition to IL-1β and plays a role in macrophage activation in particular, a promising drug might be available in the form of IL-18 binding protein (tadekinig alfa) (291).

Schnitzler's Syndrome

Schnitzler's syndrome is a late-onset autoinflammatory diseases that has been described first in 1972 by Schnitzler (292). The disease is characterized by the combination of urticaria-like exanthema (neutrophilic urticarial exanthema) and gammopathy, associated with fever, joint, muscle or bone pain, elevated inflammation markers, morphologic bone changes, hepato-splenomegaly, and palpable lymph nodes (**Figure 1Q**) (29). It is considered to be a rare entity—with only about 100 patients described in the literature—although a retrospective database search for urticarial exanthema associated with dysproteinemia led to the identification of 16 patients at Mayo Clinic (293), pointing toward a much higher incidence. The etiology and pathogenesis of the disease is unknown. A somatic mutation is assumed (293), which is comparable to the pathogenesis of mastocytosis. In the case of mastocytosis, even low frequencies of mutant cKit that are barely detectable by means of digital PCR can lead to pronounced symptoms (294). The possible causal relationship between gammopathy and Schnitzler syndrome is also unclear.

Diagnosis

The diagnosis of Schnitzler's syndrome should be considered in patients with gammopathy and urticarial exanthema, especially those without itching, increased inflammation markers and fever (295). On the other hand, chronic spontaneous urticaria (CSU) is a much more common diagnosis, which renders the differentiation very difficult. Especially, pressure urticaria may present with systemic symptoms such as fever and myalgia (296). On the other hand, CSU is such a much more common disease than Schnitzler syndrome that not every gammopathy in combination with urticarial exanthema should be misdiagnosed as Schnitzler syndrome. Unfortunately, the diagnosis of chronic urticaria is not established by specific biomarkers that would allow differentiation from other entities including allergic forms. Nevertheless, a lack of response to antihistamines, biologics such as omalizumab, or even corticosteroids may serve as further evidence of an autoinflammatory syndrome. The Strasbourg criteria are helpful in establishing the diagnosis, although they are still considered provisional and specificity and sensitivity have not been adequately determined (297). The dermatohistopathological differentiation between neutrophil-rich infiltrates in Schnitzler syndrome (298), urticarial vasculitis, and urticaria is not straightforwardly possible in practical settings, although a morphologic criterion, neutrophilic epidermotropism, might be specific for autoinflammatory diseases such a Schnitzler's

syndrome. Moreover, the gammopathy strictly required by the Strasbourg criteria may be not that absolutely necessary, as cases that appear to be clearly late-onset autoinflammatory diseases may present without it (299, 300). Gammopathy may also develop later in the course of the disease. Hence, establishment of validated diagnostic criteria for Schnitzler's syndrome is needed.

Treatment

IL-1β inhibiting treatment with anakinra and also canakinumab is highly efficient and can lead to resolution of symptoms within a few hours (301). Other treatment modalities such as colchicine, hydroxychloroquine, pefloxacin (29), and IL-6 inhibition with tocilizumab (302) are described. Like CAPS, Schnitzler's syndrome may lead to AA amyloidosis (303). AL amyloidosis due to gammopathy occurs, although rarely (304). Both types are difficult to treat, and no specific amyloid resolving treatment is known.

Perspectives

At the time being, only 9 controlled studies for Schnitzler's syndrome are listed in ClinicalTrials.gov, 5 of which that are using established IL-1β and IL-6 inhibitors have the status of being completed. A novel IL-1β inhibitor with affinity to IL-1α and IL-1Ra is recruiting, and a study that tests the histone deacetylase inhibitor ITF2357 (305) has an unknown status. Drugs that target the inflammasome may be able to prevent the activation of the autoinflammatory cascade (290). A pilot study using the NLPR3 inhibitor dapansutrile is listed as recruiting. Interestingly, a clinical observation of a resolution of Schnitzler's syndrome after haematopoietic stem cell transplantation may hint at the pathogenesis, e.g., a somatic mutation in bone marrow cells (306). This observation may also hint at a similar pathogenic pattern as in systemic mastocytosis, where myeloablative conditioning followed by (allogenic) stem-cell transplantation is used for treatment (307).

RHEUMATIC DISEASES

Cutaneous Lupus Erythematosus

Lupus erythematosus (LE) is a multisystem autoimmune condition that ranges from skin to multiorgan involvement. While systemic lupus erythematosus (SLE) involves many systems, cutaneous lupus erythematosus (CLE) affects the skin and/or mucosal surfaces (**Figures 1R,S**). CLE can present with a variety of cutaneous manifestations and is accordingly subdivided into three major categories: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE). Discoid lupus (DLE), a subset of CCLE, and SCLE are the most common forms of cutaneous lupus. Skin lesions are often a cause of significant disability and may be associated with underlying multisystem involvement secondary to SLE activity (308, 309). There are several pathways involved in the pathomechanism of CLE. Excess production of type I interferons (IFNs) has been implicated in the pathogenesis of SLE (29224681). Both plasmacytoid dendritic cells (pDCs) and cytotoxic CD8+T cells are known modulators of type 1 IFNs and seem to be critical in disease progression (310). Additionally, type I IFNs induce JAK/STAT signaling which are commonly upregulated in lesional skin (311).

Diagnosis

There are no standardized diagnostic criteria for CLE, though preliminary criteria have been developed for DLE (312). The diagnosis of CLE is largely based on clinical presentation, laboratory serologies, and histopathological findings (312). Hallmark cutaneous manifestations include malar erythema for ACLE, psoriasiform or annular lesions with central clearing for SCLE, and erythematous, scarring lesions for CCLE. Other clinical symptoms seen especially with DLE include scarring or non-scarring alopecia, scarring, and dyspigmentation. While these findings are suggestive, CLE is often misdiagnosed (313), especially as other autoimmune connective tissue diseases such as dermatomyositis (DM) (314). Diagnosis is supported with serologies demonstrating positive antinuclear antibody (ANA) or antibodies to double-stranded DNA (dsDNA), and anti-Smith (anti-Sm), but these are frequently absent. ANA is largely ubiquitous among rheumatologic conditions; only one-third of positive ANA serologies correspond with a diagnosis of LE (315). While a positive ANA is regarded as highly sensitive for SLE, there are numerous cases of ANA negative CLE with systemic findings that in the past would have been classified as SLE (316). Autoantibodies against dsDNA and Sm are more specific for SLE, though their median prevalence ranges from 30 to 70% (317, 318). Histopathological findings are used to aid in the diagnosis of CLE but are similarly not specific for CLE. Patterns such as interface dermatitis, dermal mucin deposition, and periadnexal lymphocytic infiltrates are present in both dermatomyositis and CLE. Even characteristic CLE findings on direct immunofluorescence (DIF), including granular immunoglobulin and complement deposition, are found in DM (314). Misdiagnosing CLE not only delays treatment resulting in more skin damage but prevents screening for potentially serious organ involvement.

Treatment

Since the approval of hydroxychloroquine in 1955, the Food and Drug Administration (FDA) has included three additional therapies for SLE: belimumab, a B-lymphocyte stimulator inhibitor, Anifrolumab, an anti-IFNAR receptor antibody, and voclosporin, a calcineurin inhibitor (319, 320). Belimumab and voclosporin are specifically approved for lupus nephritis. Currently, hydroxychloroquine is the only FDA-approved for CLE (313). Despite this, antimalarials [hydroxychloroquine (HCQ), chloroquine, and quinacrine] and topical corticosteroids remain first-line for the treatment of CLE. Topical calcineurin inhibitors may be used as an alternative to corticosteroids for sensitive areas of the skin and long-term use (313). About 65% of patients with CLE respond to some variation of these therapies (321). In CLE refractory to antimalarials, methotrexate (MTX), and mycophenolate mofetil (MMF) are the most effective immunosuppressives, but they may not be tolerated (322, 323). There are several reports of Azathioprine treating CLE, though MTX and MMF are typically more effective (324). Dapsone may be considered in recalcitrant CLE as there is some evidence of

its success (325). Retinoids have demonstrated success in CLE as well, though long-term use is required, which increases the risk of adverse effects (326). Lenalidomide, a thalidomide analog, has recently been used for patients with refractory CLE (327). It shares similar efficacy to thalidomide with an improved safety profile (328). Though these therapies effectively reduce disease burden in patients, off-label use makes them difficult to obtain. For example, patients must pay out of pocket for quinacrine, a drug that has shown efficacy in patients that do not respond to HCQ alone (313). As there are no curative therapies for CLE, the medications listed above are intended only to mitigate disease burden. Even when properly managed, damage that developed due to previous disease activity is notoriously difficult to resolve.

Perspectives

Although only approved for SLE, Anifrolumab demonstrated improvements in cutaneous disease and may benefit those who meet criteria SLE with cutaneous involvement. There are several clinical trials measuring improvement of cutaneous disease in CLE as a primary outcome. As with Anifrolumab, these novel therapies frequently target the type I interferon pathway, identified as a leading driver of cutaneous lesions. One such monoclonal antibody, BIIB059, causes internalization of the blood dendritic cell antigen 2 receptor on plasma dendritic cells (PDCs), subsequently inhibiting type I interferons and other pro-inflammatory modulators. A phase 2 trial testing this therapy met its primary outcome, which measured improvement of cutaneous LE compared to placebo (329) and a phase 3 trial will begin shortly. VIB7734, another monoclonal antibody that targets PDCs, showed efficacy in CLE in a phase 1 trial (330) and is of interest for future trials in CLE, although an ongoing phase 2 trial is in SLE. Janus Kinase (JAK) inhibitors have demonstrated improvement in a range of dermatological conditions and are actively being investigated for SLE (331, 332). Further studies that include patients with moderate to severe skin disease are necessary to elucidate their potential benefit in CLE. Iberdomide, a potent thalidomide analog, recently demonstrated an impressive reduction in cutaneous activity in patients with SLE. Improvement in SCLE and a trend to improvement with DLE activity was seen, although those with ACLE did not show improvement (333). The variable response based on CLE subtype may highlight the need for subgroup analysis in future trials. It is important to note that CLE is difficult to classify, especially early in disease, and 20% of CLE patients have more than one subtype of CLE. As clinical trials continue to focus on cutaneous disease as a primary endpoint, new, well-supported therapies may be identified for use in CLE.

Dermatomyositis

Dermatomyositis (DM) is thought to result from environmental triggers such as UV exposure, medications, infections, or malignancies in genetically predisposed individuals. Regarding genetic predisposition, mostly associations with HLA have been reported (334). Several characteristic cutaneous findings may be seen, including but not limited to symmetric macular erythema of the elbows, knees, or dorsal hands (Gottron's sign), papules of the dorsal metacarpophalangeal or interphalangeal joints (Gottron's papules), periorbital violaceous erythema (heliotrope rash), periungual telangiectasias, and macular erythema of the upper back (Shawl sign) and V-area of the upper chest (V-sign) (**Figure 1T**) (335). DM can also affect several other organ systems, potentially involving the skeletal muscle, lungs, heart, and esophagus. Especially interstitial lung disease is prevalent in almost 60% of DM patients (336). Thus, DM can have a large impact on patients' quality of life which tends to correlate with the amount of skin disease activity (337).

Diagnosis

The EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIM) and their major subgroups, including DM, are the only validated DM classification criteria (338). Patients are scored based on age of symptom onset, presence of muscle weakness, skin manifestations, other clinical manifestations, laboratory testing, and muscle biopsy features and can be further subcategorized into a form of IIM, like DM, if their score meets the cut-off probability of 55% (338). Despite validated criteria and characteristic cutaneous features, many clinicians do not accurately diagnose DM patients as evidenced by a retrospective study that showed that 56% of DM patients referred to an academic medical center were incorrectly diagnosed, the majority of whom were labeled as lupus or undifferentiated connective tissue disease (339). Patients with no muscle involvement and at least 2 of 3 possible skin-related items (heliotrope rash, Gottron's papules, and Gottron's sign) can be classified by the EULAR/ACR criteria as having amyopathic DM (ADM), and a skin biopsy is encouraged in such patients (339). However, these criteria have limitations as at least one retrospective study showed that 26% of patients with confirmed ADM would not meet the EULAR/ACR classification criteria due to the specific cutaneous findings required (340). It is suggested that cancer-screening investigations should be undertaken once a diagnosis of DM is established due to the associated increased risk of malignancy (341). However, no evidence-based malignancy screening protocol for DM patients currently exists. Thorough characterization of the autoantibody response in DM patients is also important in this regard, as certain autoantibodies are associated with a high risk of cancer (342). In addition, a detailed characterization of the autoantibody response in DM also allows to differentiate organ involvement and prognosis (343). In summary, missing awareness, lack of definite diagnostic criteria and no evidence-based recommendation for cancer screening are diagnostic challenges in DM.

Treatment

Systemic corticosteroids, with or without immunosuppressives, are the mainstay of DM treatment when muscle disease is confirmed and often allows patients to improve their muscle symptoms (344). Many patients unfortunately have persistent cutaneous disease despite aggressive topical and systemic therapy. A common therapeutic ladder for the treatment of cutaneous DM involves antimalarials like hydroxychloroquine or chloroquine with or without quinacrine followed by methotrexate or mycophenolate mofetil and then IVIG, currently

the only FDA-approved therapeutic for DM (345). However, even these more commonly used options have several limitations as DM patients have increased risk of cutaneous reactions to hydroxychloroquine than lupus patients, while steroid-sparing agents can have many side effects which are intolerable to patients (346). Very few randomized controlled trials have been performed in DM. However, other therapies with some evidence to support their use include topical corticosteroids, topical tacrolimus (347), topical pimecrolimus (348), tofacitinib (349), dapsone (350), and thalidomide (351), among others. One challenge facing the development of new therapies for DM is that clinical trials often use primary outcome measures which heavily weigh muscle involvement, like the TIS score. In the recently completed phase 3 study of lenabasum, the primary outcome was not met despite improvement in skin disease activity, highlighting the need for careful consideration of outcomes (352).

Perspectives

Much work is currently ongoing to overcome the diagnostic and therapeutic challenges facing DM. A recent international project that developed skin-focused classification criteria for DM that is more inclusive than the EULAR/ACR criteria while still excluding disease mimickers like lupus is undergoing prospective validation (353). While no consensus guidelines exist for cancer screening in DM patients, The International Myositis Assessment and Clinical Studies Group has an ongoing effort to create evidence-based malignancy screening guidelines for IIM patients (354). There is hope for improved therapeutic options for DM patients based on ongoing clinical trials as well as promising proof-of-concept studies. Additional therapeutics with trials that are ongoing or have reported data include JAK inhibitors, anti-interferon beta, subcutaneous immunoglobulin, and KZR-616 (349, 355).

Systemic Sclerosis

Systemic sclerosis (SSc) is an autoimmune disease belonging to the connective tissue/rheumatic diseases, characterized by a triad of vasculopathy, inflammation, and fibrosis. SSc is a rare disease with a prevalence of 40–200:1,000,000 inhabitants (35). Clinically, SSc is characterized by a wide heterogeneity, ranging from skin findings to severe organ damage including gastrointestinal dysfunction, interstitial lung disease, pulmonary arterial hypertension, cardiac inflammation, arrhythmias, neurological deficits, or end-stage renal failure. Skin findings can include oedema, scleroderma as well as acral ulcers, necrosis, or gangrene (**Figures 1U,V**). In recent years, the understanding of pathomechanisms in SSc and concomitantly, the therapeutic options for the treatment of affected patients have improved, especially regarding pulmonary artery hypertension and interstitial lung diseases. This has led to a reduction in disease-related mortality (356). Nevertheless, a multinational study examining mortality in patients with SSc between 2005 and 2014 continued to demonstrate early patient death (357). In addition, health-related quality of life is significantly lower in patients with SSc compared to healthy controls (358) and compared to other autoimmune diseases (359). The involvement of the gastrointestinal tract, pulmonary arterial hypertension, Raynaud's phenomenon and digital ulcers represent disease manifestations that affect the quality of life of patients (360). In addition, symptoms such as pain, dyspnea or impaired hand function are frequently reported by the patients as determinants for the quality of life. In addition, symptoms such as erectile dysfunction, pruritus, psychological problems such as anxiety received insufficient consideration in diagnostics and the development of treatment strategies for patients. Therefore, despite significant improvements in the understanding of the disease and expansion of therapeutic options, there is still a high unmet medical need in SSc.

Diagnosis

Years before the development of disease-defining symptoms in SSc, a risk for disease development in the presence of Raynaud's phenomenon or puffy fingers can be predicted by determination of biomarkers such as antinuclear antibodies and changes in capillary microscopy (361). These changes are summarized in the concept of "early SSc." Currently, patients at risk receive close clinical follow-ups. However, it is unclear whether and which early treatment would attenuate the course of the disease (362). Due to the heterogeneity of disease progression in SSc, the identification of biomarkers is central to predict the development and severity of organ manifestations, disease progression, and response to treatment. Although numerous biomarkers have been investigated in studies, only a few of these biomarkers have found their way into routine clinical practice (e.g., AT1R autoantibodies, ETAR autoantibodies) in specialized centers (363, 364). The identification of biomarkers for individual prediction of organ manifestations and severity of disease progression represents the basis for establishing the concept of individualized medicine in SSc.

Treatment

To date, drug treatment of patients follows a manifestation-based approach according to the EULAR recommendations (365). However, sufficient, evidence-based treatment strategies are lacking for several disease manifestations of SSc. One obstacle in the development of appropriate treatment options is that the pathophysiological mechanisms leading to specific disease manifestations are poorly understood to date, leaving only symptomatic treatment options available. These include exemplarily treatment of contractures, calcinosis cutis, acral necrosis, gastrointestinal involvement, fatigue, arthritis, or enthesitis. The highest agreement on treatment recommendations for patients with SSc is to consider immunosuppressive therapies particularly for the early inflammatory phase of the disease including autologeous stem cell transplantation. The use of angiotensin-converting enzyme inhibitors is recommended for scleroderma renal crisis. Prostacyclins, endothelin receptor blockers, phosphodiesterase-V inhibitors, and stimulators of soluble guanylate cyclase (sGC) were shown to be effective in the therapy of the obliterative vasculopathy. Here, combination therapies are increasingly applied particularly for the therapy of pulmonary arterial hypertension (PAH). Recently, nintedanib, a small molecule

tyrosine-kinase inhibitor was approved for the therapy of SSc-associated lung fibrosis. Of note, the anti-CD20 antibody rituximab has recently been demonstrated to have beneficial effects on skin and lung fibrosis and seems to be effective also in PAH. It is approved in Japan for the treatment of SSc (366, 367). Since these disease manifestations affect most patients, studies are urgently needed to decipher pathophysiology and develop causal therapeutic approaches. Furthermore, medication adherence is poorly investigated. Only a few clinical studies address compliance of SSc patients. Improving drug adherence could increase remission rates and prevent secondary disease complications. Moreover, since there are options for the therapy of cardiac arrhythmias, such as pacemakers or defibrillators, the establishment of a structured assessment for corresponding diagnosing is required. In addition to the insufficiently investigated treatment options for organ-related disease manifestations, the global disease activity cannot yet be adequately controlled with the approved therapeutic agents in all patients. Due to the described heterogeneity of organ manifestations, an interprofessional and interdisciplinary team is necessary to achieve optimal management of individual disease manifestations. A survey of patients with SSc conducted in the USA with regard to their individual unmet medical needs revealed deficits with regard to the psychological care of patients (368). In many places, there is a lack of structures that ensure interdisciplinary treatment of patients, which also includes psychological co-care of patients. Besides psychological co-care patients require physiotherapy and physical therapy to attenuate contracture development. Therefore, a prioritized objective for the next few years should be to create awareness of the need for interdisciplinary treatment and to establish appropriate structures on this basis. While diagnostics and therapy often focus on organ manifestations leading to the high disease-associated mortality, affected patients often evaluate pain, fatigue as well as alleviation of Raynaud's phenomenon and gastrointestinal symptoms as a treatment priority (360, 369). Therefore, practitioners need to define the individual treatment goal with the patient, considering not only global health but also health-related quality of life.

Perspectives

Despite the progress made in deciphering the pathogenesis of SSc in recent years, the triggers of the disease and the mechanisms that lead to the heterogeneous disease manifestations and disease severity remain poorly understood. However, since an understanding of these mechanisms is the basis for the identification of key molecules in pathogenesis and thus new therapeutic options, deciphering the disease-driving mechanisms of SSc is urgently needed. A key requirement for this is the enrollment of patients in international registries as well as a close collaboration between patients, clinicians, and scientists.

PERSPECTIVES

In conclusion, there are a multitude of challenges for the diagnosis and treatment of chronic skin inflammation. These are, however, different for each disease: At a generalized glance, for the common inflammatory skin diseases, especially psoriasis, atopic dermatitis and lichen planus, disease heterogenicity and the identification of biomarkers that allow to predict treatment responses are at the forefront of the medical needs. We assume that with the advent of more and more detailed molecular data from these patients, a stratification allowing personalized treatment options are on the horizon (63).

For the rare and orphan chronic skin inflammatory diseases, medical practitioners from all specialties need to be made aware of these diagnoses, for example pemphigus or dermatomyositis. Patient organizations, such as the International Pemphigus & Pemphigoid Foundation (IPPF), that educate patients and medical practitioners alike are key for this. This will then also lead to an earlier and more validated diagnosis, which are both essential to start the appropriate treatments. Regarding these, there is a high need to develop more selective, and potentially causal, treatments for chronic skin inflammation. The use of the chimeric antigen receptor (CAR)-T cell technology to selectively deplete autoreactive B cells in pre-clinical models of pemphigus is a milestone in reaching this goal (370).

These differences in unmet medical needs across the here discussed chronic, non-communicable inflammatory skin diseases, do, however, not allow to determine which of these diseases has the "most" or the "highest" unmet medical need. In a generalized manner, one could approach this open issue by a systematic and longitudinal assessment of patient reported outcomes across a wide range of chronic inflammatory skin diseases. This would allow to determine the burden of individual diseases at diagnosis, as well as at a time point where treatment should have had a positive impact on both objective and subjective disease symptoms.

Another challenge that is observed across almost all chronic (skin) inflammatory diseases is comorbidity. At the forefront of these are metabolic syndrome, (cardio)vascular and mental health diseases (348, 371–374). One hypothesis is that chronic skin inflammation drives the associated comorbidity (279, 375). By contrast, others provided evidence that the environment is a key driver for the observed comorbidity in chronic (skin) inflammation (376).

Thus, in perspective, we believe that we will observe significant changes how chronic skin inflammation is diagnosed and treated during the next years. Overall, this will improve the quality of life of patients. We also envision the emerge of curative treatments for those autoimmune skin diseases, where culprit cells can specifically be targeted, i.e., autoreactive B cells.

AUTHOR CONTRIBUTIONS

RL: conceptualization. KBi (lead), HU, DR, MS, SS, MMe, MMa, DT, ES, CC, KA, DD, MH, AR, HG, AH, AS, GR, GS, JD, DZ, TS, AC, KW, RS, KK, VW, and RL: visualization. All authors: writing–original draft and review and editing. All authors contributed to the article and approved the submitted version.

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