# THERAPEUTIC ADVANCEMENTS IN PSORIASIS AND PSORIATIC ARTHRITIS

EDITED BY: Anupam Mitra, Hermenio Lima, Saumya Panda and Satyaki Ganguly

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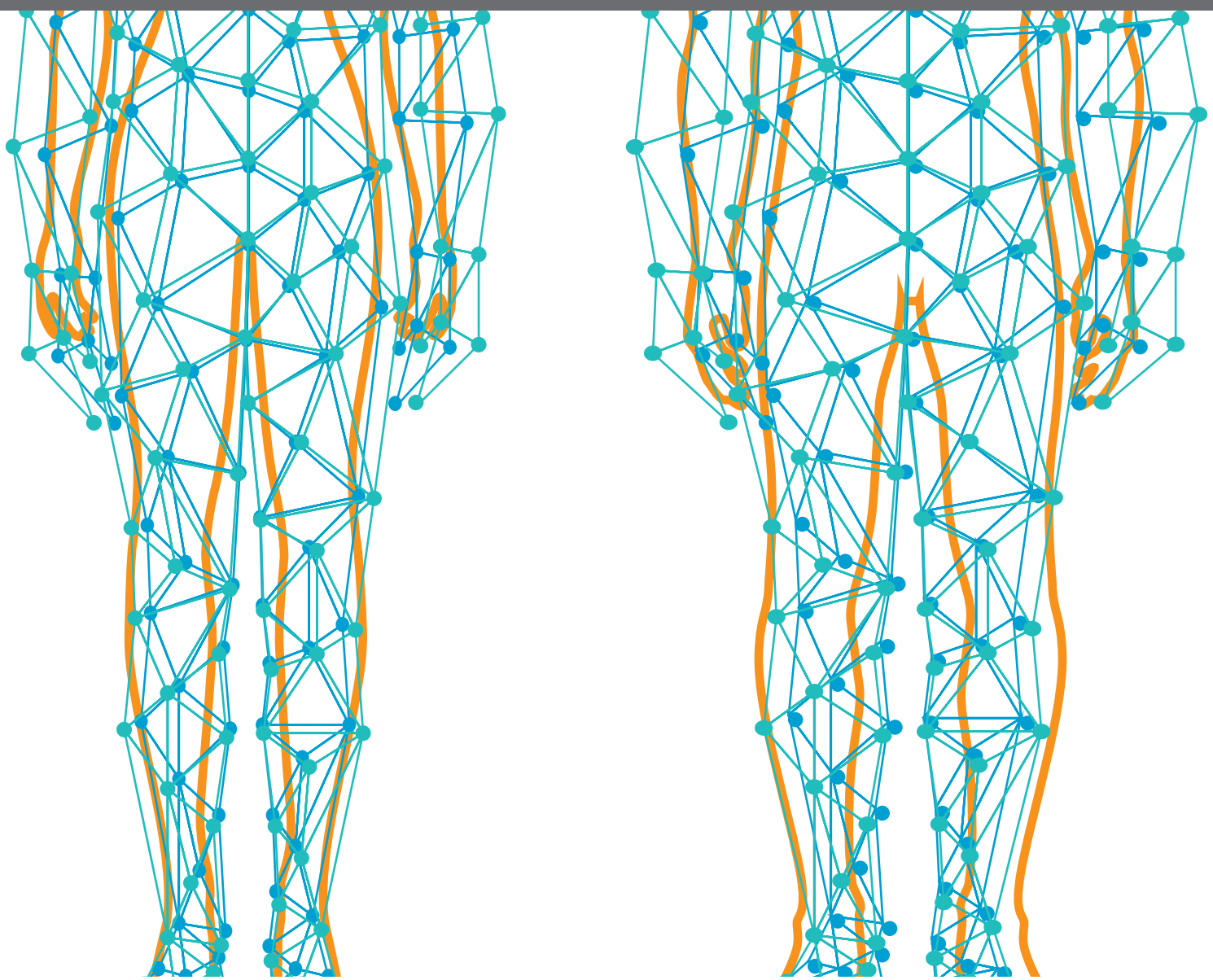

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# THERAPEUTIC ADVANCEMENTS IN PSORIASIS AND PSORIATIC ARTHRITIS

Topic Editors:
**Anupam Mitra,** University of California, Davis, United States
**Hermenio Lima,** McMaster University, Canada
**Saumya Panda,** Belle Vue Clinic, India
**Satyaki Ganguly,** All India Institute of Medical Sciences Raipur, India

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EDITORIAL
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# Editorial: Therapeutic Advancements in Psoriasis and Psoriatic Arthritis

*Saumya Panda**

*Department of Dermatology, Belle Vue Clinic, Kolkata, India*

**Keywords: psoriasis, psoriatic arthritis, therapy, epigenetics, acitretin**

## Editorial on the Research Topic

## Therapeutic Advancements in Psoriasis and Psoriatic Arthritis

Psoriasis and psoriatic arthritis are complex autoimmune diseases affecting about 2–3% of world population. With the advancement in translational research, the pathogenesis of these diseases is better known now compared to a decade ago. New therapeutic targets have been identified, and subsequently more effective therapies are now available for these patients. With these new therapies, psoriatic diseases are much better controlled, and quality of life has improved greatly. Most of these newer therapies are targeting the immune system and their molecular signaling pathways. In this Research Topic, we had planned to gather articles on new therapeutic strategies for psoriatic disease, their limitations and future directions.

We present here a gleaning of contemporary research in this area, encapsulated in 9 articles written by 60 authors. In one of the 3 original articles, Liu et al. explores a novel mechanism of action of acitretin *via* promoting the differentiation of myeloid-derived suppressor cells (MDSC). It is known that increased number of MDSCs are involved in the pathogenesis of psoriasis. Though the role of acitretin as a regulator of keratinocyte proliferation and differentiation is well-known, its effect on immune cells has been less well-understood. This work throws new light on a largely unexplored area.

In another study in this section, Bauer et al. explores epidermal drug delivery through fractional ablative (Er:YAG) laser microporation in a phase I study on plaque-type psoriasis. Topical delivery of etanercept solution to psoriatic plaques *via* laser-generated micropores was found to be generally well-tolerated and safe. The study opens the door to future follow-up studies to find out clinical benefit of this drug delivery system.

Rattanakaemakorn et al. compared a combination of liquid coal tar (liquor carbonis detergens) and 308-nm Excimer lamp with Excimer lamp alone in scalp psoriasis. The combination appeared to have a synergistic effect. This is an important finding in a particularly treatment-resistant site, that not only underscores the importance of an age-old modality like coal tar, but also situates the role of a novel light therapy.

The emergence of proteomics as a technology allows us to have a panoramic view of all potential peptides involved in the interactive pathways operating between cutaneous psoriasis and psoriatic arthropathy, and provides helpful clues as to why a certain subset of cutaneous psoriasis develops arthropathy. Qi et al. has elucidated this aspect in an important mini-review that summarizes the application of proteomics in the development of biomarkers in psoriatic arthritis and identifies possible clinical risk factors in the evolution of psoriatic arthropathy in patients with cutaneous psoriasis.

The role of oxidative stress and that of reactive oxygen species in the pathogenesis of psoriasis is well-known. In an illuminating narrative review, Campione et al. explore the role of dimethyl fumarate (DMF) and its metabolite, monomethyl fumarate, in modulation of pro-inflammatory



***Edited and reviewed by:***
*Robert Gniadecki,*
*University of Alberta, Canada*

***Correspondence:**
*Saumya Panda*
*saumyapan@gmail.com*

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transcription factors. The comparatively recent association of psoriasis with metabolic syndromes has brought the focus to glutathione-S-transferase dysregulation that is present in obesity, diabetes and cardiovascular disorders. The increase of this enzymatic activity in psoriatic epidermis and its reduction by DMF through formation of covalently linked conjugates is one of the highlights of this review.

In second of the two reviews, Thakur and Mahajan elucidate the therapeutic targets in psoriasis and the novel agents being developed to selectively block or inhibit those targets. Their discussion on the interplay of different epigenetic pathways in pathogenesis of psoriasis and the enzyme inhibitors acting on these pathways make for an illuminating discussion on the novel therapeutic targets in psoriasis.

In an interesting systematic review, Arora et al. deal with the very important issue of combination therapies and manage to come up with some recommendations. They discuss combinations of every kind that have been described in the literature, involving new therapeutic agents (small molecules, biologics), conventional agents and phototherapy.

Gómez-García et al. have done a scoping review of the inhibitors of the Janus kinase–signal transducer and activator of transcription (JAK/STAT) pathway in psoriasis. The application of this class of agents in dermatological disorders is in its infancy. They advocate caution in the interpretation of early phase trials, most of which have been industry-sponsored with a high risk of bias. They also suggest the use of standardized psoriasis-specific outcome measures, which would help reach better decisions.

The last of the three systematic reviews by Zhang et al. is on systematic treatment in nail psoriasis. They recommend to prioritize the use of anti-IL-17 agents in this situation.

To conclude: This Research Topic is a collection of diverse articles providing a gleaning on therapeutic advances in psoriasis and psoriatic arthritis. Through 3 original articles, 1 mini-review, 2 reviews and 3 systematic reviews, a whole lot of new ground, covering pathogenesis of the disease, the interlinking of pathogenetic pathways between cutaneous psoriasis and psoriatic arthritis, new drug delivery systems, systematic reviews of JAK-STAT inhibitors, to name just a few, have been covered by the authors. Many of these subjects are relatively new and/or unexplored, like the role of acitretin in the differentiation of MDSCs, and the role of the latter in the development of severe disease; fractional laser-delivered microporation as a new drug delivery technique in plaque psoriasis; the utilization of proteomics in identifying biomarkers that might be helpful in understanding the subset of cutaneous psoriasis patients who would be at risk for developing psoriatic arthritis, etc. Another important, yet a relatively virgin field of research, highlighted in one of the reviews, is the epigenetic pathways in the pathogenesis of the disease. New light has been thrown on possible mechanisms of action of some agents that are not so new, like fumarates and acitretin. All in all, this bouquet of articles will whet the appetite of anyone who wishes to have a panoramic view of new developments of all aspects of therapy of psoriasis and psoriatic arthritis, particularly if read in conjunction with novel findings in the pathogenesis of both the conditions.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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SYSTEMATIC REVIEW
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# Efficacy of Systemic Treatments of Nail Psoriasis: A Systemic Literature Review and Meta-Analysis

*Xuan Zhang*[1], *Bingbing Xie*[2] *and Yanling He*[1]*

[1] *Department of Dermatology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China,* [2] *Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China*

**Importance:** Nail involvement is a common condition in patients with psoriasis. The treatment of nail psoriasis is considered challenging and is often left untreated by physicians.

**Objective:** To assess the efficacy of current systemic treatments on nail psoriasis.

**Data Sources:** PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant articles from inception to September 1, 2020. Included articles were restricted to English language and human studies.

**Study Selection:** This was a systematic literature review with meta-analysis. Thirty-five random control trials that evaluated systemic therapies for nail psoriasis were selected in the systemic review. Among them, we retained 14 trials for meta-analysis.

**Data Extraction and Synthesis:** This study was conducted in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. All steps were performed by two independent investigators, and any disagreements were resolved by a third investigator. Meta-analysis of aggregated study data was conducted to assess therapeutic efficacy. The use of random-effects model was based on high heterogeneity as a variable endpoint in different studies.

**Main Outcomes and Measures:** Therapeutic effects on nail psoriasis were expressed in terms of effect sizes with 95% CIs.

**Results:** We included 35 random control trials (RCTs) in this systemic review. At baseline, a high prevalence (62.1%) of nail psoriasis was confirmed. The meta-analysis included 14 trials highlighting that biologic and small-molecule therapies were effective in treating nail psoriasis with variable effect size magnitudes [−0.89 (−1.10, −0.68), $I^2$ = 84%]. In particular, tofacitinib and ixekizumab showed the most significant scale of effect size magnitudes in treating nail psoriasis (−1.08 points and −0.93 points, respectively). We also found that a higher dose of tofacitinib and ixekizumab had similar effectiveness, and anti-IL-17 agents seem to be superior in effectiveness compared to anti-TNF-α therapies in the treatment of nail psoriasis. However, these results must be displayed carefully as variable endpoints in different studies.

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***Edited by:***
*Juan D. Cañete,*
*Hospital Clínic de Barcelona, Spain*

***Reviewed by:***
*Serena Lembo,*
*University of Salerno, Italy*
*Philippe Lefrançois,*
*McGill University, Canada*
*Jose-manuel Carrascosa,*
*Hospital Germans Trias i Pujol, Spain*

***Correspondence:**
*Yanling He*
*cydermhe@gmail.com*

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**Conclusions and Relevance:** This study provides a comprehensive overview of systemic treatments for nail psoriasis. For patients with psoriatic nail damage who are candidates of systemic therapies, the priority should be given to administering biologic and small-molecule therapies, especially anti-IL-17 drugs.

**Keywords: nail, psoriasis, systemic treatments, systemic review, meta-analysis**

## INTRODUCTION

Psoriasis is a chronic systemic inflammatory disease that frequently affects the nails. Approximately 40–50% of patients with psoriasis have concurrent nail involvement, with a lifetime incidence of 80–90% (1, 2). Nail psoriasis is associated with pain, cosmetic problems, and impaired finger function, with remarkably negative effects on the patient's quality of life (3, 4). Nail involvement in patients with psoriasis is considered a predictor for the development of psoriatic arthritis (5). High-resolution magnetic resonance imaging (MRI) showed that the integral supporting structure of the nail is formed by extensor tendon enthesis (6). Through this anatomical link between the nail and the joint, inflammatory responses at the affected joint in patients with psoriatic arthritis (PsA) often extend to the nail bed, suggesting that psoriatic nails can be considered as the tip of the iceberg of systemic inflammation (7). Based on this, nail psoriasis is often resistant to conventional treatments, such as topical and intralesional therapies, which are targeting at local inflammation response. Moreover, the structure of the nail presents therapeutic challenges, such as poor penetration of topical therapy across the nail plate and pain associated with intralesional therapies (8, 9). Furthermore, it has been reported that nail psoriasis promptly recurs once patients halt local therapies (10–12).

Nail psoriasis has a wide spectrum of clinical manifestations, depending on the part of the affected structure, which can be divided into the nail matrix (pitting, leukonychia, red spots in the lunula, and nail plate crumbling) or nail bed (oil drop discoloration, onycholysis, nail bed hyperkeratosis, and splinter hemorrhage) (8). In addition to a clinical description of improvement or exacerbation of nail psoriasis features, there are severity scoring systems, including the Nail Psoriasis Severity Index (NAPSI), Nail Area Severity (NAS), and Psoriasis Nail Severity Score (PNSS).

In recent years, a significant alleviation of psoriatic nails has been reported with the widespread use of small-molecule therapies and biologic agents for cutaneous psoriasis (13). Therefore, this study aimed at providing a systematic review and meta-analysis on the effectiveness of systemic therapies that are currently available for patients with psoriatic nails.

## MATERIALS AND METHODS

We conducted a systematic review and meta-analysis of random control trials for the evaluation of treatments for nail psoriasis. This study was conducted in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement (14). It is also registered in PROSPERO (https://www.crd.york.ac.uk/prospero/; registration number CRD42020204238).

### Literature Search

A computer-based literature search was performed to identify relevant articles published from inception to September 1, 2020, in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The main search terms were "*psoriasis*" and "*nail*." Vocabulary and syntax were adapted for each database. The literature search was restricted to English language and human studies. In addition, the references of these articles were also screened for relevant articles, and clinical trials registered at ClinicalTrials.gov were searched for details of relevant trials.

### Study Selection

The inclusion and exclusion criteria were determined before the search. The included studies fulfilled the following inclusion criteria: (1) study design was limited to RCT; (2) the study participants should be adults (age > 18 years) with a diagnosis of any type of psoriasis without any other nail disorder; (3) the evaluated interventions were restricted to traditional systemic immunomodulating agents, small-molecule therapies, and biologic agents; (4) severity scoring systems should be used to evaluate the involvement of nail psoriasis at baseline and at the end of study or the improvement of psoriatic nail during the treatment phase.

### Data Abstraction and Quality Assessment

Two independent reviewers abstracted data using a predefined data extraction form. The following information was extracted from each study: author, year of publication, design of study, blind time period, patient type, details of the interventions, sample size, baseline nail psoriasis involvement, and the improvement at each visit till the end of study. We independently assessed the quality of each included study in accordance with the Cochrane handbook of systematic reviews of interventions 5.2, which covers the following: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and treatment providers (performance bias); (4) blinding of outcome assessors (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other biases. Disagreements over any risk of bias in particular studies were resolved by a third reviewer.

### Statistical Analysis

We performed statistical analyses using the Review Manager V5.3 (The Nordic Cochrane Center, The Cochrane Collaboration) and STATA V15.0 (StataCorp). The identified studies used severity

scoring systems in the range 0–8 to 0–160; thus, scores will be scaled down to range 0–8 for meta-analysis for aggregation across the trials. We applied the mean difference (MD) with 95% CIs as the change in psoriatic nail involvement. The reduction in the scores over the observation period indicated an improvement in nail psoriasis. We used the random effect model to pool data to evaluate the overall effect. Heterogeneity was assessed using the $I^2$ statistic. The possibility of publication bias was assessed using a funnel plot and Egger test. Some trials included more than one intervention group, for which the control groups were equalized among the intervention groups.

# RESULTS

## Systematic Review

We identified 2,030 articles matching the search criteria after removing duplicate publications. We extracted 1,825 articles after reading the title or abstract. Furthermore, we retained 33 articles after a full-text review. The results of two different trials were presented in two articles (15, 16). Thus, we included 35 trials in the systematic review. In addition, four trials (17–20) did not mention the portion of nail involvement or enrolled patients with nail psoriasis, the remaining 31 trials included 17,254 patients with psoriasis, and 10,720 (62.1%) had nail involvement. The flow diagram is shown in **Figure 1**, and **Supplementary Figure 1** provides the quality assessment for the included trials.

### PDE4 Inhibitor: Apremilast (3 Trials)

In a placebo-controlled study on 266 patients, Paul et al. (21) reported that apremilast resulted in a trend of greater percentage reduction in NAPSI score vs. placebo (29.0 vs. 7.1%, $P = 0.052$) at week 16. Papp et al. (22) compared apremilast with placebo in 558 patients with nail psoriasis. They demonstrated that apremilast significantly reduced the activity of nail psoriasis after a treatment period of 16 weeks, whereas placebo had no effect ($P < 0.0001$). However, Reich et al. (23) studied 142 patients to assess the efficacy of apremilast and etanercept. Compared with the placebo group (−10.1%), the etanercept group (−37.3%, $P = 0.002$) experienced a significant improvement in NAPSI score, whereas apremilast (−18.7%, $P = 0.495$) had no effect at week 16.

### JAK Inhibitor: Tofacitinib (3 Trials)

Merola et al. (16) pooled data from 2 placebo-controlled studies (1,018 patients) showing a mean improvement of the NAPSI score (0–80) by 7.9 points in the tofacitinib 5 mg BID group and 10.5 points in the tofacitinib 10 mg BID group compared with the 0.4 points in the placebo group ($p < 0.001$) at week

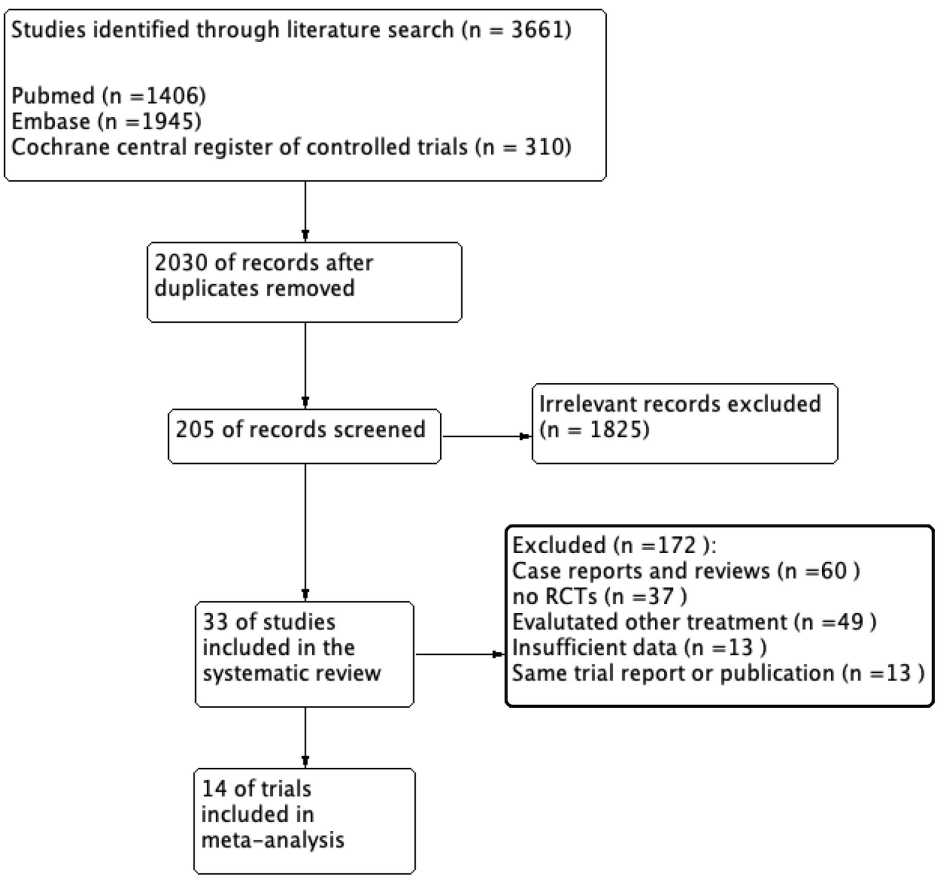


**FIGURE 1 |** Flow chart of Search Strategy and Study Selection.

16. In another (24) study with 266 patients (24), 116 had nail psoriasis. At week 16, the tofacitinib 10 mg BID group produced significantly greater changes in the NAPSI score vs. the placebo group (−33.32 vs. 7.91%, $P = 0.01$). Asahina et al. (25) evaluated the efficacy of different doses of tofacitinib in 66 patients. After 16 weeks of treatment, there were no significant differences in the reduction of NAPSI score between the tofacitinib 5 mg/BID and 10 mg/BID groups (−11.3 vs. −10.2%).

## Anti-GM-CSF Agent: Namilumab (1 Trial)

Papp et al. (26) compared namilumab to placebo in 122 patients. At the end of 12 weeks of treatment, the alleviation of nail psoriasis evaluated by NAPSI score was −2.5 points and −1.0 points in the namilumab 80 and 150 mg group, respectively, compared with 1.5 points in the placebo group ($P = 0.05$ and 0.121, respectively).

## Anti-TNF-α Agent

### *Etanercept (1 Trial)*

Mease et al. (27) examined the efficacy of methotrexate monotherapy relative to that of etanercept monotherapy and their combination in 588 patients. There was no significant difference in mNAPSI changes between the two monotherapies at week 24, while combining therapy showed a greater decrease in mNAPSI compared with methotrexate monotherapy (−1.7 vs. −1.1, $P = 0.02$).

### *Adalimumab (2 Trials)*

Elewski et al. (18) compared adalimumab with placebo in 217 patients, demonstrating that adalimumab induced greater improvement in the quality of life of patents with nail psoriasis. Significant improvement in the NAPSI score was as early as week 8 in 18.8% for the adalimumab group and 3.5% for the placebo group ($P < 0.01$). Leonardi et al. (28) compared adalimumab vs. placebo in 72 patients. The mean percentage improvement in NAPSI score was significantly greater for adalimumab than for placebo (50 vs. 8%, $P = 0.02$) at week 16.

### *Infliximab (2 Trials)*

In a study by Reich et al. (29) with 378 patients, 80.7% of patients had a psoriatic nail with a mean NAPSI score of 4.53 at baseline. The mean change in the NAPSI score was 26.0% at week 10 and 56.3% at week 24 in the infliximab group compared with −5.6 and −3.2% in the placebo group ($p < 0.0001$), respectively. In another study (30) of 43 patients, infliximab-treated patients achieved a higher reduction in NAPSI score (0–8) compared with placebo-treated patients (1.4 vs. −0.3), as early as week 10.

### *Certolizumab Pegol (1 Trial)*

Mease et al. (31) included 409 patients with PsA treated with certolizumab pegol vs. placebo. We recorded 73.3% of patients with baseline nail disease, and after a treatment period of 24 weeks, mNAPSI (0–8) changed from baseline was −1.6 for the certolizumab pegol 200 mg Q2W group and −2.0 for the certolizumab pegol 400 mg Q4W group compared with −1.1 for the placebo group ($p = 0.003$ and $p < 0.001$, respectively).

### *Golimumab (3 Trials)*

Kavanaugh et al. (32) used golimumab vs. placebo on 405 patients with PsA. The median improvement in NAPSI score from baseline to weeks 14 and 24 was significantly greater ($P < 0.001$) in the golimumab 50 mg group (25, 43%) and the golimumab 50 mg group (33, 54%) compared to that in the placebo group (0, 0%, respectively). Vieira-Sousa et al. (20) evaluated methotrexate monotherapy or combination therapy with golimumab in 44 patients. After 12 weeks of treatment, the medium percentage of reduction in target fingernail NAPSI score (0–8) from baseline for combination therapy was greater than that of methotrexate monotherapy (−2 vs. 0, $P = 0.044$). Mease et al. (33) compared golimumab vs. placebo in 367 patients. In this study, they observed a discernible clinical benefit in alleviating nail psoriasis for golimumab through 14 weeks of treatment (−9.6 vs. 1.9, $P < 0.001$).

### *Brodalumab (1 Trial)*

Elewski et al. (34) pooled two trials to evaluate the efficacy of brodalumab compared with that of ustekinumab in 593 patients with nail psoriasis. Among these, 283 had nail involvement. At week 52, 63.8% of patients achieved NAPSI = 0 for the brodalumab group vs. 39.1% for the ustekinumab group ($P < 0.05$).

## Anti-IL-23 Agent

### *Ustekinumab (2 Trials)*

Rich et al. (35) compared ustekinumab vs. placebo during 12 weeks of treatment in 766 patients. Treatment with ustekinumab 45 or 90 mg resulted in significantly better percentage improvement in NAPSI score than the placebo group ($P < 0.001$ and $P = 0.001$, respectively). However, Igarashi et al. (36) reported that there was no significant NAPSI improvement in ustekinumab 45 and 90 mg groups vs. placebo at week 12.

### *Guselkumab (2 Trials)*

Ohtsuki et al. (37) compared guselkumab with placebo in 192 patients. Among patients with nail psoriasis ($n = 126$), a significant decrease in mNAPSI score (0–8) of −1.2 and −1.5 was observed for the guselkumab 50 and 100 mg groups, compared with −0.2 for the placebo group, at week 16. Foley et al. (38) pooled two studies comparing guselkumab and adalimumab to placebo in 928 patients with fingernail psoriasis. The mean improvements in target NAPSI score were significantly greater for the treatment group (37.5 and 41.70%, respectively) than for the placebo group (0.7%; $P < 0.001$) at week 16.

## Anti-IL-17 Agent

### *Secukinumab (3 Trials)*

Reich et al. (17) compared secukinumab vs. placebo in 198 patients during week 16. Treatment with secukinumab resulted in significant improvements in nail psoriasis compared with placebo ($P < 0.001$); NAPSI improvements were −45.3, −37.9, and −10.8% for secukinumab 300 and 150 mg and placebo, respectively. Further alleviation of psoriatic nails was shown by week 32: NAPSI change from baseline was −63.2% for secukinumab 300 mg and −52.6% for secukinumab 150 mg. Two

placebo-controlled studies (39, 40) evaluated the effectiveness of secukinumab in nail psoriasis. The mean changes in NAPSI were significantly greater for secukinumab than for the placebo group ($P < 0.0001$).

***Ixekizumab (7 Trials)***

In a placebo-controlled study with 58 patients, Leonardi et al. (41) highlighted that 75 mg/150 mg q4w ixekizumab markedly alleviated the clinical symptoms of nail psoriasis compared with the placebo group as early as week 2. The SPIRIT-P1 study (42) compared ixekizumab with adalimumab and placebo in 417 patients. Among them, 289 had nail psoriasis. At week 24, the mean changes from baseline in the NAPSI score were significantly greater for the ixekizumab q4w (−14.0), ixekizumab q2w (−15.5), and adalimumab (−10.7) groups than for the placebo group (−2.4) ($p < 0.001$). A head-to-head trial (43) of 189 patients with nail psoriasis revealed a significantly greater number of patients achieved NAPSI = 0 with ixekizumab vs. ustekinumab as early as week 16. The UNCOVER-1 study (15) compared ixekizumab (80 mg q2w, 80 mg q4w) to placebo in 847 patients. The mean improvements in the NAPSI (0–80) were 7.24, 7.19, and −2.17 points, respectively ($p < 0.001$) at week 12. The UNCOVER-2 study (15) compared the same two doses of ixekizumab with etanercept (50 mg twice a week) and placebo in 751 patients. Treatment with ixekizumab 80 mg q2w or q4w resulted in an equivalent reduction in the NAPSI score (8.6 and 7.39, respectively), which was significantly better than that of patients treated with etanercept (5.34 points) and placebo (0.82 points, $P < 0.001$). Kerkhof et al. (44) performed a *post-hoc* analysis of the UNCOVER-3 study on 809 patients with baseline fingernail psoriasis comparing the efficacy of ixekizumab with etanercept and placebo. Ixekizumab provided significant improvement in fingernail NAPSI score as early as week 2 vs. etanercept (5.1 vs −7.9%, $P = 0.024$). At week 12, greater mean NAPSI improvements were achieved in the ixekizumab q4w group (36.7%) than in the placebo group (−34.3%, $P < 0.001$) and the etanercept group (20.0%, $P = 0.048$). In a head-to-head trial with 368 nail psoriasis patients, Mease et al. (45) compared ixekizumab with adalimumab. After 24 weeks of treatment, the mean change from baseline NAPSI was −15.89 for the ixekizumab group vs. −12.53 for the adalimumab group ($P = 0.001$).

### Traditional Systemic Immunomodulating Treatments (3 Trials)

Reich et al. (46) compared alitretinoin to placebo in 31 patients with palmoplantar pustulosis. The changes from baseline in the NAPSI score were similar for the alitretinoin and the placebo groups at weeks 12 and 24. Warren et al. (47) enrolled 120 patients to evaluate the efficacy of subcutaneous methotrexate in treating nail psoriasis. At week 16, there were no significant ($P = 0.40$) changes in NAPSI scores between the methotrexate group and the placebo group. Gümüşel et al. (19) enrolled 17 patients with nail psoriasis to compare the effectiveness of methotrexate and cyclosporine. After 24 weeks of treatment, the reduction of the NAPSI score from baseline was 43.3 and 37.2% for the methotrexate and cyclosporine groups, respectively.

The summary of systemic treatments for nail psoriasis are provided in **Supplementary Table 1**.

## Meta-Analysis

Among the trials selected for the systematic review, we included 14 trials that provided the outcome measurement of the alleviation of nail psoriasis between baseline and the end of the study. The characteristics of the selected trials are summarized in **Table 1**.

### Efficacy of Treatments

We evaluated 13 trials comparing the effectiveness of the interventions with placebo at variable endpoints at week 12 in seven trials (15, 26, 35, 41, 42, and 44), at week 14 in two trials (30, 33), and at week 16 in four trials (16, 24, 37). For some trials comparing different doses of interventions with placebo, the highest dose group was included in the global analysis. Positive comparisons contained in three trials were also included in this meta-analysis. Combined results from included trials were included in this global analysis (**Supplementary Figure 2**) and comparing interventions with placebo led to a significant decline in mean NAPSI score −0.89 points (95% CI [−1.10, −0.68]; $P < 0.00001$) and highlighted an immense level of heterogeneity ($I^2 = 84\%$). Accordingly, the subgroup analysis of treatment was employed to handle this bias: **Figure 2A** for JAK inhibitors [tofacitinib (16, 24)], **Figure 2B** for anti-TNF [etanercept (15, 44), adalimumab (42), infliximab (30) and golimumab (33)], **Figure 2C** for Anti-IL-23 [ustekinumab (35) and guselkumab (37)], and **Figure 2D** for Anti-IL-17 [ixekizumab (15, 42, 44)].

We also conducted other comparisons (**Figure 3**). Based on available data, we conducted effectiveness comparisons between interventions. Interestingly, a higher dose of tofacitinib did not have a better effectiveness in nail psoriasis at week 16 (**Figure 3A**). Moreover, Ixekizumab 80 mg/Q2W had a similar outcome in nail psoriasis compared with ixekizumab 80 mg/Q4W at week 12 (**Figure 3B**). We also found that at week 12, anti-IL-17 therapies were superior to anti-TNF therapies in treating nail psoriasis (**Figure 3C**).

### Risk of Bias and Publication Bias Assessment

The included studies were all screened to have a low and unclear risk of bias (**Supplementary Figure 3**), except in one study (35) where six patients (four in the intervention group and two in the placebo group) dropped out, and the missing data were not imputed. No significant publication bias was detected by using a funnel plot (**Supplementary Figure 4**) and Egger test (bias, −1.73; 95% CI, −5.16 to 1.70; $P = 0.298$).

## DISCUSSION

This systemic review provides an up-to-date synthesis of published evidence regarding the efficacy of systemic treatments on nail psoriasis and represents a meta-analysis on the efficacy of small-molecule therapies and biologic agents in treating psoriatic nails. In this review, 62.1% of patients with psoriasis had nail involvement, which is consistent with a previous study (1). Nail psoriasis is considered an indicator of systemic immune

**TABLE 1 |** Characteristics of the 14 Included Studies for meta-analysis.

| Reference | NCT | Treatment | Design | Patients | Outcome measure of nail psoriasis |
|---|---|---|---|---|---|
| **Placebo control trials** | | | | | |
| (41) | NCT01107457 | 150 mg of ixekizumab at 0, 2, 4, 8, 12, and 16 weeks | Parallel groups 12 w | Ixekizumab 10 Placebo 15 | Total nail NAPSI (0–160) |
| (15) | NCT01474512 | 160 mg ixekizumab at baseline followed by 80 mg Q4W or Q2W | Parallel groups 12 w | Ixekizumab Q2W 283 Ixekizumab Q4W 281 Placebo 283 | Total fingernail NAPSI (0–80) |
| (44) | NCT01646177 | 160 mg ixekizumab at baseline followed by 80 mg Q4W or Q2W etanercept 50 mg twice weekly | Parallel groups 12 w | Ixekizumab Q2W 229 Ixekizumab Q4W 228 Etanercept 236 Placebo 116 | Total NAPSI fingernail (0–80) |
| (15) | NCT01597245 | 160 mg ixekizumab at baseline followed by 80 mg Q4W or Q2W etanercept 50 mg twice weekly | Parallel groups 12 w | Ixekizumab Q2W 206 Ixekizumab Q4W 215 Etanercept 219 Placebo 111 | Total fingernail NAPSI (0–80) |
| (42) | NCT01695239 | Ixekizumab 160 mg at baseline followed by 80 mg Q4W or Q2W INF 40 mg/Q2W | Parallel groups 12 w | Adalimumab Q2W 71 Ixekizumab Q4W 70 Ixekizumab Q2W 74 Placebo 74 | Total fingernail mNAPSI (0–80) |
| (35) | NCT00267969 | Ustekinumab 90 mg at weeks 0, 4, 16, and 28 | Parallel groups 12 w | Ustekinumab 187 Placebo 176 | Target fingernail NAPSI (0–8) |
| (37) | NCT02325219 | Guselkumab 100 mg at weeks 0, 4, and every 8 weeks | Parallel groups 16 w | Guselkumab 40 Placebo 42 | Target fingernail NAPSI (0–8) |
| (16) | NCT01276639 | Tofacitinib 5 mg/BID or 10 mg/BID | Parallel groups 16 w | Tofacitinib 5 mg 224 Tofacitinib 10 mg 229 Placebo 102 | Total fingernail NAPSI (0–80) |
| (16) | NCT01309737 | Tofacitinib 5 mg/BID or 10 mg/BID | Parallel groups 16 w | Tofacitinib 5 mg 184 Tofacitinib 10 mg 175 Placebo 104 | Total fingernail NAPSI (0–80) |
| (24) | NCT01815424 | Tofacitinib 5 mg/BID or 10 mg/BID | Parallel groups 16 w | Tofacitinib 5 mg 38 Tofacitinib 10 mg 40 Placebo 38 | Total fingernail NAPSI (0–80) |
| (30) | - | Infliximab 5 mg/kg at weeks 0, 2, and 6 and every 8 weeks | Parallel groups 14 w | Infliximab 29 Placebo 14 | Target fingernail NAPSI (0–8) |
| (33) | NCT02181673 | Golimumab 2 mg/kg at weeks 0 and 4 and every 8 weeks | Parallel groups 14 w | Golimumab 197 Placebo 170 | Total fingernail mNAPSI (0–130) |
| (26) | NCT02129777 | Namilumab 80 mg at week 2, 6, and 10 with a loading (double) dose at week 0 | Parallel groups 12 w | Namilumab 25 Placebo 24 | Total fingernail NAPSI (0–80) |
| **Head-to-head trial** | | | | | |
| (25) | NCT01519089 | Tofacitinib 5 or 10 mg/BID | Parallel groups 16 w | Tofacitinib 5 mg 32 Tofacitinib 10 mg 34 | Total fingernail NAPSI (0–80) |

*BID, twice a day; Q2W, every 2 weeks; Q4W, every 4 weeks; NAPSI, Nail Psoriasis Severity Index; mNAPSI, modified Nail Psoriasis Severity Index; NCT, ClinicalTrials.gov Identifier.*

response (5). One included trial (43) showed that nail psoriasis is associated with a greater PASI, longer course of plaque psoriasis, and a higher proportion of PsA (data not provided). Interestingly, two trials (16, 35) pointed out that the effectiveness of interventions on nail psoriasis is regardless of the presence or absence of PsA. Although PASI scores were not firmly associated with NAPSI scores at baseline, several trials (35, 43, 44, 48) showed that there is a connection between NAPSI and PASI effects during the treatment phase. In general, nail responses were considerably lagged behind cutaneous responses. It's interesting to find out that greater cutaneous responses indicated better nail responses, as the Spearman's correlation between improvements in NAPSI and PASI scores showed a moderate but significant increased over time (35, 48).

Ninety-two percent of the studies included in the systematic review were published after 2010, and majority of trials evaluated small-molecule therapies and biologic agents in psoriasis treatment. They highlighted that available and effective remedies for nail psoriasis have been multiplied in the past decade. However, we noticed that three studies had contradictory

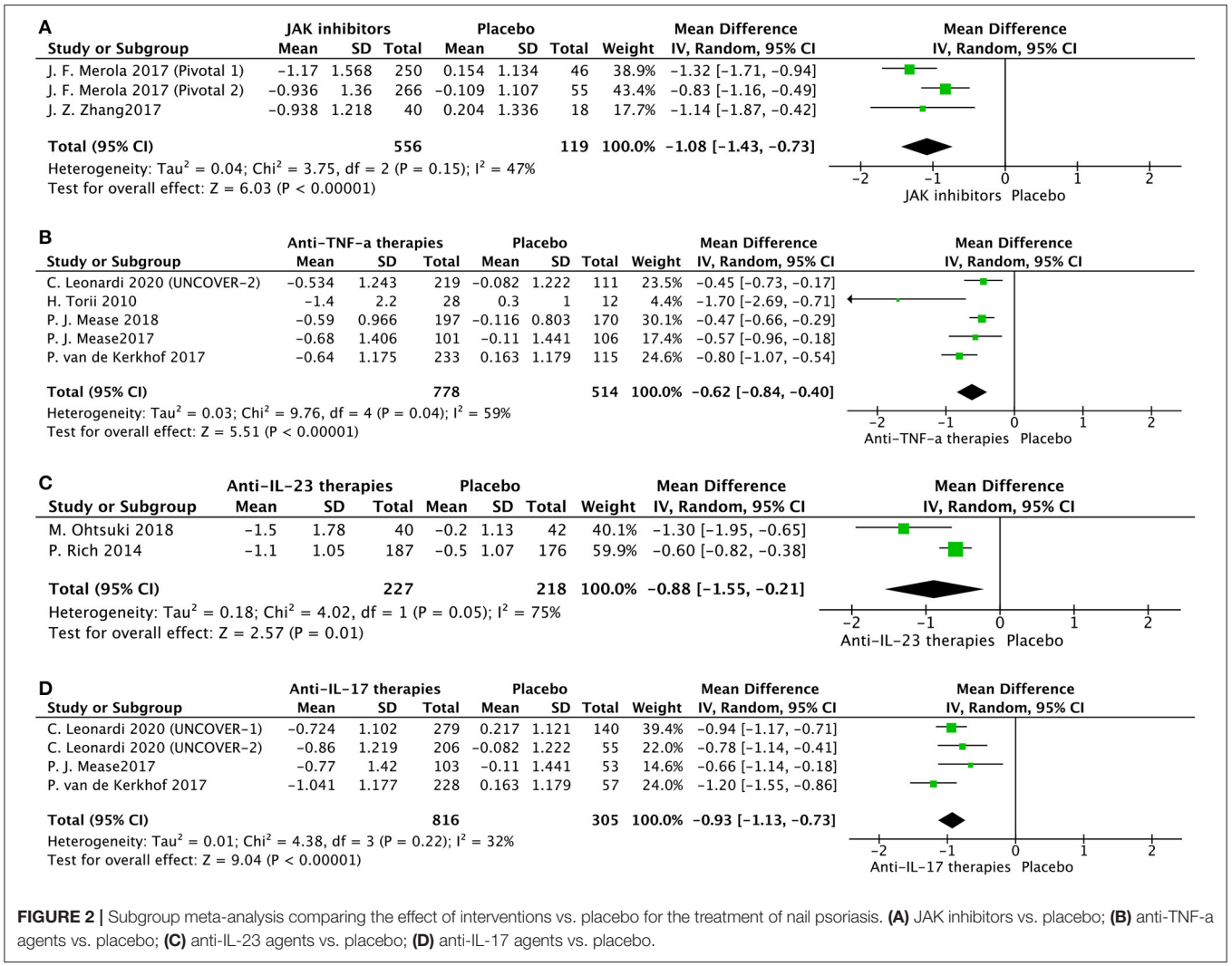


**FIGURE 2 |** Subgroup meta-analysis comparing the effect of interventions vs. placebo for the treatment of nail psoriasis. **(A)** JAK inhibitors vs. placebo; **(B)** anti-TNF-a agents vs. placebo; **(C)** anti-IL-23 agents vs. placebo; **(D)** anti-IL-17 agents vs. placebo.

outcomes of apremilast in nail psoriasis. Furthermore, one other study (36) unexpectedly reported that ustekinumab failed to provide a significant improvement in NAPSI compared with placebo. Ustekinumab is usually injected subcutaneously at week 0, 4, and then every 12 weeks. It seems unfair for the evaluation of ustekinumab on nail psoriasis that patients received only two doses at week 12 of evaluation.

Relatively few studies were retained in this systematic review evaluating conventional therapies for nail psoriasis and this review also showed their unsatisfied efficacy. This phenomenon was unexpected because acitretin, methotrexate, and cyclosporine play a historical role in systemic psoriasis treatments. However, the available evidence of their efficacy in clinical trials is inadequate, as most studies were either case reports, retrospective or unblinded in design. Anyway, it should be noted that conventional therapies may take a significantly longer time to show improvements in nail psoriasis, which will not be observed by short-term RCTs.

Our meta-analysis emphasized that all evaluated interventions have an eminent beneficial effect in the treatment of nail psoriasis. Tofacitinib showed the most significant scale of effect size in alleviating nail psoriasis (−1.08 points) at week 16. We noticed that the onset of alleviation in nail psoriasis was as early as week 8 in the tofacitinib group (16, 24). The improvement continued throughout the 16 weeks treatment phase. The efficacy of tofacitinib in patients with chronic plaque psoriasis has been previously demonstrated (49). However, one study (50) reported that the tofacitinib 5 and 10 mg/BID groups failed to achieve a significant change in NAPSI compared to the placebo group at month 3 (data not provided). The other therapies also showed significant results: anti-IL-17 (ixekizumab, −0.93 points), anti-TNF (etanercept, adalimumab, infliximab, and golimumab, −0.62 points), and anti-IL-23 (ustekinumab and guselkumab, −0.88 points). The different end timepoints may account for the high heterogeneity between the studies; three studies on week 12 and two studies on week 14 for anti-TNF subgroup analysis ($I^2$ = 59%) and one on week 12 and one on week 16 for anti-IL-23 subgroup-analysis ($I^2$ = 75%). We also found that for nail psoriasis, a higher dose of therapies was not the herald of better effectiveness, which is consistent

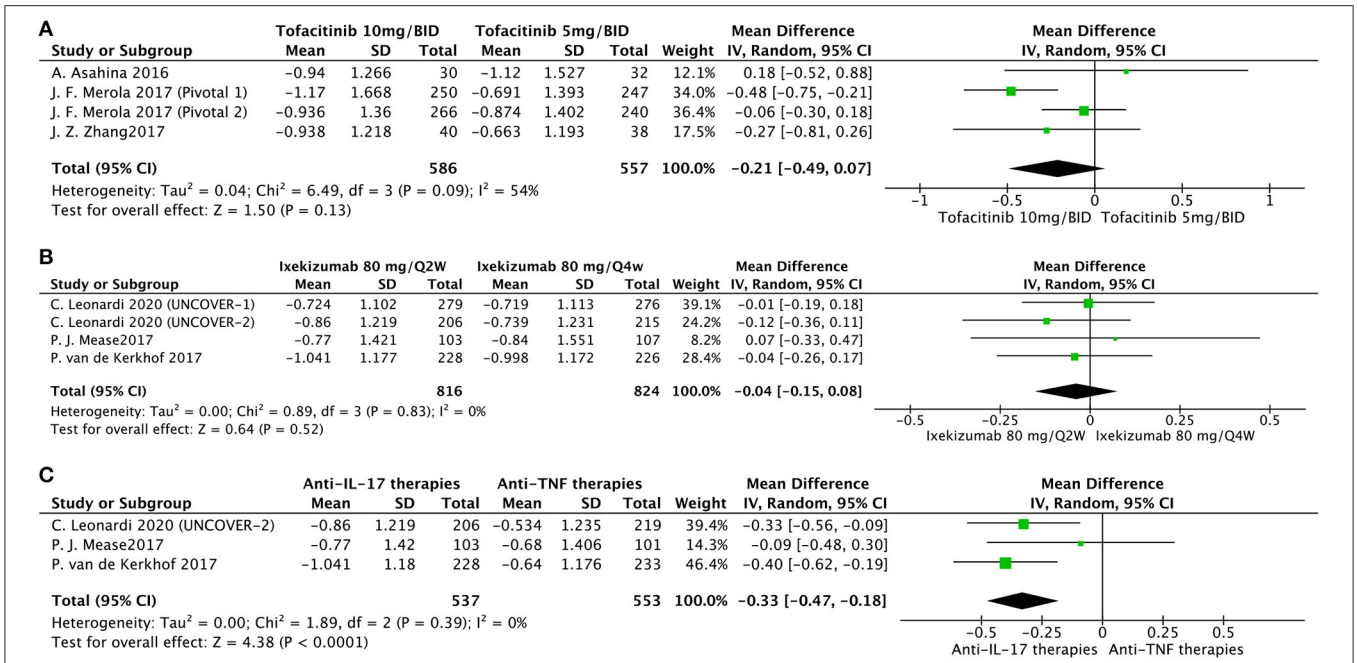


**FIGURE 3 |** Meta-analysis comparing the effect of multiple intervention groups for the treatment of nail psoriasis. **(A)** tofacitinib 10 mg/BID vs. tofacitinib 5 mg/BID at week 16; **(B)** ixekizumab 80 mg/Q2W vs. ixekizumab 80 mg/Q4W at week 12; **(C)** anti-IL-17 therapies vs. anti-TNF therapies at week 12.

with dose-independent improvement in cutaneous psoriasis, as these therapies may have exceeded the most effective dose (51). Moreover, our meta-analysis showed that anti-IL-17 agents seem to be superior to anti-TNF-α therapies in the treatment of nail psoriasis, consistent with their corresponding effectiveness in cutaneous psoriasis (52).

For patients with psoriatic nails, it was recommended to start with topical anti-psoriatic treatment for at least 4–6 months (13). Conventional systemic therapies were indicated for second-line treatment options for more severe nail psoriasis (13). However, it was also reviewed that these included therapies for cutaneous psoriasis could alleviate coexisting nail disease without noteworthy adverse effects (8). Therefore, the priority of these therapies should be increased for patients with nail psoriasis.

The most important limitation of this meta-analysis is that we could not include all the clinical trials selected in the systematic review because not all of them provided computable changes in the NAPSI score from baseline to the end of the study. Moreover, as variable endpoints (from week 12 to 16), phases (phase II, III) in different studies, and statistical errors due to a relatively small number of patients enrolled in some trials, these results must be displayed meticulously. Also, regarding the slow rate of nail growth to replace the deformed part of the nail plate, the efficacy endpoint for nail evaluation should be optimized in future trials.

Another limitation is that in our systematic review, nearly all of the studies evaluated the effectiveness of interventions on fingernails. One trial (17) showed that the decrease in the toenail NAPSI score is much slower than the fingernail NAPSI score. It is not out of the blue that the average growth rate of the toenails is slower than that of the fingernails, estimated at 1.62 vs. 3.47 mm/month (53). As a result, toenail psoriasis should take a much longer treatment course to achieve the desired outcome.

## CONCLUSION

In this study, we highlighted that the available biologic therapies and small molecule agents for psoriasis are efficient for nail psoriasis. As nail damage affects more than half of patients with psoriasis, systemic treatment of psoriatic nails should be systematically evaluated in future RCTs as the primary or secondary outcome.

## DATA AVAILABILITY STATEMENT

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

## AUTHOR CONTRIBUTIONS

XZ and YH: conceptualization. BX: writing. YH: supervision. XZ: software and methodology, data curation. XZ and BX: investigation and formal analysis. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.620562/full#supplementary-material

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# Acitretin Promotes the Differentiation of Myeloid-Derived Suppressor Cells in the Treatment of Psoriasis

*Panpan Liu*[1,2,3], *Cong Peng*[1,2,3], *Xiang Chen*[1,2,3,4], *Lisha Wu*[1,2,3], *Mingzhu Yin*[1,2,3], *Jie Li*[1,2,3], *Qunshi Qin*[1,2,3], *Yehong Kuang*[1,2,3]* *and Wu Zhu*[1,2,3,4]*

[1] *The Department of Dermatology, Xiangya Hospital, Central South University, Changsha, China,* [2] *Hunan Key Laboratory of Skin Cancer and Psoriasis, Changsha, China,* [3] *Hunan Engineering Research Center of Skin Health and Disease, Changsha, China,* [4] *Gerontology Center of Xiangya Hospital, Central South University, Changsha, China*

Increased numbers of myeloid-derived suppressor cells (MDSCs) are involved in the development of psoriasis. Acitretin is used to treat psoriasis by regulating the proliferation and differentiation of keratinocytes, but little is known about the effect of acitretin on immune cells. Here, we reported that psoriasis patients had an expansion of MDSCs and monocytic-MDSCs (M-MDSCs) in peripheral blood and skin lesions. The number of MDSCs and M-MDSCs in peripheral blood correlated positively with disease severity. Acitretin could reduce the number of MDSCs and M-MDSCs in the peripheral blood of psoriasis patients as well as the spleen and skin lesions of IMQ-induced psoriasis-like model mice. Moreover, acitretin promoted the differentiation of MDSCs into macrophages, especially $CD206^+$ M2 macrophages, and $CD11c^+MHC\text{-}II^+$ dendritic cells. Mechanically, acitretin dramatically increased the glutathione synthase (GSS) expression and glutathione (GSH) accumulation in MDSCs. Interruption of GSH synthesis abrogated the acitretin effect on MDSCs differentiation. Acitretin regulated GSS expression via activation of extracellular signal-regulated kinase 1/2. Thus, our data demonstrated a novel mechanism underlying the effects of acitretin on psoriasis by promoting MDSCs differentiation.

**Keywords: psoriasis, acitretin, MDSCs, M-MDSCs, differentiation, glutathione**

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*University of Salerno, Italy*

***Correspondence:**
*Yehong Kuang*
*yh_927@126.com*
*Wu Zhu*
*zhuwu70@hotmail.com*

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## INTRODUCTION

Psoriasis is an immune-mediated chronic inflammatory disease, affecting 2–3% of the population (1). The high proliferation and low differentiation of keratinocytes and dermal immune cells infiltration are the two major pathological manifestations of psoriasis (2, 3). The inflammatory effect induced by the interaction between keratinocytes and activated immune cells is also the main factor leading to the pathogenesis of psoriasis (4, 5). Acitretin, a synthetic retinoid belonging to the family of retinoid analogs (RA) drugs (6), has been used as the first-line treatment of psoriasis (7). It has been reported that acitretin could suppress the proliferation of keratinocytes and regulate their differentiation in the treatment of psoriasis (8), but it has little effect on Th1, Th17, and Tregs (9, 10). However, retinoic acid caused a pronounced inhibition of neutrophils in the treatment of pustular psoriasis (11), suggesting the anti-inflammatory effect of retinoids. Therefore, we sought to determine whether acitretin could regulate immunity in the treatment of psoriasis.

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature cells, including immature granulocytes, monocytes, and dendritic cells (12). Human MDSCs are HLA-DR$^-$CD11b$^+$CD33$^+$ and can be divided into two major subsets, CD15$^-$CD14$^+$ monocytic MDSCs (M-MDSCs), and CD15$^+$CD14$^-$ granulocytic MDSCs (G-MDSCs) (13, 14). Murine MDSCs are Gr-1$^+$CD11b$^+$ and can be further subdivided into CD11b$^+$Ly6G$^-$Ly6C$^+$ M-MDSCs and CD11b$^+$Ly6G$^+$Ly6C$^-$ G-MDSCs (15). Traditionally, MDSCs have been studied in regard to their increased numbers in cancer patients and immunosuppressive functions (12, 16). Recent research focused on the pathologic role of expanding MDSCs in inflammatory diseases and autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, autoimmune hepatitis, and psoriasis (17–19). In addition, the increased numbers of MDSCs in inflammatory diseases presented a pro-inflammatory role and impaired immunosuppressive function (20). The MDSCs from patients with active systemic lupus erythematosus or rheumatoid arthritis showed the induction of the Th17 response and Th17 differentiation (21, 22). Psoriatic MDSCs could produce increased IL-23, IL-1β, and CCL4 cytokines, were unable to suppress T-cell proliferation, displayed decreased expression levels of PD-1 as well as PD-L1, and failed to produce Tregs (23–26). All-trans retinoic acid (ATRA), a member of the retinoid family, potently eliminated MDSCs in cancer patients (27). Therefore, we investigated whether acitretin could regulate MDSCs.

In this study, we found psoriasis patients have a significant increase in MDSCs and M-MDSCs populations that correlated positively with disease severity. Acitretin reduced the number of MDSCs and M-MDSCs in the peripheral blood of psoriasis patients and spleen and skin lesions of imiquimod (IMQ)-induced model mice of psoriasis. Furthermore, we found that acitretin promoted the differentiation of MDSCs via increasing glutathione accumulation, which were activated by the ERK1/2 MAPK signaling pathway. In summary, these findings indicated that acitretin promoted the differentiation of MDSCs in the treatment of psoriasis.

# MATERIALS AND METHODS

## Human Subjects

All patients in this study were diagnosed with plaque psoriasis by a dermatologist based upon clinical presentation or histologic examination. Patients who were treated with any treatment in the past 3 months were excluded from this study. Psoriasis disease activity was assessed using the psoriasis area and severity index (PASI) score (28). Healthy volunteers were randomly recruited with matched age and gender of psoriasis patients. Peripheral blood mononuclear cells (PBMCs) were collected from 77 patients with plaque psoriasis and 30 healthy controls. The skin was collected from 20 patients with plaque psoriasis and 9 healthy controls. Seventeen psoriasis patients were treated with acitretin (HUAPONT PHARM, Chongqing, China) 30 mg/d for 8 weeks with the PASI score significantly improved, and PBMCs were collected before and after the treatment. Patient information was shown in **Supplementary Tables 1, 2, 3**. For all the experiments using clinical samples, we have ensured the blinded outcome assessment. All human studies were approved by the ethics committees of Xiangya hospital of Central South University, Changsha, Hunan, China, and informed consent was obtained from all subjects.

## IMQ-Induced Psoriasis-Like Model Mice

8-week-old BALB/c female mice (purchased from the department of laboratory animals of Central South University) were used. A daily dose of 62.5 mg of 5% imiquimod (IMQ) cream (Medshine Pharmaceutical Co., Ltd., Sichuan, China) was applied to the shaved back of mice for 6 consecutive days (29). Mice were treated with acitretin (5 mg/kg, daily) (HUAPONT PHARM, Chongqing, China) by oral administration once per day. All animal experiments were performed according to the Animal Care and Use Committee guidelines of Xiangya medicine school of Central South University.

## Histological Evaluation

Human and mouse skin tissues were embedded in paraffin and split for routine histopathology on paraffin slicing machine-cut 3 mm sections. Sections were stained with hematoxylin and eosin (H&E stain) for histological evaluation.

## Measurement of Skin Scores and Epidermal Thickness

The clinical skin scores of mice were determined from day 1 (the 1st day of IMQ treatment) and every other day until day 7 using the modified PASI as previously described (30, 31). The degree of skin erythema, induration, and scale was classified as follows: 0, no symptoms; 1, mild; 2, moderate; 3, severe; or 4, very severe. The thickness of the epidermis was measured from the stratum basale to the stratum granulosum using Image Pro-Plus (Image Pro-Plus 6.0 image-analysis software). The average value from seven random fields of view was calculated for each mouse.

## Immunohistochemistry and Immunohistochemical Analysis

Immunohistochemistry was performed according to a previous study (32). Briefly, sections were incubated with monoclonal antibody: PCNA (Abcam, Cat. ab15497), K17 (Abcam, Cat. ab109725), K10 (Abcam, Cat. ab76318), CD86 (NOVUS, Cat. NBP2-25208), CD206 (Abcam, Cat. ab64693), or MHC-II (Abcam, Cat. ab55152) at 4°C overnight. Bound antibodies were detected by using a conventional streptavidin-biotin method according to the manufacturer's instructions (ZSGB-BIO Cat. PV-9000). The reaction was visualized by DAB+ Chromogen, and slides were counterstained with hematoxylin.

**Abbreviations:** MDSCs, Myeloid-derived suppressor cells; M-MDSCs, Monocytic myeloid-derived suppressor cells; G-MDSCs, Granulocytic myeloid-derived suppressor cells; IMQ, Imiquimod; RA, Retinoid analogs; ATRA, all-trans retinoic acid; PBMCs, peripheral blood mononuclear cells; PASI, psoriasis severity index score; DCs, dendritic cells; PCNA, proliferating cell nuclear antigen; K17, cytokeratin 17; K10; cytokeratin 10; GSS, glutathione synthase; GSH, glutathione; ROS, reactive oxygen species; ERK1/2, extracellular signal-regulated kinase 1/2; MAPK, mitogen-activated protein kinase; IOD, integrated optical density.

For immunohistochemical analysis, immune-stained sections were characterized semi-quantitatively by digital image analysis using the Image Pro-Plus (Image Pro-Plus 6.0 image-analysis software) by using the method as previously reported (33, 34). Briefly, images at 1,360 × 1,024-pixel resolution at 400× magnification were obtained with an Olympus CX41 microscope fitted with a micro image video camera (Mshot). A series of seven random images on several sections were taken for each immune-stained parameter to obtain a mean value for statistical comparison. Staining was defined via color intensity, and a color mask was made. The mask was then applied equally to all images, and measurements were obtained. The measurement parameter included integrated optical density (IOD) and the area. The optical density was calibrated, and the area of interest was set through: PCNA (hue 9–36, saturation 0–255, intensity 0–241), K17 (hue 10–31, saturation 0–255, intensity 0–170), K10 (hue 15–31, saturation 0–255, intensity 0–170), CD86 (hue 9–70, saturation 0–255, intensity 0–180), CD206 (hue 9–70, saturation 0–255, intensity 0–196), MHC-II (hue 9–115, saturation 0–255, intensity 0–190), and then the values were counted. Two independent examiners evaluated these sections without prior knowledge of the clinical status. PCNA IOD, K17 IOD, K10 IOD/Area, CD86 IOD, CD206 IOD, or MHC-II IOD was calculated.

## Cell Isolation

PBMCs were prepared by density gradient centrifugation using Lymphocyte Separation Medium (human). Single-cell suspensions of the mice were prepared from the spleen, and red blood cells were removed using Lysing Buffer (BD, Cat. 555899). Skin lesions were dissected and digested with 2.0 mg/mL collagenase IV (Sigma-Aldrich, Cat. V900893) and 1.0 mg/mL dispase II (Sigma-Aldrich, Cat. D4693) for 60 min at 37°C. All single-cell suspensions are filtered through 40-micron pores (BD, Cat. 352340). Gr-1$^+$ MDSCs were isolated by using biotinylated anti-Gr-1 antibody (Miltenyi Biotec, Cat.130-101-849) and streptavidin microbeads (Miltenyi Biotec, Cat.130-048-102) with MiniMACS columns, and the purity of the cells after separation was >95%.

## Flow Cytometric Analysis

Flow cytometry was used to determine the phenotypes of human and mouse MDSCs, macrophages, and dendritic cells. Cells were incubated with live/dead stain (Zombie Aqua™ Fixable Viability Kit; BioLgend Cat. 432102) and Fc block (BioLegend Cat. 101302). Cells were then washed and stained for using various combinations of the following fluorochrome-conjugated mAbs: anti-human HLA-DR (L243), CD11b (ICRF44), CD33 (P67.6), CD15 (HI98), CD14 (63D3), and anti-mouse Gr-1 (RB6-8C5), CD11b (M1/70), Ly6G (1A8), Ly6C (HK1.4), F4/80 (BM8), CD86 (BU63), MHC-II (39-10-8), and CD11c (N418) from Biolegend (San Diego, USA). For intracellular staining, cells were fixed and permeabilized using the Foxp3/Transcription Factor Staining Buffer Kit (eBioscience Cat. 00-5523-00) according to the manufacturer's protocol. Cells were stained intracellularly with anti-CD206 (C068C2) antibody. All samples were detected on FACSCalibur (BD, California, USA) and analyzed by FlowJo software (version 10.0.7). Isotype-matched antibodies were used with all the samples as controls.

## Differentiation of MDSCs

MDSCs were isolated from the bone marrow of IMQ-induced model mice, resuspended in RPMI 1640 (Biological Industries Cat. 01-100-1ACS) supplemented with 10% FBS (Gibco Cat. 16140071), HEPES (Gibco Cat. 15630080), sodium pyruvate (Gibco Cat. 11360-070), Non-Essential Amino Acids Solution (Gibco Cat. 11140050), 2-Mercaptoethanol (Gibco Cat. 21985023) and 20 ng/mL murine GM-CSF (PeproTech, Cat. 96-315-03-20), and plated at concentration $1.0 \times 10^6$/mL in 24-well plate. MDSCs were cultured for 4–5 days. Acitretin (HUAPONT PHARM, Chongqing, China), sulfasalazine (SAS) (MCE, Cat. HY-14655), or selumetinib (MCE, Cat. HY-50706) was added on days 1 and 3. After 4–5 days of culture, cells were collected, and the presence of different cell populations was evaluated by flow cytometry.

## RNA Seq Analysis

Total RNA was isolated and reverse-transcribed into cDNA to generate an indexed Illumina library, followed by sequencing at the Shenzhen Genomics Institute (Shenzhen, China) using a BGISEQ-500 platform. High-quality reads were aligned to the mouse reference genome (GRCm38) by Bowtie2. The expression of individual genes was normalized to fragments per kilobase of the exon model per million mapped reads from RNA-Seq by Expectation Maximization. Significant differential expression was set if a gene with > 2-fold expression difference vs. the control with an adjusted $p$-value of < 0.05. The differentially expressed genes (DEGs) were analyzed by gene ontology using AMIGO and DAVID software. The enrichment degrees of DEGs were analyzed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) annotations.

## RT-qPCR

RNA was extracted from cells using TRIpure Reagent (Bioteke Cat. RP1001), according to the manufacturer's instructions. RNA was converted to cDNA using HiScript II Q RT SuperMix for qPCR (+gDNA wiper) (Vazyme Cat. R223-01), and gene expression was determined by RT-qPCR using the UltraSYBR One-Step RT-qPCR Kit (CWBIO Cat. CW0659) on a 7,500 Fast thermocycler (Applied Biosystems). The relative expression of target genes was confirmed using the quantity of target gene/quantity of β-Actin. The fold change of gene expression was calculated by $2^{-(\Delta Ct\ \text{experimental group} - \Delta Ct\ \text{control group})}$, which normalized to the control group. The primer sequences used for RT-qPCR were as follows: *Gss*: forward, 5′ -CTGATGCTA GAGAGATCTCGTG-3′, and reverse, 5′ -TTCACCCATGTCC AGTGAATAG-3′; *β-Actin*: forward, 5′ -GCTCTGGCTCCT AGCACCAT-3′, and reverse, 5′ -GCCACCGATCCACACA GAGT-3′. All primers were purchased from Sangon Biotech.

## Western Blotting

Cells were lysed in radio immunoprecipitation assay buffer supplemented with protease and phosphatase inhibitor (Bimake Cat. B14002). The protein concentration had been tested with a BCA Kit (Bimake Cat. PP1002), and appropriate amounts of protein were prepared for SDS-PAGE and then transferred to a PVDF membrane (Millipore). The membranes were blocked for 1 h with 5% bovine serum albumin (BSA) at room temperature and then incubated with primary antibodies overnight at 4°C. The membranes were washed with phosphate-buffered saline (PBS) buffer with 0.1% Tween 20 (PBS-T), reacted with horseradish peroxidase-conjugated secondary antibodies for 1 h, and visualized using an enhanced chemiluminescence substrate. Membranes were visualized using WesternBright ECL HRP substrate (Advansta) on a GelDoc system (Bio-Rad). Images were analyzed with the Image Lab software (Bio-Rad). Rabbit anti-GSS Ab (1:500; ABclonal Cat. ab11557), rabbit anti-p-MEK1/2 (Ser217/221) Ab (1:1000; CST Cat. 9154), rabbit anti-MEK1/2 Ab (1:1000; CST Cat. 9126), rabbit anti-p44/42 MAPK (ERK1/2) (Thr202/Tyr204) Ab (1:1000; CST Cat. 4370), Rabbit anti-p-p38 MAPK (Tyr182) Ab (1:1000; Santa Cruz Biotechnology Cat. sc-166182), or mouse anti-GAPDH Ab (1:2000, Proteintech Cat. 6004-1-Ig) was used.

## Measurement of GSH and Reactive Oxygen Species (ROS)

MDSCs were isolated from the bone marrow of IMQ-induced model mice, resuspended in 20 ng/mL murine GM-CSF (PeproTech, Cat. 96-315-03-20), and plated at concentration $1.0 \times 10^6$/mL in 24-well plate. MDSCs were treated with acitretin 500 ng/mL, SAS 200 μM or vehicle control for 48 h and then collected for the measurement of GSH or ROS. GSH level was determined using GSH Assay Kit (Beyotime Cat. S0053) according to the manufacturer's protocol. Absorbance was read at 412 nm using a microplate reader. GSH level was expressed as nanograms per $10^6$ cells. For the measurement of ROS, cells were collected and then loaded with DCFH-DA (Solarbio Cat. CA1410) in RPMI 1640 at 37°C and incubated for 20 min according to the manufacturer's instructions. Excess DCFH-DA was removed by washing with RPMI 1640. The ROS levels were measured by flow cytometry and analyzed using the FlowJo software.

## Statistical Analysis

Statistical analyses were performed on GraphPad Prism 8.0 software. Data are expressed as means ± SEM. A Student's *t* test was used to compare two conditions, and an analysis of variance (ANOVA) with Bonferroni or Newman-Keuls correction was used for multiple comparisons. Correlation analysis was performed with Pearson Correlation Test. The level of significance was defined as $p < 0.05$. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

# RESULTS

## MDSCs and M-MDSCs Expansion Was Found in the Peripheral Blood and Skin Lesions of Psoriasis Patients

To confirm the number of MDSCs in the psoriasis patients, we first measured the percentage of MDSCs and their subsets in PBMCs isolated from healthy controls and psoriasis patients. The characteristics of psoriasis patients and healthy subjects were shown in **Supplementary Table 1**. MDSCs were defined as HLA-DR$^-$CD11b$^+$CD33$^+$, which were further divided into CD15$^-$CD14$^+$ M-MDSC and CD15$^+$CD14$^-$ G-MDSC subsets (**Supplementary Figure 1**). Compared to the healthy control subjects, the plaque psoriasis patients showed significant increases in the percentages of both MDSCs and M-MDSCs (**Figure 1A**), which were positively correlated with disease severity assessed by PASI score (**Figure 1B**). However, there was no significant difference in the percentage of G-MDSCs between the groups (**Figures 1A,B**). In addition, the number of MDSCs and M-MDSCs in the skin lesions of the psoriasis patients was markedly higher than that in the non-lesion tissue and normal skin (**Figure 1C**, **Supplementary Table 2**). There was no significant difference in the percentage of G-MDSCs between these groups in skin lesions (**Figure 1C**). Therefore, the number of MDSCs, especially M-MDSCs, in peripheral blood and skin lesion of psoriasis patients was significantly higher than that of healthy controls.

## Acitretin Deceased the Number of MDSCs and M-MDSC *in vivo*

We then tried to determine whether acitretin reduced the number of MDSCs in the treatment of psoriasis. We measured the percentage of MDSCs, M-MDSCs, and G-MDSCs in the PBMCs of psoriasis patients treated with acitretin for 8 weeks with the PASI score significantly improved. The characteristics of the psoriasis patients who were treated with acitretin were shown in **Supplementary Table 3**. The number of MDSCs and M-MDSCs in the peripheral blood of the psoriasis patients was significantly decreased after acitretin treatment (**Figure 2A**). There was no significant difference in the percentage of G-MDSCs after acitretin treatment (**Figure 2A**).

To determine whether acitretin has the same effect on MDSCs in the IMQ-induced model mice of psoriasis, we first treated IMQ-induced psoriasis-like model mice with oral acitretin once per day. After the IMQ-induced model mice were treated with acitretin for 6 days, the scaling and thickness of the skin on the back of the mice were significantly alleviated, which was confirmed by the histological evaluation showing a significant decrease in epidermal thickness; the PASI score was also significantly decreased (**Figures 2B,C**, **Supplementary Figures 2A–D**). Besides, the expression of PCNA and K17 (the makers of cell proliferation) significantly decreased in the skin lesion of the acitretin treatment group. In contrast, the expression of K10 (the markers of keratinization) increased in the skin lesion of the acitretin treatment group compared with the IMQ groups (**Supplementary Figures 2E–G**).

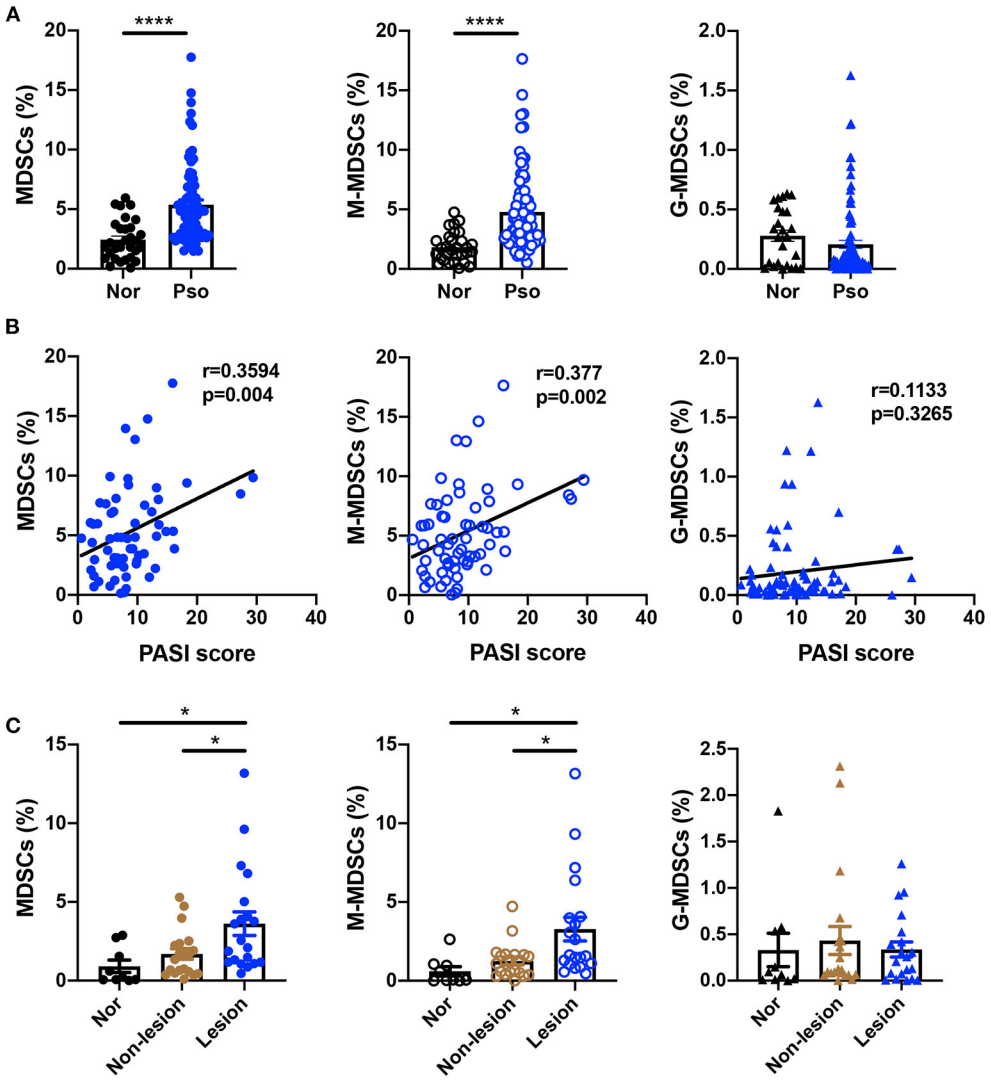


**FIGURE 1 |** MDSCs and M-MDSCs expansion was found in the peripheral blood and skin lesions of psoriasis patients. **(A,B) (A)** Percentages of HLA-DR$^-$CD11b$^+$CD33$^+$ MDSCs (left panel), HLA-DR$^-$CD11b$^+$CD33$^+$CD15$^-$CD14$^+$ M-MDSCs (middle panel), and HLA-DR$^-$CD11b$^+$CD33$^+$CD15$^+$CD14$^-$ G-MDSCs (right panel) in PBMCs of healthy controls (Nor) ($n = 30$) and plaque psoriasis (Pso) ($n = 77$), and **(B)** the correlation analysis between the indicated cells frequency and disease activity (that is, PASI score) in plaque psoriasis. **(C)** The number of MDSCs (left panel), M-MDSCs (middle panel), and G-MDSCs (right panel) in normal skins ($n = 9$), non-lesion tissues ($n = 20$), and skin lesion of psoriasis ($n = 20$). Data represent the mean ± SEM. *$p < 0.05$, ****$p < 0.0001$.

We then measured the percentage of MDSCs, M-MDSCs, and G-MDSCs in the spleen and skin lesions of acitretin-treated IMQ-induced psoriasis-like model mice. The results showed that the number of Gr-1$^+$CD11b$^+$ MDSCs, CD11b$^+$Ly6G$^-$Ly6C$^+$ M-MDSCs, and CD11b$^+$Ly6G$^+$Ly6C$^-$ G-MDSCs significantly increased in the spleen and skin lesions of IMQ-induced model mice compared with control group mice (**Figures 2D,E**, **Supplementary Figure 3**). The number of MDSCs and M-MDSCs in the spleen and skin lesions was decreased significantly in the acitretin treatment group compared with the IMQ groups (**Figures 2D,E**). However, there was no significant difference in the number of G-MDSCs after acitretin treatment (**Figures 2D,E**). Therefore, these results indicated that acitretin reduced the number of MDSCs and M-MDSCs in the psoriasis patients and psoriasis-like model mice.

## Acitretin Promoted the Differentiation of MDSCs

MDSCs are immature cells and have the ability to differentiate into macrophages and dendritic cells (DCs) (35). To test whether acitretin affected the differentiation of MDSCs, Gr-1$^+$ MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured for 4 days with GM-CSF. Acitretin (100 ng/mL or 500 ng/mL, considering that the concentration of acitretin in human blood is 196–728 ng/mL) was added on days 1 and 3. The results showed that acitretin substantially reduced the

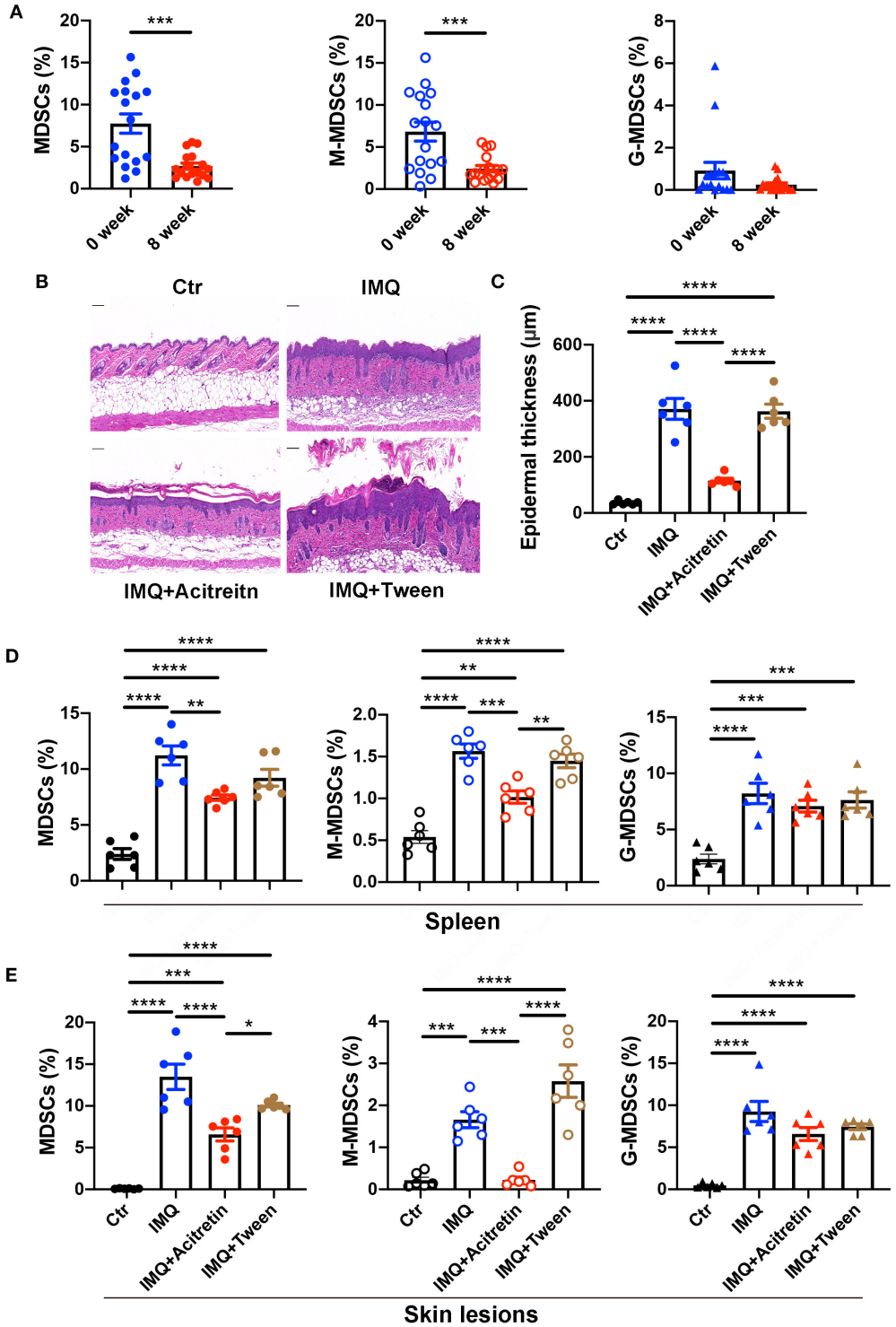


**FIGURE 2 |** Acitretin deceased the number of MDSCs and M-MDSC *in vivo*. **(A)** The percentages of MDSCs (left panel), M-MDSCs (middle panel), and G-MDSCs (right panel) in PBMCs of psoriasis patients before and after the treatment of acitretin for 8 weeks ($n = 17$). IMQ-induced psoriasis-like model mice treated with oral acitretin or tween (solvent) once per day for 6 days. **(B)** The H&E staining of the back skin derived from Control (Ctr) and IMQ-induced model mice treated with acitretin or tween (solvent) ($n = 6$). Scale bars: 100 μm. **(C)** The epidermal thickness of mice in **B** ($n = 6$). **(D,E)** The statistical data of Gr-1$^+$CD11b$^+$ MDSCs (left panel), CD11b$^+$Ly6G$^-$Ly6C$^+$ M-MDSCs (middle panel), and CD11b$^+$Ly6G$^+$Ly6C$^-$ G-MDSCs (right panel) in the spleen **(D)** and skin lesions **(E)** of IMQ-induced psoriasis-like model mice treated with oral acitretin or tween (solvent) ($n = 6$). All results represent at least 3 independent experiments. Data represent the mean ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

percentage of MDSCs (**Figure 3A**) and increased the proportion of F4/80$^+$ macrophages, especially CD206$^+$ M2 macrophages (**Figure 3B**, **Supplementary Figure 4**). However, the percentage of CD86$^+$ M1 macrophages was slightly decreased after acitretin treatment (**Figure 3B**, **Supplementary Figure 4**). In addition, acitretin increased the proportion of CD11c$^+$MHC-II$^+$ dendritic cells (**Figure 3B**, **Supplementary Figure 4**). To clarify the effect of acitretin on the differentiation of MDSCs *in vivo*, we analyzed the expression of macrophages and dendritic cells in the skin lesion of IMQ-induced model mice treated with acitretin by immunohistochemistry. The results showed that the expression of CD86 significantly decreased in the skin lesion of the acitretin treatment group, while the expression of CD206 and MHC-II increased in the skin lesion of the acitretin treatment group compared with the IMQ groups (**Figures 3C–E**). Thus, these data indicated that acitretin induced the differentiation of MDSCs into macrophages, especially CD206$^+$ M2 macrophages, and CD11c$^+$MHC-II$^+$ dendritic cells.

## Mechanism of Acitretin Effect on the Differentiation of MDSCs

To investigate the mechanisms of acitretin effect on the differentiation of MDSCs, MDSCs isolated from IMQ-induced psoriasis-like model mice treated with control or acitretin 500 ng/mL for 24 h was performed using RNA-seq. Using gene set enrichment analysis (GSEA) to identify the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, we found the top three enriched pathways included glutathione metabolism (**Figure 4A**). And RT-qPCR analysis confirmed that the expression of glutathione synthase (GSS) in MDSCs was significantly increased by treatment with acitretin (**Figure 4B**). Furthermore, among 16,183 changed genes between the control group and acitretin group, 317 were differentially expressed genes (DEGs; $|\log_2 FC| > 1.0$ and $p < 0.001$). The KEGG pathways enrichment analysis highlighted that the MAPK signaling pathway was activated after the treatment of acitretin in MDSCs (**Figure 4C**), an essential signaling cascade that controls cell proliferation, survival, and differentiation (36).

GSS involved in the synthesis of glutathione (GSH), an important antioxidant in mammalian cells (37). Because the increased level of ROS contributed to the inability of MDSCs differentiation (38), we intended to explore whether acitretin promoted the differentiation of MDSCs by regulating glutathione metabolism. To address this hypothesis, we isolated MDSCs from the bone marrow of IMQ-induced model mice and cultured cells in the presence of GM-CSF with or without acitretin. We found the protein level of GSS up-regulated in MDSCs exposed to acitretin and was observed as early as 15 min after the start of the treatment with acitretin (**Figure 5A**). The up-regulated expression of GSS is related to the increased level of GSH, so we measure the GSH level in MDSCs by using an enzymatic assay. The results showed that acitretin increased the level of GSH in MDSCs (**Figure 5B**). Besides, we found the ROS level significantly decreased in MDSCs after the treatment of acitretin (**Figure 5C**, **Supplementary Figure 5A**), indicating that acitretin-induced the increased level of GSH neutralized the ROS production of MDSCs. Sulfasalazine (SAS) is an inhibitor of system $x_c^-$ cystine/glutamate antiporter, which is required for the GSH synthesis (39). 48 h treatment of MDSCs isolated from the bone marrow of IMQ-induced model mice with SAS dramatically decreased the level of GSH and resulted in the accumulation of ROS (**Supplementary Figures 5B,C**). To investigate whether SAS interfered with the effect of acitretin on MDSCs differentiation, MDSCs were isolated from the IMQ-induced model mice and cultured for 5 days with GM-CSF and acitretin with or without SAS. The results showed that in the presence of SAS, acitretin had no effect on the proportion of F4/80$^+$ macrophages, CD206$^+$ M2 macrophages, and CD11c$^+$MHC II$^+$ dendritic cells, although still decreased the percentage of CD86$^+$ M1 macrophages (**Figure 5D**). Therefore, acitretin-induced the increased level of GSH was responsible for the MDSCs differentiation.

To gain insight into the mechanisms by which acitretin regulated the expression of GSS, we focused on the transcriptome profiling in the acitretin-treated MDSCs. As we mentioned above, the MAPK signaling pathway was activated in MDSCs treated with acitretin (**Figure 4C**). To explore whether acitretin induced the differentiation of MDSCs via the MAPK signaling pathway, MDSCs were isolated from the bone marrow of IMQ-induced model mice and were cultured in the presence of GM-CSF with or without acitretin. The results found that acitretin did not affect the p-p38. In contrast, acitretin substantially activated p-MEK1/2, MEK1/2, and p-ERK1/2 (**Figure 5E**), indicating that the effect of acitretin on GSS expression might through the ERK1/2 MAPK signaling pathway. To address this hypothesis, we treated MDSCs with selumetinib, a specific inhibitor of MEK1/2 (40), which blocks the phosphorylation of ERK1/2 (**Figure 5F**). We found that inhibition of p-ERK1/2 prevented the expression of GSS in MDSCs (**Figure 5F**). To evaluate the role of p-ERK1/2 in acitretin-promoted MDSCs differentiation, MDSCs were cultured for 5 days in the presence of GM-CSF and acitretin with or without selumetinib. Consistent with the previous observation, inhibition of p-ERK1/2 abrogated the effect of acitretin on the differentiation of MDSCs into F4/80$^+$ macrophages, CD206$^+$ M2 macrophages, and CD11c$^+$MHC II$^+$ dendritic cells, although had no effect on the differentiation of MDSCs into CD86$^+$ M1 macrophages (**Figure 5G**). Collectively, these data indicated that acitretin increased the expression of GSS via the ERK1/2 MAPK signaling pathway.

# DISCUSSION

The significant finding of this study is that acitretin promoted the differentiation of MDSCs in the treatment of psoriasis. Prior to our study, the consensus view on the effect of acitretin on psoriasis was that it inhibited the proliferation of keratinocytes and regulated its differentiation (1). However, our findings suggested that the critical role of acitretin on MDSCs in the treatment of psoriasis. Acitretin decreased the number of MDSCs by promoting them to differentiate into macrophages and dendritic cells. Mechanically, acitretin promoted MDSCs differentiation via increasing the GSH production in MDSCs

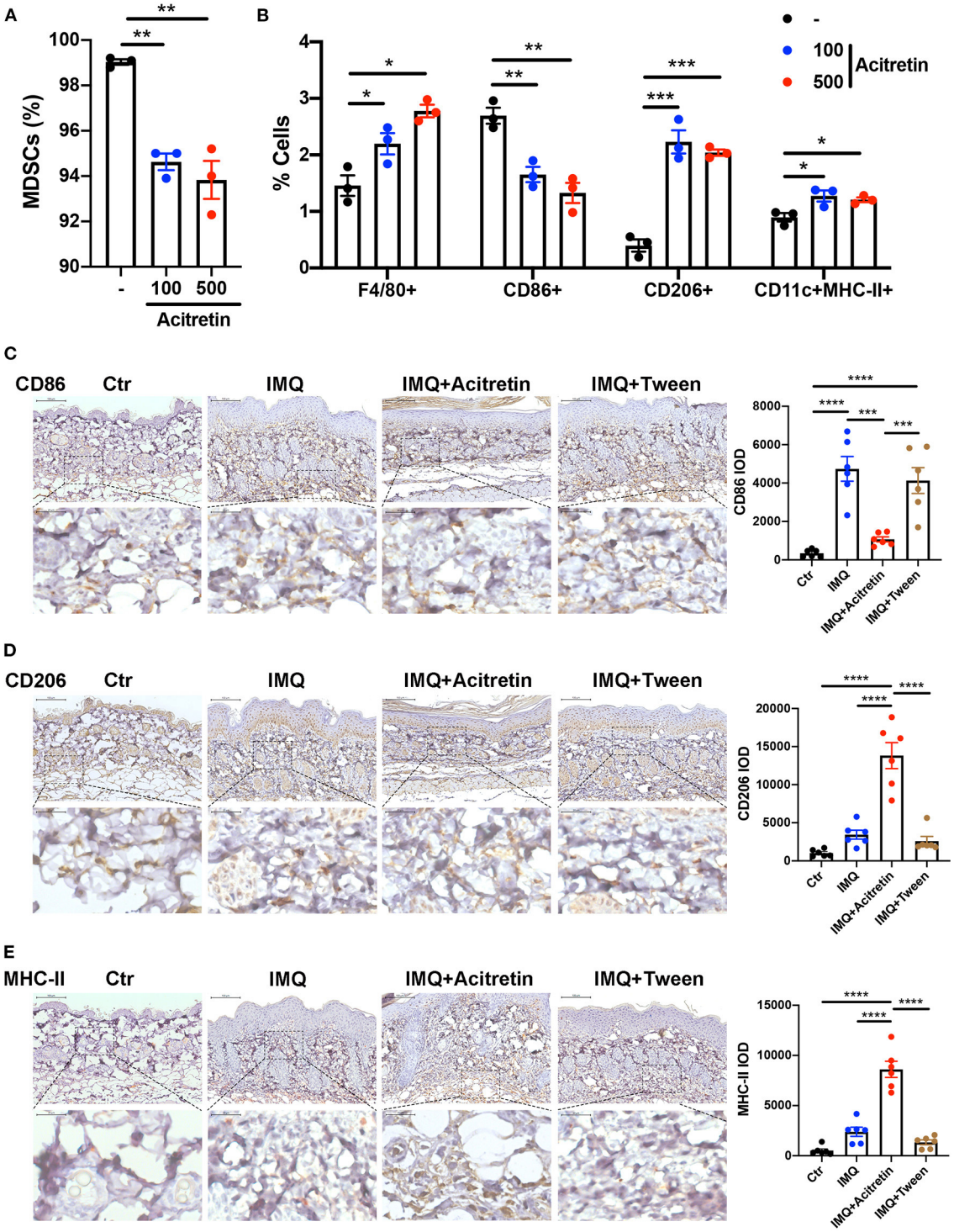


**FIGURE 3 |** Acitretin promoted the differentiation of MDSCs. **(A,B)** MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured for 4 days with 20 ng/mL GM-CSF. Acitretin (100 ng/mL or 500 ng/mL) or vehicle control (-) was added on days 1 and 3. **(A)** The percentages of MDSCs treated with acitretin. **(B)** The effect of acitretin on differentiation of MDSCs into F4/80$^+$ macrophage, CD86$^+$ M1 macrophage, CD206$^+$ M2 macrophage, and CD11c$^+$MHC II$^+$ dendritic cells. The presence of different cell populations was evaluated by flow cytometry. **(C–E)** IMQ-induced psoriasis-like model mice treated with oral acitretin or tween (solvent) once per day for 6 days. Paraffin sections of the back skin of Control (Ctr), IMQ, IMQ+Acitretin, and IMQ+Tween group were stained for CD86, CD206, and MHC-II by immunohistochemistry. CD86 IOD, CD206 IOD, and MHC-II IOD measured by image pro plus 6.0 expressed the CD86, CD206, and MHC-II expression. **(C)** CD86 stain, **(D)** CD206 stain, **(E)** MHC-II stain. Scale bars: 100 μm (upper panel), scale bars: 20 μm (lower panel). Statistical data are shown in the right panel. All results represent at least three independent experiments. Data represent the mean ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

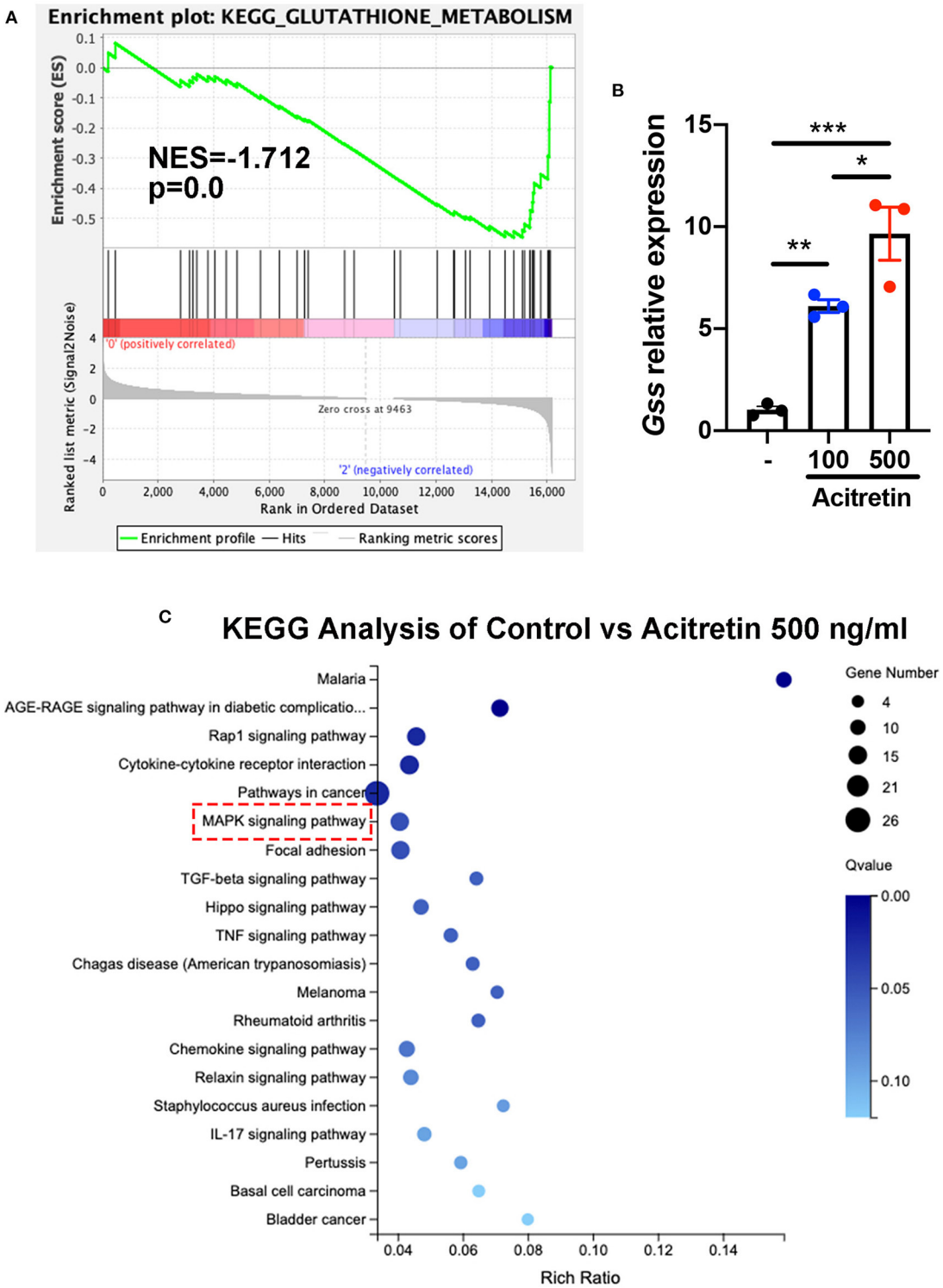


**FIGURE 4 |** Transcriptome analysis of MDSCs treated with acitretin. MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured in the presence of 20 ng/mL GM-CSF with or without acitretin 500 ng/mL. After 24 h of treatment, MDSCs were collected and used for whole-genome transcriptome analysis. **(A)** Glutathione metabolism enriched by GSEA identified from RNA-seq data of control vs. acitretin group. Normalized enrichment score (NES) and Normalized *p*-value (p) are shown in the plot. **(B)** MDSCs were treated with control (-), acitretin 100 ng/mL, or acitretin 500 ng/mL for 48 h. Expression levels of *Gss* were examined by RT-qPCR. The results are representative of at least three independent experiments with three samples per group in each. Data represent the mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. **(C)** KEGG pathways analysis of differentially expressed genes in MDSCs treated with control or acitretin 500 ng/mL for 24 h.

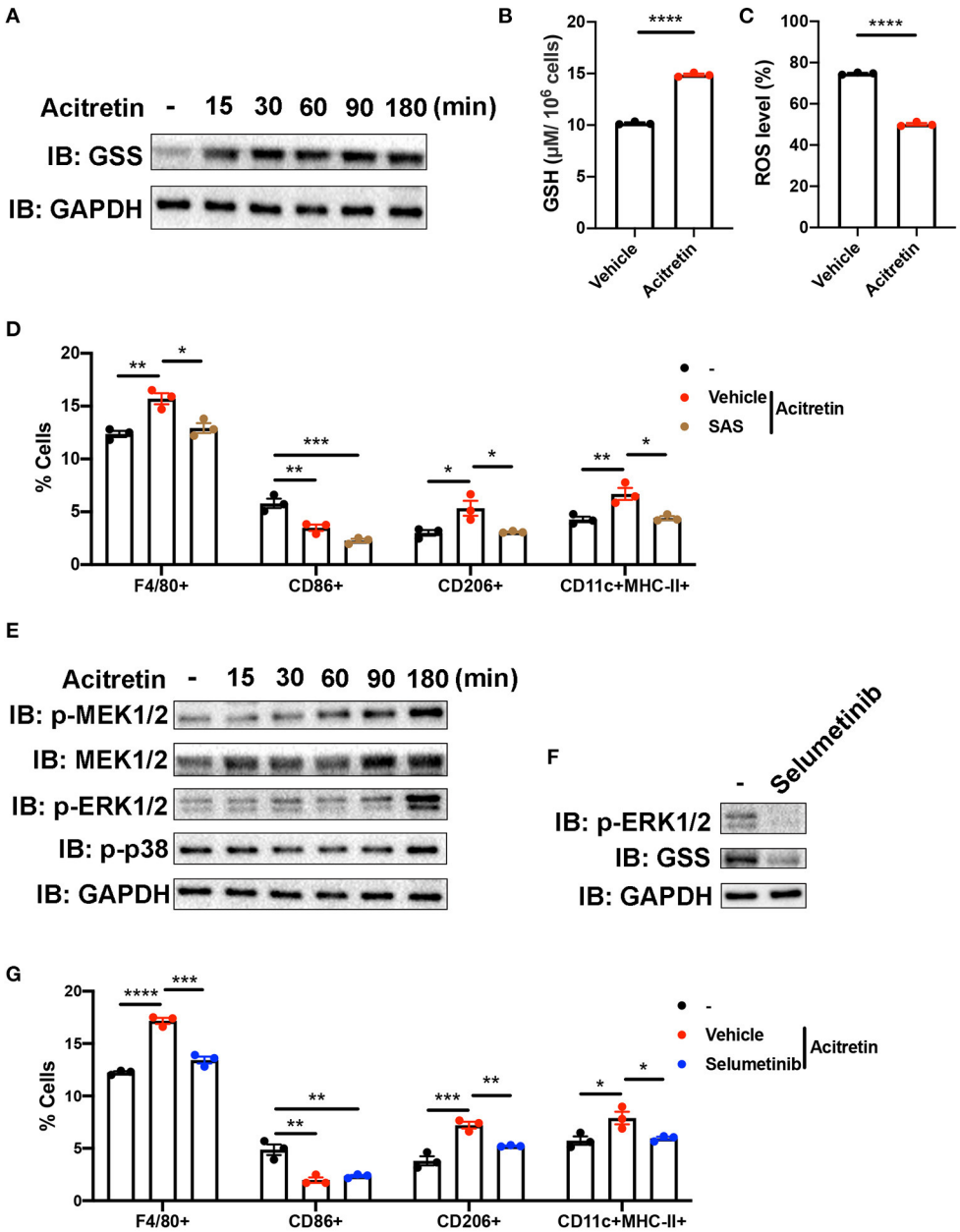


**FIGURE 5 |** Mechanism of acitretin effect on the differentiation of MDSCs. **(A)** The effect of acitretin on GSS. Gr-1$^{+}$MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured in the presence of 20 ng/mL GM-CSF with or without 500 ng/mL acitretin for 15, 30, 60, 90, or 180 min. Whole-cell lysates were obtained, and the protein expression of GSS was evaluated in Western blotting as described in **Materials and Methods**. GAPDH was blotted as a loading control. **(B,C)** MDSCs from IMQ-induced model mice were treated with vehicle control or 500 ng/mL acitretin for 48 h as described above. MDSCs were obtained, and the level of GSH was measured with a GSH detection kit. The level of ROS was detected by flow cytometry. **(B)** The level of GSH in MDSCs. **(C)** The level of ROS in MDSCs. **(D)** The effect of SAS combination with acitretin on the differentiation of MDSCs. MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured for 5 days with 20 ng/mL GM-CSF. Acitretin 500 ng/mL or SAS 200 μM was added on days 1 and 3. The presence of different cell populations was evaluated by flow cytometry. **(E)** Western blot analysis of different proteins in MDSCs after treatment with acitretin. **(F)** The effect of selumetinib on MDSCs. MDSC were isolated from IMQ-induced model mice and cultured in the presence of 20 ng/mL GM-CSF with or without 10 nM specific MEK1/2 inhibitor selumetinib for 3 h. Cell lysates were prepared, and the protein expression of GSS and p-ERK1/2 was evaluated in Western blotting. GAPDH was blotted as a loading control. **(G)** The effect of selumetinib combination with acitretin on the differentiation of MDSCs. MDSCs were isolated from the bone marrow of IMQ-induced model mice and cultured for 5 days with 20 ng/mL GM-CSF. Acitretin 500 ng/mL or selumetinib 10 nM was added on days 1 and 3. The presence of different cell populations was evaluated by flow cytometry. Data represent the mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

and neutralizing the high level of ROS, which were mediated by the ERK1/2 MAPK signaling pathway. Therefore, in addition to acting as a mediator of keratinocytes, our study suggests that acitretin plays a crucial role in the differentiation of MDSCs in the treatment of psoriasis.

This study identified that the number of MDSCs and M-MDSCs increased in the peripheral blood and skin lesions of psoriasis patients compared with healthy control subjects, which was similar to the previous findings (23, 25, 26). However, Soler et al. found there was no statistically significant relationship between the disease severity and the number of MDSCs (26). In our study, we enlarged the enrolled psoriasis patients and further divided the MDSCs into two groups according to the latest surface markers (41). We observed that the expansion of MDSCs, especially M-MDSCs ($HLA\text{-}DR^{-}CD11b^{+}CD33^{+}CD15^{-}CD14^{+}$), in the PBMCs positively correlated with disease severity, while there was no significant correlation between the number of G-MDSCs ($HLA\text{-}DR^{-}CD11b^{+}CD33^{+}CD15^{+}CD14^{-}$) and disease severity. Therefore, our study further confirmed the critical role MDSCs played in the pathogenesis of psoriasis, especially M-MDSCs.

There is overwhelming evidence that ATRA decreased the number of MDSCs in cancer patients and could differentiate MDSCs into mature myeloid cells (42–44). However, the role of acitretin on MDSCs in psoriasis is still unknown. In this study, our findings showed acitretin reduced the number of MDSCs and M-MDSCs in psoriasis patients and psoriasis-like model mice. In addition, acitretin promoted MDSCs to differentiate into macrophages, especially $CD206^{+}$ M2 macrophages, and $CD11c^{+}MHC\text{-}II^{+}$ dendritic cells, while inhibited MDSCs differentiate into $CD86^{+}$ M1 macrophages *in vitro*. Acitretin-treated the skin lesions of IMQ-induced model mice further confirmed that the expression of CD206 and MHC-II increased in the skin lesion after the treatment of acitretin, while the expression of CD86 significantly decreased. Macrophages are highly plastic, exhibiting different phenotypes ranging from pro-inflammatory M1 to anti-inflammatory M2 phenotype (45, 46). Besides, conventional DC2s, preferentially express MHC-II, were required for Th2 rather than Th1 cells differentiation (47). Therefore, the differentiation of MDSCs induced by acitretin might further regulate the imbalance of immune cells in skin lesions of psoriasis, which might synergistically inhibit inflammation.

In this study, GSEA analysis of transcriptional profiling of acitretin-treated MDSCs found signaling pathways were enriched in glutathione metabolism. Moreover, acitretin induced the expression of GSS, increased GSH production, and neutralized the ROS level in MDSCs. Interrupting GSH synthesis abolished the effect of acitretin on MDSCs differentiation. Previous researches reported that ROS was essential to maintain the undifferentiated state of MDSCs (38). $H_2O_2$ scavenging induced immature myeloid cells to differentiate into macrophages in tumor-bearing mice (48). GSH, the most important antioxidant in cells, are responsible for the differentiation of MDSCs isolated from tumor-bearing mice by neutralization of ROS (27, 49, 50). Therefore, this previous evidence supported our finding that the increased level of GSH in MDSCs induced by acitretin was responsible for the MDSCs differentiation. However, the precise molecular mechanism of GSH on MDSCs differentiation remains to be elucidated.

Retinoic acid mediated the specific effects of cells by regulating the MAPK signaling pathway. It has been reported that ATRA inhibited proliferation and migration, and repressed p53-dependent apoptosis through inhibition of the MAPK signaling pathway, including p38 MAPK, JNK1/2, and ERK1/2 (51–53). However, ATRA promoted the differentiation of immature cells via activating the ERK1/2 MAPK signaling pathway. For instance, MEK/ERK signaling pathway was activated and regulated in ATRA-induced differentiation of acute promyelocytic leukemia (54). ERK1/2 MAPK signaling pathway, but not of the JNK, p38 MAPK, was essential for the ATRA effects on MDSCs differentiation (55), which was similar to our findings. In this study, transcriptional profiling of acitretin-treated MDSCs found differentially expressed genes enriched in the MAPK signaling pathways. Besides, we found acitretin dramatically increased phosphorylation of MEK1/2 and ERK1/2 in MDSCs but had no effect on the phosphorylation of p38. Inhibition of p-ERK1/2 completely abrogated the effect of acitretin on GSS expression and MDSCs differentiation. These data indicated that acitretin might regulate GSS expression and MDSCs differentiation via ERK activation.

In summary, the present study provided evidence demonstrating that an increased number of MDSCs was found in psoriasis, and acitretin reduced the number of MDSCs in the treatment of psoriasis. Furthermore, acitretin promoted the differentiation of MDSCs via activating the ERK1/2 MAPK signaling pathway, which contributed to the increased expression of GSS and accumulation of GSH in these cells. GSH neutralized the level of ROS in MDSCs and was responsible for acitretin-induced MDSCs differentiation. These results indicated the novel biological mechanisms underlying the effects of acitretin on psoriasis.

## RNA SEQUENCING DATA

The accession number for the sequencing data in this paper is PRJNA711342.

## DATA AVAILABILITY STATEMENT

The datasets generated for 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 Xiangya hospital of Central South University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The animal study was reviewed and approved by Xiangya medicine school of Central South University.

## AUTHOR CONTRIBUTIONS

PL performed all experiments and data analysis and wrote the manuscript. CP and XC contributed to study design. LW assisted in mouse experiments. MY assisted in flow data analysis. JL performed histological analysis. QQ involved in patient recruitment and sample collection. YK and WZ designed and supervised all experiments and wrote the paper. 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.2021.625130/full#supplementary-material

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# 308-nm Excimer Lamp vs. Combination of 308-nm Excimer Lamp and 10% Liquor Carbonis Detergens in Patients With Scalp Psoriasis: A Randomized, Single-Blinded, Controlled Trial

*Ploysyne Rattanakaemakorn†, Korn Triyangkulsri†, Wimolsiri Iamsumang† and Poonkiat Suchonwanit*†*

*Division of Dermatology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

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**Edited by:**
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***Correspondence:**
*Poonkiat Suchonwanit*
*poonkiat@hotmail.com*

**†ORCID:**
*Ploysyne Rattanakaemakorn*
*orcid.org/0000-0002-8336-1834*
*Korn Triyangkulsri*
*orcid.org/0000-0001-8552-9277*
*Wimolsiri Iamsumang*
*orcid.org/0000-0002-0185-9752*
*Poonkiat Suchonwanit*
*orcid.org/0000-0001-9723-0563*

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**Background:** Scalp psoriasis is usually refractory to treatment. Excimer devices have been proved to be a promising therapeutic option in psoriasis. Greater efficacy of phototherapy can be achieved by concurrent use of coal tar derivatives.

**Objective:** We aimed to compare efficacy and safety between 308-nm excimer lamp monotherapy and a combination of 308-nm excimer lamp and 10% liquor carbonis detergens in the treatment of scalp psoriasis.

**Methods:** In this randomized, evaluator-blinded, prospective, comparative study, 30 patients with scalp psoriasis received either 308-nm excimer lamp monotherapy or a combination of 308-nm excimer lamp and 10% liquor carbonis detergens twice per week until complete remission of the scalp or for a total of 30 sessions. Efficacy was evaluated by the improvement of Psoriasis Scalp Severity Index (PSSI) score, itch score, and Scalpdex score.

**Results:** Both treatments induced significant improvement in PSSI score with greater reduction observed in the combination group. At 30th visit, a 75% reduction in PSSI (PSSI75) was attained by 4 (28.6%) and 9 (69.2%) patients treated with monotherapy and combination therapy, respectively ($P < 0.05$).

**Conclusions:** Excimer lamp is well-tolerated in patients with scalp psoriasis and liquor carbonis detergens can be used as a combination therapy to improve the efficacy of excimer lamp.

**Keywords: excimer lamp, phototherapy, coal tar, targeted phototherapy, UVB**

## INTRODUCTION

Psoriasis is a common dermatologic disease with a prevalence of ∼0.5–11% worldwide (1). It has several clinical presentations which eventually develop into chronic plaque psoriasis. The scalp is commonly affected and the frequency tends to increase with the disease duration (2). Compare to other areas of the body, the scalp is relatively refractory to many of the treatment modalities (3).

Ultraviolet (UV) radiation, both A and B, is known to be an effective treatment of psoriasis. Excimer laser and non-laser devices offer a narrow spectrum of UV light and greater localization of irradiation allowing a lower number of treatments and cumulative dose as well as sparing of uninvolved skin to produce higher efficacy (4). Earlier studies found that 308-nm excimer laser was able to achieve exceptional results in the previously recalcitrant area of the scalp (5–7). A previous study using a 308-nm excimer lamp, a non-laser device, also demonstrated a similar favorable result in the treatment of scalp psoriasis with minimal and transient side effects (8). Comparing to the excimer laser, the excimer lamp has the superior advantage of being able to give uniform irradiation of 50 times wider area in a single exposure at a lower cost (9).

Coal tar is one of the traditional treatments for psoriasis. Other than having anti-inflammatory, antibacterial, antipruritic, and antimitotic effects, coal tar is also a photosensitizer (10). Coal tar, when used together with UVB light, provides a synergistic effect with better treatment outcomes than either treatment alone (11). Goeckerman regimen is an example of the application of coal tar with phototherapy (12). The regimen requires the patient to apply coal tar to the lesion for 5 h and rinsed off before undergoing phototherapy. The process boasts a fast resolution of psoriasis with 100% of patients attained a 75% reduction in Psoriasis Area and Severity Index at ∼12 weeks (13).

We hypothesized that with liquor carbonis detergens (LCD), a coal tar derivative, the treatment of excimer lamp could be enhanced to give a superior treatment outcome to the excimer lamp alone. This study aimed to compare the efficacy and safety of 308-nm excimer lamp monotherapy and 308-nm excimer lamp in combination with 10% LCD in the treatment of scalp psoriasis.

## MATERIALS AND METHODS

### Study Design and Patients

This is a randomized, evaluator-blinded, controlled study of 308-nm excimer lamp as monotherapy and combination of 308-nm excimer lamp with 10% LCD in scalp psoriasis. This study was conducted as a pilot study. The sample size estimation was based on data from the previous 308-nm excimer lamp study in the Asian population. To achieve a power of 80% and a two-sided significance level of 5%, the minimum sample size required was 9 in each group (8). Thirty patients with clinically diagnosed plaque-type scalp psoriasis were enrolled in the study. The study was approved by the Committee of Human Rights Related to Research Involving Human Subjects, Mahidol University (ID 09-60-09, thaiclinicaltrials.org identifier: TCTR20171128003) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. Patients age 18 years or older who have been diagnosed with plaque-type psoriasis of the scalp involving at least 1% of total body surface area were included. The exclusion criteria were (i) pustular or erythrodermic psoriasis; (ii) presence of severe systemic disease; (iii) a history of photosensitivity or taking photosensitive medication; (iv) a history of skin cancer; (v) being pregnant or lactating; and (vi) allergy to any coal tar derivatives. Patients' current systemic treatments without recent modification (within 6 months) were maintained throughout the study period; however, topical agents for the scalp were required to be discontinued before enrolling in the study and until the last follow-up appointment.

Upon enrollment, a detailed history was obtained from each patient with special attention on the duration of the disease, area of involvement, as well as the history of previous therapies and current therapies. Each patient was randomly assigned using a random number table to receive either excimer lamp monotherapy or excimer lamp in combination with 10% LCD therapy (combination therapy).

### Treatment

The 308-nm excimer lamp (Therabeam® UV308, Ushio Inc., Tokyo, Japan) was used for both groups. Treatment was performed twice per week. Each patient was treated for 30 sessions, or until complete clearing of the scalp occurred. Beginning with 500 mJ/cm$^2$ for all patients, we increased the irradiation dose by 10% every treatment during the whole treatment period. The irradiation dose was fixed when clinically noticeable improvement was observed. If severe side effects including blistering, burn or severe pain occurred, the treatment was skipped until complications subsided. The treatment would then resume with the dose that did not cause any side effects on the subsequent visit. Participants who failed to attend treatment for more than 3 weeks consecutively were excluded. Patients in the combination therapy group were additionally asked to apply 10% LCD cream efficiently throughout the plaques on their scalp for at least 5 h or overnight and rinsed off before each treatment session.

### Assessment

At baseline, 20th visit, 30th visit, and 4 weeks after the last treatment, Psoriasis Scalp Severity Index (PSSI) score was assessed by a blinded dermatologist. The PSSI score is calculated by assessing erythema, scaliness, and induration with a score of 0–4 for each symptom. The extent of scalp psoriasis involvement ranging from 0 to 6 is then calculated and multiplied with the score of the symptoms resulting in a total score of 0–72 (14).

Patients were requested to rate their scalp-related itch and Scalpdex score at baseline, 20th visit, 30th visit, and after last treatment. Itch score was rated using a 0–10 scale, with higher scores indicating greater severity. Scalpdex score requires the patients to rate frequency of impact for 23 scalp-related items using a 0–100 scale with 0 = never, 25 = rarely, 50 = sometimes, 75 = often, and 100 = all the time. The items are categorized into

symptoms, functioning, and emotions. Higher scores indicate greater impairment of quality of life in each aspect (15).

## Statistical Methods

Data were analyzed using STATA/SE version 14.2 (STATA Corp., College Station, TX). Categorical variables were expressed as percentages and were analyzed using either the chi-squared test or Fisher's exact-test. Continuous variables were expressed in terms of either mean (standard deviation) for normally distributed variables or median (range) for non-normal distributed variables and were evaluated using a mixed model. A $P$-value of $<0.05$ was considered statistically significant.

# RESULTS

## Patient Characteristics

Thirty patients (13 males, 17 females; age 21–72, mean age 41 years) were enrolled in this study and were randomly divided into 2 groups. There was a significant difference in mean age between the two groups. Other baseline demographics were similar between treatment groups (**Table 1**). Twenty-seven patients completed the study while 3 were excluded because of their inability to adhere to treatment frequency due to personal or unforeseen circumstances. Baseline disease characteristics after excluding 3 patients displayed some but not statistically significant difference in median baseline PSSI. There was also a significant difference in median baseline itch score after excluding 3 patients. Thus, these 2 variables (age and itch score) were adjusted in the statistical analysis. Baseline Scalpdex scores were similar between treatment groups (**Table 2**).

## Efficacy

Both treatment groups achieved a significant reduction in PSSI score. In the monotherapy group, the median PSSI score was reduced from 18 (8–30) to 12.5 (2–25) at 20th visit, 12 (0–25) at 30th visit, and 8 (0–20) at 4 weeks after the last treatment ($P < 0.001$). Similarly, the combination therapy group's median PSSI score was reduced from 10.5 (3–24) to 3 (0–6) at 20th visit, 3 (0–4) at 30th visit, and 3 (0–4) at 4 weeks after the last treatment ($P < 0.001$). The combination therapy group was able to achieve a significantly greater reduction in PSSI score than the monotherapy group at every assessment time ($P = 0.001$; **Table 2**). At 30th visit, the combination therapy group had a larger percentage of patients reaching PSSI50, PSSI75, or PSSI100 than the monotherapy group ($P < 0.05$) (**Figures 1**, **2**). However, by 4 weeks after treatment cessation, monotherapy group had more patients who continued to improve (PSSI50 = 46.1%, PSSI75 = 23.1%, PSSI100 = 7.7%) resulting in a more similar achievement to combination therapy group (PSSI50 = 25.0%, PSSI75 = 41.7%, PSSI100 = 25.0%) ($P = 0.362$). In terms of itch score, both treatment groups were found to have a significant reduction ($P < 0.05$) but there was no significant difference between the two ($P = 0.597$). Overall Scalpdex score displayed significant reduction in both groups ($P < 0.001$) without significant difference between groups ($P = 0.366$; **Table 2**).

The monotherapy group seemed to require a slightly higher irradiation dose than the combination therapy group at a mean effective dose of 1364.3 ($\pm$315.9) mJ/cm$^2$ and 1165.4 ($\pm$315.9) mJ/cm$^2$, respectively ($P = 0.134$). Mean cumulative dose at 30th visit demonstrated a similar pattern as the monotherapy group having 32702.9 ($\pm$3997.3) mJ/cm$^2$ while the combination therapy group having 27779.2 ($\pm$8860.9) mJ/cm$^2$ ($P = 0.101$).

## Safety

Common adverse events that occurred in both groups were itch and pain after the treatment, which resolve spontaneously without any treatment within 1–2 days. No patient experienced any pain or discomfort during the treatment. Five patients (35.7%) from the monotherapy group developed blisters compared to 1 patient (8.3%) from the combination therapy group ($P = 0.170$). The first-degree burn was observed in 1 patient from each group. The combination therapy group had severe adverse events observed at a lower mean dose of 680 ($\pm$28.3) mJ/cm$^2$ when compared to the monotherapy group, 1,180 ($\pm$345.7) mJ/cm$^2$ ($P = 0.111$). No patient dropped out due to adverse events.

# DISCUSSION

Immunomodulation is the key therapeutic mechanism of phototherapy in psoriasis. Phototherapy interfered with antigen presentation of Langerhans cells to the T cell which in turn affects cytokines and adhesion molecules that are overexpressed in psoriatic plaques (16, 17). It also downregulates Th17 expression, cytokine expression, and causes a shift in cytokine profiles from a Th1 to a Th2 response (18, 19). By interposing with the synthesis of proteins and nucleic acids, UV radiation also inhibits epidermal hyperproliferation and angiogenesis (20–22). Various UVB sources with wavelength ranging from 290 to 320 nm are commonly used in the treatment of psoriasis. Among these, excimer devices that are able to produce a spectrum of 308 nm radiation have been shown to be efficacious in treating psoriatic plaques. A study demonstrated the efficacy of a single high dose 308-nm excimer laser treatment, clearing psoriasis plaque (23). An immunohistochemical study found that psoriatic skin after excimer light therapy showed significant T-cell depletion and alterations of apoptosis-related molecules associated with a decreased proliferation index and clinical remission (24). The excimer lamp irradiation also shows an antipruritic effect *via* induction of epidermal nerve degeneration (25).

In this study, the excimer lamp alone is efficacious and well-tolerated for scalp psoriasis whereas LCD cream was shown to enhance its efficacy without a significant increase in adverse events. Given many of the patients in our study were considered refractory to the ongoing treatment, they reportedly achieved improvement after excimer lamp treatment with or without LCD cream. Additionally, the effects of both treatment regimens were maintained up to 4 weeks after the last treatment. Furthermore, the monotherapy group showed a higher number of patients with ongoing improvement. We hypothesize that UVB phototherapy could induce a long remission period by promoting apoptosis of

**TABLE 1 |** Demographics and characteristics of the patients at baseline.

| Characteristics | Monotherapy (*N* = 15) | Combination therapy (*N* = 15) | *P*-value |
|---|---|---|---|
| **Sex**; *N* (%) | | | 0.713 |
| Male | 6 (40.0%) | 7 (46.7%) | |
| Female | 9 (60.0%) | 8 (53.3%) | |
| **Age** in year; mean (SD) | 47 (15.0) | 35.53 (12.7) | 0.032* |
| **BMI** in kg/m$^2$; mean (SD) | 29.10 (6.5) | 27.15 (5.5) | 0.386 |
| **Fitzpatrick skin type**; *N* (%) | | | 0.705 |
| III | 9 (60.0%) | 10 (66.7%) | |
| IV | 6 (40.0%) | 5 (33.3%) | |
| **Onset** in years; mean (SD) | 33.92 (13.9) | 27.63 (11.1) | 0.182 |
| **Duration** in years; median (range) | 9 (0.25–40) | 5 (0.5–29) | 0.228 |
| **Family history**; *N* (%) | | | 0.682 |
| Yes | 3 (20.0%) | 5 (33.3%) | |
| No | 12 (80.0%) | 10 (66.7%) | |
| **Psoriatic arthritis**; *N* (%) | | | 0.682 |
| Yes | 5 (33.3%) | 3 (20.0%) | |
| No | 10 (66.7%) | 12 (80.0%) | |
| **Current systemic treatment**; *N* (%) | | | 0.700 |
| Yes | 6 (40.0%) | 4 (26.7%) | |
| No | 9 (60.0%) | 11 (73.3%) | |
| **Effective dose** in mJ/cm$^2$; mean (SD) | 1,364.3 (315.9) | 1,165.4 (315.9) | 0.134 |

*BMI, Body mass index.*
**Statistically significant.*

**TABLE 2 |** Treatment results on patients throughout the study duration.

| Data | Monotherapy (*N* = 14) | Combination therapy (*N* = 13) | *P*-value |
|---|---|---|---|
| **PSSI; median (range)** | | | |
| Baseline | 18 (8–30) | 12 (3–30) | 0.149 |
| 20th visit | 12.5 (2–25) | 3 (0–6) | 0.021* |
| 30th visit | 12 (0–25) | 3 (0–4) | 0.016* |
| 4 weeks after last treatment | 8 (0–20) | 3 (0–4) | 0.022* |
| **Itch score; median (range)** | | | |
| Baseline | 7 (2–8) | 4.5 (0–9) | 0.050* |
| 20th visit | 4 (0–8) | 2 (0–5) | 0.316 |
| 30th visit | 2 (0–7) | 2 (0–7) | 0.515 |
| 4 weeks after last treatment | 2 (1–7) | 3 (0–7) | 0.175 |
| **Scalpdex total score; median (range)** | | | |
| Baseline | 39.7 (6.5–80.4) | 42.4 (30.4–73.9) | 0.961 |
| 20th visit | 17.9 (4.3–88.0) | 14.1 (3.3–45.7) | 0.213 |
| 30th visit | 17.4 (0.0–82.6) | 16.3 (1.1–44.6) | 0.256 |
| 4 weeks after last treatment | 15.2 (2.2–90.2) | 9.2 (0.0–64.1) | 0.403 |

*PSSI, Psoriasis Scalp Severity Index.*
**Statistically significant.*

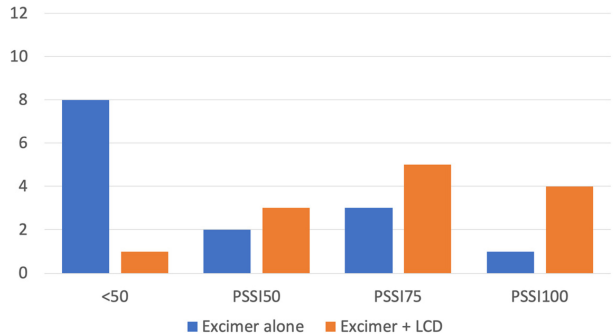


**FIGURE 1 |** Number of patients achieving clearance of various percentages at 30th visit. Patients achieving <50% clearance (<PSSI50), 50% clearance (PSSI50), 75% clearance PSSI75, and 100% clearance (PSSI100). *PSSI*, Psoriasis Scalp Severity Index; *LCD*, Liquor carbonis detergens.

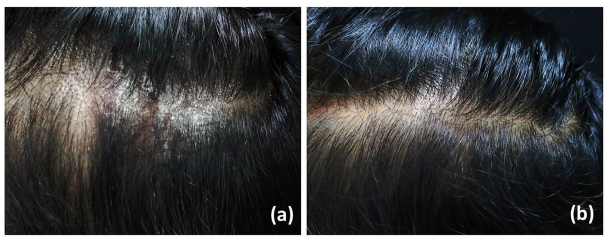


**FIGURE 2 |** Psoriatic plaque, before **(a)** and after **(b)** treatment with excimer lamp and 10% LCD cream at 30th visit.

pathologically relevant T cells, especially tissue-resident memory T cells (26, 27). A higher cumulative irradiation dose used in the monotherapy group may result in more patients with continuous improvement. However, concurrent application of 10% LCD cream also resulted in less irradiation effective dose, therefore hastens reduction rate of PSSI score. This can result in less long-term cumulative UV exposure. The author would also like to point out that in this study, 10% LCD cream was only used on the night before excimer lamp treatment for its photodynamic property and thus effects of the treatment may be enhanced further if 10% LCD cream was applied regularly or more frequently.

The main setbacks of 10% LCD cream are its unfavorable smell, its ability to readily stain onto fabric material, and possible contact dermatitis. Lastly, usage of LCD cream or other coal tar derivatives can interfere with UV transmission and should be removed thoroughly before exposure to phototherapy (28–32). Although the detail of photodynamic activity of coal tar was still unclear and only proven with an action spectrum in UVA and visible light (33, 34), several studies had demonstrated the effectiveness of coal tar in enhancing the therapeutic outcome of UVB spectrum treatment similar to our study suggesting rooms for further research in elucidating the actual mechanism and possible light spectrum range for UVB of coal tar photodynamic activity (13, 35–37).

A previous study of excimer lamp showed that 6 out of 28 patients (30%) were able to achieve PSSI75 after only 10 sessions and 5 patients (25%) achieved PSSI50 (8). These numbers showed a favorable result of excimer lamp similar

to this study. However, the treatment sessions required were much shorter than our study which we suspect to be due to the patient's concurrent treatment of topical medication. A previous study evaluating excimer laser found that the majority of patients (56.52%) achieved PSSI75 while 34.78% of patients were able to achieve PSSI50 at 24th visit (7). These results triumph over our monotherapy group. However, our combination therapy group attained comparable improvement at 30th visit (15 weeks), accounting for 69.2 and 23.1% for PSSI75 and PSSI50, respectively. Furthermore, it is important to note that among 69.2% with PSSI75, 4 patients (30.7%) achieved PSSI100.

As for safety issues, the monotherapy group showed a higher incidence of adverse events due to the higher irradiation dose used. Nevertheless, dose adjustment was able to prevent the reoccurrence of the adverse events. Blistering was seen mainly when the dose was higher than 1,100 $mJ/cm^2$ and readily resolve spontaneously or with a short course of moderate potency topical corticosteroid within 7–10 days. Similar case series documenting cases with blistering after narrowband UVB therapy were able to continue and complete the treatment course with lowered irradiation dose. These cases too were able to complete their phototherapy and the occurrence of blisters subsided after topical corticosteroid treatment and dose adjustment as well (38). Few studies using excimer devices both light and laser had reported some patients with blistering (6, 7, 39). This suggests that blistering might just be due to too high irradiation dose. However, this also proved that patients can tolerate excimer lamp at a much lower dose than narrowband UVB in general. Therefore, attention must be paid to dose adjustment and increment while using excimer devices. Safety of having concurrent vitamin A derivatives intake was not addressed in our study as they were in the exclusion criteria.

The limitations of this study include a limited number of patients and a relatively short follow-up period after treatment cessation. Although the assignments were randomized, there was a significant difference in baseline severity of scalp psoriasis between the two groups. The monotherapy group had more severe baseline disease, which might contribute to their lower response rate. Future studies involving larger populations and longer study duration are warranted in elucidating long-term safety and remission time.

## CONCLUSION

Combination therapy of excimer lamp and 10% LCD showed promising results with 92.3% of patients achieving PSSI50 and above with minimal and reversible adverse events. Concerning scalp psoriasis, the combination of excimer lamp therapy and 10% LCD is highly efficacious and well-tolerated.

## 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 the Committee of Human Rights Related to Research Involving Human Subjects, Mahidol University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

PS: conceptualization. PS and PR: methodology, validation, and writing–review and editing. KT and WI: formal analysis and data curation. PS, KT, and WI: investigation. KT and PR: writing–original draft preparation. All authors have read and agreed to the published version of the manuscript.

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# Phase I Study to Assess Safety of Laser-Assisted Topical Administration of an Anti-TNF Biologic in Patients With Chronic Plaque-Type Psoriasis

*Martin Bauer[1]*, Edith Lackner[1], Peter Matzneller[1], Valentin Al Jalali[1], Sahra Pajenda[1], Vincent Ling[2], Christof Böhler[3], Werner Braun[4], Reinhard Braun[4], Maximilian Boesch[4], Patrick M. Brunner[5] and Markus Zeitlinger[1]*

[1] Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria, [2] Takeda - Pharmaceutical Sciences, Materials and Innovation, Cambridge, MA, United States, [3] Boehler Life Science Advice, Berneck, Switzerland, [4] Pantec Biosolutions AG, Ruggell, Liechtenstein, [5] Department of Dermatology, Medical University of Vienna, Vienna, Austria

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**Edited by:**
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*Pirogov Russian National Research Medical University, Russia*

***Correspondence:**
*Martin Bauer*
*martin.m.bauer@meduniwien.ac.at*

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Ablative fractional laser treatment facilitates epidermal drug delivery, which might be an interesting option to increase the topical efficacy of biological drugs in a variety of dermatological diseases. This work aims at investigating safety and tolerability of this new treatment approach in patients with plaque-type psoriasis. Eight patients with plaque-type psoriasis were enrolled in this study. All patients received (i) ablative fractional laser microporation (AFL) of a psoriatic lesion with an Er:YAG laser + etanercept (ETA; Enbrel® solution for injection) (AFL-ETA), (ii) ETA alone on another lesion, and, if feasible, (iii) AFL alone on an additional lesion. Overall, all treatment arms showed a favorable safety profile. AFL-ETA improved the lesion-specific TPSS score by 1.75 vs. baseline, whereas ETA or AFL alone showed a TPSS score improvement of 0.75 points, a difference that was not statistically significant and might be attributable to differences in baseline scores. Topical administration of ETA to psoriatic plaques *via* AFL-generated micropores was generally well-tolerated. No special precautions seem necessary in future studies. Clinical benefit will need assessment in sufficiently powered follow-up studies.

**Keywords: plaque-type psoriasis, topical, etanercept (enbrel), biologic active molecule, laser, phase 1 clinical studies, local tolerability, drug delivery**

## INTRODUCTION

Psoriasis is a chronic remitting-relapsing, inflammatory disease of the skin, affecting about 2% of the general population (1). Chronic plaque-type psoriasis, also known as *psoriasis vulgaris*, is the form most commonly seen. It is characterized by sharply demarcated, thickened lesions (called plaques) in which both the vasculature and the epidermis are involved, as evidenced by erythema and scale formation, respectively (2). Furthermore, psoriatic lesions can cause pain, itching, and local bleeding. These physical discomforts combined with the potential psychological burden of the disease may interfere with everyday life activities and negatively impact an individual's quality of life (3).

During the last few years, biologics have revolutionized the treatment of moderate-to-severe psoriasis patients. However, there is still a lack of treatment options especially for patients with mild, localized disease when they do not sufficiently respond to, or are intolerant to, topical treatments. Detailed knowledge about the pathogenesis of chronic plaque psoriasis and the central role for the TNF/IL-23/TH17 pathway has led to the development of therapies targeting the pathogenic cytokines, including anti-TNFs, anti-p40 (IL-12/IL-23), anti-p19 (IL-23 specific), anti-IL-17A, and anti-IL-17 receptor antibodies (4). Novel topical agents that can efficiently treat limited skin disease would therefore be highly desirable.

Etanercept (Enbrel®), a genetically-engineered fusion protein acting as a soluble decoy receptor, has been approved as a safe and efficacious treatment option for patients with moderate-to-severe plaque psoriasis in the US, Europe, and a number of other countries. Mechanistically, etanercept binds to the pro-inflammatory cytokines TNFα and lymphotoxin-α (LT-α, also known as TNF-β), thereby neutralizing their biological activity. Etanercept thus mimics the inhibitory effects of naturally occurring soluble TNF receptors, while offering a greatly extended half-life in circulation which allows superior therapeutic activity (5, 6). Due to the rather large size of this molecule (934 amino acids and an apparent molecular weight of 150 kDa), the approved route of administration is subcutaneous injection. Nevertheless, previous studies have shown that also topical administration of TNF blockers might have efficacy in psoriasis (7). However, epidermal uptake of biological drugs is naturally limited by the *stratum corneum*, which functions as the main physical barrier for size exclusion in human skin. Pre-treatment of the skin with fractional lasers increases topical drug uptake, while fractional radiofrequency does not (8). The use of an Er:YAG laser device, with a wavelength that is highly absorbed by $H_2O$ and therefore requires minimal energy input, results in the creation of a series of micropores with minimal coagulation (9). These micropores permit even large molecules such as biologics to efficiently cross the *stratum corneum* and penetrate into deeper skin layers (10). In a preclinical study, it has recently been shown that etanercept can be delivered efficiently into intact porcine skin at depths ranging from 40 microns to 225 microns. The effect of laser parameters was studied with the goal to optimize clinical delivery rates (11).

In view of the potential synergy between laser microporation and topical etanercept administration, we performed a phase I clinical trial to assess safety and efficacy of ablative fractional laser microporation and topical occlusive application of etanercept in patients with chronic plaque-type psoriasis.

## PATIENTS, MATERIALS, AND METHODS

This partially observer-blinded, lesion-randomized, intra-patient controlled, 3-arm, monocentric phase I study to assess safety and efficacy of a localized, laser-assisted topical administration of etanercept in patients with plaque-type psoriasis was conducted over 1 year between January 2019 and January 2020.

### Ethics Statement

The study was performed in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and its amendments. The study was registered under EudraCT no. 2018-001093-19 and EUDAMED no. CIV-AT-20-06-033310, and approved by the local ethics committee and competent authority. All study participants received oral and written information about the study and provided their written informed consent before study enrolment.

Lesions were selected based on similar characteristics, size, and similar location. Treatment was randomly assigned to the respective lesion areas on the first day of treatment. The treatment procedures (etanercept as well as laser) were repeated twice weekly over 6 weeks on the respective lesions. All patients received (i) ablative fractional laser microporation (AFL) of psoriatic lesions + etanercept (ETA; Enbrel® 25 or 50 mg solution for injection in pre-filled pen, marketing authorization holder for Europe: Pfizer Europe) and (ii) ETA alone on another lesion. Four out of eight participants additionally received (iii) AFL microporation alone to treat another lesion (this was only applicable if three comparable lesions could be randomized).

The Er:YAG laser P.L.E.A.S.E.® Professional (Pantec Biosolutions AG, Ruggell, Liechtenstein), with a wavelength of 2'940 nm, a repetition rate of 100 Hz and a pulse length of 225 μs, was used to generate micropores in a 4 or 8 $cm^2$ area of a designated plaque. Etanercept (50 mg) solution at a dose of 30 μl/4 $cm^2$ or 60 μl/8 $cm^2$ was applied to the previously microporated or native surface of the plaque. The treated areas were covered with a transparent dressing for 4 h (occlusion). Patients were asked to document local reactions, adverse events and co-medications in a patient diary. After the screening period, the use of concomitant treatment for psoriasis in all body regions (excluding the three randomized lesions) was restricted to emollients (not supplied), with no pharmacologically active ingredients such as lactic acid, salicylic acid, urea, α-hydroxy acids or fruit acids allowed.

### Patients

Eligible patients were aged ≥ 18 years with chronic plaque-type psoriasis diagnosed at least 6 months prior to baseline who were candidates for topical therapy or phototherapy with at least 2 lesions. Main exclusion criteria were other forms of psoriasis, drug-induced psoriasis, ongoing use of topical corticosteroids, other topical treatments or phototherapy involving study treatment areas and any biological medicinal product (for full in- and exclusion criteria see the above-indicated registries).

### Assessments

Safety assessments included the continuous assessment of the incidence and severity of adverse events (AE), Administration Site Reactions (ASR, defined as itching, redness, swelling, pain, or ulceration), Adverse Device Effects (ADE), local tolerability at the treatment area, laboratory values (blood chemistry, hematology, and lipid panels), monthly pregnancy tests for females of child-bearing potential, and electrocardiograms (ECG) and vital signs.

**TABLE 1 |** Patient characteristics at baseline.

| | |
|---|---|
| Participants (female), *n* (%) | 8 (50) |
| Age (years), mean (SD) | 43 (14) |
| Range | 23–67 |
| Race, *n* (%) | |
| Caucasian | 8 (100.0) |
| Other | 0 |
| Weight (kg), mean (SD) | 89 (37) |
| Range | 55–177 |
| Duration of psoriasis since first diagnosis (years), mean (range) | 8 (0.6–19) |
| Fitzpatrick Score, mean (SD) | 3 (1) |
| TPSS, mean (SD) | 6.9 (2.0) |
| Range | 4.0–10.0 |
| BSA (%), mean (SD) | 13.7 (6.6) |
| Range | 1.5–23.0 |

*BSA, body surface area; TPSS, Target Plaque Severity Score; SD, standard deviation.*

Assessment of treatment efficacy was based on the established Target Plaque Severity Score (TPSS). To this end, the target plaque was assessed separately for induration, scaling and erythema using a five-point severity scale (0, none; 1, slight; 2, moderate; 3, marked; 4, very marked), and the scores were summed up to yield the TPSS sum score [13-point scale = 0 (no severity), 12 (high severity)]. Assessments were done before the treatment on day 1 (baseline), as well as on days 4, 8, and 13.

## Objectives

Treatment safety as assessed by ASR and AE/ADE was the primary study objective. Treatment efficacy as assessed by TPSS evolution served as the secondary study outcome.

## Randomization and Statistics

Treatment was randomly assigned on the first day of treatment to eligible psoriatic lesions.

The sample size of this study ($n = 8$) was based on clinical and practical considerations rather than formal power calculations. The primary efficacy variable was the TPSS. Changes from baseline (V1) until the last observation (V13) in the TPSS were described and compared between AFL + ETA and ETA only with Wilcoxon's signed rank test in an exploratory manner for the intention-to-treat population. A two-sided significance level of 0.05 was considered for all statistical tests.

# RESULTS

Eight participants (4 females) with a mean age of 43 ± 14 years and a baseline TPSS of 6.9 ± 2 (range 4-10) were included into the study. Detailed patient characteristics are given in **Table 1**.

## Safety Results

### Adverse Site Reactions

A total of 64 ASR, all of mild ($n = 53$) or moderate ($n = 11$) severity, were documented in the study. 32 ASR occurred in areas treated with microporation (AFL) and etanercept (ETA). 14 ASR occurred in areas treated with ETA only and 18 ASR occurred in areas treated with AFL only (**Table 2**). No ASR was graded as severe. Descriptive analysis showed increased ASR—of mostly mild severity—when areas were treated with AFL+ETA as compared to ETA only.

**TABLE 2 |** Adverse site reactions.

| Treatment | Adverse site reaction type | | | | |
|---|---|---|---|---|---|
| | Itching | Redness | Pain | Ulceration | Total |
| **AFL + ETA (*n* = 8)** | 8 (25.00) | 17 (53.13) | 3 (9.38) | 4 (12.50) | 32 |
| **ETA only (*n* = 8)** | 4 (28.57) | 8 (57.14) | 1 (7.14) | 1 (7.14) | 14 |
| **AFL only (*n* = 4)** | 8 (44.44) | 9 (50.00) | 1 (5.56) | 0 (0.00) | 18 |
| **Total** | 20 | 34 | 5 | 5 | 64 |

*Frequency of adverse site reactions (ASR). The percentage is given in brackets.*

### Adverse Events

A total of eleven AE of mild or moderate severity were documented for five out of the eight study participants, of which most were classified as unrelated to the study procedures: influenza, contact dermatitis on the neck, gastrointestinal bleeding, abdominal cramps (twice in the same subject), headache, constipation, arterial hypertension, hyperlipidaemia, bleeding at laser application site, common cold (two subjects). Furthermore, one serious AE (hospitalization due to arterial hypertension) was recorded and classified as unrelated to the study procedures. No ADE was observed. In addition, one subject experienced two episodes of bleeding at the AFL only laser application site (classified as moderate ASR). No clinically significant deviations in lab results were observed.

## Secondary Objective (Efficacy)

The evolution of the TPSS for the respective treatment over the study period is given in **Figure 1**.

Efficacy analysis showed no significant differences between the treatments AFL + ETA and ETA only. However, five patients (62.5%) had higher V1-minus-V13 differences under AFL + ETA than under ETA only, two patients (25%) had the same changes over time in both treatments and only one patient (12.5%) showed a higher difference under ETA than under AFL + ETA (**Figure 2**). Changes from V1 to V13 under AFL + ETA were not significantly different to changes from V1 to V13 under ETA only ($p = 0.2813$; Wilcoxon's signed rank test).

The raw data from TPSS Total-Score by visit and treatment are listed in **Supplementary Table 1**.

Plaque lesions selected for treatment of a representative subject are displayed in **Supplementary Figure 1**.

# DISCUSSION

Results from this study suggest that laser-assisted epidermal delivery of ETA to psoriasis lesions is generally safe and well-tolerated. A comprehensive assessment of risks and benefits associated with either treatment arm (AFL + ETA, ETA only,

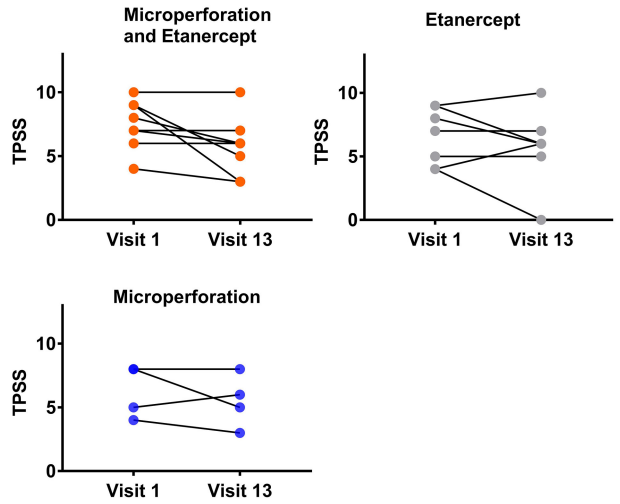


**FIGURE 1 |** TPSS values (mean ± SD). TPSS was assessed before the respective twice weekly treatments [Er:YAG laser microporation, etanercept (ETA) or combination] over the 6 week study period.

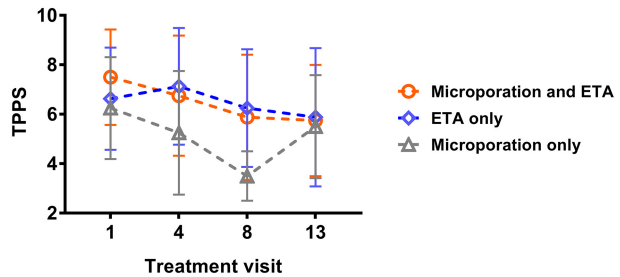


**FIGURE 2 |** Individual TPSS values at visit 1 and visit 13 for the respective treatment areas. TPSS for etanercept ($n = 8$), etanercept + Er:YAG laser microporation ($n = 8$) and Er:YAG laser microporation ($n = 4$).

AFL only) is naturally hampered by the low sample size of a phase I study.

A total of 64 ASR were documented throughout the study. In areas treated with the combination of AFL and ETA 32 ASR, thereof mainly redness ($n = 14$), occurred. By contrast, in areas treated with ETA only 14 ASR and AFL only 18 ASR occurred. Most ASR were graded as mild, none as severe. This leads to the conclusion that topical administration of ETA to psoriatic plaques via AFL-generated micropores in patients with plaque-type psoriasis is well-tolerated. The incidence of ASR was in line with other studies using the same Er:YAG laser system (12).

A comparison of all three treatment groups showed the mean TPSS Total Score evolution ($n = 8$) from treatment visit 1 (V1) to 13 (V13) as follows: AFL + ETA: V1: 7.5, V13: 5.75; ETA only: V2: 6.63, V13: 5.88; microporation only: V1: 6.25, V13: 5.5. While these data indicate the largest numerical improvement in TPSS for AFL + ETA, the numbers did not reach statistical significance. Of note, in contrast to the single treatment lesions, only lesions receiving the combination treatment did not show worsening of the TPSS over the 6 week treatment period (**Figure 1**). Overall, a mean difference of 1.75 points on the TPSS is in the magnitude of effect commonly used for approval of psoriasis drugs, even though this might be rooted in different baseline scores, therefore warranting future investigation in larger studies.

The strategy of enhancing drug delivery through skin micropores has recently been extensively used for various applications including vaccination (12), topical delivery of small molecules (13), proteins (9), and living human cells *in vitro* (14). Our pilot data provide a basis for further investigation of the combination of AFL + ETA in larger studies. A numerical trend toward lower TPSS in the AFL + ETA group may indicate clinical benefit and justifies follow-up investigation within the framework of larger clinical trials. General benefits of topical drug administration modalities are (i) the possibility to apply high local doses of the active compound and (ii) the prevention—or reduction—of systemic side effects. The combination of skin micropores and topical application of a biological drug was well-tolerated within this study. Local reactions were observed but generally of mild intensity.

The drug formulation was not optimized and due to high fluidity special attention was needed during topical administration. In our case ETA doses of 30 µl/4 $cm^2$ or 60 µl/8 $cm^2$ was applied to the treatment area of 4-8 $cm^2$ in comparison to 50 mg dose in 1 ml needed for systemic efficacy. The lowered economic burden afforded by localized delivery system has been demonstrated in other medical fields as well, most notably with the case of systemic bevacizumab adapted for local intra-ocular delivery for wet age-related macular degeneration (AMD) (15) allowing affordable treatments for many AMD patients, at a global scale. Further development of laser-based microporation technology, using current electronic components and controls can also reduce the cost of instrumentation. The current device used is large, programmable, and designed for clinical application, but miniaturization engineering can reduce unit size to a lower cost with potential for unsupervised at-home applications. Further development in the field of laser-assisted biologics delivery in dermatology can allow applications that stretch beyond psoriasis and are accessible to patients worldwide.

Based on the favorable safety profile of the here investigated laser-medicinal product combination, no special precautions seem necessary for future studies.

In summary, topical administration of ETA to psoriatic plaques *via* AFL-generated micropores in patients with plaque-type psoriasis was generally safe and well-tolerated. The study presented here demonstrates a medical path for utilizing biologics on a local basis for dermatological conditions. Safety of ETA treatment in this context opens up the opportunity to examine the use of other anti-inflammatory and immunosuppressive biologics for topical administration, especially in settings where systemic exposure to the treatment agent would result in greatly reduced local concentrations at the target lesion.

## 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

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

## AUTHOR CONTRIBUTIONS

CB, WB, RB, MBo, and MZ designed the study. MBa, EL, PM, VA, SP, and PB conducted the study. MBa, PB, and MZ discussed the data. MBa, VL, MBo, PB, and MZ wrote the manuscript. MZ supervised the study. All authors agreed on publication of this manuscript.

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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.2021.712511/full#supplementary-material

**Supplemental Figure 1 |** Plaque lesions selected for treatment with the respective TPSS scores at baseline and before the last treatment on visit 13 (AFL, ablative fractional laser microporation; ETA, etanercept). Each treated area is about 4 $cm^2$.

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SYSTEMATIC REVIEW
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# Systematic Review and Recommendations to Combine Newer Therapies With Conventional Therapy in Psoriatic Disease

*Sandeep Arora*[1]*, *Pankaj Das*[1] and *Gulhima Arora*[2]

[1] Department of Dermatology, Army College of Medical Sciences & Base Hospital Delhi Cantt, New Delhi, India, [2] Consultant Dermatologist, Mehektagul Dermaclinic, New Delhi, India

**Background:** Psoriasis continues to have unmet needs in its management despite introduction of newer molecules. Monotherapy with these newer agents may not achieve therapeutic goals in all cases, hence necessitating their combinations with other molecules. Improved understanding of newer as well as conventional treatment modalities and experiences in their combinations hence necessitates therapeutic guidelines for their use in psoriasis.

**Objective:** To review the combinations of treatments reported in literature and recommendations for their use based on best current evidence in literature.

**Methods:** A literature review of MEDLINE database for studies evaluating combinations of newer therapies with conventional therapies in psoriasis was done. Newer therapies were identified as biologic disease modifying anti rheumatic drugs and other molecules such as apremilast while conventional therapies included methotrexate, cyclosporine, or retinoids, phototherapy and others. The therapeutic guidelines are proposed with the aim to provide evidenced based approach to combine newer and conventional agents in day-to-day psoriasis management.

**Findings:** Combination of acitretin and narrow band ultraviolet B (NB-UVB)/Psoralen with ultraviolet A (PUVA) achieves faster clearance and allows reduction of dose of the latter. A variable outcome is reported of methotrexate with TNF-α inhibitors vs. TNF-α inhibitors alone, although addition of methotrexate appears to reduce immunogenicity of TNF-α inhibitors thereby preventing formation of anti-drug antibodies especially in case of infliximab. While combination of acitretin and PUVA is beneficial, combining TNF-α inhibitors and phototherapy too produces better and faster results but long term risks of Non Melanoma Skin Cancers (NMSCs) may preclude their use together. Combination of cyclosporine and phototherapy is not recommended due to greater chances of NMSCs. Adding phototherapy to Fumaric Acid Esters (FAEs) improves efficacy. Apremilast can be safely combined with available biologic agents in patients with plaque psoriasis or psoriatic arthritis not responding adequately to biologics alone. Hydroxyurea and acitretin may be used together increasing their efficacy and reducing doses of both and hence their adverse effects.

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*Civil Hospital of Brescia, Italy*
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*Hospital Germans Trias i Pujol, Spain*

***Correspondence:**
*Sandeep Arora*
*aroraderma@gmail.com*

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**Conclusion:** Selected clinical scenarios shall benefit from combinations therapies, improving efficacy of both conventional and newer agents and at the same time helping reduce toxicity of higher dosages when used individually.

**Keywords: psoriasis, combination (combined) therapy, conventional therapy, biologics, guidelines and recommendations**

## INTRODUCTION

Psoriasis is a chronic relapsing-remitting inflammatory papulo-squamous disease, which affects ∼0.51–11.43% of adults worldwide (1). This immune-mediated disease causes chronic inflammation in milieu which not only affects skin, but also joints, blood vessels, heart, liver, and kidneys (2) as well as metabolic syndrome (3, 4). PsA (Psoriatic Arthritis) may be present in >40% of psoriasis patients leading to joint damage and deformities thereby severely affecting QoL (Quality of Life) and physical functioning (5–7). Early diagnosis and treatment intervention are crucial for optimal patient care (8, 9). The chronic relapsing course of disease with these co-morbidities are associated with increased physical and psychological burden, which leads to impaired Quality of Life (QoL) and depression (10). Mild psoriasis responds to topical therapy while moderate to severe psoriasis may need augmentation with phototherapy or systemic agents. Severe psoriasis may sometimes be refractory to one systemic agents requiring combination with another to maintain remission (11, 12). Combining therapeutic agents holds potential in synergistic action for a better control over disease activity. Moreover, a combination may be needed to reduce adverse effects by allowing reduction of dose despite severe disease. However, combining therapies pose challenges in tolerability, acute and long-term adverse effects in the absence of clear overall guidelines. Conventionally, immunosuppressive and non-biologic disease modifying immune-modulatory drugs such as methotrexate, cyclosporine, retinoids, phototherapy, and others have been used. Management of psoriasis has been revolutionized by biologics which have improved management of psoriasis but aren't panaceas either. Combining newer and conventional therapies provide a tantalizing option for managing psoriasis, to achieve prolonged remission and better Quality of Life (QoL). Although there are numerous Randomized Control Trials (RCTs), case series, case reports, and expert opinions proving efficacy of different combinations in various clinical scenarios, literature is lacking in clear cut guidelines on how and when to combine the newer and conventional therapeutic options. This review aims at analyzing data available from studies with highest quality of evidence i.e., RCTs and generate recommendations for combining newer and conventional therapies in psoriatic disease.

## MATERIALS AND METHODS

### Protocol Development and Eligibility Criteria

A protocol was designed and followed as laid down by PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (**Figure 1**). The conventional therapies considered being immunosuppressive and non-biologic disease modifying immune-modulatory drugs such as methotrexate, cyclosporine, retinoids, phototherapy, hydroxyurea, and fumaric acid esters (13). The newer therapies were identified as biologic disease modifying anti-rheumatic drugs namely- TNFα (Tumor Necrosis Factor-α) inhibitors- etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol; IL-17A (Interleukin-17A) inhibitors- secukinumab and ixekizumab; IL-17RA (Interleukin-17 Receptor Antagonist)- brodalumab; IL-12/IL-23 inhibitor- ustekinumab, IL-23 inhibitor- guselkumab; oral PDE-4 (Phosphodiesterase-4) inhibitor- apremilast and tofacitinib selective JAK (Janus Kinase) 1 and 3 inhibitor (14).

### Search Strategy

A literature search was performed for studies conducted in psoriasis therapeutics published before 01 Jan 2021. MEDLINE (OVID, from 1948), EMBASE (OVID, from 1980), Cochrane Central Register of Controlled Trials (CENTRAL), ahead of print subset fraction from Pubmed- not yet published in (OVID MEDLINE), and ongoing trial registries (http://clinicaltrials.gov/) were searched with no language restrictions. The search was carried out through use of keywords targeting all drugs used in conventional as well as newer therapies. In MEDLINE and EMBASE, a methodologic filter for search was used to identify RCTs and clinical controlled trials in Medical Subject Headings and titles and abstracts (adapted from the Cochrane Central Register of Controlled Trials). For potential drug combinations where RCTs were not found, the search was extended to include lower tiers of hierarchy of evidence up to case series. A systematic method in search was used for each database to broaden the search through inclusion of pertinent search terms as relevant citations were recognized (i.e., by scrutinizing references and citing articles).

### Search Terms

The search terms which were used are as follows: ("methotrexate" OR "cyclosporine" OR "ciclosporine" OR "acitretin" OR "phototherapy" OR "hydroxyurea" OR "fumaric acid esters" OR "conventional" [MeSH term] OR "drugs" [MeSH term] OR "etanercept" OR "infliximab" OR "adalimumab" OR "secukinumab" OR "golimumab" OR "ixekizumab" OR "ustekinumab" OR "guselkumab" OR "certolizumab pegol" OR "apremilast" OR "tofacitinib" OR "biologics" [MeSH term] OR "psoriasis" [MeSH term] OR "combination" [MeSH term] OR "therapy" [MeSH term]).

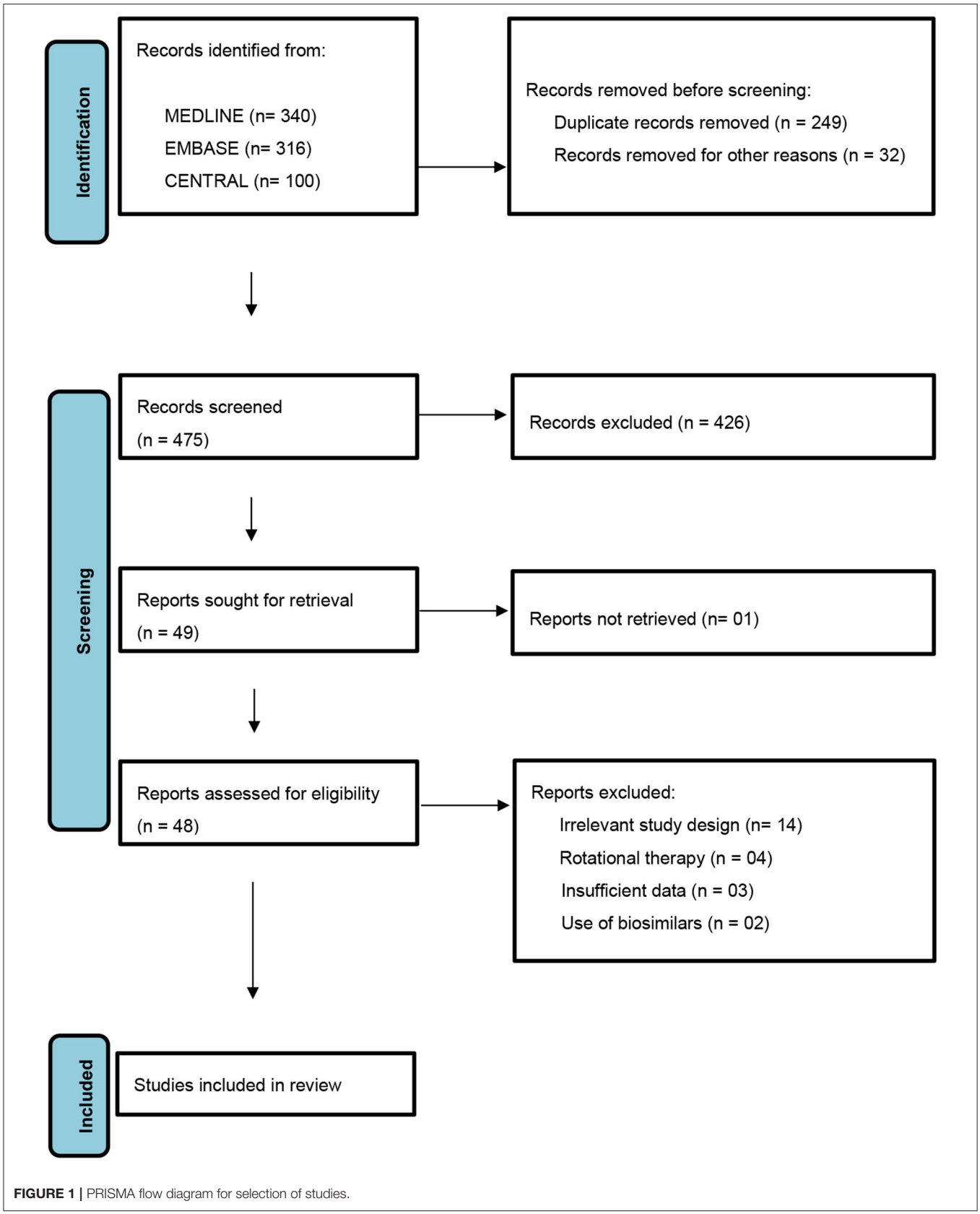


**FIGURE 1 |** PRISMA flow diagram for selection of studies.

## Inclusion Criteria

Randomized Controlled Trials ($N > 10$) which reported on the efficacy and safety of combined use of conventional and newer drugs in psoriatic disease were included. Potential combinations in which RCTs have not been carried out, studies with lower levels of evidence were also included.

## Exclusion Criteria

*In-vitro*, preclinical and animal studies, case reports and expert opinions were excluded from the review as well as all studies not meeting the inclusion criteria. Studies with rotational or sequential therapies using these drugs as well as those combining alternative medicines (i.e., Chinese herbal) were excluded. Biosimilars were excluded from the study to maintain uniformity on drug efficacy data.

## Selection of Studies

Using the above keywords, the titles and abstracts from electronic literature search were screened, and full text of articles that met the pre-defined inclusion criteria were obtained. Successively, articles were scanned for inclusion or exclusion. The selection of studies were implemented by 2 reviewers independent of each other (S.A. and P.D.). The quality of each included articles was assessed in agreement with the Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011). Any disagreements between the two reviewers were resolved by commonly drawn consensus by discussion or intervention by a third reviewer (G.A.).

## Data Extraction

Information on the year of publication, study design, study reference, number of patients (N), baseline disease severity, treatment schedule, duration of combination therapy, and period of follow-up were extracted. Critical as well as important outcomes were carefully chosen to determine the quality of evidence. Critical outcomes were defined as the proportion of patients who attained a PASI (Psoriasis Area and Severity Index) of 90, PASI of 75, and a PGA (Physician Global Assessment) of clear or almost clear; discontinuation of a particular drug because of AEs (Adverse Effects); proportion of patients who encountered SAEs (Serious Adverse Events); and mean change in DLQI (Dermatology Life Quality Index). Important outcomes were defined as lack of efficacy leading to withdrawals (number), proportion of patients with AEs (not leading to drug withdrawal), mean time to clearance, mean change in PASI (0–72, 0–18, and 0–16) and mean time to relapse.

# RESULTS

Our literature search yielded 25 RCTs (**Table 1**) combining different drugs which met the criteria to be included for analysis in the present study. Potential drug combinations for which RCTs have not been done, studies with lesser levels of evidence up to case series were searched for to look for evidence and gaps in research (**Table 2**).

# Discussion and Recommendations

Literature search yielded 25 RCTs combining different agents to treat psoriasis and/or psoriatic arthropathy. Most of the studies involved combinations with Narrow Band Ultraviolet B (NB-UVB) /Psoralen with Ultraviolet A (PUVA) or methotrexate.

## NB-UVB/PUVA and Acitretin

There are 02 RCTs involving acitretin and UVB/PUVA by Tanew et al. (15) and Lowe et al. (16). The former found that the cumulative PUVA dose required for complete clearance in PUVA-acitretin group was 58.7 ± 17.9 J/cm$^2$ whereas in PUVA-placebo group was 101.5 ± 15.8 J/cm$^2$. In RCT by Lowe et al. (16), 14 participants in the UVB-acitretin group took a total of 873 min of UVB exposure for complete clearance as compared to a significantly higher time- 1,236 min in the UVB-placebo group ($n = 15$). At the end of 12 weeks, the mean PASI ± SD in acitretin + UVB group reduced significantly from 8.83 ± 1.8 to 2.27 ± 1.04 ($p < 0.01$), whereas it reduced from 9.75 ± 2.34 to 6.36 ± 3.07 in placebo + UVB group. Both the RCTs concluded that adding UVB/PUVA to acitretin achieves greater as well as faster clearance than either placebo- UVB/PUVA or acitretin alone. Clinical adverse effects of added acitretin in both the studies were generally well-tolerated and similar to previous studies in treatment of psoriasis with acitretin (46–48).

## Recommendation

We recommend combining these two modalities when patients do not respond to either one of the two. In addition to increased efficacy, the combination allows reduction of cumulative dose of UVB/PUVA. Also important is the prevention of non-melanoma skin cancers by acitretin which may be caused by long term UVB/PUVA (49, 50).

## NB-UVB With TNFα Inhibitors

Etanercept with NB-UVB combination has been evaluated by Lynde et al. (17), Park et al. (18), Calzavara-Pinton et al. (19), and Gambichler et al. (20). Lynde et al. (17) concluded that addition of NB-UVB to etanercept did not significantly improve the overall clinical response except for a subset of patients with high adherence to NB-UVB without increasing the adverse effects significantly. Park et al. (18) studied combination of etanercept and NB-UVB in obese patients. They concluded that the combination has a similar efficacy to etanercept monotherapy even in the setting of obesity. However, Calzavara-Pinton et al. (19) who performed an intra-individual RCT in receiving etanercept and a randomized half of the body with NB-UVB for found that The PSI (Psoriasis Severity Index) scores of non-irradiated control lesions were 6.4 ± 2.3 and 5.8 ± 2.5 ($p$ = not significant) before and after the treatment respectively, whereas the PSI of irradiated psoriatic plaques were 6.3 ± 2.3 and 0.5 ± 0.8 ($p < 0.05$). In the combination group, the mean PASI ± SD value reduced from 16.2 ± 9.2 to 2.4 ± 2.8 in 12 weeks. The patients received 14.6 ± 3.3 exposures resulting in a cumulative dose of 8.4 ± 4.2 J cm$^{-2}$. While the combined treatment was always well-tolerated, it was aimed at short duration of NB-UVB therapy for faster clearance to avoid long term adverse effects. It also may help reduce total doses as well as cost of

**TABLE 1 |** Randomized controlled trials which met the inclusion criteria and selected in this study ($n = 25$).

| S no. | References | Study design | No of patients | Baseline disease severity | Intervention | Control group(s) | Study length (weeks) | Follow up (weeks) | Outcome measures used in study analysis | | LoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Efficacy | Safety | |
| 1. | Tanew et al. (15) | Randomized double blinded trial | 60 | ≥20% BSA or PASI ≥10 | Acitretin 1 mg per kg per day plus four PUVA exposures per week | Placebo plus four PUVA exposures per week | Until complete clearance/maximum of 11 weeks. | 11 | Complete remission or marked improvement i.e.at least 90% clearing of psoriasis | Percentage of patients with AEs and SAEs/withdrawal because of AEs | 2b |
| 2. | Lowe et al. (16) | Randomized controlled trial | 37 | Moderate to severe chronic plaque type psoriasis | Acitretin 50 mg per day plus UVB | Placebo plus UVB | 12 | 12 | Mean PASI at the end of 12 weeks | Percentage of patients with AEs | 2b |
| 3. | Lynde et al. (17) | Single- blinded randomized controlled trial | 99 | ≥10% BSA or PASI ≥10 | Etanercept 50 mg once a week plus thrice weekly NB-UVB | Etanercept 50 mg once a week | 24 | 24 | PASI 90, PASI 75, PGA- clear, minimal, mild, moderate, severe, very severe BSA and DLQI | AEs, SAEs infectious adverse events and injection-site reactions | 1b |
| 4. | Park et al. (18) | Randomized, 'head-to-head' pilot trial | 30 | ≥10% BSA or PASI ≥10 with BMI of 30 or greater | Etanercept induction dose at 50 mg twice weekly for 12 weeks followed by combination of etanercept at maintenance dose of 50 mg weekly with NB-UVB thrice weekly | Etanercept induction dose at 50 mg twice weekly for 12 weeks followed by etanercept monotherapy at maintenance dose of 50 mg weekly | 24 | 24 | (i) PASI 75 response after 12 weeks of combination etanercept and NB-UVB therapy (ii)Improvement in average PASI, (iii)Improvement in BSA and (iv) Improvement in PGA | Serious Adverse Events (SAEs) at weeks 12 and 24. | 1b |
| 5. | Calzavara-Pinton et al. (19) | Randomized controlled intra-individual trial | 20 | PASI ≥10, Patients on etanercept alone who did not achieve PASI 75 within 12 weeks | Etanercept at 50 mg twice weekly plus NB-UVB thrice weekly on a selected psoriatic plaque | Covered plaque served as non-irradiated control | 24 | 24 | Mean PASI reduction, PASI 90, PASI 75 | Percentage of patients with AEs | 2b |
| 6. | Gambichler et al. (20) | Randomized controlled intra-individual trial | 14 | PASI ≥10 | Etanercept at 50 mg twice weekly plus NB-UVB thrice weekly on a selected psoriatic plaque | Covered plaque served as non-irradiated control | 6 | 6 | Modified PASI reduction, performance of skin biopsies | Percentage of patients with AEs | 2b |
| 7. | Wolf et al. (21) | Open-label randomized trial | 10 | PASI ≥10 | Ustekinumab at 45 or 90 mg at week 0 and 4 and plus NB- thrice weekly | Ustekinumab at 45 or 90 mg at week 0 and 4 | 6 | 12 | PASI of 75, mean change in PASI | Percentage of patients with AEs, withdrawal because of AEs | 2b |
| 8. | Mahajan et al. (22) | Randomized, single blinded, placebo controlled trial | 40 | ≥10% BSA | Methotrexate at 0.5 mg per kg once weekly to a maximum of 30 mg per week plus NB-UVB thrice weekly | Placebo plus NB-UVB thrice weekly | 24 | 24 | PASI 75, PASI 50 | Percentage of patients with AEs and SAEs/withdrawal because of AEs. | 2b |
| 9. | Asawanonda et al. (23) | Open-label randomized trial | 24 | ≥20% BSA | Methotrexate at 15 mg per week plus NB-UVB thrice weekly | Placebo plus NB-UVB thrice weekly | 24 | 24 | PASI 90, PASI 50, Dermatology Life Quality Index (DLQI) | Percentage of patients with AEs and SAEs | 1b |
| 10. | Al-Hamamy et al. (24) | Open-label randomized trial | 120 | ≥10% BSA | Methotrexate at 0.2 mg per kg weekly with a maximum of 20 mg per week plus NB-UVB thrice weekly | (i) Methotrexate at 0.2 mg per kg weekly with a maximum of 20 mg per week (ii) NB-UVB thrice weekly | 24 | 48 | PASI 90, PASI 50 | Percentage of patients with AEs and SAEs | 2b |
| 11. | Zachariae et al. (25) | Open-label randomized trial | 60 | ≥10% BSA or PASI ≥8 | Etanercept 50 mg twice weekly for 12 weeks, and then 25 mg twice weekly for 12 weeks plus continued methotrexate therapy | Etanercept 50 mg twice weekly for 12 weeks, and then 25 mg twice weekly for 12 weeks plus methotrexate tapered and discontinued during the 4 weeks | 24 | 24 | Physician's Global Assessment (PGA), PASI 50, PASI 75, PASI 90, DLQI. | Percentage of patients with AEs and SAEs/withdrawal because of AEs | 2b |

*(Continued)*

**TABLE 1** | Continued

| S no. | References | Study design | No of patients | Baseline disease severity | Intervention | Control group(s) | Study length (weeks) | Follow up (weeks) | Outcome measures used in study analysis | | LoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Efficacy | Safety | |
| 12. | Gottlieb et al. (26) | Randomized, double-blind, placebo controlled trial | 478 | ≥10% BSA or PASI ≥10 | Etanercept 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg once weekly for 12 weeks plus methotrexate titrated from 7.5 mg to maximum of 15 mg or tolerated dose. | Etanercept 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg once weekly for 12 weeks plus placebo | 24 | 24 | PASI 90, PASI 75, PASI 50, static Physician's Global Assessment (sPGA), BSA improvement from baseline at weeks 12 and 24. Assessments were performed at screening, at baseline, and every 4 weeks thereafter throughout the study. | Percentage of patients with AEs. | 1b |
| 13. | Yu et al. (27) | Randomized trial, unclear blinding | 30 | PASI ≥10 | Etanercept 50 mg once weekly plus oral methotrexate 7.5–15 mg per week | Etanercept 50 mg once weekly | 24 | 24 | PASI score, static Physician's Global Assessment (sPGA), Patient's Global Assessment (PtGA), Dermatology Life Quality Index (DLQI) | Percentage of patients with AEs. | 2b |
| 14. | Mease et al. (28) | Randomized, double-blind, placebo-controlled triple armed trial | 851 | 3 tender joints and 3 swollen joints (based on 68- and 66-joint, and an active psoriatic skin lesion that was ≥2 cm in diameter). | Etanercept (target dose 50 mg) plus oral methotrexate (target dose 20 mg) given weekly. | Methotrexate (target dose 20 mg) plus subcutaneous placebo given weekly or subcutaneous etanercept (target dose 50 mg) plus oral placebo given weekly. | 48 | 48 | ACR20, Minimal Disease Activity (MDA) response, Leeds Dactylitis Index (LDI), static Physician's Global Assessment (sPGA). | Percentage of patients with AEs and SAEs/withdrawal because of AEs. | 1b |
| 15. | Baranauskaite et al. (29) | Open-label randomized trial | 115 | Psoriasis and psoriatic arthropathy | Infliximab 5 mg per kg infusions at weeks 0, 2, 6, and 14 plus methotrexate 15 mg per week | Methotrexate 15 mg per week | 16 | 16 | ACR20, ACR50 and ACR70 responses, PASI 75, PASI 90, EULAR response, physician and patient global assessment of disease activity, disease activity score in 28 joints (DAS28) scores, minimal disease activity (MDA) | Percentage of patients with AEs and SAEs/withdrawal because of AEs. | 2b |
| 16. | van Mens et al. (30) | Randomized, double-blind, placebo controlled trial | 59 | Patients meeting CASPAR criteria and current active disease, defined as the presence of at least three swollen and three tender joints. | Methotrexate 25 mg per week or as tolerated plus Golimumab 50 mg administered every 4 weeks | Methotrexate 25 mg per week or as tolerated plus placebo prefilled syringes administrated every 4 weeks | 22 | 22 | Disease Activity Score (DAS), MDA, ACR20/50/70 responses, Leeds Enthesitis Index, and Dermatology Life Quality Index (DLQI). | Percentage of patients with AEs and SAEs/withdrawal because of AEs. | 2b |
| 17. | Vieira-Sousa et al. (31) | Randomized, double-blind, placebo controlled trial | 48 | Classification for Psoriatic Arthritis criteria ≥1 digit with tender dactylitis and ≥1 other site of active inflammation (joints, enthesis, spine, skin, or nails). | Methotrexate 25 mg per week or as tolerated plus Golimumab 50 mg administrated every 4 weeks | Methotrexate 25 mg per week or as tolerated plus placebo prefilled syringes administrated every 4 weeks | 24 | 24 | Dactylitis Severity Score (DSS) DSS20, 50 or 70, Leeds Dactylitis Index (LDI) LDI20, 50 or 70, Enthesitis Index (LEI). | Percentage of patients with AEs. | 2b |
| 18. | Lee et al. (32) | Randomized, open labeled trial | 60 | ≥10% BSA or PASI ≥10 | Etanercept 25 mg biweekly plus acitretin 10 mg twice daily for 24 weeks | (i) Etanercept 50 mg biweekly for 12 weeks followed by etanercept 25 mg biweekly for 12 weeks; (ii) Acitretin 10 mg BID for 24 weeks. | 24 | 24 | PASI 75, PASI 50, clear/almost-clear by PGA | Percentage of patients with AEs | 2b |

*(Continued)*

**TABLE 1** | Continued

| S no. | References | Study design | No of patients | Baseline disease severity | Intervention | Control group(s) | Study length (weeks) | Follow up (weeks) | Outcome measures used in study analysis | | LoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Efficacy | Safety | |
| 19. | Gisondi et al. (33) | Randomized, controlled, investigator-blinded pilot trial | 60 | ≥10% BSA or PASI ≥10 | Etanercept 25 mg once weekly plus oral acitretin 0.4 mg per kg per day daily. | Etanercept 25 mg twice weekly subcutaneously; (ii) Acitretin 0.4 mg per kg per day daily in a single oral dose; and | 24 | 24 | PASI 75, PASI 50 and mean BSA reduction at week 24 | Percentage of patients with AEs | 2b |
| 20. | van Bezooijen et al. (34) | Randomized controlled trial | 33 | PASI ≥10 | Oral fumarates up to 4 × 215 mg plus Etanercept 2 × 50 mg/week for 12 weeks followed by 1 × 50 mg weekly from week 12 onwards | Etanercept at 2 × 50 mg/week for 12 weeks followed by etanercept to 1 × 50 mg weekly from week 12 onwards | 48 | 48 | PASI 75, PGA clear or almost clear | Percentage of patients with AEs | 2b |
| 21. | Tzaneva et al. (35) | Open-label randomized trial | 30 | ≥10% BSA or PASI ≥10 | Accelerated FAE dosing scheme with NB-UVB thrice weekly | Accelerated FAE | 26 | 26 | Mean PASI reduction, PASI 75, Mean, absolute and relative DLQI reduction | Percentage of patients with AEs | 2b |
| 22. | Prystowsky et al. (36) | Randomized, single blinded, placebo-controlled trial | 19 | >20% BSA | Calcitriol 0.5–2.0 μg per day plus NB-UVB four times weekly | Placebo plus NB-UVB four times weekly | 5 | NR | Mean change in PASI (scale, 0-16) | NR | 2b |
| 23. | Ezquerra et al. (37) | Open-label randomized trial | 40 | PASI ≥15 | Acitretin at 25 mg per day plus calcitriol 0.25 μg per day | Acitretin at 25 mg per day | 12 | NR | Mean change in PASI | Percentage of patients with AEs | 2b |
| 24. | Mittal et al. (38) | Randomized, double-blind, placebo-controlled trial | 41 | >20% BSA | Acitretin at 25 mg per day plus pioglitazone, Hydrochloride at 15 mg per day | Acitretin at 25 mg per day plus placebo | 12 | 12 | PASI 75, PGA of clear or almost clear, mean change in PASI, withdrawal because of lack of efficacy | Percentage of patients with AEs, withdrawal because of AEs | 2b |
| 25. | el-Mofty et al. (39) | Randomized trial, unclear masking | 16 | >25% BSA | Sulfasalazine, 2 gm per day plus Pentoxifylline 1,200 mg per day | Methotrexate, 25 mg per week | 8 | NR | Mean change in PASI, Withdrawal because of lack of efficacy | Percentage of patients with AEs | 2b |

*PUVA, Psoralen and Ultra Violet A; UVB, Ultra Violet B; NB-UVB, Narrow Band Ultra Violet B; BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; AE, Adverse Events; SAE, Serious Adverse Events; BMI, Body Mass Index; DLQI, Dermatology Life Quality Index; PGA, Physician's Global Assessment; sPGA, static Physician's Global Assessment; PtGA, Patient's Global Assessment; ACR 20/50/70, American College of Rheumatology 20/50//70; MDA response, Minimal Disease Activity response; LDI 20/50/70, Leeds Dactylitis Index 20/50/70; EULAR response, European League Against Rheumatism response; DAS28 scores, Disease Activity Score in 28 joints; LSI, Leeds Enthesitis Index.*

**TABLE 2 |** Summary of levels of evidence and strength of recommendations.

| S. no. | Drug combinations | Highest levels of evidence on efficacy | Recommendations for combination on basis of evidence |
|---|---|---|---|
| 1 | UVB/PUVA + Acitretin (15, 16) | 2b | B |
| 2 | Etanercept + NB-UVB (17–20) | 1b, 2b | A |
| 3 | Adalimumab + NB-UVB (40, 41) | 2b, 4 | B |
| 4 | Ustekinumab + NB-UVB (21) | 2b | B |
| 5 | Methotrexate + NB-UVB (22–24) | 1b, 2b | A |
| 6 | Etanercept + Methotrexate (25–28) | 1b, 2b | A |
| 7 | Infliximab + Methotrexate (29) | 2b | B |
| 8 | Golimumab + Methotrexate (30, 31) | 2b | B |
| 9 | Etanercept + Acitretin (32, 33) | 2b | B |
| 10 | Apremilast + NB-UVB (42) | 4 | C |
| 11 | Apremilast + Secukinumab (43, 44) | 4 | C |
| 12 | Etanercept + Fumarates (34) | 2b | B |
| 13 | Fumarates + NB-UVB (35) | 2b | B |
| 14 | Calcitriol (oral) + Acitretin (37) | 2b | B |
| 15 | Hydroxyurea + Acitretin (45) | 4 | C |

*Levels of evidence: 1a, Systematic review of (homogeneous) RCTs; 1b, Individual RCTs (with narrow confidence intervals); 2a, Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects; 2b, Individual cohort study/low-quality RCTs; 3a, Systematic review of (homogeneous) case-control studies; 3b, Individual case-control studies; 4, Case series, low-quality cohort or case-control studies; 5, Expert opinions based on non-systematic reviews of results or mechanistic studies.*
*Strength of recommendations: A, Good evidence to support a recommendation for use; B, Moderate evidence to support a recommendation for use; C, Poor evidence to support a recommendation.*

etanercept therapy. Calzavara-Pinton et al. (19) inferred that the combination is more effective than each therapy alone in the treatment of moderate-to-severe plaque psoriasis, and is well-tolerated. In an intra-individual RCT by Gambichler et al. (20) ($n = 14$) the relative M-PASI (modified-PASI) reduction of etanercept alone treated sites after 6-weeks was 53.7 ± 36.9%, whereas etanercept plus NB-UVB combination treated sites resulted in a significantly higher relative M-PASI reduction of 64.7 ± 27.8% ($P = 0.011$, 95% CI −19 to −3%) concluding that etanercept combined with NB-UVB is more effective than etanercept monotherapy at 6 weeks. Similarly, in an another intra-individual RCT by Wolf et al. (40) consisting of 04 participants who were followed up for 06 weeks concluded that adding thrice weekly NB-UVB to 40 mg bi-weekly adalimumab reduced mean PASI from 14.8 to 2.0 on UV-irradiated body halves vs. 6.9 on non-irradiated body halves (95% confidence interval, 0.4–9.4) accelerating the clearance of psoriatic lesions with no significant adverse effects. Bagel (41) performed a 24-week single-arm open-label study in 20 adults with moderate to severe psoriasis who received bi-weekly adalimumab 40 mg and thrice weekly NB-UVB phototherapy for 12 weeks and followed up for another 12 weeks. The mean baseline scores of patients were 17.0 for PASI, 21.2 for BSA (Body Surface Area) and 3.5 for PGA (Physicians Global Assessment). At the end of treatment at week 12, 19 (95%) patients achieved PASI-75, 15 (75%) PASI-90 and 11 (55%) achieved PASI-100. Seventeen (85%) were clear or almost clear (PGA score =1). Mean baseline PASI, BSA, and PGA scores improved by 95, 93, and 80%, respectively. Moreover, the improvement was sustained through the end of follow up period at week 24 without any serious adverse events. Although none of the studies combining TNFα blockers and NB-UVB reported any major adverse effects, concerns were shown regarding the long-term effects of combining TNFα blockers with NB-UVB-especially malignancy.

## Recommendation

As the implication of malignancy in treatment with TNF-α blockers alone or in combination with NB-UVB complex with levels of TNF-α having varied effects on tumoral growth, (51) we recommend to restrict this highly effective combination for short duration up to 24 weeks, to obtain a quicker response and to avoid long-term complications (52–54). European Academy of Dermatology and Venereology (EADV) guidelines on management of psoriasis mention that TNFα blockers and NB-UVB may or may not be combined and it is not as strict a contraindication as cyclosporine with NB-UVB (55).

## NB-UVB and IL12/23 Inhibitor

There is only a single intra-individual RCT combining injection ustekinumab at 45/90 mg 4 weeks apart and thrice weekly 311-nm UVB by Wolf et al. (21) in 10 patients. At baseline, the mean PASI was similar in both irradiated and unirradiated body halves (13.6 vs. 13.3). At 6 weeks, PASI was significantly lower on irradiated body halves (2.5 vs. 6.1), (95% confidence interval 1.3–5). PASI 75 was achieved significantly more often on UV-irradiated body halves than on un-irradiated ones [7/9 patients (78%) vs. 1/9 (11%)]. They concluded that treatment with NB-UVB accelerates the clearance of psoriatic lesions at week 6 as well as at week 12 in ustekinumab-treated patients without increase in incidence of severe adverse effects.

## Recommendation

No specific recommendation could be offered as there is limited review of this combination. However, in patients on ustekinumab with a poor response NB-UVB may be added as it has a good safety profile.

## NB-UVB and Methotrexate

03 studies combining methotrexate and NB-UVB met the criteria to be included in our review- Mahajan et al. (22), Asawanonda et al. (23), and Al-Hamamy et al. (24). Mahajan et al. (22) combined oral methotrexate at 0.5 mg/kg once weekly [maximum of 30 mg/week and thrice weekly NB-UVB and compared it with placebo plus NB-UVB for a duration of 12 weeks. PASI 75 was attained in 19/20 patients in the combination group versus 14/20 patients in NB-UVB plus placebo group ($p = 0.04$)]. PASI 75 was achieved in 7.57 ± 3.09 weeks (4–16) in the combination group and 11.42 ± 4.98 weeks (6–20) in NB-UVB + placebo group ($p < 0.006$). The mean number of NB-UVB sessions to which the patients were exposed were

17.47 ± 6.62 (10–35) in the combination group and 35.72 ± 17.05 (16–6) in NB-UVB + placebo group ($p < 0.0001$). Mean NBUVB dose for achieving PASI 75 was 9.14 ± 5.39 J/cm$^2$ (3.34–20.84) in the combination group as compared with 25.99 ± 18.55 J/cm$^2$ in NB-UVB + placebo group ($p < 0.001$). Asawanonda et al. (23) showed that the median time to clear psoriasis in the former group was 4 weeks, which was significantly less than that the latter. Ten of 11 patients on combination of methotrexate and NBUVB achieved PASI 90 compared with only 5/13 in the placebo/ NB-UVB group ($p < 0.0001$). The mean cumulative dose in methotrexate/NB-UVB group was 26.92 ± 15.54 J/cm$^2$, as compared to 59.25 ± 16.71 J/cm$^2$ ($p = 0.002$) in the placebo/NBUVB group. Al-Hamamy et al. (24) compared the combination of methotrexate with NB-UVB, methotrexate alone and NB-UVB alone and found no statistically significant difference in the number of patients achieving PASI 90 between the three groups in six months of treatment. However, the mean number of weeks required for achieving clearance was 6.11 ± 1.28 weeks in combination group and 11.42 ± 2.36 weeks in NB-UVB group, while 20.87 ± 4.21 weeks in methotrexate group ($p < 0.0001$). The mean number of NBUVB sessions to which the patients were exposed was 17.86 ± 3.74 in combination group and 33.51±6.90 in NB-UVB group ($p < 0.0001$). The mean total cumulative dose of NBUVB phototherapy for achieving clearance was 12.13 ± 4.02 J/cm$^2$ in the combination group; compared with 34.48 ± 13.13 J/cm$^2$ in NB-UVB group ($p < 0.0001$). All 03 RCTs combining methotrexate with NB-UVB concluded that the mean time to achieve reduction in PASI 75 was significantly less in the combined group as against those treated only with NB-UVB and addition of methotrexate to NB-UVB rapidly clears psoriatic lesions without any significant adverse effects.

## Recommendation

We recommend combining NB-UVB with methotrexate for faster clearance of lesions. However, either may be discontinued after achieving PASI 75 and the other continued for maintenance therapy the duration of which shall be dictated by the disease burden.

## TNFα Inhibitors and Methotrexate

The following RCTs combining TNFα blockers with methotrexate met the inclusion criteria- Zachariae et al. (25), Gottlieb et al. (26), Yu et al. (27), Mease et al. (28), Baranauskaite et al. (29), van Mens et al. (30), and Vieira-Sousa et al. (31) who compared the combination of TNFα blockers with methotrexate with either TNFα blockers alone or methotrexate alone. Zachariae et al. (25) randomized 60 patients who were already on methotrexate for at least 03 months into two groups receiving etanercept-methotrexate combination and etanercept with tapering and stopping methotrexate and noted significantly more number of patients achieving PASI 75 as well as significantly lower mean PASI scores at both 12 and 24 weeks in the combination group compared with etanercept alone with similar AEs for both groups, an effect that was maintained until the end of the study. Gottlieb et al. (26) studied 478 patients combining weekly methotrexate to patients who were already on etanercept since 24 weeks to the treatment group against placebo in control group. The percentage of patients achieving PASI 75 was significantly higher at week 24 for the combination therapy group (77.3%) compared with the monotherapy group (60.3%; $p < 0.0001$). Overall, 74.9% of patients in the combination group experienced AEs compared with 59.8% in the monotherapy group. Withdrawals due to AEs were infrequent in both groups [combination, $n = 10$ (4.2%); monotherapy, $n = 6$ (2.5%)], and none of the AEs leading to withdrawal was considered to be serious or infectious. They concluded that addition of methotrexate to etanercept was more effective than etanercept monotherapy in patients with moderate to severe plaque psoriasis with acceptable tolerability. Yu et al. (27) compared similar treatment arms as above but started administering the combination from baseline and followed up subjects for 24 weeks. They found no significant change in the PASI score from baseline to 24 weeks. However, both sPGA (static Physician's Global Assessment) and PtGA (Patient's Global Assessment) scores were significant ($p < 0.05$). Adverse effects were reported in 60% of patients in the combination group and in 33% in the monotherapy group. None of the adverse effects were serious enough to discontinue treatment. Mease et al. (28) performed a triple arm study consisting of 851 patients of psoriatic arthropathy randomized to oral methotrexate 20 mg plus placebo weekly, etanercept 50 mg plus placebo weekly, or etanercept 50 mg plus oral methotrexate 20 mg weekly. ACR20 (American College of Rheumatology 20) criteria and MDA (Minimal Disease Activity) responses at week 24 were significantly greater for etanercept monotherapy vs. methotrexate monotherapy (ACR20: 60.9 vs. 50.7% [$p = 0.029$]; MDA: 35.9 vs. 22.9% [$p = 0.005$]) and for combination therapy vs. methotrexate monotherapy (ACR20: 65.0 vs. 50.7% [$p = 0.005$]; MDA: 35.7 vs. 22.9% [$p = 0.005$]). Many patients in this trial had a moderate to severe level of psoriasis as assessed by BSA (Body Surface Area). Results from the dermatologic endpoints showed that etanercept and methotrexate had good efficacy, with a suggestion that the combination arm had slightly greater efficacy than either of the monotherapy arms for improved BSA. They concluded that etanercept monotherapy and combination therapy showed greater efficacy than methotrexate monotherapy in ACR, MDA, and BSA responses and radiographic progression. However, combining methotrexate and etanercept did not improve etanercept efficacy in either PsA or psoriasis. Baranauskaite et al. (29) combined infliximab at 5 mg per kg infusions at 0, 2, 6, and 14 weeks and methotrexate at 15 mg per week vs. methotrexate alone for a period of 16 weeks. 86.3% of patients receiving combination and 66.7% of those receiving methotrexate alone achieved an ACR20 response ($p < 0.02$). While 97.1% of patients receiving infliximab plus methotrexate achieved PASI 75, the figure was 54.3% in patients receiving methotrexate alone ($p < 0.0001$). They demonstrated significantly greater ACR 20 response rates and PASI 75 improvement in the combination group and was generally well-tolerated. A double-blind RCT measuring end points in psoriatic arthritis by van Mens et al. (30) studied combination of methotrexate 15–25 mg per week and subcutaneous injections of golimumab at 50 mg per month with that of methotrexate and placebo and found that

Disease Activity Score (DAS) remission at week 22 was almost doubled (21/26;81%) in methotrexate plus golimumab group vs. methotrexate alone (10/24; 42%) ($p = 0.004$). Also the patients belonging to the combination group reached an MDA (Minimal Disease Activity) in 21/26 (81%) vs. 7/24 (29%) in the methotrexate arm ($p < 0.001$). An ACR 20/50/70 response was achieved by, respectively, 85, 81, and 58% in the combination arm vs. 58, 33, and 13% in the methotrexate arm ($p = 0.039$, $p = 0.001$, and $p = 0.001$, respectively). The most frequent adverse effect was nausea and occurred in similar incidences in both treatment arms and considered to be treatment related but was not severe enough to discontinue treatment. Likewise, a double-blind RCT by Vieira-Sousa et al. (31) comparing similar doses of golimumab plus methotrexate vs. placebo plus methotrexate in dactylitis in psoriatic arthropathy concluded that the combination of golimumab and methotrexate was superior to methotrexate alone in reducing Dactylitis Severity Score (DSS) and Leeds Dactylitis Index (LDI) with comparable incidence of adverse effects between treatment arms. All patients had active dactylitis at baseline, with a median baseline DSS of 6 in both arms. The patients treated with golimumab/methotrexate exhibited significantly greater improvements by DSS at week 24 (median change of 5) relative to the placebo/methotrexate group (median change of 2) ($p = 0.026$), and as early as 12 weeks ($p = 0.004$). The proportion of DSS50 (Dactylitis Severity Score 50) and DSS70 (Dactylitis Severity Score 70) responders at week 24 were also significantly higher for patients treated with golimumab/methotrexate (DSS50: $p = 0.005$, DSS70: $p = 0.010$) Endpoints to measure cutaneous efficacy like PASI, BSA and skin-related quality of life (Dermatology Life Quality Index) improved in both groups at week 24 but difference in both treatment groups was not significant. 102 adverse events were reported during study period, with similar incidence between the treatment arms and mostly of mild to moderate severity. According to systematic review by Hsu et al. (56), there are 06 studies measuring anti-drug antibodies in etanercept and its possible effect on drug efficacy- they found the prevalence of anti- etanercept antibodies (AEA) ranging from 0 (57) to 18.3% (58) in psoriasis, and none of which had significant effect on treatment efficacy (56). Similarly, 10 studies proved prevalence of anti-infliximab antibodies (AIA) ranging from 5.4 (59) to 43.6% (60) with most of these studies showing significant decreased mean PASI scores and greater loss of clinical response when compared to AIA-negative patients (56). A study by Adisen et al. (61) with five patients of psoriasis who developed AIA, determined that AIA positivity disappeared after 8 weeks of combined methotrexate pulse therapy, ranging from 5 to 15 mg/week. Six studies assessed for Anti-Ustekinumab Antibody (AUA) formation in patients with moderate-to severe psoriasis showed ranges from 3.8 (62) to 5.4% (63) in psoriasis (56). But their clinical significance on treatment response is yet to be evaluated (56).

## Recommendation

We recommend combining TNFα blockers with methotrexate in moderate to severe psoriatic disease especially while using infliximab. Poor response to etanercept alone at lower doses as elaborated below necessitates an additional drug, methotrexate being a good option.

## TNFα Inhibitors With Cyclosporine

Atzeni et al. (64) who performed an RCT comparing etanercept plus cyclosporine with etanercept plus methotrexate show similar efficacy in reducing DAS28 (Disease Activity Score 28) in patients with moderate/severe psoriatic arthropathy and peripheral arthritis, but former combination was more efficacious in reducing psoriatic skin involvement. PASI 50 and PASI 75 scores were achieved by 88 and 53%, respectively, in the patients in etanercept plus cyclosporin group, and 73 and 32%, respectively, in the patients in etanercept plus methotrexate group ($p < 0.05$). There was no significant difference in serious adverse events between the two treatment groups.

## Recommendation

We recommend TNFα blockers with cyclosporine in moderate to severe psoriasis with arthropathy for rapid remission, however side effects limit the duration of treatment with cyclosporine and sequential therapy with methotrexate is recommended.

## TNFα Inhibitors With Acitretin

Lee et al. (32) randomized 60 subjects into three treatment arms-ETN-ETN (etanercept-etanercept), ETN-ACT (etanercept-acitretin), and ACT (acitretin). The median time to achieve PASI 75 for patients in the ETN–ETN arm was 126 days vs. 146 days for patients in the ETN-ACT arm. The median time to achieve PASI 50 was same in ETN–ETN and ETN-ACT arms (56 days) and much shorter than for patients in ACT arm (126 days). The difference was statistically significant among the three treatment arms (PASI 75: $p = 0.0448$ and PASI 50: $p = 0.0033$). Lee et al. (32) proved that the combination is more effective than acitretin alone without increase in adverse effects. In another study with similar treatment arms Gisondi et al. (33) randomized 60 patients into three groups to receive etanercept 25 mg twice weekly; acitretin 0.4 mg per kg daily; and etanercept 25 mg once weekly plus oral acitretin 0.4 mg per kg daily. PASI 75 response at week 24, was achieved by 10 of 22 patients (45%) in the etanercept group, six of 20 (30%) in the acitretin group and eight of 18 (44%) patients with etanercept plus acitretin group ($P = 0.001$ for both etanercept groups compared with acitretin alone). PASI 50 response at week 24 too showed similar significant results ($P = 0.001$ for both etanercept groups compared with acitretin alone).

## Recommendation

Etanercept 25 mg twice weekly with acitretin is a superior option to acitretin alone. We recommend addition of acitretin to etanercept dose of 25 mg twice weekly before considering a higher dose of etanercept 50 mg twice weekly.

## Apremilast Combinations

Apremilast, a PDE4 inhibitor has minimal immunosuppressive effects when compared to biologics. There are no RCTs combining apremilast with any other drug. However, case series and retrospective studies have suggested that combination of apremilast with other drugs and biologics like methotrexate,

acitretin, cyclosporin, secukinumab, etanercept, adalimumab, ixekizumab, and ustekinumab have been effective, look promising and may be exercised to reduce adverse effects of either of two.

In an open-labeled prospective study combining apremilast 30 mg twice daily and increasing doses of NB-UVB three times per week for 12 weeks. 73% (16 of 22 completers) achieved a PASI 75 response at week 12. The most commonly reported adverse events were mild and moderate first-degree burns related to NB-UVB ($n = 11$ [38%] patients). Bagel et al. (42) concluded that the combination provided a new treatment option without any increased adverse effects. Both Sacchelli et al. (43) and De et al. (44) published case series and case reports combining apremilast with secukinumab and found improvement in PASI scores. Metyas et al. (65) and Takamura et al. (66) performed retrospective studies reporting the efficacy of apremilast in combination with any other biologics and inferred that apremilast can be safely combined with all biologic agents in patients with plaque psoriasis or psoriatic arthritis not responding adequately to biologics alone. Another retrospective study by AbuHilal et al. (67) studied the combination of apremilast with other biologics as well as conventional drugs like methotrexate, acitretin, cyclosporine with similar conclusion.

## Recommendation

We recommend apremilast 30 mg twice daily and NB-UVB as a combination modality not responding or minimally responding to either of the two. The combination of apremilast and a biologic may be a safe, useful treatment option for managing patients with psoriasis showing biologic fatigue, but not as a routine. However, large scale studies with higher level of evidence like RCTs are needed in future.

## Miscellaneous Combination Therapies

RCTs combining less used unconventional drugs in psoriasis included in this review dealt with fumaric acid esters (FAEs) calcitriol, sulfasalazine, pentoxifylline, and pioglitazone with conventional modes of therapy. An exploratory RCT by Bezooijen et al. (34) combining etanercept 50 mg twice weekly for 12 weeks followed by once weekly for another 12 weeks with oral fumarates 215 mg four times daily for the whole period vs. etanercept alone found out that the reduction in PASI score per week for the combination therapy was 5.97% (95% confidence interval, CI: 5.08–6.85) and in the monotherapy group 4.76% (95% CI: 3.57–5.93; $p = 0.11$). They concluded that combination therapy caused quicker improvement in PASI 75 in first 24 weeks although difference in the PASI score between the two groups was statistically insignificant but with satisfactory tolerability. In an another RCT by Tzaneva et al. (35), an increasing dose of FAEs was combined with NB-UVB. At 26 weeks of treatment, the median baseline PASI of 15.4 [interquartile range (IQR) 11.7–21.0] was reduced to 2.8 (IQR 1.6–4.8) in the combination group and from 14.0 (IQR 12.5–15.1) to 9.0 (IQR 6.5–12.1) in the FAE group, respectively. The mean absolute and relative reduction in PASI was significantly greater in the combination group (10 and 69%) compared with patients receiving only FAE (5 and 36%) ($p = 0.016$). Side-effects related to FAE were mainly mild gastrointestinal complaints reported by 12/16 patients (75%) in the monotherapy group and 3/14 patients (21%) in the combination group. These were abdominal pain, nausea, flatulence, diarrhea that occurred at the beginning of treatment, were dose-dependent and improved after a temporary dose reduction. They found an accelerated as well as augmented response improving the quality of life in the patients with combination therapy as compared with fumaric acid esters monotherapy with no increase in adverse effects in the combination group.

A single blinded, placebo-controlled trial combining calcitriol 0.5–2.0 μg per day plus NB-UVB against NB-UVB alone by Prystowsky et al. (36) concluded that there was no added benefit to treatment when oral calcitriol was administered with phototherapy. Our search yielded only a single RCT combining acitretin and calcitriol- Ezquerra et al. (37) who compared the combination with acitretin alone. Initial PASI of 26.90 reduced to 13.3 in acitretin alone group; whereas it reduced from 28.35 to 10.3 in acitretin+calcitriol combination group which was statistically significant ($p < 0.05$). A double-blind RCT by Mittal et al. (38) compared combination of acitretin plus pioglitazone hydrochloride with acitretin alone. The percentage of reduction in the PASI score from baseline to 12 weeks of treatment was 64.2% (95% CI, 49.2–79.3%) in the combination group compared with 51.7% (95% CI, 38.7–64.7%) in the acitretin plus placebo group ($p = 0.04$). The adverse effects in both the groups were mild to moderate and were comparable. el-Mofty et al. (39) conducted a quadri-armed RCT comparing the combination of sulfasalazine and pentoxifylline to methotrexate alone (active control group), sulfasalazine alone and pentoxifylline alone and concluded that combination of sulfasalazine and pentoxifylline though effective than when used alone, is not as effective as methotrexate, may be promising and tried because they present as safer and well-tolerated alternatives to methotrexate. There are no RCTs on hydroxyurea in psoriasis. Hydroxyurea becomes one of the drugs of choice in settings of psoriasis in HIV, where not only it helps in controlling psoriasis, but also in controlling viral loads especially when combined with didanosine (NRTI) (68, 69). In a retrospective study, Narang et al. (45) combined lower doses of hydroxyurea 1 g daily with acitretin 25 mg daily for the management of refractory cases and found them to be superior to either to hydroxyurea and acitretin alone as found in previous studies. Combining acitretin with hydroxyurea may theoretically reduce the risk of non-melanoma skin cancers and actinic keratosis, which are rare but serious adverse effect of hydroxyurea (49, 70). Methotrexate too have been combined with hydroxyurea in lower doses (5–10 mg/week and 500 mg per day, respectively) to good effect with no increase in adverse effects of either of the two (71). Though theoretically both the drugs may cause GI intolerance and myelosuppression, they were not found in the study.

## Recommendation

We recommend combining hydroxyurea and acitretin in recalcitrant cases of psoriasis not responding to conventional stand-alone drugs. This combination also may be used in HIV

where both the drugs do not cause immune suppression with added benefit of anti-viral action of hydroxyurea.

Combining methotrexate with hydroxurea in lower doses may help reducing dose-dependent or cumulative toxic effects of either of the two.

Our search for combinations comprising relatively newer drugs like guselkumab, tildrakizumab, certolizumab pegol, and tofacitinib yielded no results and provide gap in research with a massive potential.

## CONCLUSION

Combining newer therapies with conventional ones is a promising prospect to manage difficult to treat psoriasis. Combining drugs when suited to patients needs can enhance efficacy, achieve remission, while reducing adverse effects. With available evidence, there are limited options with highest level of evidence and hence recommendation. Due to a smaller number of studies in combination of drugs, research providing more high-quality evidence is required.

## 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

SA: conception and design, acquisition of data, literature search, analysis and interpretation of data, drafting the manuscript, and revising it. PD and GA: acquisition of data, literature search, analysis and interpretation of data, drafting the manuscript, and revising it. All authors contributed to the article and approved the submitted version.

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# Psoriasis to Psoriatic Arthritis: The Application of Proteomics Technologies

*Fei Qi*†, *Yaqi Tan*†, *Amin Yao*, *Xutong Yang* and *Yanling He**

*Department of Dermatology, Capital Medical University Affiliated Beijing Chaoyang Hospital, Beijing, China*

Psoriatic disease (PsD) is a spectrum of diseases that affect both skin [cutaneous psoriasis (PsC)] and musculoskeletal features [psoriatic arthritis (PsA)]. A considerable number of patients with PsC have asymptomatic synovio-entheseal inflammations, and approximately one-third of those eventually progress to PsA with an enigmatic mechanism. Published studies have shown that early interventions to the very early-stage PsA would effectively prevent substantial bone destructions or deformities, suggesting an unmet goal for exploring early PsA biomarkers. The emergence of proteomics technologies brings a complete view of all involved proteins in PsA transitions, offers a unique chance to map all potential peptides, and allows a direct head-to-head comparison of interaction pathways in PsC and PsA. This review summarized the latest development of proteomics technologies, highlighted its application in PsA biomarker discovery, and discussed the possible clinical detectable PsA risk factors in patients with PsC.

**Keywords: psoriasis, psoriatic disease, psoriatic arthritis, proteomics, biomarkers**

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****Correspondence:***
*Yanling He*
*heyanlingdermatology@gmail.com*

*†These authors have contributed equally to this work*

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## INTRODUCTION

Psoriatic disease (PsD), as an umbrella term, describes a systemic inflammatory disease that predominantly affects the skin [cutaneous psoriasis (PsC)] and musculoskeletal features [psoriatic arthritis (PsA)], with ∼125 million patients worldwide (1, 2). The concept of PsD indicates the realization of the common inflammatory and metabolic pathways working on the skin and synovium (3). Although it is still controversial whether PsC and PsA shared the same immunological factors or belonged to the same spectrum of diseases, studies from genetic and proteomics confirmed the overlap between PsC and PsA (4–8).

Psoriatic arthritis is characterized by multiple joints stiffness, pain, and swelling with insidious onset (1, 9). Poor prognosis with debilitating joint destruction brings a tremendously negative impact on the life quality of all patients (10). It affects one in five people who have a psoriasis diagnosis, while only 15% of PsA cases get cutaneous lesions after arthritis onset (11, 12). After the initiation of psoriasis, the prevalence of PsA grows over time, hitting 20% after 30 years (13, 14). It is significant to identify patients who are at risk for PsA and enable targeting therapies to prevent and intercept the joint involvement at a very early stage of the psoriatic arthropathy (15, 16). A 6-month delay in joint destruction detection is linked to a significantly lower treatment response (17).

Psoriatic arthritis was strongly associated with nail, scalp, skinfold, elbow/knee involvement, the severity, early onset age, and total disease time of the cutaneous presentation (18–20). Symptoms like arthralgia in female psoriasis patients indicated a high chance of developing PsA (21). Although

not all PsO patients with joints pain have PsA, a longitudinal study confirmed that compared with psoriatic patients without joint complaints (PsO), those with arthralgia (PsOAr) were more likely to develop PsA in the subsequent follow-up period (22).

Psoriatic arthropathy, an early stage of joint involvement that may not fulfill the PsA diagnostic criteria, is more common than PsA in PsO patients (23). For those with asymptomatic joint abnormalities, early synovio-entheseal inflammation or bone erosion can be detected by imaging features like ultrasonography or MRI (24, 25). However, with these predictors, it is still hard to foresee the possibility of the transition to PsA (26). Unlike rheumatoid arthritis (RA), the absence of serum diagnostic biomarkers impedes the identification of very early PsA from PsC patients (8, 9, 27).

"Omic" technologies have achieved enormous progress in their development and application over the past decades, which provided an unprecedented opportunity to decipher the entire genes (genomics), mRNA (transcriptomics), proteins (proteomics), and metabolites (metabolomics) of a specific biological sample (28, 29). Notably, advances in proteomics have made it possible for the head-to-head comparisons of potential biomarkers in the heterogeneity of PsD (8, 30). The present article reviewed the latest development of proteomics technologies, summarized its application in PsA biomarker discovery, and discussed the possible clinical detectable PsA risk factors in PsC patients.

## RECENT DEVELOPMENTS IN PROTEOMICS TECHNOLOGIES

Proteome, as the ultimate goal for biomarker discovery, is the analysis of the whole protein materials of a disease or a biological sample, which offers possibilities to track the changes in protein expression under different conditions (31, 32). Present proteomic technologies could be addressed either as system-wide and unbiased tools such as antibody-based assay, aptamer-based assay, and mass spectrometry (MS) or a highly sensitive targeted immunoassay, such as the proximity extension assay (PEA) (33–35).

Mass spectrometry is a powerful and flexible instrument for characterizing proteins in their entirety (36–38). Of note, the introduction of high-throughput and high sensitivity protein identification and quantification methods to the single-cell proteomics and multi omics technologies help identify the candidate biomarkers in a protein-centric molecular way (29, 39–41). Ample studies have shown that the protein expression profile in the serum of patients with PsC or PsA can be illustrated *via* multiple MS approaches, including data-dependent methods (such as label-based, label-free, MuDPIT, and shotgun proteomics) and targeted data-independent approaches (such as SWATH and MSE, multiple reaction monitoring, phospho-, and ubiquitinoylation-targeted proteomics) (35, 42). Furthermore, an emerging concept of "proteogenomics" produced fused the insights of proteomic and genomic, in which genomic events, such as SNPs, mutations, insertions, deletions, and substitutions and be detected with a better understanding of its effects at the protein level (43–45). With the help of a series of peptide-to-spectra matches (PSM) by assigning fragment ion mass spectra to peptide sequences, which is similar to proteomics, proteogenomics query the search engines with a customized protein FASTA, which contain both genomes- and protein-modified sequence (46). More recently, an integrated proteomics pipeline (IPP) was established to combine a variety of search engines to improve the sensitivity of novel peptide identifications with a novel "cascade search" method, which maximizes the accuracy and reliability of new candidate biomarker discovery. The current proteogenomics application mainly focuses on precision oncology, which assists in differentiating the subtypes and relevant pathways of tumors (47–53). Although no studies have shown its application on rheumatic diseases, proteogenomics is now the primary suggestion for PsC/PsA biomarker discovery (2, 30).

Proximity extension assay is a novel technology with up to 96-plex immune assays invented by Olink Proteomics (Uppsala, Sweden), which consolidates quantitative real-time PCR (54, 55). It was based on a dual recognition of selected antibodies with which biomarker-specific DNA "barcodes" oligonucleotides were labeled. The unique DNA will be merged by high-throughput relative quantification microfluidic qPCR for up to 1,161 human proteins in the plasma (54, 55). Compared with LC-MS/MS, PEA covers a broader dynamic range with higher sensitivity, which provides sensitive and specific detection of low-abundant proteins in human blood and other body fluid samples (55–58). Moreover, PEA also tends to be less influenced by multiplex ELISA technical problems, such as antibody crossreactivity and interassay variability (59). PEA has been widely applied in non-clinical biomedical research to decipher minute protein concentrations in minute sample volumes. In contrast, current studies have seen more applications of PEA in exploring both diagnostic markers and inflammation key components (60, 61).

## PROTEOMICS IN POTENTIAL BIOMARKER DISCOVERY OF PSA TRANSITION

Identifying early asymptomatic PsA in patients with PsO has been recognized as a historically complex issue with no exact serum diagnostic biomarkers used in daily clinical practice (8). Proteomics is extensively adopted in biomarker exploration. The emergence of proteomic technologies allows deciphering the changes in protein expression under diseased conditions. The following session of this work will review the detected possible predictors that may indicate early preclinical and subclinical PsA under the novel proteomics technologies (62) (**Figure 1**).

### Proteomics in Peripheral Blood

Plasma and serum are extensively applied for proteomics-based biomarker discovery (63). Plenty of studies highlighted both PsA diagnostic and prognostic biomarkers with the help of MS proteomics technology (64). Serum proteome can also be obtained by PEA, an emerging technology previously explored in immune-mediated diseases of the skin, such as atopic dermatitis (65, 66). In a head-to-head comparison of serum biomarkers

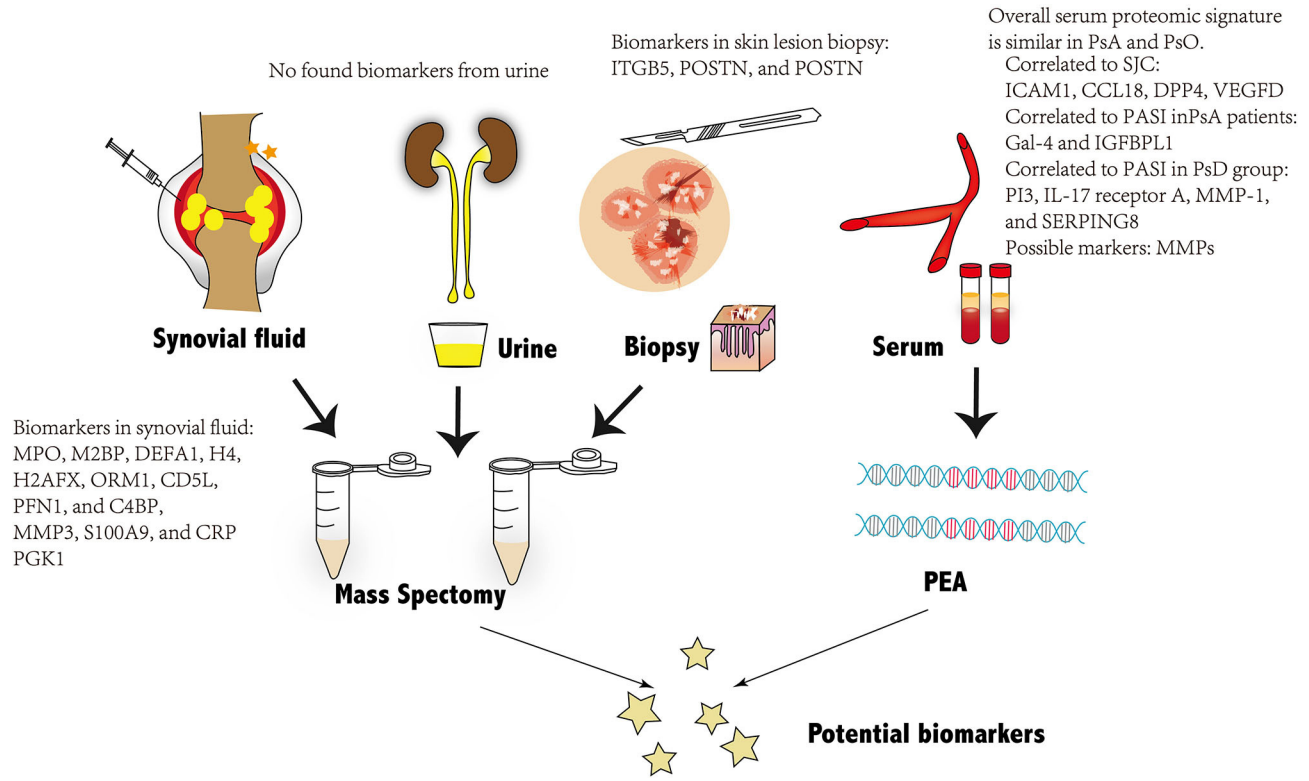


**FIGURE 1 |** Overview of the potential biomarkers of PsA found through proteomic technologies from four different kinds of biological samples: Biomarkers from synovial fluid and skin tissues are presented in the figure. No possible biomarkers are found from urine and serum. PsA, psoriatic arthritis; PEA, proximity extension assay.

between PsC and PsA, Leijten et al. chose a high-throughput serum biomarker platform (Olink) to evaluate the concentrations of 951 serum proteins in both patients with PsA and PsC. Although no biomarkers with a significant difference were found between PsC and PsA, PASI scores were found most strongly correlated to the proteins PI3, IL-17 receptor A, MMP-1, and SERPING8, when patients with PsA and PsO belonged to one group. When analyzing PsA patients as one group separately, PASI score was found correlated to Gal-4 and IGFBPL1. Four proteins including Intercellular adhesion molecule-1 (ICAM1), CC chemokine ligand 18 (CCL18), Dipeptidyl-peptidase 4 (DPP4), Vascular endothelial growth factor D (VEGFD), were found correlate to arthritis activity evaluated by swollen joint count (SJC), among which ICAM-1 and CCL18 were reported relevant to synovial tissue in rheumatoid arthritis activity. The swollen joint count (SJC) was identified, among which ICAM-1 and CCL18 were reported relevant to synovial tissue in RA, whereas VEGFD was proposed to participate in the pathogenesis of arthritis. DPP4 was only found to be related to type 2 diabetes mellitus rather than in arthritis development (8, 67–71).

It was found that there were 20 dysregulated proteins, which specially existed in the serum of patients with PsA, which showed at the normal range in the PsO group when compared with the health control (8). Though the published research suggested, it is difficult to find a simple diagnostic protein from the serum to discriminate patients with PsA from patients with PsO, there is still a scarcity of serum proteome with PEA technology, and the mentioned study was completed with a small number of samples. Besides the 11 selected platforms encompassing only inflammatory proteins, more proteins reflected bone turnover and tissue biological changes, such as matrix metalloproteinase (MMPs) (72).

Although human plasma is believed to be a feasible and less invasive source with a rich proteome, potential biomarkers secreted by the targeted tissues may be diluted in the blood with an undetectable concentration by current MS methods (73). In addition, many coexisting factors in the peripheral blood may interfere with the candidate soluble potential proteins. Thus, other biological samples, such as synovial fluid (SF) and skin, have drawn more interest to be analyzed (74). Besides, some authorities recommended a more specific method to finding serum markers after the proteomics of inflamed synovial biomarkers (75).

## Proteomics in Synovial Samples

Synovium is the primary affected site in most inflammatory arthritis (74). Many pathological modifications in inflamed synovial tissue are mirrored in the SF, which was more easily

accessible and widely studied (76). SF is a versatile source for proteins from the synovial membrane, cartilage, and plasma, depicting the pathophysiological issues that cause arthritis (77). A previously performed label-free MS quantitation of SF proteomics identified and verified 12 candidate PsA markers, including MPO, M2BP, DEFA1, H4, H2AFX, ORM1, CD5L, PFN1, and C4BP, as well as the top three upregulated proteins: MMP3, S100A9, and CRP (78). In another age-matched study, 10 SF samples from patients with PsA who were examined by using liquid chromatography-tandem MS quantitation revealed that Periostin (POSTN) and phosphoglycerate kinase 1 (PGK1) were upregulated with folded ratio compared with healthy controls (79). Although both studies showed a promising direction in SF proteome, no available data compared SF biomarkers between PsA and PsC samples.

The acquisition of SF is more feasible than synovial tissue, but it is undeniable that SF sometimes provides only indirect biomarkers (80). In the study of RA, the analysis of synovial tissue samples offered great insights into both epigenetic and proteomic changes in patients with very early-stage RA. Therefore, synovial tissue might also be helpful and become a more precise target source in investigating PsA (74, 81).

## Proteomics in Skin Lesion Biopsy

Skin manifestations, which include psoriasis Vulgaris or plaque psoriasis, were strongly associated with PsA (82). One hypothetical model for PsA transition was a systematic expansion of inflammation from the skin to synovio-entheseal tissues (62, 83). Factors that caused cutaneous diseases in the skin were released to promote a systemic dysregulated immune-mediated response and to develop musculoskeletal lesions after a second hit, such as trauma, infection, etc. (84, 85). Hence, it is of great need to explore the skin proteome in patients with PsA and PsC. Label-free quantitation of skin proteins verified 47 different peptides between samples in the two groups. After validation in serum by ELISA, integrin β5 (ITGB5), a group of transmembrane receptors function on cell adhesion, increased significantly in the PsA group when compared with the PsC group. Besides POSTN, a secreted extracellular matrix protein originally derived from the osteoblasts, was believed as a potential serum biomarker with a slightly higher concentration in PsA patients than in PsC patients (86). Another latest research using isobaric tags for relative and absolute quantitation (iTRAQ), a labeled MS technology, found 2-5-oligoadenylate synthase levels in both serum and psoriatic epidermis that were positively correlated with the severity of psoriasis through PASI and BSA (87, 88). As some data suggest, severe psoriasis can account for another cutaneous feature with a higher risk and prevalence of psoriatic arthropathy. The plasma membrane ATPase (derived from the OSA2 gene) might become another possible predictor for early joint inflammations in psoriatic patients (89, 90). Although these results are promising, limitations such as small sample numbers and the absence of further repetitive investigations in skin proteome impede the uncover of candidate PsA biomarkers, as well as the understanding of the underlying mechanism. There is no published research involving synovial tissue proteome in patients with PsA or PsC. Farnebo et al. performed MS analysis on a rabbit tendon injury model to compare protein expression in intrasynovial tendon grafts and extra synovial tendon grafts, which offered a possible substitute for the hard-to-access human samples (91).

## Proteomics in Urine

Urine is another excellent source for both systemic and renal inflammatory biomarker exploration for its non-invasive sample collection approach as well as the low dynamic analytes range (92). Most proteins identified in urine are filtered from the plasma or generated by inflammatory renal cells, contributing to a relatively small number of proteins appearing in the urine in patients with normal kidney function (93). Meanwhile, active proteases in the urine limit the degradation of biomarkers, leading urinary proteomics with MS-based analysis to become one of the most attractive directions in disease biomarker discovery (94, 95). Most published literature utilized urine proteome as a target for detecting biomarkers to kidney and cardiovascular diseases, with only a few describing urine proteomics technologies on inflammatory arthritis (64, 96, 97). In research exploring urine biomarkers in four different arthritis [RA; PsA; osteoarthritis (OA); and inflammatory bowel diseases (IBD)], 50 most significant peptides, including 80% specific for one group only, and a minor overlap were found through urinary proteomics (98). However, the most detectable peptide markers in this study were collagen fragments previously derived from proteins functionally different from arthritis, which may be due to the filtration of the glomerulus or the limited uncovered nature of the peptides in the urine (98). The result indeed showed the potent application of urine proteomics and peptidomics in the future (99). More longitude cohort studies in a large number of samples should be carried out in the future.

# CONCLUSION

Over the past two decades, PsD is gradually considered a systematic inflammation that causes multiple associated comorbidities across the body rather than a simple disease cutaneous lesion (100). The emergence of skin presentation of psoriasis offers a unique opportunity for early management for those at high-risk systematic progression (101). Although existing reviews have already pointed out that imaging methods, such as ultrasound and MRI, can also become a valuable method to detect early the inflammatory lesions of joints, the expensive costs of exam fees and related equipment, and the long waiting time are limitations. Examination time and hard-interpreted imaging results for non-professional clinicians were all hurdles that hamper the prevalence of application on imaging examinations on patients with PsC (22, 25, 102). Consequently, a fast exam kit with an accessible kit becomes more necessary, suggesting an imperative need to explore a possible biomarker. The immense development and utilization in proteomics have provided an extraordinary chance to detail the molecular and mechanistic understanding of PsD pathways, decode the potential biomarkers, and investigate more effective intervention therapies (103, 104).

This review summarized the current approaches applied in the early PsA proteome. Compared with the traditional LC-MS/MS methods in proteogenomics, PEA provides more sensitive and specific detection for a more considerable range of low-abundant proteins in human blood and other body fluid samples (55–58). However, the need for the custom panel of biomarkers also restricted the exploration of the unknown proteins. Only a few studies that focused on psoriatic arthropathy finished their study with PEA technology. It highlighted the great need to perform high-throughput analyses in serum and tissues and other possible samples to discover PsA precursors. The future work on performing extensive integrative analysis will be undoubtedly challenging. Still, the increasing recognition of human proteome and consistent progression on proteomics technologies will become the most supportive foundation for challenging tasks.

## AUTHOR CONTRIBUTIONS

YH: did the project administration, conceptualization, and methodology. FQ and YT: did the investigation and formal analysis. FQ, YT, AY, and XY: offered the resources. FQ wrote the original draft. YT: reviewed and edited the draft. YH: visualized the whole project and supervised the whole project. All authors contributed to the article and approved the submitted version.

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REVIEW
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# The Role of Glutathione-S Transferase in Psoriasis and Associated Comorbidities and the Effect of Dimethyl Fumarate in This Pathway

*Elena Campione[1]*, Sara Mazzilli[2], Monia Di Prete[3,4], Annunziata Dattola[1], Terenzio Cosio[1], Daniele Lettieri Barbato[5,6], Gaetana Costanza[7], Caterina Lanna[1], Valeria Manfreda[1], Ruslana Gaeta Schumak[1], Francesca Prignano[8], Filadelfo Coniglione[9], Fabrizio Ciprani[2], Katia Aquilano[5] and Luca Bianchi[1]*

[1] Dermatology Unit, University of Rome Tor Vergata, Rome, Italy, [2] Italy State Police Health Service Department, Ministry of Interior, Rome, Italy, [3] Anatomic Pathology Unit, University of Rome Tor Vergata, Rome, Italy, [4] Anatomic Pathology, Santa Maria di Ca' Foncello Hospital, Treviso, Italy, [5] Department of Biology, University of Rome Tor Vergata, Rome, Italy, [6] Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione Santa Lucia, Rome, Italy, [7] Virology Unit, University of Rome Tor Vergata, Rome, Italy, [8] Unit of Dermatology, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy, [9] Department of Surgical Sciences, University Nostra Signora del Buon Consiglio, Tirana, Albania

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***Correspondence:**
*Elena Campione*
*elena.campione@uniroma2.it*

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Psoriasis vulgaris is a chronic inflammatory skin disease characterized by well-demarcated scaly plaques. Oxidative stress plays a crucial role in the psoriasis pathogenesis and is associated with the disease severity. Dimethyl fumarate modulates the activity of the pro-inflammatory transcription factors. This is responsible for the downregulation of inflammatory cytokines and an overall shift from a pro-inflammatory to an anti-inflammatory/regulatory response. Both steps are necessary for the amelioration of psoriatic inflammation, although additional mechanisms have been proposed. Several studies reported a long-term effectiveness and safety of dimethyl fumarate monotherapy in patients with moderate-to-severe psoriasis. Furthermore, psoriasis is a chronic disease often associated to metabolic comorbidities, as obesity, diabetes, and cardiovascular diseases, in which glutathione-S transferase deregulation is present. Glutathione-S transferase is involved in the antioxidant system. An increase of its activity in psoriatic epidermis in comparison with the uninvolved and normal epidermal biopsies has been reported. Dimethyl fumarate depletes glutathione-S transferase by formation of covalently linked conjugates. This review investigates the anti-inflammatory role of dimethyl fumarate in oxidative stress and its effect by reducing oxidative stress. The glutathione-S transferase regulation is helpful in treating psoriasis, with an anti-inflammatory effect on the keratinocytes hyperproliferation, and in modulation of metabolic comorbidities.

**Keywords: comorbidities, dimethyl fumarate, glutathione-S-transferase, psoriasis, pathway**

## INTRODUCTION

Psoriasis vulgaris is a chronic inflammatory skin disease characterized by well-demarcated erythema and scaly plaques. It is reported that an enhanced oxidative stress is associated with the severity of psoriasis (1). Karabowicz et al. investigated the intensity of oxidative stress and the expression and activity of the proteasomal system, as well as the autophagy, responsible for the degradation of oxidatively modified proteins in the blood cells of patients with psoriasis (2). Oxidative-antioxidant system plays a crucial role in the psoriasis pathogenesis (3). Numerous studies reveal significantly increased levels of oxidative stress markers, as malondialdehyde, nitric oxide end products, and 8-hydroxy-2′ -deoxyguanosine in the plasma of psoriatic patients. Meanwhile, a decreased total antioxidant capacity, reduced vitamin A and E levels, and a diminished activity of the main antioxidant enzymes were also detected in these patients (4). The antioxidant system involved in oxidative stress reduction is constituted by the glutathione-S transferase (GST). An increased reactive oxygen species (ROS) and insufficient antioxidant activity have been detected in psoriatic lesions (5). Pro-inflammatory cytokines are involved in redox skin balance perturbation in patients with psoriasis (3). Dimethyl fumarate (DMF) and its metabolite monomethyl fumarate (MMF) modulate some signaling proteins activity and intracellular concentration, such as the nuclear factor (erythroid-derived 2)-like 2 (Nrf2), nuclear factor-kappa B (Nf-κB), and cyclic adenosine monophosphate. Some studies showed that DMF can also affect the hypoxia-inducible factor-1 alpha. These actions seem to be responsible for i) the downregulation of inflammatory cytokines and ii) an overall shift from a pro-inflammatory (Th1/Th17) response to an anti-inflammatory/regulatory (Th2) response. Both steps are necessary for the amelioration of psoriatic inflammation, although additional mechanisms have been proposed. There is a growing body of evidence to support the notion that DMF/MMF may also exert effects on granulocytes and non-immune cell lineages, including keratinocytes and endothelial cells. A better understanding of the multiple molecular mechanisms involved in the cellular action of fumaric acid esters (FAEs) will help to adapt and to further improve the use of such small molecules for the treatment of psoriasis and other chronic inflammatory diseases (6). Superoxide dismutase (SOD) and glutathione peroxidase (GP) activity in erythrocytes are involved in the psoriasis onset (7). Imbalance in the oxidant-antioxidant system in psoriasis is involved. The DMF is considered as a prodrug, after oral administration, rapidly hydrolyzed by esterases in the small intestine and converted to MMF representing an intermediate of tricarboxylic acid cycle (TCA) (7). This molecule has been successfully used in psoriasis treatment for more than 40 years. Several clinical trials have demonstrated the FAEs efficacy in this role (6, 8). In 1994, a mixture of MMF and DMF (Fumaderm®) was approved for the oral treatment of psoriasis in Germany, Switzerland, and Austria (9). In 2019, DMF was approved for the treatment of mild-to-moderate plaque psoriasis. Several studies reported a long-term effectiveness and safety of DMF monotherapy in patients with moderate-to-severe psoriasis (9). In humans, people with polymorphisms in GST genes were described to be susceptible to various disorders, including psoriasis (10, 11), coronary artery diseases (12), chronic obstructive pulmonary diseases (13), rheumatoid arthritis (14), or neoplastic diseases, as breast, esophageal, and gastric cancers (15, 16). Furthermore, psoriasis is a chronic disease often associated with metabolic comorbidities, as obesity, diabetes, and cardiovascular diseases, wherein GST deregulation is present (17). Environmental and genetic risk factors have been implicated in obesity etiopathology (18). Also, the oxidative stress could lead to obesity, and the related comorbidities, by promoting a white adipose tissue deposition (19). Several *in vitro* studies documented that an increased oxidative stress and an ROS could augment adipocyte proliferation, differentiation, and growth (20–22), and control hunger and satiety behaviors (23). Interestingly, there is a mutual relation between oxidative stress and obesity, as abnormal fat accumulation can stimulate a pro-inflammatory and a pro-oxidant state through various biochemical and cellular mechanisms (24–26). The GST, which removes the electrophilic compounds, including the lipid peroxidation products, showed a white adipose tissue-specific downregulation (26). Additionally, the antioxidant enzyme activities of GP and superoxide dismutase were reported to be dysregulated in red blood cells and serum of obese individuals compared to controls (27, 28). Enzyme-converting glutathione is constitutionally expressed by keratinocytes (29). An increase of GST activity in psoriatic epidermis in comparison with uninvolved and normal epidermal biopsies has been reported. The DMF depletes glutathione by formation of covalently linked conjugates. Consequently, oxidized glutathione is converted to a reduced glutathione and is also depleted by DMF (30). The GST includes glutathione enzyme catalyzing conjugation with various hydrophobic compounds (29). Many data evaluated the role of conjugating activity of hydrophobic molecules, such as bilirubin and hematin linkage and selenium-independent GP activity, toward organic hydroperoxides in the oxidative stress cycle (31).

This review investigates the anti-inflammatory role of DMF in oxidative stress and its effect by reducing ROS through glutathione modulation. The GST regulation is helpful in treating psoriasis, with anti-inflammatory effect on the keratinocytes hyperproliferation and in modulation of metabolic comorbidity.

## DMF ANTIOXIDANT ACTIVITY

Dimethyl fumarate (DMF) is considered a prodrug as, after oral administration, it is rapidly hydrolyzed by esterases in the small intestine and converted to MMF (32). The MMF is highly bioavailable and is rapidly hydrolyzed inside cells to fumaric acid, which in mitochondria, represent an intermediate of TCA (33, 34). It is mostly believed that DMF exerts its therapeutic effects through antioxidant and anti-inflammatory pathways (**Figure 1**). Both MMF and fumarate are believed to be responsible for the primary therapeutic effects of DMF through activation and inhibition of the transcription factors, Nrf2 (35, 36) and Nf-κB (37), respectively. It has been well-described that DMF activates the Nrf2 signaling pathway through the

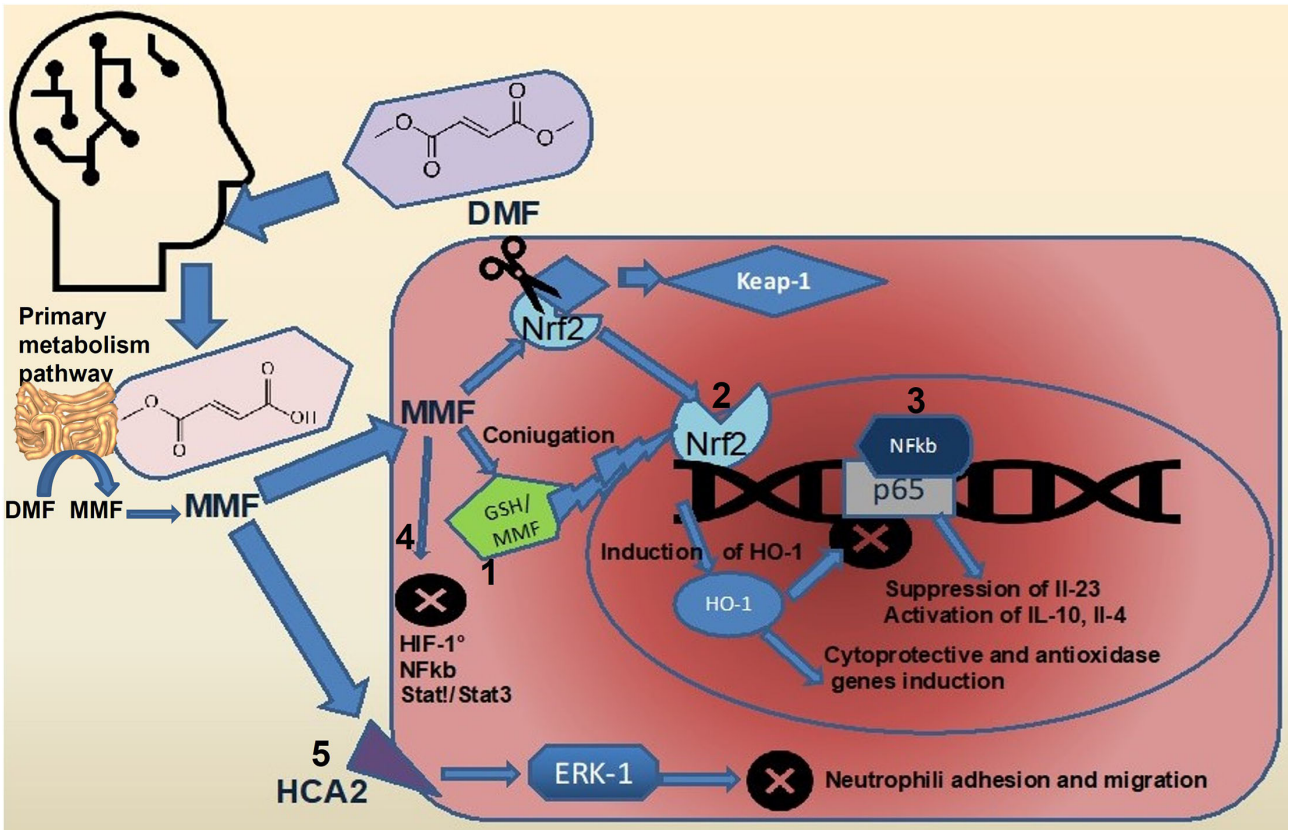


**FIGURE 1 |** Effects of DMF on intracellular signaling pathways. Upon ingestion, most of the DMF (about 90%) is rapidly converted to MMF by hydrolization in the small intestine (5). The full pharmacokinetic profile of DMF and MMF remains to be elucidated. DMF, dimethyl fumarate; MMF, monomethil fumarate; FAEs, fumaric acid esters; GP, glutathione peroxidase; GST, glutathione-S transferase; NF-kappaB, nuclear factor-kappa B; Nrf2, nuclear factor (erythroid-derived 2)-like 2; ROS, reactive oxygen species; and TCA, tricarboxylic acid cycle.

electrophilic modification of Kelch-like ECH-associated protein 1 (35). The DMF exerts its immuno-modulatory activity also *via* the agonism of the hydroxycarboxylic acid receptor 2 (38). Such important mechanisms, nonetheless, fail to fully account for the *in vitro* and *in vivo* immunologic actions of DMF (39). Recent evidence has suggested that modulation of innate and adaptive immune processes is Nrf2 independent (40). Some of the neuro-protective effects seen with this drug are secondary to its anti-inflammatory and antioxidant actions and appear to rely on the modulation of cellular metabolism. Accordingly, a short-term DMF treatment of an oligodendrocyte cell line did not prevent a hydrogen peroxide-mediated death, and a DMF treatment in a model of toxic demyelination was not able to prevent demyelination (41). Importantly, methylated esters of TCA intermediates, such as DMF, are cell permeable and can modify the activity of this pathway by increasing the level of metabolic intermediates' proximate to fumarate. In the TCA, succinate is oxidized to fumarate and then hydrated to malate through the activity of two enzymes, succinate dehydrogenase, and fumarase. Administration of DMF *in vitro* causes a rise in the concentration of succinate (42, 43). Prolonged treatment with DMF in a human oligodendrocyte cell line elicited increases in both succinate and fumarate (44). This event is associated with augmented lipid synthesis, thus, preserving mature oligodendrocytes viability, and protecting myelin through the modulation of cellular lipid metabolism. These data were confirmed *in vivo* by using global metabolomics profiling of blood plasma of patients with relapsing-remittent multiple sclerosis treated for 6 weeks with DMF. Significant changes in TCA intermediates fumarate and succinate, and in the secondary TCA metabolites succinyl-carnitine and methyl succinyl-carnitine were observed, arguing that the potential anti-inflammatory properties of these metabolites are mediated by metabolic rewiring. Interestingly these changes were not observed in the control population (45). A metabolic switch toward aerobic glycolysis is mandatory for immune cells activation. Impinging a metabolic rewiring toward mitochondrial oxidative metabolism is considered a valid strategy to counteract the inflammatory process in immune diseases (46). The DMF was shown to covalently modify protein cysteine residues in a process termed succinylation. In activated myeloid and lymphoid cells, DMF was able to downregulate aerobic glycolysis *via* the succinylation and inactivation of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase, thereby inhibiting the autoimmune response (47). Immune

cell activation also depends on calcium signaling. Among the proposed mechanisms for the immunoregulatory role of DMF, the rise of intracellular calcium is also included. In particular, DMF promotes an immediate extracellular calcium influx, long-term increase of cytosolic calcium, and reduced intracellular calcium storage. Upon DMF treatment, the glutathionylation of a cysteine of sarco/endoplasmic reticulum $Ca^{2+}$-ATPase SERCA2b is critical to the modulation of intracellular calcium concentration. The SERCA2b is downregulated but more active due to glutathionylation of the redox-sensitive cysteine. A net increase of cytosolic calcium due to a diminished calcium storage is, therefore, obtained (48). Fumarate also functions as an immuno-modulator by controlling chromatin modifications. Fumarate can also rewire the epigenetic landscape of the cells through inhibiting either histone or DNA demethylases. Fumarate accumulation has been demonstrated in activated immune cells, and this event inhibits KDM5 histone demethylase activity, thus, promoting the transcription of promoters of TNF-α and IL-6 cytokines (49). Upon DMF treatment, different proteins in T cells are susceptible to covalent modifications of cysteines. Protein kinase C θ modification avoids its association with the co-stimulatory receptor CD28, preventing a T-cell activation (50). Besides such immuno-modulatory actions, DMF has an important antioxidant activity; the way by which it reduces oxidative stress is very peculiar. Actually, it scavenges the major intracellular non-enzymatic thiol antioxidant glutathione (51–54), likely, *via* the immediate formation of glutathione-DMF adducts (55), and this results in the stabilization and in the raise of Nrf2. Nrf2 then translocates into the nucleus and binds to antioxidant response elements in the promoter region of several antioxidant genes, such as heme-oxygenase-1 and NADPH-quinone-oxidoreductase-1. This, in turn, increases the intracellular concentration of glutathione (35, 56), making the cell more resistant to oxidative stress. However, DMF is able to raise glutathione levels also when the rate-limiting enzyme of glutathione synthesis, i.e., glutamate-cysteine ligase, is inhibited, thanks to the Nrf2-mediated induction of glutathione reductase that enhances the molecule recycling (57).

## THE ROLE OF GLUTATHIONE AND DMF IN PSORIASIS

Several studies have demonstrated that glutathione binding to DNA is able to regulate Nf-κB proinflammatory activity. In particular, the Nf-κB complex and the upstream proteins, as TRAF6, are negatively regulated by glutathione (58). Genetic polymorphisms affecting GST produce a decrease in intracellular concentration of glutathione, with consequent raising of skin inflammation, as seen in atopic and allergic dermatitis, psoriasis, lichen planus, urticaria, and vitiligo (59–62).

Glutathione plasmic levels and GP activity in patients with psoriasis were significantly lower than in general population (63). Consequently, GST activity reduction leads to the accumulation of ROS in inflamed lesions, as it was reported in psoriatic plaques, where ROS levels are 3-fold higher than in non-lesioned skin (64). The DMF action in this context is not yet completely clear. It irreversibly binds the glutathione in a 1:1 ratio, decreasing its production and favoring its excretion through urine as glutathione-DMF adducts (65). In this way, fumarate compounds influence cellular redox state, affecting intracellular signaling pathways (66).

Glutathione intracellular depletion in human antigen-presenting cells causes IL-10 production, with immuno-modulatory action, instead of the pro-inflammatory cytokines IL-12 and IL-23, responsible for Th1/Th17 immune system response switch in psoriasis. In this context, DMF promotes Th2 cell differentiation, with immunoregulatory functions (67).

In summary, the rationale of employing DMF in psoriasis consists in reducing cellular inflammation both by decreasing glutathione intracellular levels and by inducing a switch in immune response toward an anti-inflammatory/immunoregulatory setting (68, 69). European guidelines recommend FAEs in induction and long-term therapy of moderate-to-severe plaque psoriasis (70). With more than 220,000 patients per year treated with FAEs, Germany has been one of the first nations in Europe to adopt this systemic therapy for psoriasis (71), but also other countries, like Italy, are aligned with European guidelines (7). The recommendation in the treatment with DMF is to begin with a low dose followed by gradual increases. This flexible approach is tailored on the need of each patient, and the most used regimen is between 240 mg and 480 mg of DMF per day. Several randomized clinical trials have demonstrated efficacy and safety of FAEs in psoriasis. At week 16 of the phase III, randomized, BRIDGE study, PASI 75 was reached by more than one third of patients enrolled (8), while in the large retrospective FUTURE study it was demonstrated a mean reduction of 79% in PASI from baseline (72). Combination of topical treatments, biological agents, or phototherapy to FAEs in the induction phase showed to reach a faster response (73–75). The FAEs are also characterized by a mild spectrum of side effects, including gastrointestinal disorders and flushing during the treatment, which are not responsible for therapy discontinuation. Among the others, the most important is lymphopenia, which is, generally, of a mild entity and experienced during induction or when it is necessary to increase the dose regimen. It is necessary in such cases to adjust the dosage at the higher tolerance. Treatment discontinuation is required only in rare cases to minimize opportunistic infections' risk (76).

## THE ROLE OF SMALL MOLECULES IN THE METABOLIC SYNDROME

Patients with psoriasis are characterized by a higher prevalence of cardiovascular disease and metabolic syndrome (77). In particular, visceral fat has a critical role in the development of cardiovascular disease in patients with psoriasis, including coronary arteries disease, heart infarction, stroke, and related mortality. Moreover, the inflammatory background of the patients with psoriasis both increases and accelerates the atherosclerosis (77). Small molecules, as the phosphodiesterase-4 inhibitor apremilast, approved for the treatment of adults with

moderate-to-severe plaque psoriasis and/or psoriatic arthritis, have demonstrated a broad anti-inflammatory activity, which may influence metabolism (17, 78). It has been demonstrated that liver steatosis is reduced by limiting the fat deposition and increasing lipolysis (17). The patients with diabetes reached better results in terms of psoriasis response when treated with apremilast. Moreover, it was observed as a better control of serum glucose levels, a significant reduction of insulin resistance and cholesterol levels, and the restoration of endothelial function, which are all factors strongly associated with propensity to cardiovascular diseases. Finally, apremilast also decreases the systemic inflammatory status of patients with psoriasis, decreasing TNF-α, IFN-γ, IL-12, and IL-23 production (17). As an apremilast, DMF also exhibits strong anti-inflammatory and immunomodulatory effects and was tested in a laboratory to evaluate its role in ameliorating basal inflammation and metabolic disturbances (79). Compared to control rats, those treated with FAEs showed lower levels of C-reactive protein, IL-6, and TNF-α. Moreover, it was demonstrating less fat accumulation, with lower visceral fat weight in liver and muscles. These results suggest the potential crucial role of DMF, as an apremilast, in the treatment of patients with psoriasis with concurrent metabolic comorbidities, which are probably the largest part.

## AUTHOR CONTRIBUTIONS

Conceptualization was contributed by EC, SM, MD, AD, TC, DL, GC, CL, VM, RG, FP, FCo, KA, and LB. Methodology was contributed by EC, MD, AD, TC, DL, GC, CL, VM, RG, FP, FCo, FCi, KA, and LB. Validation was contributed by EC, SM, MD, TC, DL, GC, CL, VM, RG, FP, FCo, FCi, KA, and LB. Formal analysis was contributed by EC, SM, MD, AD, DL, GC, CL, VM, RG, FP, FCo, KA, and LB. Investigation was contributed by EC, SM, MD, AD, TC, GC, CL, VM, RG, FP, FCo, KA, and LB. Resources was contributed by EC, SM, MD, AD, TC, DL, CL, VM, RG, FP, FCo, KA, and LB. Data curation was contributed by EC, SM, MD, AD, TC, DL, GC, VM, RG, FP, FCo, KA, and LB. Writing—original draft preparation was contributed by EC, SM, MD, AD, TC, DL, GC, CL, RG, FP, FCo, KA, and LB. Writing—review and editing were contributed by EC, SM, MD, AD, TC, DL, GC, CL, VM, FP, FCo, FCi, KA, and LB. Visualization was contributed by EC, SM, MD, AD, TC, DL, GC, CL, VM, RG, FCo, KA, and LB. Supervision was contributed by EC, SM, MD, AD, TC, DL, GC, CL, VM, RG, FP, FCi, KA, and LB. Project administration was contributed by EC, SM, MD, AD, TC, DL, GC, CL, VM, RG, FP, FCo, and LB. All authors approved the submitted version and agreed to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

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REVIEW
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# Novel Therapeutic Target(s) for Psoriatic Disease

*Vishal Thakur and Rahul Mahajan**

*Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Psoriasis and psoriatic arthritis, together known as psoriatic disease, is highly prevalent chronic relapsing inflammatory disease affecting skin, joints or both and is associated with several comorbidities such as cardiovascular, metabolic, psychiatric, renal disease etc. The etiopathogenesis of psoriasis is complex and mainly driven by aberrant immune response owing to the genetic susceptibility and various environmental factors such as trauma, infections and drugs. Recent advances in understanding molecular and cellular pathways have identified tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), IL-23, IL-22 as major contributors in psoriasis pathogenesis. Advances in the knowledge of pathophysiology, the interaction of autoinflammation and clinical phenotypes have led to the development of highly effective targeted therapeutic agents which include TNF-α, IL-17, IL-23, IL-1 α/β or IL-36 inhibitors or receptor blockers, small molecule drugs like phosphodiesterase-4 inhibitors (apremilast), Janus kinase (JAK) inhibitors, retinoic acid receptor-related orphan receptor γt (RORγt) inhibitors. These novel drugs have promised the potential of improved disease control. In recent years, the transition from biologics to biosimilars especially with TNF-α inhibitors had significant impact on decreasing health care cost and increasing therapeutic options to the patients. However, selection of right treatment for an individual patient still remains challenging. Moreover, interplay between different epigenetic mechanisms such as the DNA methylation, chromatin modifications and noncoding RNA regulation has recently been started to be deciphered. Enzymes inhibitors involved in epigenetic pathways such as DNA methyltransferases and histone deacetylases demonstrated to restore normal epigenetic patterns in clinical settings and have provided the potential as novel therapeutic targets for psoriasis. In this review, we will discuss novel biologic agents and newer therapeutic approaches in treatment of psoriatic disease.

**Keywords: psoriasis, psoriatic arthritis, infliximab monotherapy, autoimmune hepatitis, treatment, biologics and biosimilars, small molecule**

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***Correspondence:**
*Rahul Mahajan*
*drrahulpgi@yahoo.com*

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## INTRODUCTION

Psoriatic disease is a chronic relapsing inflammatory condition affecting ∼2–3% of population (1, 2). Psoriatic disease consists of psoriasis vulgaris affecting skin and psoriatic arthritis affecting joints. Psoriasis affects patients' quality of life significantly and have tremendous psychosocial burden among patients (3). The immunopathogenesis of psoriasis is complex primarily driven by an aberrant immune response further modified by an interplay between genetic susceptibility

and environmental factors. The inflammatory events lead to systemic inflammation resulting in cardiovascular, metabolic and renal disease and increased morbidity (4). In last few years, advances in understanding molecular and cellular pathways have identified tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), IL-23, IL-22 as major contributors in psoriasis pathogenesis (5). This has led to the development of highly effective targeted therapeutic agents which include TNF-α, IL-17, IL-23, IL-1 α/β or IL-36 inhibitors or receptor blockers, small molecule drugs like phosphodiesterase-4 inhibitors (apremilast), Janus kinase (JAK) inhibitors, retinoic acid receptor-related orphan receptor-γT (RORγT) inhibitors (5). **Figure 1** shows the pathogenesis and various therapeutic targets in psoriatic disease. These novel drugs have promised the potential of improved disease control. In this review, we will discuss novel therapeutic targets in the management of psoriatic disease.

## JAK INHIBITORS

The Janus Kinase–Signal Transducer and Activator of Transcription (JAK–STAT) pathway plays an important role in intracellular signaling in various physiological and pathological processes in inflammatory disorders including psoriasis. Cytokines implicated in psoriasis pathogenesis mainly IL-17, IL-23, TNF-α, IL-1, IL-22, IFN-α and IFN-γ are linked to JAK-STAT pathway (6, 7). Upon interaction of various cytokines with their respective receptor, activation of JAK leads to phosphorylation of STAT proteins and nuclear translocation resulting in gene expression (8). In psoriasis, increased expression and upregulation of STAT1 and STAT3 have been demonstrated in the lesional skin (9, 10). STAT1 and STAT3 are involved in the activation of dendritic cells and differentiation of Th1 and Th17 cells (9, 10). STAT3 also leads to the keratinocyte proliferation mediated through IL-19, IL-36 and IL-22 (11). IFN-γ secreted from keratinocytes leads to the migration of inflammatory cells from the lymphoid tissue to the skin (10).

Various JAK inhibitors have been used in psoriatic disease with good efficacy, of which Tofacitinib, an oral JAK1/3 inhibitor, has been extensively studied in phase II and III trials (6). In phase III studies, a significant proportion of patients achieved PASI75 at weeks 12 or 16 showing greater efficacy with higher doses i.e., 10 mg twice daily (12). Studies evaluating the efficacy after treatment withdrawal also showed higher efficacy as compared to placebo (13). In another study, 74.1 and 79.4% of patients receiving tofacitinib 5 mg twice daily and 10 mg twice daily respectively, maintained the response at 52-weeks (14). Tofacitinib has shown significantly better efficacy and safety in psoriatic arthritis as compared to placebo (15, 16). A topical formulation of tofacitinib has also been developed and used in plaque psoriasis with modest efficacy (17). Common adverse effects include cytopenia and infections (6, 18). Safety concerns especially dose-dependent (i.e., 10 mg twice daily) risk of herpes zoster, higher chances of infections, gastric perforation and thromboembolic events has been raised (6, 18), although long-term studies with larger samples are needed. Due to these safety concerns, tofacitinib was not approved for psoriasis by FDA, however it is approved for use in psoriatic arthritis (6).

Baricitinib, an oral highly selective JAK1 and JAK2 inhibitor has also been studied in patients with moderate-to-severe psoriasis in Phase II trials and has shown better efficacy as compared to placebo at doses 8 mg and 10 mg (19). Adverse effects included anemia, cytopenia and increase in creatinine levels (6). Similar safety concerns have been raised with baricitinib, thus, it is approved for use in rheumatoid arthritis only.

Ruxolitinib, another JAK1 and JAK2 inhibitor, has been developed as topical cream and studies in psoriasis showed a better efficacy and safety profile compared to vehicle and Non-inferior to calcipotriol-betamethasone combination (17). Other JAK1/2 inhibitors such as itacitinib (20), abrocitinib (21), solcitinib (22) and filgotinib (23) have shown efficacy in phase II trials in psoriasis and psoriatic arthritis. Peficitinib, an oral pan-JAK inhibitor with JAK3 selectivity, showed a good efficacy in psoriasis in phase IIa trial with no major adverse events (24).

## IL-23

IL-23, a cytokine of IL-12 family, consists of two subunits: p19 (unique for IL-23) and p40 that is common with IL-12 (25). IL-23 is mainly produce by dendritic cells and macrophages (26, 27). Initially, antibodies targeting p40 subunit of IL-12 were found effective in psoriasis as these neutralized IL-23 also (27). Later on, increased expression of p19 and p40 was found in psoriatic lesions while p35 that is specific to IL-12 was normal which suggested that IL-23 not IL-12 is an important cytokine involved in the psoriasis pathogenesis (26). IL-23 binds to its heterodimeric receptor leading to the activation of Janus kinases (Jak) and further activation of STAT3 (28). IL-23 leads to the production of cytokines from Th-17 cells i.e., IL-17, a major cytokine implicated in the pathogenesis of psoriasis (28). This led to development of anti-IL23 biologics in the therapeutics of psoriatic disease. As these agents target upstream cytokine involved in the psoriasis pathogenesis, dosing interval of longer duration is an advantage as compared to the downstream cytokines such as IL-17 and TNF-α (29). Currently, ustekinumab, guselkumab, tildrakizumab, and risankizumab are FDA approved for psoriasis vulgaris and only ustekinumab and guselkumab have been approved by the FDA for psoriatic arthritis (29). IL-23 inhibitors have shown superior efficacy to conventional agents and TNF-α inhibitors. A network metanalysis found guselkumab and risankizumab more effective than tildrakizumab (30). The IL-23 inhibitors have been found to be more effective in maintaining remission as compared to other drugs even after drug discontinuation. In PHOENIX 1 trial of ustekinumab, median time to loss of PASI-50 was ∼22 weeks from the last dose of drug (31). Similar results have been observed with other IL-23 inhibitors including guselkumab, tildrakizumab and risankizumab, showing sustained improvement in disease after drug discontinuation (32–34). The efficacy of IL-23 inhibitors especially ustekinumab and guselkumab in psoriatic arthritis was also found significantly high as compared to placebo

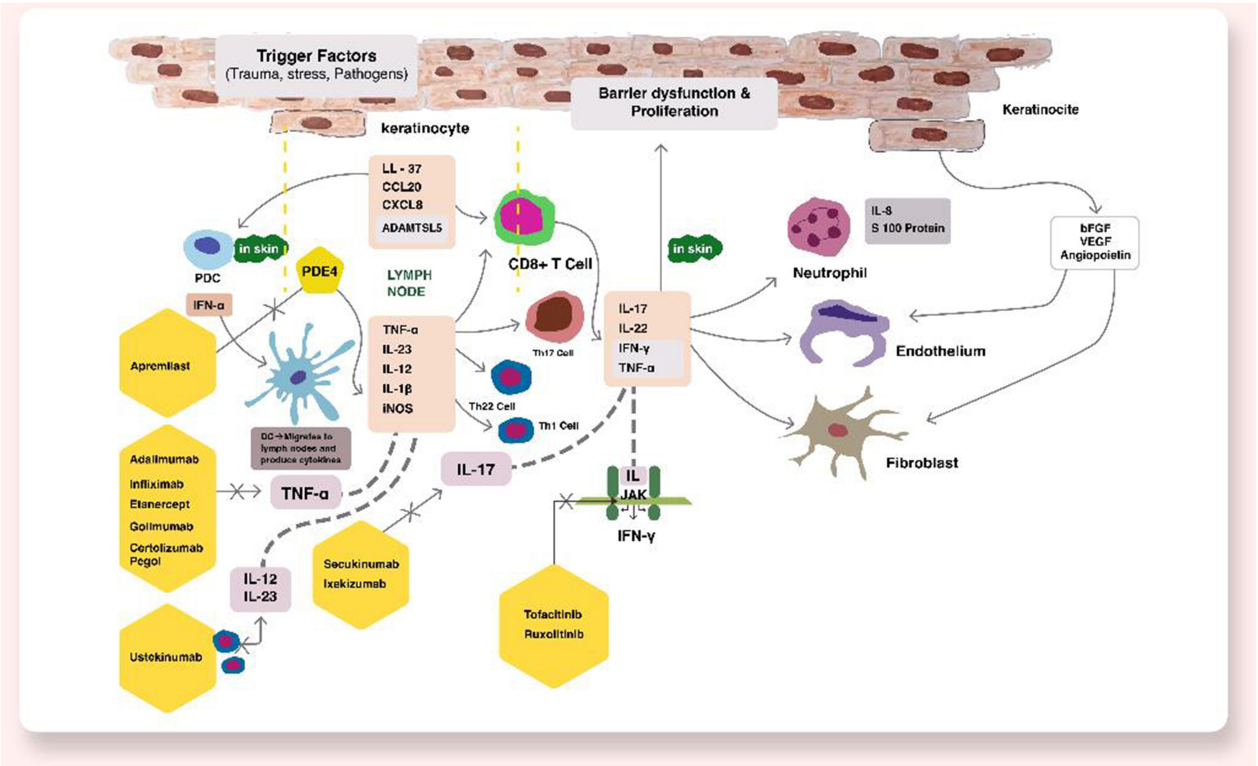


**FIGURE 1 |** Pathogenesis and various therapeutic targets in psoriatic disease.

(35–37). However, more studies evaluating efficacy of these agents and comparison with other drugs such as TNF-α are required. Common adverse effects of IL-23 inhibitors include upper respiratory infections, nasopharyngitis, and headache (29). Other advents events include serious infections, major adverse cardiovascular events and malignancy, however, the rates observed were comparable to seen in general population of psoriasis patients (29). A long-term data on the safety of these novel drugs is thus warranted.

## IL-36

IL-36 (member of IL-1 family) binds to its receptor and leads to the activation of NF-κB and MAPKs pathways through MyD88/IRAK complex (38). Expression of IL-36γ have been found to be significantly upregulated in the serum and skin samples of psoriasis patients (39). Furthermore, loss of function mutation in IL-36Ra gene has been found in a severe variant of generalized pustular psoriasis (GPP) (40, 41). Studies in mouse model have observed psoriasis like epidermal changes, inflammatory cell infiltrate and gene dysregulation after IL-36 administration which was not seen when Pre-treatment with an IL-36 antagonist was administered (42). This supports a direct role of IL-36 in psoriasis pathogenesis and attenuating this signaling pathway may be an effective alternative approach to the already approved small molecules such as apremilast or other biologics. Moreover, studies have shown that individuals with loss of function mutation in IL-36Ra gene have normal immune function suggesting that targeting this cytokine may not lead to adverse events associated with immune dysregulation and may have a good safety profile (43). Recently, an oral small molecule inhibitor of IL-36, A-552 was shown to inhibit IL-36γ and production of other cytokines induced by IL-36γ in human and mouse cells (44). Monoclonal antibody against IL-36R, spesolimab has shown efficacy in a Phase I study, and phase II and III studies of spesolimab in GPP are currently undergoing (45, 46). Thus, anti-IL-36 agents may have a robust potential in therapeutics of psoriasis and further research evaluating their efficacy and safety is needed. **Table 1** summarizes the studies of JAK inhibitors, IL-23 and IL-36 inhibitors in psoriasis and psoriatic arthritis.

## IL-1

IL-1, a proinflammatory cytokine, comprise of IL-1α and IL-1β. Both these cytokines has been implicated in the pathogenesis of psoriasis (46). Increased expression of IL-1β has been found in the psoriatic skin and correlated with disease severity (47). Furthermore, IL-1β has been shown to induce Th17 cells and stimulate keratinocytes to secrete chemokines such as CCL20 (47). IL-1β production is also regulated by NLRP3 inflammasome as these inflammasomes cleave procaspases into caspases leading

**TABLE 1 |** Summary of various trials of JAK inhibitors, IL-23, IL-12/23 and IL-36 inhibitors.

| Drug | Study/year | Setting/Dose | Number of patients | Response | Adverse effects | Conclusion | Phase |
|---|---|---|---|---|---|---|---|
| JAK inhibitors Tofacitinib | Papp et al. (87)/ 2012 | Psoriasis vulgaris–Tofacitinib 2 mg twice daily vs. 5 mg twice daily vs. 15 mg twice daily vs. placebo | Tofacitinib 2 mg-49; 5 mg—49; 15 mg—49; placebo-50 | At week 12, higher proportion of patients achieved PASI 75 in all tofacitinib groups: 25·0% (2 mg), 40·8% (5 mg) and 66·7% (15 mg) compared with placebo (2·0%). | Infections and infestations, | Oral tofacitinib results in significant clinical improvement in patients with moderate-to-severe plaque psoriasis. | Phase 2b |
| | Bisonette et al. (13)/ 2015 | Moderate-to-severe plaque psoriasis–tofacitinib 5 mg or 10 mg twice daily for 24 weeks. The patients achieving both PASI75 and Physician's Global Assessment of "clear" or "almost clear" received a placebo or the previous dose. At relapse (>50% reduction in the PASI improvement during initial treatment) or week 40, the patients received the initial dose. | Tofacitinib 5 mg—331; 10 mg—335 | 33·5% and 55·2% achieved both PASI 75 and PGA responses in tofacitinib 5 and 10 mg twice daily group, respectively. | Elevations in low-density lipoprotein–cholesterol levels | Patients who received continuous treatment maintained a response more effectively than placebo. Patients who relapsed, 60% reattained a response with tofacitinib. | Phase 3 |
| | Bachelez et al. (88) / 2015 | Moderate-to-severe plaque psoriasis–Tofacitinib 5 mg twice daily vs. 10 mg twice daily vs. Etanercept 50 mg twice weekly vs. placebo | Tofacitinib 5 mg—330; 10 mg—332; Etanercept- 336; placebo- 108 | At week 12, PASI75–39·5% in tofacitinib 5 mg group, 63·6% in tofacitinib 10 mg group, 58·8% in the etanercept group, and 5·6% in the placebo group. | Serious adverse events—2% in tofacitinib 5 mg group, 2% in tofacitinib 10 mg group, 2% in etanercept group, and 2% in placebo group. | Tofacitinib 10 mg twice daily was Non-inferior to etanercept and was superior to placebo, but 5 mg twice daily did not show Non-inferiority to etanercept. | Phase 3, randomized, multicentre, placebo-controlled, 12-week, Non-inferiority trial. |
| | Papp et al. (12)/ 2015 | Plaque psoriasis–tofacitinib 10 or 5 mg or placebo, twice daily. | Tofacitinib 5 mg—745; 10 mg—741; placebo- 373 | At week 16, a greater proportion of patients achieved PGA responses with tofacitinib 5 and 10 mg twice daily vs. placebo. | Similar across groups. Twelve patients reported herpes zoster across the tofacitinib treatment groups. | Oral tofacitinib demonstrated significantly high efficacy as compared to placebo, during 16 weeks of treatment. | Phase 3 |
| | Mease et al. (15)/ 2017 | Psoriatic arthritis–tofacitinib 5-mg twice daily, 10-mg twice daily, adalimumab 40-mg once every 2 weeks, placebo with a blinded switch to 5-mg tofacitinib at 3 months, or placebo with a blinded switch to 10-mg tofacitinib at 3 months. | Tofacitinib 5 mg—107; 10 mg—104; adalimumab- 106; placebo- 52 (5 mg switch), 53 (10 mg switch). | ACR20 response rates at month 3 were 50% in 5-mg tofacitinib group and 61% in 10-mg tofacitinib group, 33% in placebo group, 52% in the adalimumab group. | The rate of adverse events was 66% in 5-mg tofacitinib group, 71% in 10-mg tofacitinib group, 72% in adalimumab group. | Efficacy of tofacitinib was superior to placebo at month 3 in patients who previously had an inadequate response to conventional synthetic DMARDs. | 12-month, double-blind, active-controlled and placebo-controlled, phase 3 trial |

*(Continued)*

**TABLE 1** | Continued

| Drug | Study/year | Setting/Dose | Number of patients | Response | Adverse effects | Conclusion | Phase |
|---|---|---|---|---|---|---|---|
| | Gladman et al. (16)/ 2017 | Psoriatic arthritis–tofacitinib 5 mg twice daily; 10 mg twice daily; placebo, with a switch to 5 mg tofacitinib twice daily at 3 months; or placebo, with a switch to 10 mg tofacitinib twice daily at 3 months. | Tofacitinib 5 mg—132; 10 mg—132; placebo- 66 (5 mg switch), 65 (10 mg switch). | ACR20 response- 50% with 5-mg tofacitinib and 47% with 10-mg dose, as compared to 24% with placebo. | 4 serious infections, 3 herpes zoster infections, 1 myocardial infarction, and 1 ischemic stroke. | Tofacitinib was more effective than placebo over 3 months in reducing disease activity. | 6-month randomized, placebo-controlled, double-blind, phase 3 trial |
| Baricitinib | Papp et al. (19)/ 2016 | Moderate-to-severe psoriasis- placebo or oral baricitinib at 2, 4, 8 or 10 mg once daily for 12 weeks. | baricitinib 2 mg- 32, 4 mg- 72, 8 mg- 64, 10 mg- 69, Placebo- 34 | At week 12, patients in 8-mg (43%) and 10- mg (54%) baricitinib groups achieved PASI-75 than in placebo group (17%).<br>Statistically significant PASI-90 responses were achieved in 8-mg and 10-mg groups at 8 and 12 weeks. | treatment-emergent AE rates were 44, 50, 47, 58 and 64% for placebo and 2-, 4-, 8- and 10-mg baricitinib groups. | Treatment with baricitinib for 12 weeks achieved significant improvements in PASI-75. | Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study. |
| IL-12/23 inhibitors Ustekinumab | Phoenix-I (89)/ 2008 | Moderate-to-severe psoriasis- Ustekinumab 45 mg or 90 mg at weeks 0, 4 and then every 12 weeks; or placebo at weeks 0 and 4, with subsequent crossover to ustekinumab at week 12. | Placebo-255; 45 mg- 255; 90 mg- 256 | 67·1% patients receiving ustekinumab 45 mg, 66·4% receiving ustekinumab 90 mg, and 3·1% receiving placebo achieved PASI 75 at week 12. | Adverse events occurred in 54·5% in ustekinumab and 48·2% in placebo group. | Ustekinumab seems to be efficacious for the treatment of moderate-to-severe psoriasis; dosing every 12 weeks maintains efficacy for at least a year in most patients. | Phase 3, parallel, double-blind, placebo-controlled study. |
| | Phoenix-II (90)/ 2008 | Moderate-to-severe psoriasis- Ustekinumab 45 mg or 90 mg at weeks 0, 4 and then every 12 weeks; or placebo.<br>Partial responders (patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. | Placebo- 410; 45 mg- 409; 90 mg—411 | 66·7% patients receiving ustekinumab 45 mg, 75·7% receiving ustekinumab 90 mg, and 3·7% receiving placebo achieved 75% improvement in PASI at week 12.<br>More partial responders who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at week 52 than those who received the same dose every 12 weeks. | Serious adverse events were seen in 2% patients in 45 mg group, 1·2% in 90 mg group, and 2% in placebo group. | Ustekinumab every 12 weeks is effective for most patients with moderate-to-severe psoriasis. Intensification of dosing to once every 8 weeks with ustekinumab 90 mg might be necessary to elicit a full response in patients who only partially respond to the initial regimen. | Multicentre, phase 3, double-blind, placebo-controlled study. |
| | Griffiths et al. (91)/ 2010 | Moderate-to-severe psoriasis- 45 or 90 mg of ustekinumab (at weeks 0 and 4) or high-dose etanercept (50 mg twice weekly for 12 weeks) | 45 mg—209; 90 mg—347; etanercept—347 | 75% improvement in the PASI at week 12 in 67.5% of patients receiving 45 mg of ustekinumab and 73.8% of patients receiving 90 mg, as compared with 56.8% of those with etanercept. | One or more adverse events occurred in 66% of patients in 45 mg ustekinumab and 69.2% in 90 mg ustekinumab and in 70% in etanercept group. | Efficacy of ustekinumab 45 or 90 mg was superior to high-dose etanercept over a 12-week period. | Randomized, multicentre study. |

*(Continued)*

**TABLE 1 |** Continued

| Drug | Study/year | Setting/Dose | Number of patients | Response | Adverse effects | Conclusion | Phase |
|---|---|---|---|---|---|---|---|
| | PSUMMIT I (35) | Active psoriatic arthritis—45 mg ustekinumab, 90 mg ustekinumab, or placebo at week 0, week 4, and every 12 weeks thereafter. | Placebo- 206; 45 mg- 205; 90 mg—204 | More ustekinumab-treated [42·4%] in the 45 mg group and [49·5%] in the 90 mg group than placebo-treated [22·8%] patients achieved ACR20 at week 24. | Adverse events were similar in the ustekinumab [41·8%] and placebo groups [42·0%]. | Ustekinumab significantly improved active psoriatic arthritis. | Phase 3, multicentre, double-blind, placebo-controlled trial |
| | PSUMMIT II (36) | Active Psoriatic Arthritis- ustekinumab 45 mg or 90 mg at week 0, week 4, q12 weeks or placebo at week 0, week 4, week 16 and crossover to ustekinumab 45 mg at week 24, week 28 and week 40. | Placebo- 104; 45 mg- 103; 90 mg- 105 | More ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients achieved ACR20 at week 24; all benefits were sustained through week 52. | No unexpected adverse events were observed. | Ustekinumab (45/90 mg q12 weeks) yielded significant and sustained improvements in Psoriatic arthritis. | phase 3, multicentre, placebo-controlled trial |
| IL-23 inhibitor Guselkumab | VOYAGE-I (92) | Moderate to severe plaque psoriasis- guselkumab 100 mg (weeks 0 and 4, then every 8 weeks); placebo/guselkumab (weeks 0, 4, and 12 then guselkumab at weeks 16 and 20, then every 8 weeks); or adalimumab (80 mg week 0, 40 mg week 1, then 40 mg every 2 weeks through week 47). | Placebo- 174; 100 mg—329; adalimumab—334 | Guselkumab was superior to placebo at week 16 (73.3 vs. 2.9% [PASI-90]). Guselkumab was also superior to adalimumab for PASI 90 at week 16 (73.3 vs. 49.7%), week 24 (80.2 vs. 53.0%), and week 48 (76.3 vs. 47.9%). | The proportions of patients with adverse events were similar in the guselkumab and adalimumab group. | Guselkumab demonstrated superior efficacy compared with adalimumab. | phase 3, randomized, double-blind, placebo- and active comparator-controlled trial |
| | VOYAGE-II (93) | Moderate to severe plaque psoriasis- Similar to VOYAGE I; at week 28, guselkumab PASI90 responders were rerandomized to guselkumab or placebo with guselkumab after loss of response. Placebo→ guselkumab responders and adalimumab responders received placebo, then guselkumab after loss of response. | Placebo- 248; 100 mg—496; adalimumab—248 | Guselkumab was superior to adalimumab and placebo at week 16. From weeks 28 to 48, better persistence of response was observed in guselkumab maintenance vs. withdrawal groups. Of adalimumab Non-responders who switched to guselkumab, 66.1% achieved PASI 90 at week 48. | Adverse events were comparable among groups. | Guselkumab is highly effective maintenance therapy, including in adalimumab Non-responders. | phase 3, double-blind, placebo- and active comparator–controlled |
| | DISCOVER I (37) | Active psoriatic arthritis | Placebo- 126; 100 mg every 4 weeks- 128; 100 mg at 0 and 4 weeks, then every 8 weeks- 127 | Significantly greater proportions of patients receiving guselkumab every 4-week (59·4%) and every 8-week (52·0%) vs. placebo (22·2%) achieved ACR20 at week 24. | Serious adverse events occurred in none of patients in guselkumab every 4-week, 3·1% in guselkumab every 8-week, and 4·0% in placebo group. | Guselkumab demonstrated a favorable benefit-risk profile and is an effective treatment option in patients with active psoriatic arthritis. | Phase-3, double-blind, placebo-controlled study |

*(Continued)*

**TABLE 1 |** Continued

| Drug | Study/year | Setting/Dose | Number of patients | Response | Adverse effects | Conclusion | Phase |
|---|---|---|---|---|---|---|---|
| Tildrakizumab | reSURFACE I (94) | Moderate-to-severe chronic plaque psoriasis- Tildrakizumab at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab. | Placebo- 154 100 mg- 309 200 mg-308 | At week 12, 62% in 200 mg group and 64% in 100 mg group achieved PASI 75, compared with 6% in placebo group. | Nasopharyngitis. | Tildrakizumab 200 mg and 100 mg were efficacious compared with placebo. | Parallel group, double-blind, randomized controlled study |
| | reSURFACE II (94) | Moderate-to-severe chronic plaque psoriasis- Tildrakizumab at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab; etanercept was given twice weekly in part 1 and once weekly during part 2). | Placebo- 156 100 mg- 307 200 mg-314 Etanercept—313 | At week 12, 66% in 200 mg group, and 61% in 100 mg group achieved PASI 75, compared with 6% in placebo group and 48% in the etanercept group. | The incidence of severe infections, malignancies, and major adverse cardiovascular events were low and similar across treatment groups. | Tildrakizumab 200 mg and 100 mg were efficacious compared with placebo and etanercept and were well tolerated. | Parallel group, double-blind, randomized controlled study |
| Risankizumab | UltIMMa-1 and UltIMMa-2 (95) | Moderate-to-severe chronic plaque psoriasis—150 mg risankizumab, 45 mg or 90 mg ustekinumab or placebo. Following 16-week double-blind treatment period (part A), patients initially assigned to placebo switched to 150 mg risankizumab at week 16; other patients continued their originally randomized treatment (part B, double-blind, weeks 16–52). Study drug was administered subcutaneously at weeks 0 and 4 during part A and at weeks 16, 28, and 40 during part B. | UltIMMa-1 - Placebo- 102; 150 mg—304; ustekinumab—100 UltIMMa-2- Placebo-98; 150 mg—294; Ustekinumab- 99 | At week 16 of UltIMMa-1, PASI 90 was achieved by 75·3% patients receiving risankizumab vs. 4·9% receiving placebo and 42·0% receiving ustekinumab. At week 16 of UltIMMa-2, PASI 90 was achieved by 74·8% patients receiving risankizumab vs. 2·0% receiving placebo and 47·5%. | The frequency of treatment-emergent adverse events in UltIMMa-1 and UltIMMa-2 was similar across risankizumab, placebo, ustekinumab, and placebo to risankizumab groups. | Risankizumab showed superior efficacy to both placebo and ustekinumab. | Phase 3, randomized, double-blind, placebo-controlled and active comparator-controlled trials |
| IL-36 inhibitor Spesolimab | Bachelez et al. (96) | Generalized Pustular Psoriasis- single 900-mg intravenous dose of spesolimab or placebo. Patients in both groups received an open-label dose of spesolimab on day 8, an open-label dose of spesolimab as a rescue medication after day 8, or both and were followed to week 12. | Spesolimab 900 mg- 35; placebo-18 | At week 1, 54% in the spesolimab group had a pustulation sub-score of 0, as compared with 6% in the placebo group. | Drug reactions—2 patients. (drug-induced hepatic injury- 1); infections—17% through the first week; antidrug antibodies—46%. | Spesolimab resulted in a higher incidence of lesion clearance at 1 week than placebo but was associated with infections and systemic drug reactions. | Phase 2 randomized trial |

to the production of IL-1β (48). Higher caspase-1 and IL-1β levels has been observed in patients with psoriasis that normalized after treatment with TNF-α (48). Anti-IL1 agents such as anakinra, canakinumab and gevokizumab have shown efficacy in psoriasis. Anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra) inhibits both IL-1α and IL-β and has shown efficacy in pustular psoriasis and deficiency of IL-1 receptor antagonist (DIRA) variant (49). However, the partial responses observed suggest role of other cytokines of IL-1 family such as IL-36 (49, 50). Canakinumab, an anti-IL-β antibody has also shown beneficial effects in GPP (51). Gevokizumab, another novel IL-1β antagonist has shown its efficacy in GPP (52). In 2 patients of GPP, 79 and 65% improvement in GPP scores was observed after 4 weeks (52). Thus, IL-1 inhibitors particularly IL-1β could be potentially efficacious in management of psoriasis especially pustular psoriasis, though larger studies are needed.

## RORγT ANTAGONISTS

RORγT is an important transcription factor required for the differentiation of Th17 cells and regulates the expression of Th17 cytokines i.e., IL-17A, IL-17F, IL-22 and IL-23 receptor (53). Thus, RORγT inhibition seems to be an effective strategy in therapeutics of psoriasis. VTP-43742, an oral RORγT inhibitor is undergoing phase III study in treatment of plaque psoriasis. In a phase IIa study, 29 and 23% reduction in PASI was observed at 4 weeks in patients receiving 700 mg and 350 mg of VTP-43742 respectively along with 75% reduction in IL-17A and IL-17 F levels in both groups (54). Side effects included headache, flushing, elevated liver enzymes and nausea. Other agents such as JTE-451 and ABBV-157, oral RORγT inhibitors are currently in phase 2 and phase 1 of development respectively, for the treatment of moderate to severe psoriasis. New systemic and topical RORγT inhibitors may be the potential candidates for the treatment of psoriasis (55).

## TYK2 INHIBITORS

The TYK2, a JAK family gene, has been associated with psoriasis susceptibility genes and loss of function mutation is associated with various cytokine signaling defects that are implicated in psoriasis pathogenesis (56, 57). Individuals with these mutations have been found to be unaffected by immune-mediated inflammatory diseases without being susceptible to life-threatening infections (58). These observations suggested that TYK2 inhibitors may be a safe therapeutic target. BMS-986165 is an oral highly selective TYK2 inhibitor and inhibit STAT1 and STAT3 phosphorylation in peripheral blood mononuclear cells stimulated with IFN-α and IL-23 (6). BMS-986165 has shown good efficacy in psoriasis in phase II trials at doses 3 mg, 6 mg and 12 mg daily (59). Common adverse effects include headache, nausea, diarrhea, and upper respiratory tract infections (59). Phase III trials in plaque psoriasis and phase II trial in psoriatic arthritis are currently undergoing (6). Another selective TYK2 inhibitor, PF-06826647, is also being tested in moderate-to-severe psoriasis in an ongoing phase II clinical trial (NCT03895372) (6). Brepocitinib (formerly known as PF-06700841) is not a selective TYK2 inhibitor (rather a potent TYK2/JAK1 inhibitor), has shown good efficacy in phase II trials in psoriasis with few minor adverse effects, except thrombocytopenia and decreased reticulocyte count (60). A phase IIb study is currently undergoing to evaluate the efficacy and safety in psoriatic arthritis (6). A topical formulation is also being tested in mild to moderate psoriasis. These small molecules have advantages like oral route of administration, decreased cost, less immunologic adverse events as compared to biologics.

## SPHINGTOSINE-1-PHOSPHATE RECEPTOR 1 (S1PR1) ANTAGONIST

Sphingosine-1-phosphate (S1P) is involved in cell proliferation and survival, migration, inflammation and angiogenesis (61, 62). S1P inhibits the keratinocyte proliferations and increase cell differentiation (63). Ponesimod, an oral S1P receptor 1 antagonist leads to the downregulation of S1P receptor and prevent migration of lymphocytes from lymph nodes to skin in psoriasis (64). In a phase 2 study, PASI75 was achieved in 46 and 48% of patients receiving ponesimod 20 mg and 40 mg respectively as compared to placebo at 16-weeks and the improvement continued till 28 weeks (65). However, effect is not maintained after drug discontinuation due to its rapid elimination within 1 week. Adverse effects include transaminitis, shortness of breath, dizziness and may cause conduction abnormalities, thus contraindicated in patients with cardiac disease (65).

## A3 ADENOSINE RECEPTOR AGONIST

A3 adenosine receptors are G-protein coupled receptors involved in various intracellular pathways. These receptors have been found to be highly expressed on peripheral mononuclear cells in psoriasis patients (66). Piclidenoson, an oral A3 adenosine receptor agonist has been found to downregulate NF-κB signaling pathway and pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12, and inhibit T-lymphocyte proliferation (67). In a phase II trial, a significant reduction in PASI was observed at 12 weeks as compared to placebo and drug was well tolerated (67). Currently, the drug is in phase III trials.

## mTOR INHIBITORS

**T**he PI3-K/Akt/mTORC1 cascade acts as a regulator of epidermal homeostasis (68). Akt has been shown to be highly activated in skin of psoriatic lesions, except in the basal layer and mTOR, expression is found to be increased in lesional and Non-lesional skin of psoriasis patients (69, 70). An animal model study showed that the PUVA treatment led to improvement in psoriasis and normalization of mTORC1 signaling (71). This suggested a pathophysiological role of mTORC1 signaling in psoriasis. The increased expression of mTORC1 may have a role in increased proliferation of keratinocytes and decreased differentiation. During normal

keratinization, mTORC1 signaling pathway is inactivated as the keratinocyte differentiation occurs (72). mTORC1 signaling also plays important roles in the innate and adaptive immunity (72, 73). Aberrant mTORC1 signaling was found in peripheral blood mononuclear cells (PBMCs) of psoriasis patients (74). Rapamycin, a mTOR inhibitor, has been used in few patients with psoriasis due to its antiproliferative and immunosuppressive actions (75). Everolimus was also used successfully in a psoriasis patient along with tacrolimus (76). Topical rapamycin has also been used in psoriasis showing clinical improvement (77). Thus, oral and topical mTOR inhibitors may be a successful therapeutic strategy in psoriasis and further research exploring the role of mTOR pathway as therapeutic target is warranted.

## FUTURE PERSPECTIVE

Recent advances in understanding the pathogenesis of the psoriasis has led to the development of newer therapies such as biologics and other small molecules. However, apart from the therapeutic options discussed, various other cells and pathways are implicated in the pathogenesis such as role of natural killer cells, regulatory T-cells and mesenchymal stem cells (MSCs). The regulatory T-cells have been found increased in lesional skin of psoriasis patients. Similarly, IL-10-producing regulatory B cells of psoriasis patients were reduced in number and showed decreased IL-10 production. MSCs have been implicated in the psoriasis pathogenesis and may serve as potential therapeutic target. MSCs have immunomodulatory properties and affect Th1 and Th17 lymphocytic inhibition in psoriatic skin (78). These MSCs have also been found to have pleiotropic effects of biologic therapy in psoriasis (79). MSCs based therapy has been tried in few patients with psoriasis with successful outcomes (80–82). However, larger studies are still needed to fully explore the role of these cells as a therapeutic option. Another class of drug i.e., selective serotonin reuptake inhibitors (SSRIs) have been found to be beneficial in psoriasis due to their anti-inflammatory properties and reduction in cytokine levels (83). Moreover, these agents prevent T-cell proliferation by reduced antigen presentation by dendritic cells and causes inflammatory cell apoptosis (83). Role of proanthocyanidins having antioxidant, anti-proliferative, antiangiogenic and anti-inflammatory properties as an therapeutic option needs to be investigated as oxidative stress plays an important role in the pathogenesis of psoriasis (84). A potent and selective NF-kB inducing kinase (NIK) inhibitor has been found effective in imiquimod induced psoriasis in animal model, highlighting the potential of newer strategy for the treatment of psoriasis (85). Mutations in CARD14 have been found in psoriasis patients (86). Such genetic associations indicate a role in immune regulatory pathways involved in psoriasis. Such observations may help in the better knowledge of psoriasis susceptibility genes and individualized approaches in management of psoriasis. In addition, the role of keratinocytes as initiators of psoriatic inflammation might further shift the focus to topical treatments. Further studies are needed to obtain better insights in the immunopathogenesis of the disease that may lead to the development of more targeted and more effective therapies.

## CONCLUSION

Many novel systemic and topical therapies are currently in development. The success of these agents depends on the efficacy and safety of these drugs in future studies. Better understanding of inflammatory pathways involved the pathogenesis and newer discoveries may lead to the effective therapeutic strategies in management of psoriasis.

## AUTHOR CONTRIBUTIONS

VT: study design, acquisition, analysis or interpretation of data, and drafting of the manuscript. RM: study concept and design, acquisition, analysis or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical, or material support, and study supervision. All authors contributed to the article and approved the submitted version.

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# A Scoping Review on Use of Drugs Targeting the JAK/STAT Pathway in Psoriasis

*Francisco Gómez-García*[1,2], *Pedro Jesús Gómez-Arias*[1,2], *Ana Montilla-López*[1], *Jorge Hernández-Parada*[3], *Juan Luís Sanz-Cabanillas*[1,2], *Juan Ruano*[1,2]* *and Esmeralda Parra-Peralbo*[4]

[1] *Inflammatory Immune-Mediated Chronic Skin Diseases' Laboratory, Insituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Córdoba, Spain,* [2] *Department of Dermatology, Reina Sofia University Hospital, Córdoba, Spain,* [3] *Department of Pharmacology, Reina Sofia University Hospital, Córdoba, Spain,* [4] *Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain*

**Introduction:** The Janus kinase–signal transducer and activator of transcription (JAK/STAT) pathway are known to be involved in inflammatory immune-mediated skin diseases, including psoriasis. The development of drugs targeting the JAK/STAT signaling pathway presents new treatment opportunities for psoriasis. However, the application of JAK inhibitors for the treatment of dermatological disorders is still in its early stages of development. This review summarizes available evidence in an attempt to identify knowledge gaps for conducting further research studies and improving clinical decision-making.

**Objective:** The objective of this study is to conduct a scoping review of the use of drugs targeting the JAK/STAT pathway in the treatment of psoriasis.

**Methods:** A priori protocol for scoping review was published in 2019. The Joanna Briggs Institute Reviewer's Manual and the PRISMA Extension for Scoping Review were used for the review. MEDLINE, EMBASE, CINAHL, Scopus, and Web of Science databases and ClinicalTrials registry were referred to in April 2019 and March 2021, respectively. References in English involving evidence on the use of drugs targeting the JAK/STAT pathway in patients with psoriasis were included. Data charting was performed by two authors using tables and figures.

**Results:** The evidence found on the efficacy and safety of drugs targeting the JAK/STAT pathway in patients with psoriasis comes from 118 articles reporting the results of 34 randomized clinical trials (RCTs). Nine different drugs administered through various routes were identified (systemic: peficitinib, baricitinib, solcitinib, itacitinib, abrocitinib, deucravacitinib, and brepocitinib; topical: ruxolitinib; and both: tofacitinib). Knowledge articles are mainly created and published by pharmaceutical companies and authors through their own funding or by those related to them. Only tofacitinib and deucravacitinib have undergone phase III clinical trials, being the only ones tested with active comparators etanercept and apremilast, respectively. Proportions of Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) were the efficacy variables most frequently studied in systemic treatments. Only two RCTs

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*Priscila Giavedoni, Hospital Clínic de Barcelona, Spain*
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***Correspondence:**
*Juan Ruano*
*juanruanoruiz@mac.com*

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declared the safety data collected by systematic assessment; the only systemic drug with phase III data was tofacitinib. Tofacitinib 5 mg two times daily (BID)/10 mg BID efficacy was compared with etanercept 50 mg/week and a placebo. At 12–16 weeks, PASI 75/PGA 01 ranges were as follows: 38.07–80%/37.16–67.4% for tofacitinib 5 mg BID; 54.79–100%/50–75.6% for tofacitinib 10 mg BID; 58.8/66.8% for etanercept, date from one only study; and 0–33.3%/9.04–33.3% for the placebo group. Other drugs in earlier stages of development showed values within these ranges. The most frequent adverse events (AEs) were nasopharyngitis and upper respiratory tract infections in all treatment groups.

**Conclusion:** There is increasing evidence on the use of drugs targeting the JAK/STAT pathway as a treatment for psoriasis, although they are in the early phases of development. The trials conducted to date have been financed directly or indirectly by the pharmaceutical industry, which must be taken into account when interpreting the results of the trials. Psoriasis treatment is currently symptomatic and could potentially present a significant risk of toxicity. Therefore, the design of principal efficacy outcome measures considering the impact of the outcome on quality of life and a drug assessment methodology aimed at improving safety would probably strengthen the evidence and decision-making process.

**Keywords: psoriasis, autoimmune diseases, JAK inhibitors, abrocitinib, deucravacitinib, ruxolitinib, tofacitinib**

## HIGHLIGHTS

- The use of drugs targeting the JAK/STAT pathway as a treatment for psoriasis is increasing, although they are in the early phases of development. Only tofacitinib and deucravacitinib have undergone phase III studies. None of the drugs have been approved yet.
- Most of the evidence produced so far is financed directly or indirectly by the pharmaceutical industry, which must be taken into account when interpreting the results.
- The most frequently used primary efficacy variables did not evaluate the quality of life. Few studies focus on safety, and most employ an unsystematic methodology. Standardized psoriasis-specific outcome measures would help reach better decisions.

## INTRODUCTION

Psoriasis is a chronic, immune-mediated dermatological disease with an estimated prevalence of 0.91–8.5% worldwide (1). Studies on quality of life in psoriasis patients demonstrate that disutility among psoriasis patients is within the same range as other chronic diseases, such as cancer, liver diseases, and diabetes (2). Associated comorbidities, such as cardiovascular risk, kidney disease, metabolic syndrome, or altered mood are related to a decrease in life expectancy (3). Finally, patients with psoriasis bear a higher financial burden due to absenteeism, in addition to the cost of managing their disease (4). Better knowledge of physiopathology has led to the development of molecules increasingly specific to the disease that reach high levels of efficacy. Despite this, the treatment of psoriasis remains symptomatic, and no treatment has been shown to address the basic cause of the disease and increase life expectancy in patients. In addition, they present a risk of potentially serious toxicity whereas high costs curtail the access of patients to these treatments and jeopardize the sustainability of health systems. Knowledge of all the available therapeutic alternatives allows cost-effective treatment recommendations to be adopted, which suit the values and preferences of patients.

From a pathogenic point of view, epidermal antigens activate dendritic cells resident in the dermis that converts naive T lymphocytes into functioning Th17 lymphocytes in a genetically permissive background (5). The presence of the HLA-C*06:02 risk allele, which codes an aminopeptidase that helps to process antigens for HLA class I presentation, and, specifically, the interaction with a risk variant in the ERAP1 gene, markedly increases the risk and therefore it implies to have a genetic background keen to psoriasis development for an individual (5). Interleukin 23 (IL-23) and Th-17 responses are considered important drivers of psoriasis, based on the findings from genome-wide association studies and clinical trials (5). Actually, psoriatic lesions result from hyperproliferation and disturbed differentiation of epidermal keratinocytes that are provoked by immune mediators of the IL-23 and IL-17 pathways (6). Th17 lymphocytes are believed to play a central role in the pathogenesis of psoriasis (7). In this context, the JAK/STAT pathway has been shown to participate in different key points of the pathophysiology of psoriasis, inducing the proliferation of Th17 lymphocytes (8) keratinocytes (9) and gamma–delta T cells. The regulation of these functions in the specified cell type is determined by the activation of the JAK/STAT pathway. The JAK/STAT pathway family is comprised of four types of

cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and Tyk2 (10), and seven transductors of the signal that activate translocation to the target gene expression: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6. STAT3 has recently emerged as a key player in the development and pathogenesis of psoriasis and psoriatic inflammatory conditions (7). JAK activation by IL-23 leads to the phosphorylation of STAT3 that transmits the signals of: IL-6, a key cytokine implicated in T17 cell programming; and also of IL-22, IL-19, IL-20, and IL-24 that act directly on keratinocytes (6). However, the complexity of the pathway is high, for example, although JAK 2 and TYK2 are fundamental for the transduction of the IL-23 signal, they are also involved in other pathways such as IL-10 or IL-13, which have protective roles in psoriasis (11). In this sense, polymorphins of TYK2 are known to protect against psoriasis (12).

In recent years, drugs acting on the JAK/STAT pathway have been developed by specifically inhibiting one component (filgotinib-JAK1, pacritinib-JAK2, and decernotinib-JAK3) or several of them (tofacitinib-JAK1 and JAK3; ruxolitinib, baricitinib-JAK1, and JAK2). These drugs have several advantages compared to biologics: they can be administered orally or topically and do not produce immunogenicity (7). Tofacitinib and upadacitinib, two JAK inhibitors, have been approved by both, Food and Drug Administration and European Medicine Agency (EMA), and only by EMA respectively, to treat psoriasic arthritis. However, none has been authorized for the use in skin psoriasis treatment.

A review of the scope is a mean for scientific synthesis that addresses an exploratory research question, with the objective of mapping key concepts and gaps in research related to a defined area or field (13).

In this work, we review the state of science on the study methodology used as well as the dissemination of the current knowledge on the drugs that block the JAK/STAT pathway in the treatment of psoriasis, what would allow to order it and detect gaps. This could be the base to formulate further specific research questions, which could be addressed by conducting a systematic review, later on (14).

The aim of this study is to present current evidence on the use of JAK inhibitors in the treatment of psoriasis, using a scoping review methodology.

# MATERIALS AND METHODS

## Compliance With Ethics Guidelines

This article is based on previous studies and therefore does not include any study by any of the authors involving human participants or animals.

## Methods

A scoping review protocol has been published by us a priori (15). Our study was conducted and reported using the methodology described in the Joanna Briggs Institute Reviewer's Manual (16) and the PRISMA Extension for Scoping Reviews (17).

## Eligibility Criteria for Inclusion in Review

To be included in the review, papers had to show evidence of the use of JAK/STAT drugs in patients with psoriasis. Studies were included if they were written in English, involved human participants, and described the conditions formulated in the research question, regardless of the publication date or format. Articles were excluded if they did not fit the conceptual framework of the study. Non-scientific reviews were excluded from the analysis.

## Literature Search

Eligibility criteria and strategies for literature search are described in **Supplementary Table 4**.

## Data Charting

Two researchers jointly developed a data charting form to determine the variables to be extracted. A pilot test was conducted on five studies, and the chosen variables were included in a .csv file. The two researchers independently charted the data, discussed the results, and continuously updated the data charting form in an iterative process. Variables related to the study design and metadata from the primary sources are finally reported. Where possible, the data were collected from the clinical trial webpage; otherwise, data from congress abstracts and full-text articles were used.

## Collation, Summarization, and Reporting of Results

The results of the comprehensive research are presented using a PRISMA flow diagram (**Figure 1**). We first grouped the references and primary studies, drug-wise. Second, a narrative and qualitative synthesis of psoriasis mapping references, studies, and efficacy and safety data findings were elaborated using tables.

## Protocol vs. Scope Review

The review methods that are finally reported were compared with our planned search strategy published in *BMJ* (15). An update search was carried out using the ClinicalTrials registry in March 2021, for the anti-JAK-STAT drugs previously identified as used in the treatment of psoriasis.

# RESULTS

## Search Results

From 4,897 records [EMBASE ($n$ = 1.048), EMBASE and MEDLINE ($n$ = 1,108), MEDLINE ($n$ = 41), Web of Science ($n$ = 1,217), SCOPUS ($n$ = 1,324), and CINAHL ($n$ = 159)] regarding the use of JAK/STAT-targeting drugs in the treatment of dermatological diseases, 130 references met the criteria for full-text review (**Figure 1**), after filtering out duplicates and selecting studies based on title, abstract, and keywords. Of these, 117 articles that belong to 26 different studies fulfilled the inclusion criteria. In March 2021, the list of previously identified anti-JAK drugs was updated with reference to the ClinicalTrials registry, adding one new reference and eight new studies. A total of 118 references and 34 studies (**Supplementary Table 1**) on nine drugs inhibiting the JAK/STAT pathway were found: tofacitinib, deucravacitanib, ruxolitinib, brepocitinib, peficitinib, baricitinib, solcitinib, itacitinib, and

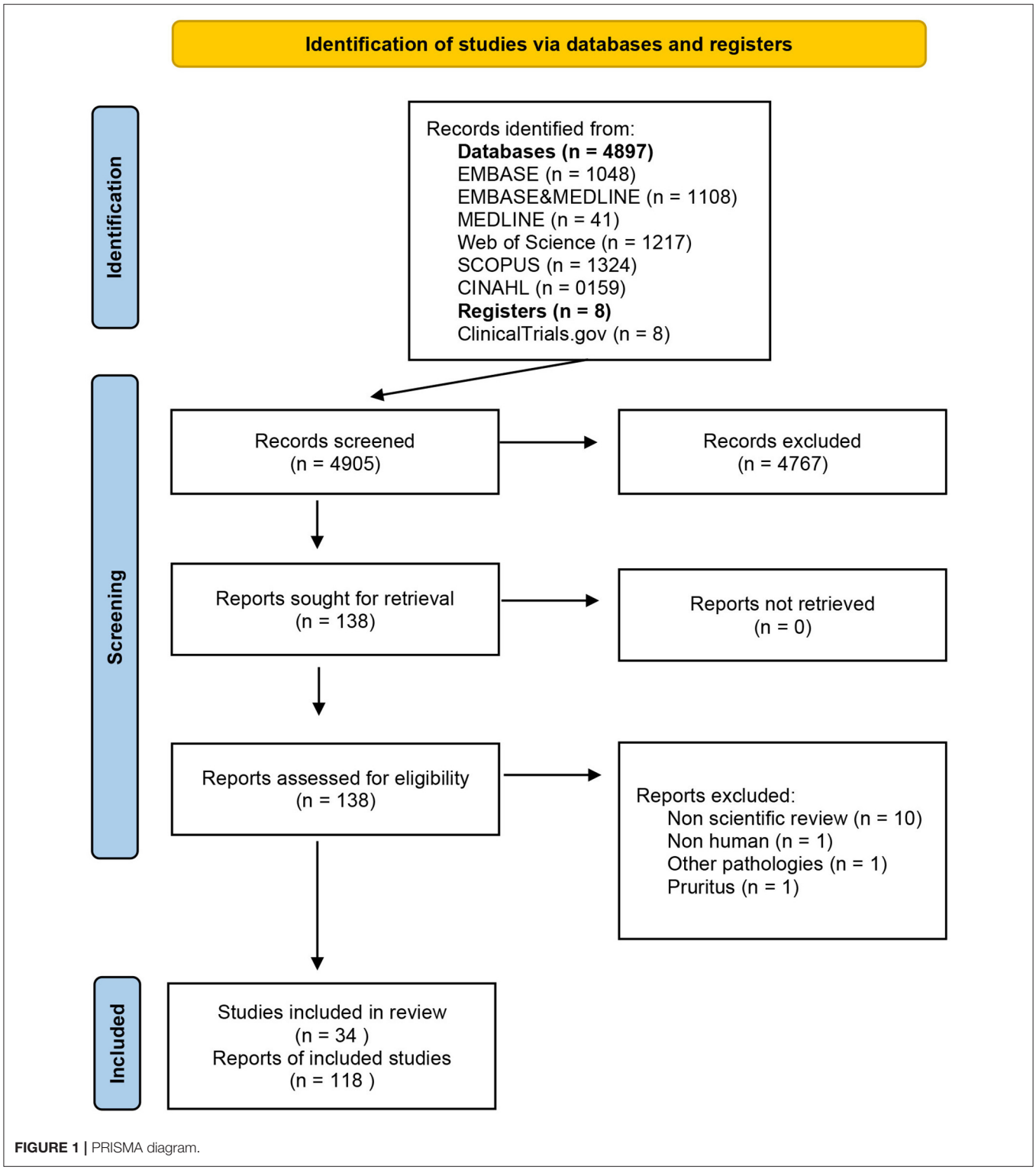


**FIGURE 1 |** PRISMA diagram.

abrocitinib. These JAK inhibitors and their mechanisms of action and selectivity are shown in **Figure 2**. A reference list of all articles with reasons for inclusion and exclusion is presented in **Supplementary Tables 5**, **6**.

Results pertaining to the nine drugs are listed below.

## Tofacitinib

### Mapping References and Studies

A total of 103 references are shown in **Supplementary Table 7**: 93.2% (96/103), 4.8% (5/103), and 0.9% (1/103) of them correspond to studies on systemic, topical, and systemic topical

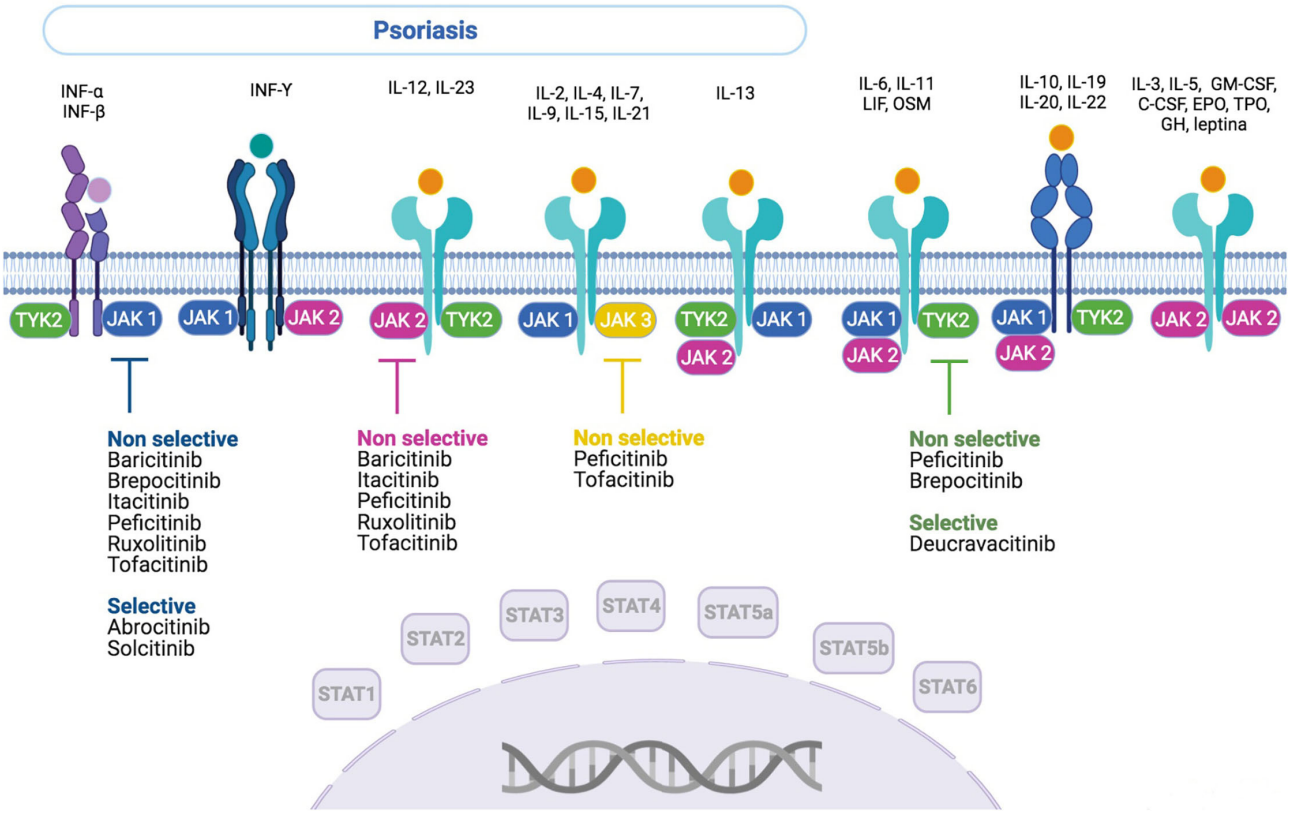


**FIGURE 2 |** Anti-JAK drugs—action mechanism and selectivity. INF, interferon; IL, interleukin; OSM, oncostatin M; LIF, leukemia inhibitory factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; C-CSF, granulocyte colony-stimulating factor; EPO, erythropoietin; TPO, thrombopoietin; GH, growth hormone.

tofacitinib treatment, respectively. Of these, 46.6% (48/103), 49.5% (51/103), and 3.8% (4/103) were full-text articles, congress abstracts, and letters, respectively. Most of them, that is, 80.5% (83/103), were published in dermatology journals. Overall, each publication was elaborated by 8.57 (1–17) authors: 4.76 (0–11), 1.31 (0–11), and 2.43 (0–9) author affiliations were to the pharmaceutical industry, research institutions, and dermatology departments of hospitals, respectively; A total of 56.3% (58/103) indicated collaboration among multinational centers, the US being the country whose centers contribute the greatest number of authors to the publications [75.8% (44/58)]. A total of 67.9% (70/103) and 66.0% (68/103) of the authors declared conflict of interests and funding sources, respectively. Among them, an average of 8.15 (0–17) authors declared a conflict of interest whereas 91.1% (62/68), 4.4% (3/68), and 4.4% (3/68) received funding from the pharmaceutical industry, public centers, and other sources, respectively. Pfizer Inc. [96.7% (60/62)] was the pharmaceutical company that funded the highest number of publications; 47.45% (28/59) of the publications, where the conflict of interest or type of funding was not declared, were congress abstracts.

Fifteen randomized studies—11 and 4 on systemic and topical treatments, respectively—were found (**Supplementary Table 1**). Studies on systemic treatment were conducted between November 2002 and June 2016. Of these, 10/11 (90.9%) and 6/11 (54.54%) were multinational studies and studies involving multiple centers, respectively. In seven studies, the US was the country with the highest number of participating centers. One phase-I study, two phase-II studies, and seven phase-III studies, with 59, 209, and 6,856 participants, respectively, of both sexes and older than 18 years, were funded by Pfizer. One study that included 18 patients was funded by the National Natural Science Foundation of China. The primary endpoints varied between 2 and 16 weeks. Three studies presented cohorts of 52 weeks. Maximum follow-up was undertaken at 67 months. Six doses of oral tofacitinib [2, 5, 10, 15, 20, 30, 50 mg, BID, and 60 mg once daily (QD)] were tested, with 5 mg BID and 10 mg BID being the most frequently investigated doses. The placebo and etanercept 50 mg administered subcutaneously two times a week were the only comparators evaluated. The primary objectives of the studies were efficacy (7/11), safety (2/11), efficacy or safety (1/11), and physiopathological aspects (1/11). The efficacy variables studied as primary objectives were PASI 75 and PGA 01 in four of the studies whereas mean reduction PASI was in one of the studies (**Supplementary Table 2**). Ten out of the 11 clinical trials declared that AEs were collected by non-systematic assessment.

Studies on the topical use of tofacitinib (**Supplementary Table 1**) were conducted between October

2008 and February 2015. Three out of the four studies were multinational studies involving multiple centers, most of which were located in the USA. One phase I and three phase-II studies, with a total of 15 and 618 participants, respectively, were funded by Pfizer. The primary endpoints were located between 12 days and 12 weeks. The latter was the period with the greatest long-term follow-up. Patients were 18 years of age or older, and both sexes were included. Tofacitinib 0.02, 0.2, 1, 2, and 4% were compared with the placebo and 50 μg/ml once or two times a day. The main objectives of the studies were related to efficacy variables. Two out of four clinical trials reported that AEs were collected by non-systematic assessment.

### Tofacitinib Systemic Treatment

The efficacy variables PASI 75 and/or PGA 01 at 12–16 weeks of tofacitinib 5 mg BID, tofacitinib 10 mg BID, etanercept 50 mg/week, and the placebo were evaluated in eight ($n$ = 1,221 patients), nine ($n$ = 2,748 patients), one ($n$ = 335 patients), and seven ($n$ = 731 patients) studies, respectively (**Supplementary Table 2**). The values of PASI 75/PGA01 were in the range of 38.07% ($n$ = 331)−80% ($n$ = 5)/37.16% ($n$ = 331)−67.4% ($n$ = 43) for tofacitinib 5 mg BID; 54.79% ($n$ = 2,200)−100% ($n$ = 7)/50% ($n$ = 8)−75.6% ($n$ = 90) for tofacitinib 10 mg BID; 58.8% ($n$ = 335)/66.8% ($n$ = 335) for etanercept; and 0% ($n$ = 6)−33.3% ($n$ = 3)/9.04% ($n$ = 177)−33.3% ($n$ = 3) in the placebo group. Regarding security, most of the data were collected by non-systematic assessment (9/11), and the time frame was not specified (8/11). AEs were described for the different treatment arms at very short (14 days/one study), short (12–16 weeks/four studies), medium (24 weeks/one study), and long term (52 weeks/four studies, 66 months/one study), as shown in **Supplementary Table 2**. The most frequent AEs were nasopharyngitis and upper respiratory tract infections in all treatment groups. Severe AEs associated with tofacitinib are presented in **Supplementary Table 8**.

### Tofacitinib—Topical Treatment

The efficacy of topical tofacitinib (**Supplementary Table 9**) at doses of 2% ($n$ = 15) and 4% ($n$ = 15) vs, placebo ($n$ = 15) and calcipotriol 50 μg/g ($n$ = 15) was evaluated at 12 days (improvement from baseline in psoriatic skin thickness/echo-poor band (EBP). Topical tofacitinib efficacy at four weeks resulted in an improvement in the Percent Change Target Plaque Severity Score (TPSS) at doses of 0.02% ($n$ = 23), 0.2% ($n$ = 23), and 2% ($n$ = 71) vs. vehicle ($n$ = 35). Finally, at 12 weeks, PGA improvement was observed in a study at a dose of 1% ($n$ = 144) and 2% ($n$ = 141) vs. the placebo ($n$ = 145). At 12 days and 4 weeks, as cutoff primary points, no serious AEs, namely frequent burning or stinging, were observed. At 12 weeks, zero, seven, and four severe AEs were described in the tofacitinib 2%, 1%, and placebo groups, respectively.

## Ruxolitinib

Four references on topical ruxolitinib treatment—one full-text and three congress abstracts—were published between 2009 and 2012 (**Supplementary Table 7**). Overall, the studies were performed by a mean of eight authors (4–13), of which 6.25 (2–11), 1 (0–3), and 1.75 (0–3) had affiliations with the pharmaceutical industry, dermatology institutions, and other research institutions, respectively. Publications involved multiple centers, with three of the authors from the USA and only one from Spain. All the authors in one out of the four references—a full-text article (9)—declared conflict of interest whereas two out of the four references declared funding by the pharmaceutical group, Incyte Corp.

Three of the references mentioned above are experimental studies on topical treatment with ruxolitinib conducted between May 2007 and May 2009, two of which were randomized studies (**Supplementary Table 1**). All three studies were phase II clinical trials, with a total of 253 participants of both sexes ranging from 18 to 75 years in age. Three different doses of ruxolitinib cream (0.5, 1, and 1.5%) were tested against calcipotriene, betamethasone, and the placebo at cutoff points of 28 and 84 days. Two of these trials studied efficacy variables as primary outcome measures, and only one of them studied a safety variable. Only the results from one of the studies, NCT00820950, have been published; none of them have been posted in the clinical trial registry. All these studies were funded by the Incyte Corporation.

The efficacy and safety of topical ruxolitinib are shown in **Supplementary Table 10**.

## Peficitinib (ASP015K)

A full-text article and a congress abstract on systemic treatment using peficitinib were published in dermatology journals in 2012 and 2015, respectively (**Supplementary Table 7**). Studies were conducted by a mean of seven authors, four of them belonging to the pharmaceutical industry, and three of them to research centers. The publications involved multiple nations and centers, with the USA contributing the greatest number of authors. Only the full-text publication declared conflict of interests (all authors) and specified the funding source (Astellas).

A phase IIa randomized study on systemic treatment with peficitinib was conducted between March 2010 and July 2011 (**Supplementary Table 1**). It included 124 patients aged 18 years and over, of both sexes. Five oral doses of the drug—four, two times-daily dosing groups (10, 25, 60, and 100 mg) and one once-daily dosing group (50 mg)—were compared with the placebo at 6 weeks. Efficacy, reduction of PASI 75, and safety variables were among the primary outcome measures studied. We did not find a description of the safety outcomes in the publications or on the clinical trial webpage. This study was funded by Astellas.

The efficacy and safety at 6 weeks are summarized in **Supplementary Tables 3, 11**.

## Baricitinib

Four references on systemic treatment using baricitinib were found, three of which were published in dermatology journals and one in a general medicine journal between 2014 and 2019 (**Supplementary Table 7**). Three of them were full-text articles, and the other was a congress abstract. Studies were conducted by a mean of 7.5 (6–9) authors, of which 5.5 (3–9) had affiliations to the pharmaceutical industry. All involved multiple centers, and three were multinational, with the USA contributing the greatest number of authors. Conflict of interests (all the authors) and

funding by the pharmaceutical industry (all funded by Eli Lilly) were declared in all three full-text references.

A randomized phase IIb study of systemic treatment with baricitinib was conducted between December 2010 and August 2014 (**Supplementary Table 1**). A total of 271 patients of both sexes, 18 years of age or older, were included. Four oral doses of baricitinib (2, 4, 8, and 10 mg) were compared with the placebo after 12 weeks of treatment. One primary outcome measure of efficacy, the PASI 75, was assessed. AEs were collected by systematic assessment.

The study was funded by Eli Lilly.

The efficacy and safety results at 12 weeks are presented in **Supplementary Tables 3, 12**. Serious baricitinib AEs are summarized in **Supplementary Table 13**.

## Solcitinib

A full-text reference on systemic treatment using solcitinib was published in a dermatological journal in 2016 (**Supplementary Table 7**). The publication was multinational involving multiple centers, with the USA contributing the greatest number of authors. A total of 12 authors, 10 of whom had a pharmaceutical industry affiliation and two of whom had a dermatology center affiliation, contributed to this study. The authors declared that conflict of interests were involved. The study was funded by GlaxoSmithKline.

A randomized phase-IIb study on systemic treatment with solcitinib was conducted from March 2013 to March 2014 (**Supplementary Table 1**). A total of 68 patients aged 18–75 years, of both sexes, were included. Three oral doses of solcitinib (100, 200, and 400 mg) were compared with the placebo after 12 weeks of treatment. PASI 75 was assessed as the primary outcome measure of efficacy. AEs were collected through systematic assessment. This study was funded by GlaxosmithKline.

The efficacy and safety results at 12 weeks are summarized in **Supplementary Tables 3, 14**. Serious solcitinib AEs are shown in **Supplementary Table 15**.

## Itacitinib

A full-text reference on systemic treatment with itacitinib was published in a dermatological journal in 2016 (**Supplementary Table 7**). The publication was multinational involving multiple centers, with the USA contributing the greatest number of authors. A total of 11 authors (nine from the pharmaceutical industry and two from research institutions) contributed to this study, nine of whom declared a conflict of interest. It was funded by the Incyte Corporation.

A phase II study on systemic treatment with itacitinib was conducted between June 2012 and February 2013 (**Supplementary Table 1**). A total of 50 patients of both sexes, aged 18–75 years, were included in the study. Four oral doses (100 mg QD, 200 mg QD, 200 mg BID, and 600 mg QD) were compared with the placebo at 28 days. The efficacy, PGA change, and primary safety objectives were evaluated. We did not find a methodology for AE assessment in the publications or on the clinical trial webpage. The study was funded by the Incyte Corporation.

The results for efficacy and safety after 28 days of treatment are presented in **Supplementary Tables 3, 16, 17**.

## Deucravacitinib (BMS-986165)

A full-text reference on (BMS-986165) systemic treatment with deucravacitinib was published in a general medicine journal in 2018 (**Supplementary Table 7**). The study was multinational involving multiple centers, with the USA contributing the greatest number of authors. The study was conducted by nine authors (three from the pharmaceutical industry, two from dermatological institutions, and four from other research institutions). The authors declare that conflict of interests were involved. The study was funded by Bristol Myers Squibb.

Eight studies, one in phase I, one in phase-II, and six in phase III with 140, 268, and 3,690 patients, respectively, of both sexes and all ages on systemic deucravacitinib treatment, were conducted from November 2016 to April 2024 (**Supplementary Table 1**). Six of these eight clinical trials studied the primary efficacy variables, PASI and PGA. Three oral doses (3 mg QD, 3 mg BID, and 6 mg BID) were compared to the placebo, apremilast, famotidine, and interferon 2alfa recombinant at 12 or 16 weeks. We did not find an AE assessment methodology. This study was funded by Bristol Myers Squibb.

The efficacy and safety at 12 weeks are summarized in **Supplementary Tables 3, 18**.

## Abrocitinib (PF-04965842)

A full-text reference on the systemic treatment with abrocitinib was published in a dermatology journal in 2018 (**Supplementary Table 7**). The publication was uninational (USA), involving multiple centers. A total of 12 authors (nine, one, and two from the pharmaceutical industry, a dermatological institution, and a research institution, respectively) contributed to this study. The authors declare no conflict of interest. This study was funded by Pfizer.

A phase-II study on systemic treatment with abrocitinib was conducted between November 2014 and September 2015 (**Supplementary Table 1**). A total of 59 patients of both sexes, aged 18–65 years, were included. Three oral doses (200 mg QD, 400 mg QD, and 200 mg BID) were compared with the placebo at 4 weeks. The PASI was evaluated as a primary objective. AE was collected by a non-systematic assessment. This study was funded by Pfizer.

The efficacy and safety results are presented in **Supplementary Tables 3, 19**.

## Brepocitinib (PF-06700841)

A full-text reference on systemic treatment with brepocitinib was published in a pharmacology journal in 2017 (**Supplementary Table 7**). The publication (USA) involved multiple centers. A total of 11 authors (10 from the uninational pharmaceutical industry and one from a research institution) contributed to this study. All authors declare that they have no conflict of interest. This study was funded by Pfizer.

Three studies, one in phase-I and two in phase-II, on systemic treatment with brepocitinib, with 96 and 452 patients, respectively, of both sexes ranging from 18 to 75 years in

age, were conducted from November 2014 to April 2021 (**Supplementary Table 1**). Seven oral doses, ranging from 30 mg QD to 100 mg QD, were compared to the placebo at four and 12 weeks. As primary objectives, PASI 75 was evaluated as a primary objective in two of these studies whereas pharmacokinetics and arterial pressure in the other one. The primary objectives namely safety, pharmacokinetics, efficacy, and PASI reduction were evaluated. AE was collected by a non-systematic assessment. These studies were funded by Pfizer.

No efficacy data were found. Safety data are presented in **Supplementary Tables 3, 20**.

# DISCUSSION

## Summary of Findings

To our knowledge, this is the first scoping review on the use of drugs targeting the JAK/STAT pathway for treating psoriasis. Nine molecules that inhibit the JAK/STAT pathway were identified. Some of these drugs act on a single-specific component of this pathway, such as abrocitinib and solcitinib (JAK1) and deucravacitinib (TYK2), whereas others do so by inhibiting several components, such as baricitinib, ruxolitinib, itacitinib (JAK1 and JAK2), brepocitinib (JAK1 and TYK2), tofacitinib (JAK2 and JAK3), and peficitinib (JAK1, JAK2, JAK3, and TYK2). All of them, except ruxolitinib applied topically, have been used orally. Tofacitinib was the only drug tested in both forms of administration. These drugs are in different stages of development. Most drugs are being tested in phase-II studies; only tofacitinib and deucravacitinib are being tested in phase-III studies. None of these drugs have been approved for use in the treatment of psoriasis.

The evidence available so far comes mainly from clinical trials that are promoted almost entirely by the pharmaceutical industry which also funds the notification of the results and conclusions from those studies. The dissemination of knowledge is mainly carried out through journals and congresses related to dermatology by authors belonging to the pharmaceutical industry with declared conflict of interests. Results from some of the registered studies have not been published after the completion of the trials. All systemic treatments have been compared mainly to the placebo, tofacitinib, and brepocitinib being the only drugs that have been tested against other active molecules, specifically, against etanercept and apremilast, and against famotidine, and interferon 2 alpha recombinant, respectively. Drugs administered topically include the placebo, calcipotriol, and betamethasone. The primary objectives of these clinical trials focus mainly on aspects of efficacy rather than safety and present primary endpoints in the short (12–16 weeks) or very short term (days—4 weeks). The effectiveness, measured as the reduction in PASI, PASI 75, and PGA, varies depending on the tested dose. Most of the data regarding security were collected by non-systematic assessments. The short-term data were similar between the different treatment arms, with nasopharyngitis being the most frequent AE. Tofacitinib was the only drug with long-term data available.

## Strengths and Limitations of the Review

Regarding the methodology of this study, the study was conducted based on an a priori protocol previously published in a scientific journal and using the latest standards in scoping review methodology; at least two researchers were involved in each phase. This manuscript was prepared according to the recommendations of the PRISMA Extension for Scoping Reviews. We also identified a high number of anti-JAK drugs whose current development phase made them eligible for inclusion in the latest Cochrane living review update (18).

Limitations related to funding and time prevented us from including articles written in languages other than English. Additionally, we were unable to contact the authors of some articles that would have helped reduce the amount of missing data, particularly for studies published as congress abstracts, as we did not exclude these types of publications. This work is a substudy, and although we believe that the global search strategy was a complete one, and that the three-phase search minimized overlooking of relevant articles, it is still possible that we did not include some articles describing studies related to the research topic. In March 2021, an update of the previously identified anti-JAK drugs was carried out, but only on the clinical trial webpage. Finally, most of the studies have been carried out, founded, and disseminated by pharmaceutical industry, and the validity of the conclusions may be comprised.

## Findings in Context and Research Gap

The creation and notification of knowledge about drugs that act on the JAK/STAT pathway are funded almost exclusively by the pharmaceutical industry. Further, knowledge diffusion is carried out by authors with conflict of interest, most of whom belong to the pharmaceutical industry. In addition, a high percentage of references are congress abstracts that are not subjected to any peer review process, and it is a known fact that the products of sponsors are favored (19). Also, it is common knowledge that between two-thirds and three-quarters of randomized trials reported in major journals have been supported by the pharmaceutical industry (20). There is strong evidence to show that compared to independent trials, industry-funded studies exaggerate treatment effects in favor of products promoted by their sponsor (21). Furthermore, industry-sponsored trials are more likely than other trials to conclude that a drug is safe (22). Thus, independent studies are necessary. Alternatively, external evaluators could access the primary studies and participate in the dissemination of the results. A meta-epidemiological study has found that randomized clinical trials using routinely collected data to assess outcomes indicate systematically less favorable treatment effects than trials using traditional methods used in the clinical trials considered in this review. In this context, using data from clinical patient registers, mobile devices, or electronic health records may improve the validity of the results of treatments (23). Further, we found clinical trials whose results have not been published or have not been included in clinicalTrials.org; there is evidence of a delay of more than 7 years in the publication of the results after the study completion of up to 25% of them (24). There is evidence on how selective reporting of studies poses a risk to the health of patients (25). All the above factors must

be considered when evaluating the knowledge available on these drugs at the time of evaluation.

The objective of the studies is found to most frequently focus on the efficacy outcomes, whose readout is the extension of the lesions, PASI, and PGA. Although these outcomes are the most widely used in the trials of drugs for psoriasis, standard measurement criteria are essential for the results to be accepted by the clinical community. However, it is also true that a key determining factor of the scientific value of clinical trials is the choice of measures of outcomes (26). In this sense, bestowing more importance on the influence of the surface body in reducing the quality of life is questionable; this impact is influenced by factors depending on the location of lesions (palms, plants, and visible and stetic-disfigured regions). In fact, symptoms of pain or itching, the presence of comorbidities, and being older or female are the factors that are most clearly associated with a decrease in quality of life (27). Therefore, it is possible that the efficacy measured in these trials was not the most useful for clinical extrapolation in patients. Here, the Cochrane Skin Core Outcome Set Initiative is of great interest, as it has been recently established to improve and standardize outcome measurement in clinical trials and to make the evidence more useful (28). Regarding safety, the facts that most of the data were collected by non-systematic assessments and that the time frames were not specified make it difficult to interpret the findings. In this sense, a better methodology for collecting and reporting results is desirable. In addition, knowledge of safety is focused on the short or very short term, making the uncertainties high, necessitating better collection and notification of new data from more studies.

## CONCLUSION

The number of drugs targeting the JAK/STAT pathway for treating psoriasis is increasing, tofacitinib being the most widely known. The evidence available must be interpreted considering that the funding for conducting studies on these drugs and notification of their results comes mainly from the pharmaceutical industry. The sources of knowledge are RCTs, whose primary objectives are focused on the issues of efficacy rather than safety, and their cutoff points are located in the very short or short term; we put evidence enough together to point out that principal efficacy primary outcome scales did not take into account fundamental aspects that impact the quality of life, such as symptoms and the location of the lesions, which are very variable depending on the doses administered. Also, only tofacitinib and deucravacitinib are being tested in phase III clinical trials. The methodology used in investigating and reporting on the safety of the drugs used suggests that the current high level of confidence in the findings of these studies is overrated.

## 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

JR and FG-G: conceptualization. FG-G and EP-P: data curation and writing—original draft. JR: funding acquisition. FG-G, PG-A, AM-L, JH-P, JS-C, and EP-P: investigation. JR and EP-P: supervision. FG-G, EP-P, and PG-A: validation. JR, FG-G, and EP-P: visualization. EP-P: writing—review and editing. 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.2022.754116/full#supplementary-material

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