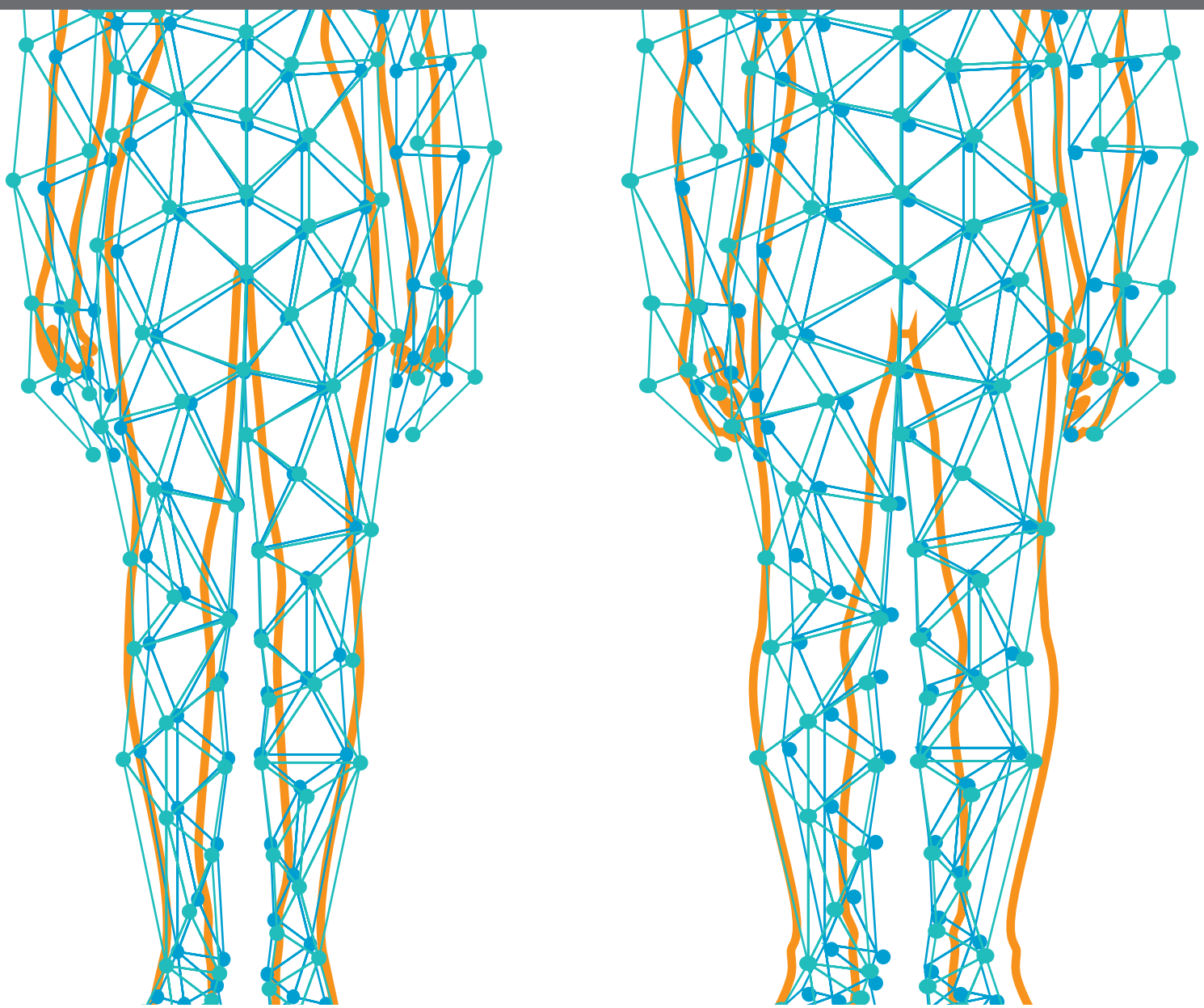
COMORBIDITIES IN PSORIATIC ARTHRITIS AND THEIR IMPACT ON THERAPEUTIC STRATEGIES

EDITED BY: Ilenia Pantano and Piero Ruscitti

PUBLISHED IN: Frontiers in Medicine



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ISSN 1664-8714
ISBN 978-2-88974-578-4
DOI 10.3389/978-2-88974-578-4

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COMORBIDITIES IN PSORIATIC ARTHRITIS AND THEIR IMPACT ON THERAPEUTIC STRATEGIES

Topic Editors:
Ilenia Pantano, University of Campania Luigi Vanvitelli, Italy
Piero Ruscitti, University of L'Aquila, Italy

Citation: Pantano, I., Ruscitti, P., eds. (2022). Comorbidities in Psoriatic Arthritis and Their Impact on Therapeutic Strategies. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-578-4

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frontiers in Medicine

EDITORIAL
published: 03 February 2022
doi: 10.3389/fmed.2021.830179

Editorial: Comorbidities in Psoriatic Arthritis and Their Impact on Therapeutic Strategies

Ilenia Pantano[1*†] *and Piero Ruscitti*[2†]

[1] *Rheumatology Unit, Department of Precision Medicine, University of Campania L. Vanvitelli, Caserta, Italy,* [2] *Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*

Keywords: psoriatic arthritis, comorbidities, BDMARDs, cardiovascular disease, obesity

Editorial on the Research Topic

Comorbidities in Psoriatic Arthritis and Their Impact on Therapeutic Strategies

Psoriatic Arthritis (PsA) is a chronic disease characterized by the inflammatory involvement of joint in patients with psoriasis, manifest or not (1). PsA may be also associated with a significant rate of comorbidities, mainly cardiometabolic, which, together with the musculoskeletal manifestations, may have a relevant impact on quality of life and outcome of these patients (2, 3). The synergy between inflammation and "traditional" cardiovascular risk factors may result in this typical clinical phenotype and may be considered as a part of the psoriatic disease itself. Multiple lines of evidence may suggest that at the basis of these comorbidities there is a cytokine activation (2, 3). The systemic inflammation is pivotal in the pathogenesis of atherosclerosis, involving low-grade inflammatory activity in the vascular wall (4). Moreover, inflammatory cytokines, such as TNF and IL-6, are also involved in the pathophysiology of hypertension and dyslipidemia associated with obesity and insulin resistance. In recent years, several drugs have been approved for PsA but little data is available on their impact of on associated comorbidities of these patients. Similarly, the impact of these comorbidities in influencing the choice as well as the efficacy of such medications remain to be fully evaluated. There are no specific data which may guide the physician in the therapeutic choice based on the presence of certain comorbidities. Given that the comorbidities may be linked to the inflammatory process underlying PsA, it could be possible to speculate that the currently available therapies could also play a role in the associated disorders.

Taking together these observations, in this special issue, the impact of comorbidities was assessed in the management of patients with PsA. The selected articles are very different from each since the topic itself is very heterogeneous. The association between PsA and different comorbidities was discussed, highlighting the relevance of this problem in managing these patients (Lu et al.; De Lorenzis et al.; Alonso et al.; Atzeni et al.; Novelli et al.; Chia et al.; Tripolino et al.; Ramírez et al.; Englbrecht et al.). The rate of depression was discussed in PsA, which is acknowledged as a frequent comorbidity in inflammatory arthritis influencing the patient clinical picture (Englbrecht et al.). In addition, a vascular dysfunction was observed in patients with PsA and depression; a correlation between flow mediated dilatation features and depressive symptoms was observed (De Lorenzis et al.). The most frequently topic of these works was the cardiometabolic risk associated with PsA (Atzeni et al.; Novelli et al.; Ramírez et al.). An update about cardiovascular risk in PsA was provided, also describing the involved inflammatory pathogenic mechanisms (Novelli et al.). In fact, a number of epidemiologic studies, systematic reviews, and meta-analyses have suggested that PsA may be considered an independent risk factor for major adverse cardiovascular events. In addition, the clinical impact of obesity was reviewed in PsA (Ramírez et al.); this is recognized as

Edited and reviewed by:
João Eurico Fonseca, University of Lisbon, Portugal

***Correspondence:**
Ilenia Pantano
ilenia.pantano@libero.it

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *06 December 2021*
Accepted: *22 December 2021*
Published: *03 February 2022*

Citation:
Pantano I and Ruscitti P (2022) Editorial: Comorbidities in Psoriatic Arthritis and Their Impact on Therapeutic Strategies. Front. Med. 8:830179. doi: 10.3389/fmed.2021.830179

an independent risk factor for PsA occurrence and its association with cardiometabolic burden (2). The clinical role of hyperuricemia in managing patients with PsA was also pointed out. Serum levels of uric acid may be associated with the severity of clinical manifestations and inflammatory features in patients with PsA (Tripolino et al.). In addition, in this special issue, the treatment was described in PsA with associated extra-articular manifestations or comorbidities (Alonso et al.; Atzeni et al.; Tripolino et al.). The management of concomitant uveitis and inflammatory bowel disease in these patients may be associated with specific therapeutic strategies according to different underlying pathogenetic steps (Chia et al.). Frequently, patients with PsA are characterized by the presence of metabolic syndrome, but the impact of approved therapies on that is far from being optimal. Thus, the main evidence related to the possible effects of synthetic and biologic DMARDs on metabolic syndrome outcomes was described in patients with PsA (Atzeni et al.). Finally, the effectiveness of secukinumab, a monoclonal antibody binding IL-17A, was explored in a "real-life" setting (Alonso et al.). Interestingly, in this study, the presence of some comorbidities (i.e., high blood pressure, diabetes, and obesity) were associated with a lower risk of discontinuation of the biologic DMARDs in patients with PsA (Alonso et al.). These findings may suggest that the effectiveness of this drug may be not influenced by the presence of comorbidity. In fact, the specific mechanism of action of secukinumab may not be influenced by the presence of associated disorder and possibly proposing its therapeutic relevance in a "real-life" setting. In this context, it must be pointed out that the evidence deriving from randomized clinical trials did not entirely clarify this issue. The strict enrolment criteria of these studies would decrease the generalizability of the results since the enrolled patients could not fully mirror the "real-life" scenario.

Taking together these findings, the increase of the rate of comorbidities, especially the cardiometabolic ones, is recognized in PsA with a consequent enhanced mortality and disability in these patients. In the clinical practice every rheumatologist routinely deals with these problems in patients with PsA and there are no specific therapeutic strategies to manage these comorbidities. This special issue has collected data about the influence of comorbidities, especially cardiometabolic, in the management of these patients. Thus, this special issue may provide the rationale of designing specific designed studies to fully evaluate these issues in PsA.

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

We thank all the authors who participated in the special issue by submitting their works.

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

frontiers in Medicine

ORIGINAL RESEARCH
published: 11 May 2021
doi: 10.3389/fmed.2021.666802

Increased Incidence of Total Knee Replacement Surgery in Patients With Psoriasis: A Secondary Cohort Analysis of a Nationwide, Population-Based Health Claims Database

Ming-Chi Lu[1,2†], *Kuo-Sheng Fan*[3†], *Chia-Wen Hsu*[4], *Malcolm Koo*[5,6*] and *Ning-Sheng Lai*[1,2*]

[1] Division of Allergy, Immunology and Rheumatology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [2] School of Medicine, Tzu Chi University, Hualien City, Taiwan, [3] Division of Pulmonology and Critical Care, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [4] Department of Medical Research, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [5] Graduate Institute of Long-term Care, Tzu Chi University of Science and Technology, Hualien City, Taiwan, [6] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

OPEN ACCESS

Edited by:
Piero Ruscitti,
University of L'Aquila, Italy

Reviewed by:
Anabela Barcelos,
New University of Lisbon, Portugal
Hsin-Hua Chen,
Taichung Veterans General Hospital, Taiwan

***Correspondence:**
Malcolm Koo
m.koo@utoronto.ca
Ning-Sheng Lai
tzuchilai@gmail.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: 11 February 2021
Accepted: 19 April 2021
Published: 11 May 2021

Citation:
Lu M-C, Fan K-S, Hsu C-W, Koo M and Lai N-S (2021) Increased Incidence of Total Knee Replacement Surgery in Patients With Psoriasis: A Secondary Cohort Analysis of a Nationwide, Population-Based Health Claims Database. Front. Med. 8:666802. doi: 10.3389/fmed.2021.666802

Patients with rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, have increased risk of receiving total knee replacement surgery or total hip replacement surgery. We speculated that psoriasis could also attack the joints of the knees and hips, leading to an increased risk of receiving total knee replacement surgery or total hip replacement surgery. The aim of this study was to investigate the risk of total knee replacement or total hip replacement surgery in patients with psoriasis using a nationwide, population-based health claims database in Taiwan. Using the Taiwan's National Health Insurance Research Database, we identified 10,819 patients with psoriasis between 2000 and 2012. A comparison cohort consisting of five patients without psoriasis for each patient with psoriasis was assembled, based on frequency matching for sex, 10-year age interval, and index year. Both groups were followed until a diagnosis of the study outcomes (total knee replacement or total hip replacement surgery) or the end of the follow-up period. Incidence rate ratios (IRRs) for the outcome variables were calculated using multiple Poisson regression models. Female patients with psoriasis exhibited a significantly higher incidence of receiving total knee replacement surgery [adjusted IRR = 1.44, $p = 0.014$)]. Analyses stratified by age groups showed that the risk of receiving total knee replacement surgery was significantly higher older (adjusted IRR = 1.31, $p = 0.047$) patients with psoriasis. There were no significant differences in the risk of receiving total hip replacement surgery in patients with psoriasis compared with controls, either with or without stratification by sex or age groups. In conclusion, patients with psoriasis were associated with an increased risk of receiving total knee. Clinicians should be vigilant in assessing the presence of arthritis in these patients, and initiate strategies to delay or prevent the need for joint replacement.

Keywords: psoriasis, psoriatic arthritis, total knee replacement, total hip replacement, surgery

INTRODUCTION

Psoriasis is a common, chronic, non-communicable, inflammatory skin disease characterized by erythematous, scaly patches, or plaques on the skin (1). The worldwide prevalence of psoriasis was estimated to vary from 0.14 to 1.99% (2). The debilitating and highly visible skin symptoms of psoriasis can severely impact on patients' quality of life (3). Up to one-third of patients with psoriasis could develop psoriatic arthritis, which is a chronic and potentially severe condition. It can cause joint damage leading to deformity, and may require surgery to alleviate pain and restore function (4). Our previous studies have shown that patients with rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, have increased risk of receiving total knee replacement (TKR) surgery or total hip replacement (THR) surgery (5–7). We speculated that psoriasis could also attack the joints of the knees and hips resulting in their destruction, which then lead to an increased risk of receiving TKR and THR. Therefore, the aim of this study was to investigate the incidence of THR and TKR in patients with psoriasis using a nationwide, population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study Design and Data Source

This study is a secondary analysis of a nationwide, population-based, retrospective cohort based on the data available from the National Health Insurance Research Database (NHIRD). The study protocol was approved by the institutional review board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan (No. B10104020). The requirement for obtaining informed consent from patients was waived because the data file contained only deidentified secondary data.

Identification of the Psoriasis Cohort and a Comparison Cohort

Patients in the psoriasis cohort were identified based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 696.0, 696.1, and 696.8, using the ambulatory care expenditures by visits datafile of the Longitudinal Health Insurance Database (LHID 2000) from January 1, 2000 to December 31, 2012. The comparison cohort was assembled from the patients in LHID 2000. Five patients without psoriasis were selected, based on frequency matching for 10-year age interval and index year, for each patient with psoriasis.

In both cohorts, patients with systemic lupus erythematosus (ICD-9-CM code 710.0), rheumatoid arthritis (ICD-9-CM code 714.0), ankylosing spondylitis (ICD-9-CM code 720.0), juvenile rheumatoid arthritis (ICD-9-CM code 714.3X), and acquired immune deficiency syndrome (ICD-9-CM code: 042) were excluded. In addition, patients with fracture of the lower limb (ICD-9-CM codes 820–829), obesity (ICD-9-CM code 278.0x), osteoarthritis (ICD-9-CM code 715.xx), and avascular necrosis (ICD-9-CM code 733.4x) were identified and these conditions were adjusted as potential confounders. Patients younger than 20 years or older than 80 years of age were also excluded.

Identification of Total Knee Replacement Surgery and Total Hip Replacement Surgery

We followed all patients until the occurrence of our study events or the end of the follow-up period, separately for the TKR and THR outcome variables. TKR and THR were defined in this study using inpatient ICD-9-CM procedure codes 81.54 and 81.51, respectively. For the analysis of the risk of TKR, patients in the psoriasis and comparison cohorts receiving TKR before the index date were excluded. For the analysis of the risk of THR, those receiving THR before the index date were excluded.

Statistical Analysis

We compared the basic characteristics between the psoriasis cohort and the comparison cohort using *t*-test or Chi-square test, as appropriate. For the psoriasis cohort and the comparison cohort, the incidence rate per 1,000 person-years was separately calculated for TKR and THR. Incidence rate ratios (IRRs) for the outcome variables were calculated using Poisson regression models (generalized linear models with a Poisson log-linear link function and person-years as the offset variable), with and without adjusting for potential confounding factors, including fractures of the lower limb, obesity, osteoarthritis, osteonecrosis, age, sex, socioeconomic status, and geographic region. In addition, subgroup analyses were conducted with stratification by age groups (20–44, 45–64, and 65–80 years). All statistical analyses were performed using IBM SPSS Statistics software package, version 24.0 (IBM Corp, Armonk, NY, USA). A p-value of < 0.05 was considered significant.

RESULTS

There were no significant differences between the psoriasis cohort and the comparison cohort in age and sex. Patients with psoriasis showed a higher socioeconomic status and different geographic distribution compared with the comparison cohort. Patients with psoriasis had a significantly higher proportion of obesity ($p = 0.004$), osteoarthritis ($p < 0.001$), and avascular necrosis ($p < 0.001$), but a significantly lower proportion of fractures of the lower limb ($p = 0.046$) compared to those in the comparison cohort (**Table 1**).

Table 2 shows the incidence rates, IRRs, and adjusted IRRs of TKR for the psoriasis cohort and the comparison cohort. Patients with psoriasis showed a significantly higher incidence of receiving TKR compared with the comparison cohort (adjusted IRR 1.38, $p = 0.007$). In addition, with subgroup analyses stratified by sex, female patients, but not male patients with psoriasis had a significantly higher incidence of receiving TKR (adjusted IRR 1.44, $p = 0.014$) compared with the comparison cohort. Furthermore, in analyses stratified by the three age groups, only patients with psoriasis showed an increased incidence in TKR in the 60–80 year group (adjusted IRR 1.31, $p = 0.047$).

TABLE 1 | Basic characteristics of the psoriasis cohort and comparison cohort ($N = 64,914$).

Variable	*N* (%)				*P*
	Psoriasis cohort 10,819 (16.7)		Comparison cohort 54,095 (83.3)		
Sex					>0.999
male	6,197	(57.3)	30,985	(57.3)	
female	4,622	(42.7)	23,110	(42.7)	
Age group (years)					>0.999
20–39	4,182	(38.7)	20,910	(38.7)	
40–59	4,045	(37.3)	20,225	(37.3)	
60–80	2,592	(24.0)	12,960	(24.0)	
Mean age (standard deviation), years	46.3	(16.6)	46.3	(16.6)	0.988
Median age (interquartile range), years	45	(32–59)	45	(32–59)	
Obesity	38	(0.4)	112	(0.2)	0.004
Fracture of the lower limb	38	(0.4)	268	(0.5)	0.046
Osteoarthritis	424	(3.9)	1,157	(2.1)	<0.001
Avascular necrosis	20	(0.2)	32	(0.1)	<0.001
Socioeconomic status ($n = 64,879$)					<0.001
low	5,483	(50.7)	30,115	(55.8)	
middle	2,887	(26.7)	14,019	(25.9)	
high	2,449	(22.6)	9,886	(18.3)	
Geographic region ($n = 63,237$)					<0.001
Northern	5,864	(55.6)	32,748	(62.2)	
Central	1,539	(14.6)	8,629	(16.4)	
Southern	2,943	(27.9)	10,260	(19.5)	
Eastern	202	(1.9)	1,052	(2.0)	

Socioeconomic status was estimated by insurance premiums based on salary. Low: ≤ 19,000 New Taiwan dollars (NT$); middle: 19,001–24,000; and high: > 24,000.

TABLE 2 | The incidence rate and incidence risk ratio of total knee replacement in the psoriasis cohort and comparison cohort ($N = 64,672$).

Disorder (ICD-9-CM)		Psoriasis cohort ($n = 10,764$)			Comparison cohort ($n = 53,908$)			IRR (95% CI)	aIRR* (95% CI)
		No. of patient	Person-years	IR	No. of patient	Person-years	IR	*P*	*P*
TKR (815.4)	Overall	96	68,510	1.40	297	325,346	0.91	1.54 (1.22–1.93) < 0.001	1.38 (1.09–1.75) 0.007
	Sex								
	male	33	39,013	0.85	111	185,879	0.60	1.42 (0.96–2.09) 0.079	1.29 (0.87–1.92) 0.209
	female	63	29,497	2.14	186	139,467	1.33	1.60 (1.20–2.13) 0.001	1.44 (1.08–1.93) 0.014
	Age group (years)								
	20–39	1	27,750	0.04	3	132,933	0.02	1.60 (0.17–15.35) 0.685	2.84 (0.26–31.36) 0.394
	40–59	21	25,817	0.81	56	125,788	0.45	1.83 (1.11–3.02) 0.018	1.68 (1.00–2.81) 0.051
	60–80	74	14,943	4.95	238	66,625	3.57	1.39 (1.07–1.80) 0.014	1.31 (1.00–1.71) 0.047

aIRR, adjusted incidence rate ratio; CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth revision, clinical modification; IR, incidence rate per 1,000 person-years; IRR, incidence rate ratio; TKR, total knee replacement.

**Adjusted for age, sex, socioeconomic status, geographic region, obesity, fracture of the lower limb, osteoarthritis, and avascular necrosis.*

Table 3 shows the incidence rates, IRRs, and adjusted IRRs of THR for the psoriasis cohort and the comparison cohort. The overall adjusted IRR for receiving THR in patients with psoriasis was not significantly different between the two cohorts. Similarly, subgroup analyses stratified by either the three age groups or sex were not significantly different between the two cohorts in the risk of THR.

DISCUSSION

This secondary cohort analysis of a nationwide, population-based health claim database showed that patients with psoriasis, especially female and those middle-aged or older, had a significantly higher risk of receiving TKR. On the other hand, male and those middle-aged patients with psoriasis had a significantly higher risk of receiving THR. It is

TABLE 3 | The incidence rate and incidence risk ratio of total hip replacement in the psoriasis cohort and comparison cohort ($N = 64,781$).

Disorder (ICD-9-CM)		Psoriasis cohort ($n = 10,782$)			Comparison cohort ($n = 53,999$)			IRR (95% CI)	aIRR* (95% CI)
		No. of patient	Person-years	IR	No. of patient	Person-years	IR	*P*	*P*
THR (815.1)	Overall	37	68,548	0.54	137	325,555	0.42	1.28 (0.89–1.84) 0.179	1.27 (0.88–1.84) 0.204
	Sex								
	male	27	38,931	0.69	89	185,755	0.48	1.45 (0.94–2.23) 0.092	1.40 (0.90–2.19) 0.137
	female	10	29,617	0.34	48	139,800	0.34	0.98 (0.50–1.94) 0.962	1.09 (0.55–2.19) 0.803
	Age group (years)								
	20–39	5	27,716	0.18	21	132,919	0.16	1.14 (0.43–3.03) 0.790	1.18 (0.42–3.32) 0.757
	40–59	19	25,725	0.74	61	125,611	0.49	1.52 (0.91–2.54) 0.111	1.55 (0.91–2.65) 0.106
	60–80	13	15,107	0.86	55	67,025	0.82	1.05 (0.57–1.92) 0.878	0.97 (0.53–1.79) 0.923

aIRR, adjusted incidence rate ratio; CI, confidence interval; ICD-9-CM, international classification of diseases, Ninth revision, clinical modification; IR, incidence rate per 1,000 person-years; IRR, incidence rate ratio; THR, total hip replacement.

**Adjusted for age, sex, socioeconomic status, geographic region, obesity, fracture of the lower limb, osteoarthritis, and avascular necrosis.*

known that women are more likely to receiving TKR in the general population (8). Knee joint inflammation has been demonstrated in patients with psoriasis (9), and our finding was consistent with their findings. Although the presence of detection bias was possible as a result of increased medical utilization in our patients, we believe its effects on my results are minimal. First, patients generally would only consider TKR and THR surgery when they have severe joint damage over the hip or knee joint, which is accompanied with obvious pain and disability. Second, prior to TKR and THR surgery, an approval from the Taiwan National Health Insurance Administration, which requires a review of X-ray films of the target joint and clinical data by an orthopedic specialist (5). As these factors are not related to increased medical surveillance, our results should not be affected by detection bias.

Prior to this study, we anticipated that some patients with psoriasis would develop psoriatic arthritis, causing chronic and destructive inflammation of joints and thereby leading to an increased risk of receiving TKR or THR. However, we found that only four (4.2%) patients with psoriasis were diagnosed with psoriatic arthritis before TKR and only three (8.1%) patients were diagnosed with psoriatic arthritis before THR in our study. The number of cases is too few to analyze. The percentage of psoriatic arthritis in patients with psoriasis has been reported to be 20–30% (4). Nevertheless, the percentage of psoriatic arthritis in patients with psoriasis was found to be only 8.2% based on a study using the NHIRD in Taiwan (10). A study based on 34 dermatology centers in seven European and North American countries found that approximately a third of patients with psoriasis seen in dermatology centers had psoriatic arthritis as assessed by rheumatologists. Among the patients with psoriatic arthritis, 41% had not been previously given the diagnosis (11). A meta-analysis based on seven epidemiological studies and five studies on psoriatic arthritis screening questionnaires also supported that there is a high prevalence of undiagnosed psoriatic arthritis in patients with psoriasis (12). In a cross-sectional clinical survey of 414 patients, the percentage of psoriatic arthritis patients with psoriasis was found to be 30.6% (13). Therefore, we believed that psoriatic arthritis was underdiagnosed in the NHIRD. In addition, there are many therapeutic agents available for treating psoriatic arthritis (14). Early treatment and tight control of inflammation in early psoriatic arthritis can clearly improve patients' outcome (15). Therefore, clinicians need to be vigilant regarding the possible psoriatic arthritis in patients with psoriasis.

There are some limitations in this study. First, the identification of psoriasis, psoriatic arthritis, THR, and TKR were based on ICD-9-CM codes. Nevertheless, the National Health Insurance Administration routinely performs audits on random samples of medical claims to ensure their accuracy. Second, the severity of psoriasis could not be obtained because the NHIRD data did not include clinical assessments. Despite these limitations, the strengths of this study included the large sample size, a population-based cohort study design, and a long follow-up period.

In conclusion, this study showed that female and older patients with psoriasis had a higher risk of receiving TKR. Patients with psoriasis did not show an increased risk for receiving THR. Clinicians should be vigilant in assessing the presence of arthritis in patients with psoriasis, and initiate strategies to delay or prevent the need for joint replacement in these patients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act," data cannot be made publicly available. Requests for data can be sent as a formal application to the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare, Taiwan. Requests to access these datasets should be directed to http://dep.mohw.gov.tw/DOS/np-2497-113.html.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan (No. B10104020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR'S NOTE

This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by the National Health Research Institutes, Taiwan. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare or the National Health Research Institutes, Taiwan.

AUTHOR CONTRIBUTIONS

M-CL, K-SF, and N-SL conceptualized the idea of the manuscript. C-WH conducted statistical analysis of data. M-CL and MK wrote the manuscript. All authors have read and approved the contents of the final manuscript.

FUNDING

This work was supported by grants from the Buddhist Tzu Chi Medical Foundation (Tzu Chi Medical Mission Project 105-01-05 and TCMF-A 108-05).

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

frontiers in Medicine

ORIGINAL RESEARCH
published: 26 May 2021
doi: 10.3389/fmed.2021.679009

Multicenter Study of Secukinumab Survival and Safety in Spondyloarthritis and Psoriatic Arthritis: SEcukinumab in Cantabria and ASTURias Study

*Sara Alonso[1], Ignacio Villa[2], Sabela Fernández[1], José L. Martín[2], Lilyan Charca[1], Marina Pino[1], Leyre Riancho[2], Isla Morante[2], Monserrat Santos[2], Anahy Brandy[3], Elena Aurrecoechea[2], Loreto Carmona[4] and Rubén Queiro[1,5]**

[1] Rheumatology Division, Hospital Universitario Central de Asturias, Oviedo, Spain, [2] Rheumatology Division, Hospital Sierrallana, Torrelavega, Spain, [3] Rheumatology Division, Hospital Universitario de Cabueñes, Gijón, Spain, [4] Instituto de Salud Musculoesquelética, Madrid, Spain, [5] Instituto de Investigación Sanitaria del Principado de Asturias (ISPA) Translational Immunology Division, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain

OPEN ACCESS

Edited by:
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Reviewed by:
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***Correspondence:**
Rubén Queiro
rubenque7@yahoo.es

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *10 March 2021*
Accepted: *29 April 2021*
Published: *26 May 2021*

Citation:
Alonso S, Villa I, Fernández S, Martín JL, Charca L, Pino M, Riancho L, Morante I, Santos M, Brandy A, Aurrecoechea E, Carmona L and Queiro R (2021) Multicenter Study of Secukinumab Survival and Safety in Spondyloarthritis and Psoriatic Arthritis: SEcukinumab in Cantabria and ASTURias Study. Front. Med. 8:679009. doi: 10.3389/fmed.2021.679009

Objectives: We aimed to evaluate the drug retention rate and safety of secukinumab (SEC) in patients with axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA) in a real clinical setting.

Methods: This multicenter retrospective observational study included all AxSpA and PsA patients who received at least one dose of SEC. Adverse events (AE) and the drug retention rate were the main study outcomes. Drug survival was analyzed by Kaplan-Meier curves while predictive factors of discontinuation were evaluated using a Cox regression analysis. The weight of these associations was estimated by hazard ratio (HR) values.

Results: We included 154 patients (59 PsA and 95 AxSpA). Mean disease duration was 6.5 years (IQR 2-8). Sixty-one percent of patients were treated with two or more biologics prior to SEC. The 1 and 2-year retention rates for SEC were 66 and 43%, respectively. The main causes of discontinuation were inefficacy (59%) and AE (36%). The factors associated with lower risk of discontinuation were male gender (HR 0.54, 95% CI 0.38-0.78 $p = 0.001$), obesity (HR 0.53, 95% CI 0.30-0.93 $p = 0.027$), hypertension (HR 0.55, 95% CI 0.30-0.93 $p = 0.008$), and diabetes (HR 0.42 95% CI 0.18-0.99 $p = 0.047$) while number of previous biologics and depression were predictors of discontinuation (HR 1.18, 95% CI 1.04-1.34 $p = 0.011$ and HR 2.53, 95% CI 1.61-3.96 $p < 0.001$).

Conclusions: SEC showed a good retention rate in a population previously exposed to several biological therapies. As a novelty, cardiometabolic comorbidities were associated with better drug survival.

Keywords: secukinumab, safety, survival, spondyloarthritis, psoriatic arthritis, comorbidities

INTRODUCTION

Secukinumab (SEC) is a human monoclonal antibody (IgG1) directed against IL-17A, approved for the treatment of plaque psoriasis (1), psoriatic arthritis (PsA) and axial spondyloarthritis (AxSpA) (2, 3). The safety profile observed for SEC during clinical development is generally not different from other biological therapies including among others, infections, neutropenia, and hypersensitivity reactions. Data from randomized controlled clinical trials (RCTs) and post-marketing surveillance have shown that SEC has a favorable safety profile over long-term treatment (4), even with fewer adverse events and low frequency of treatment discontinuation (2, 4–6). Compared to placebo, SEC has been described to increase the incidence of upper respiratory tract infections and an increased incidence of mucocutaneous Candida infections, middle ear infections, and herpes simplex infections has also been observed compared to placebo (7). Some severe cases and exacerbations of Crohn's disease have also been described (8), so caution is recommended with its use. In terms of routine clinical practice, studies show a safety profile similar to that previously reported in RCTs and their long-term extension studies (9–12), but information from real-world evidence studies is still scarce. Data on survival of biological therapy in PsA from the DANBIO registry showed a median survival of the first TNF inhibitor (TNFi) being 2.2 years and the second and third TNFi being 1.3 and 1.1 years, respectively. Switchers were more frequently women, had a shorter disease duration, a higher median Health Assessment Questionnaire (HAQ) score, DAS28 and fatigue and pain scores (on a VAS), and had more swollen and tender joints compared to non-switchers when they started the first TNFi (13). Likewise, the NOR-DMAR registry performed an analysis in patients who switched from one TNFi to another, finding that survival of the second TNFi was only 3 years in 36% (14). However, we currently have no consistent data on long-term survival of SEC in patients with AxSpA and PsA in routine clinical practice. Efficacy, the number of previous treatments, specific comorbidity and perhaps obesity and smoking are factors that may determine SEC survival.

Therefore, we aimed to evaluate the safety of SEC in actual clinical practice, as well as to study drug retention and causes for discontinuation, and to evaluate factors associated with SEC suspension in patients diagnosed with PsA or AxSpA who receive or have received such therapy.

METHODS

We designed a multicenter retrospective longitudinal observational study. The project adhered to the postulates of the Declaration of Helsinki and its extensions as well as to the rules of good clinical practice and General Data Protection Regulation. The ethics review board of Sierrallana Hospital approved the study and exempted the participants from informed consent due to the retrospective nature of the study (EPA-OD, code: HUC- SEC-2019-01).

Study Population

Eligible subjects were all adult patients with a diagnosis of AxSpA (age range: 27-77 years) by the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (15) or PsA (age range: 24-81 years) by the Classification Criteria for Psoriatic Arthritis (CASPAR) (16) who received at least one dose of SEC in three hospitals from northern Spain.

The two primary outcomes were safety and drug survival. Safety was analyzed by reviewing the clinical charts from the date of initiation of SEC, as well as the hospital admission records; the following were specifically checked: (1) Infections (type, microorganism, location and whether it was accompanied by bacteremia); (2) neoplasms (type, location, and stage); (3) Events located or affecting any other organs or systems. Drug survival (in months) was defined as the time from the start of SEC to the last dose administered if discontinued or to the last dose administered if lost to follow-up. The reason for suspension was also collected.

TABLE 1 | Disease characteristics of the study population.

Characteristic	Psoriatic arthritis *n* = 59	Axial spondyloarthritis *n* = 95	Total *n* = 154
Age, mean (SD)	51 (12)	47 (10)	49 (11)
Male	27 (46)	58 (61)	85 (55)
Disease duration, m (SD)	7 (8)	6 (5)	6 (7)
Number of previous biologics, median (IQR)	3 (2)	3 (2)	3 (2)
csDMARD prior to SEC	39 (66)	15 (16)	54 (36)
Type of csDMARD			
Methotrexate	34 (58)	10 (11)	44 (29)
Leflunomide	9 (15)	3 (3)	12 (8)
Sulfasalazine	1 (2)	5 (5)	6 (4)
Other	3 (5)	1 (1)	4 (3)
Glucocorticoids	18 (31)	10 (11)	28 (19)
Secukinumab dose 300 mg	34 (57)	11 (12)	45 (29)
Obesity (BMI > 30)	16 (27)	10 (11)	26 (17)
Smoker	15 (26)	29 (31)	44 (29)
Hypertension	17 (29)	18 (19)	35 (23)
Dyslipidemia	22 (37)	19 (20)	41 (27)
Diabetes	9 (15)	3 (3)	12 (8)
COPD	1	-	1
Cardiovascular disease*	1	2	3 (2)
Ischemic heart disease	4 (7)	3 (3)	7 (5)
Depression	10 (17)	17 (18)	27 (18)
Chronic Kidney Disease	2	-	2
Hepatic failure	1	2	3 (2)

Cells include n (%) unless otherwise indicated.

**Myocardial infarction or cerebrovascular event.*

SD, standard deviation; IQR, interquartile range; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; BMI, body mass index; COPD, Chronic obstructive pulmonary disease.

The following secondary variables were collected: descriptive and explanatory variables related to treatment, disease, and comorbidities, indication (AxSpA, PsA), dose of SEC administered, corticosteroids, tobacco (active, ex-smoker, never), age, years evolution of the illness, sex, enthesitis, dactylitis, diabetes mellitus, hypertension, obesity, dyslipemia, depression, chronic obstructive pulmonary disease (COPD), major adverse cardiovascular events (MACE), ischemic cardiopathy, renal and hepatic insufficiency, biological treatment line (1st line, 2nd, 3rd, 4th...), primary or secondary failure, previous serious AEs, previous disease-modifying antirheumatic drugs (DMARDs) (yes/no and concomitant), BASDAI, BASFI, ASDAS, MDA, BSA, ESR, CRP, hemoglobin (baseline and at 6 and 12 months).

Statistical Analysis

The sample was described in terms of the distribution of the descriptive variables by summary statistics. The rate of AEs was estimated in total, by severity and by type of event. The denominator used was the total number of patients*years of follow-up. Survival was analyzed using Kaplan-Meier curves and the hazard ratio was used as a measure of the association. Multivariate Cox regression was used to analyze the effect of the explanatory variables on survival. Potential confounding variables were previous and concomitant treatments, and comorbidities.

A random sample of 68 individuals was deemed sufficient to estimate, with 95% confidence and a precision of ±5% units, a population rate of AE expected to be around 15%, and a percentage of replacements of 5%.

RESULTS

154 patients were included, 59 with PsA (38%) and 95 with AxSpA (62%), with a mean age of disease onset of 49 years (SD ± 11), being 55% men. The median disease duration was 6.5 years (IQR 2-8). **Table 1** shows a description of the study population, by diagnosis and total.

The population was largely refractory to biological therapy: SEC was the first line of treatment in 13 patients (8%), the second line in 46 (30%), the third line in 54 (35%) and subsequent lines in 41 (27%).

The median survival of SEC was 23 months (IQR 5-32), with a 1-year retention rate of 66% and a 2-year retention rate of 43%.

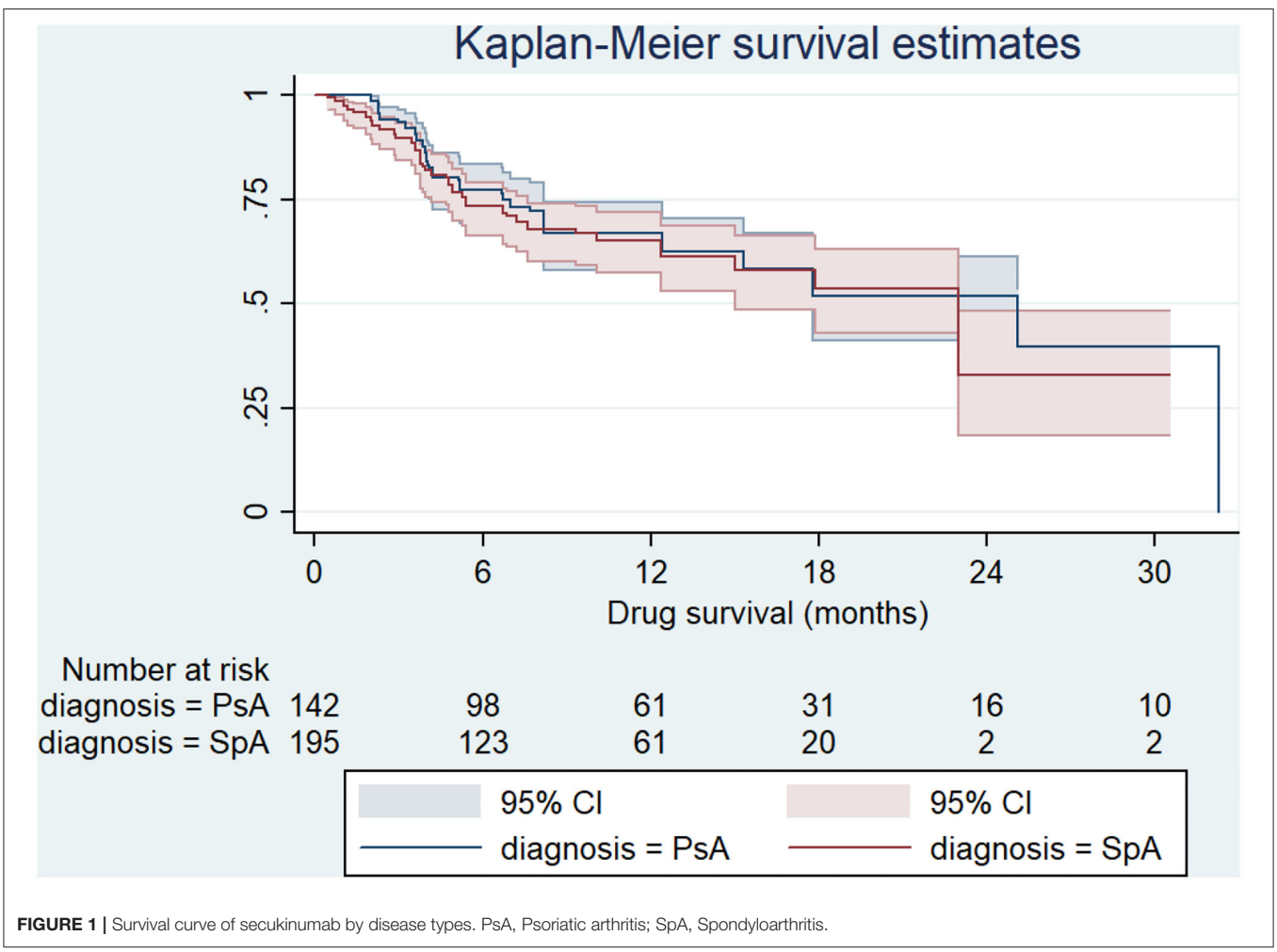

FIGURE 1 | Survival curve of secukinumab by disease types. PsA, Psoriatic arthritis; SpA, Spondyloarthritis.

No differences were found between AxSpA and PsA (log-rank p 0.526) (**Figure 1**).

The main cause of SEC discontinuation was inefficacy (59%) followed by AEs (23 cases, 36%). Most patients who discontinued due to AEs (71%) did so during the first 6 months of treatment. The rate of discontinuation due to AE was 6.4 per 1,000 persons-years (95% CI: 4.1-9.7). The most frequent AE were gastrointestinal (nausea, vomiting, and abdominal pain, including two cases of Crohn's disease), cutaneous (mainly generalized rash, pruritus, and papulo-nodular lesions), and infections (mostly upper respiratory tract). One major cardiovascular event was collected, and a neoplasm was diagnosed in two patients during treatment. Crohn's disease was diagnosed in two patients during the exposure. **Table 2** shows a description of the AEs identified.

The factors associated with lower risk of discontinuation were male gender (HR 0.54, 95% CI 0.38-0.78 $p = 0.001$), obesity (HR 0.53, 95% CI 0.30-0.93 $p = 0.027$), hypertension (HR 0.55, 95% CI 0.30-0.93 $p = 0.008$), and diabetes (HR 0.42 95% CI 0.18-0.99 $p = 0.047$) while number of previous biologics and depression were predictors of discontinuation (HR 1.18, 95% CI 1.04-1.34 $p = 0.011$ and HR 2.53, 95% CI 1.61-3.96 $p < 0.001$). The survival by treatment line (biologic order) and by obesity are shown in **Figures 2** and **3**. **Table 3** shows bivariable and multivariable survival analysis.

TABLE 2 | Description of adverse events collected.

Adverse event	*n* (%)	Withdrawal
Disorders of the blood and lymphatic system	0 (0)	-
Heart disorders	1 (0.6)	1/1
Congenital, familial and genetic disorders	0 (0)	-
Disorders of the ear and vestibular maze	1 (0.6)	1/1
Endocrine disorders	0 (0)	-
Eye disorders	0 (0)	-
Gastrointestinal disorders	6 (3.8)	6/6
General symptoms and local injection site reactions	0 (0)	-
Hepatobiliary disorders	0 (0)	-
Immune system disorders	0 (0)	-
Traumatic injuries, intoxications and complications of therapeutic procedures	0 (0)	-
Disorders of metabolism and nutrition	0 (0)	-
Musculoskeletal and connective tissue disorders	0 (0)	-
Disorders of the nervous system	0 (0)	-
Pregnancy, puerperium and perinatal diseases	0 (0)	-
Psychiatric disorders	1 (0.6)	1/1
Kidney and urinary disorders	0 (0)	-
Reproductive and breast disorders	0 (0)	-
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1/1
Disorders of the skin and subcutaneous tissue	5 (3)	5/5
Social circumstances	0 (0)	-
Vascular disorders	0 (0)	-
Infections	5 (3)	4/5
Neoplasms	2 (1)	2/2

Cells include n (%).
Withdrawal: No. patients in whom the adverse event led to discontinuation of the drug.

DISCUSSION

In this clinical practice study conducted in 154 patients with AxSpA and PsA, treatment with SEC showed a 66% 1-year retention rate in a population largely refractory to biological therapy irrespective of the disease and the number of biologics previously received. The main cause of discontinuation in our study was lack of efficacy while AEs leading to discontinuation of the drug occurred mainly in the first 6 months of treatment. Factors associated with longer SEC survival were male gender, obesity, hypertension and diabetes. Number of previous biologics and depression were identified as negative predictors for drug survival.

Discontinuation or switching of biological agents in inflammatory arthritis is quite common. Switchers receiving their second TNFi agent usually have considerably poorer responses compared with non-switchers (17), so switching to other biological disease-modifying antirheumatic drugs (DMARDs) with different mechanisms of action may be a better therapeutic strategy alternative (18). Among the main factors related to reduced TNFi survival different studies have found female sex, shorter disease duration, number or previous biologics, older age, current smoking, and comorbidities (13, 19–21). Other studies showed a better overall drug survival in patients with higher C-reactive protein (CRP) levels and patients replacing the first TNFi as a result of adverse events (21–23). The effect of concomitant methotrexate (MTX) on TNFi survival varies among registry studies, with similar TNFi persistence on combination therapy and monotherapy in the CORRONA registry (24), a trend toward longer drug survival in the SSATG study (22) and the DANBIO study (25) and significantly longer drug survival in the NOR-DMARD study (20). It is unclear at this time whether combination therapy with conventional DMARDs could influence SEC survival, and our data do not allow us to make any claims about this either, so further studies are needed.

Patients who start SEC retain the drug in a large percentage for at least 12 months according to clinical trials (5), but long term data regarding SEC survival in daily clinical practice are limited. Also, patients in clinical trials may be subject to selection bias as they are recruited on the basis of different clinical or disease characteristics, comorbidities and/or concomitant drugs. Factors that may affect SEC survival have not yet been established with certainty. In another Spanish observational study conducted in real clinical practice, Pinto et al. analyzed the efficacy and safety of SEC in 76 patients with peripheral PsA who started treatment in a 1-year period. 71% of patients had received at least one biological treatment before SEC. In line with our study, the retention rate of SEC at 12 months was lower in the group previously treated with biologics (81.5 vs. 90.9%) (26). Other real-life studies both in patients with PsA and AxSpA, had shown similar results with an ever decreasing SEC survival rate in

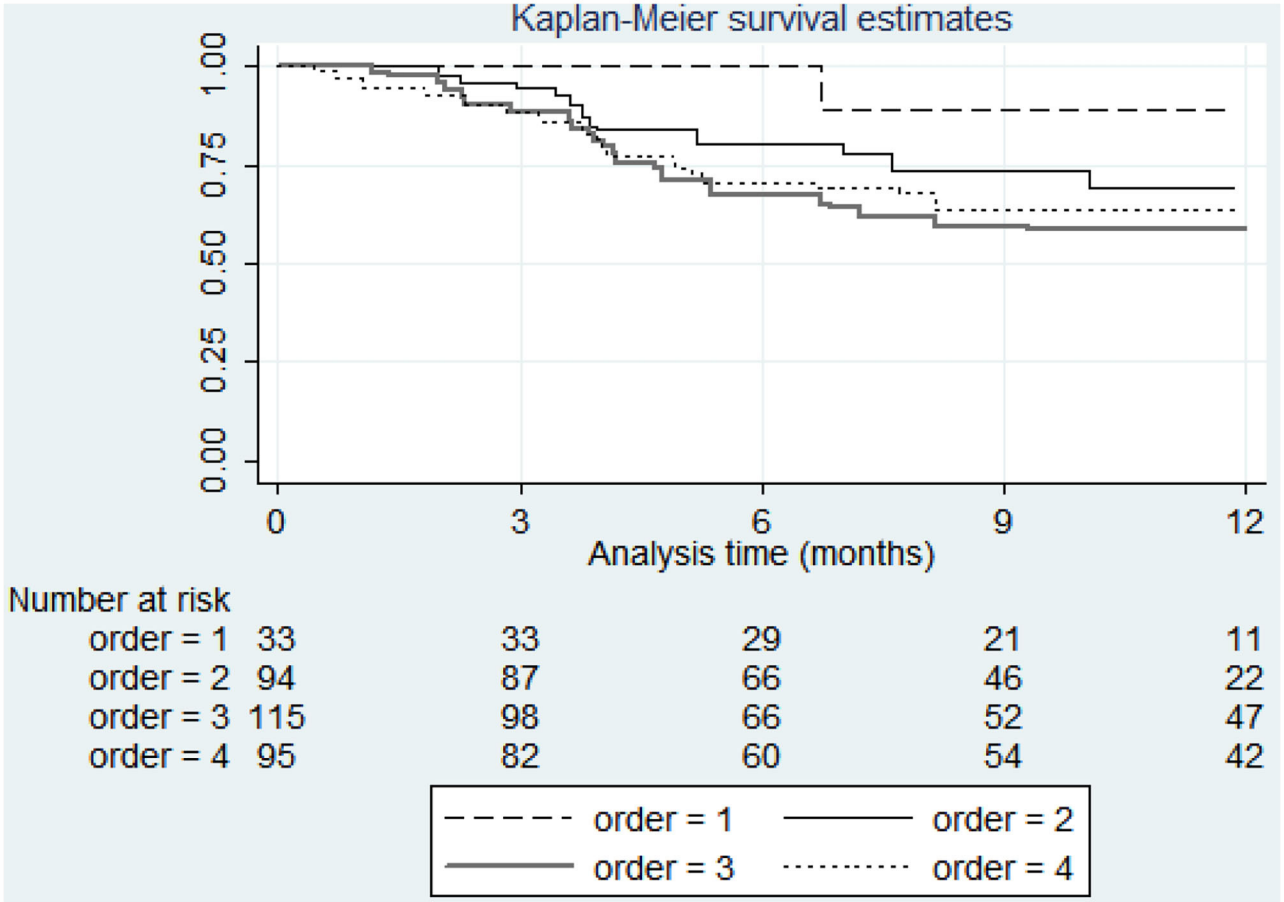

FIGURE 2 | Survival curve of secukinumab by biologic order.

patients who had previously received biological therapy (11, 26–28). We found only one study in real-life in which the survival rate of SEC was not related to the number of previous biologics. In the study by Gentileschi et al. evaluating the long-term efficacy of SEC in only 39 patients with radiographic and non-radiographic AxSpA, it was found an overall 2-year retention rate of 78.2% with no significant differences between biologic-naïve and anti-TNF-failure patients (29). Regarding other possible factors associated with SEC survival, Chimenti et al. published a real-life, prospective observational study on 169 consecutive patients (39 with ankylosing spondylitis and 130 with PsA) treated with SEC over a 1-year period. Most patients had received at least one biological drug (79%), and in line with our data they found higher persistence rate in male patients than female (30).

Obesity has been related to a higher risk of immune-mediated inflammatory diseases with an obesity range prevalence of 10–50% among these patients (31). High body weight has been associated with accelerated clearance resulting in lower trough concentrations of TNF blockers (32). Furthermore, visceral fat has been shown to independently contribute to an increased systemic inflammatory load (33). Obesity is associated to a poor prognosis in patients with rheumatic diseases, especially psoriasis and PsA (34). Obese patients with PsA are less likely to achieve minimal disease activity (MDA), more likely to discontinue treatment and also show lower skin clearance rate. This effect appears to be proportional to body mass index (BMI) and, in fact, weight reduction improves response to treatment (4, 35). In a recent meta-analysis, obesity was associated with 60% higher odds of failure to an index TNFi therapy in patients with rheumatoid arthritis, AxSpA, and psoriatic disease (36).

On the other hand, the therapeutic response to SEC tends to be poor in obese psoriasis patients (37). However, we found that obesity, and other components of metabolic syndrome, were predictors of longer survival for SEC therapy. Therefore, SEC could be a good therapeutic choice in obese patients with AxSpA and PsA as opposed to TNFi agents. In line with our data, Pantano et al. analyzed 100 PsA patients treated with EC. Patients were divided into two groups based on their BMI. After 6 months of SEC, changes of the Disease Activity Index for Psoriatic Arthritis (DAPSA) were inversely related to BMI values (38). Analysis of IL-17 serum levels showed significantly higher serum levels of this cytokine among obese patients. Also, Tiberio et al. described two cases of obese patients with psoriasis and PsA effectively treated with SEC (39). Therefore, SEC seems

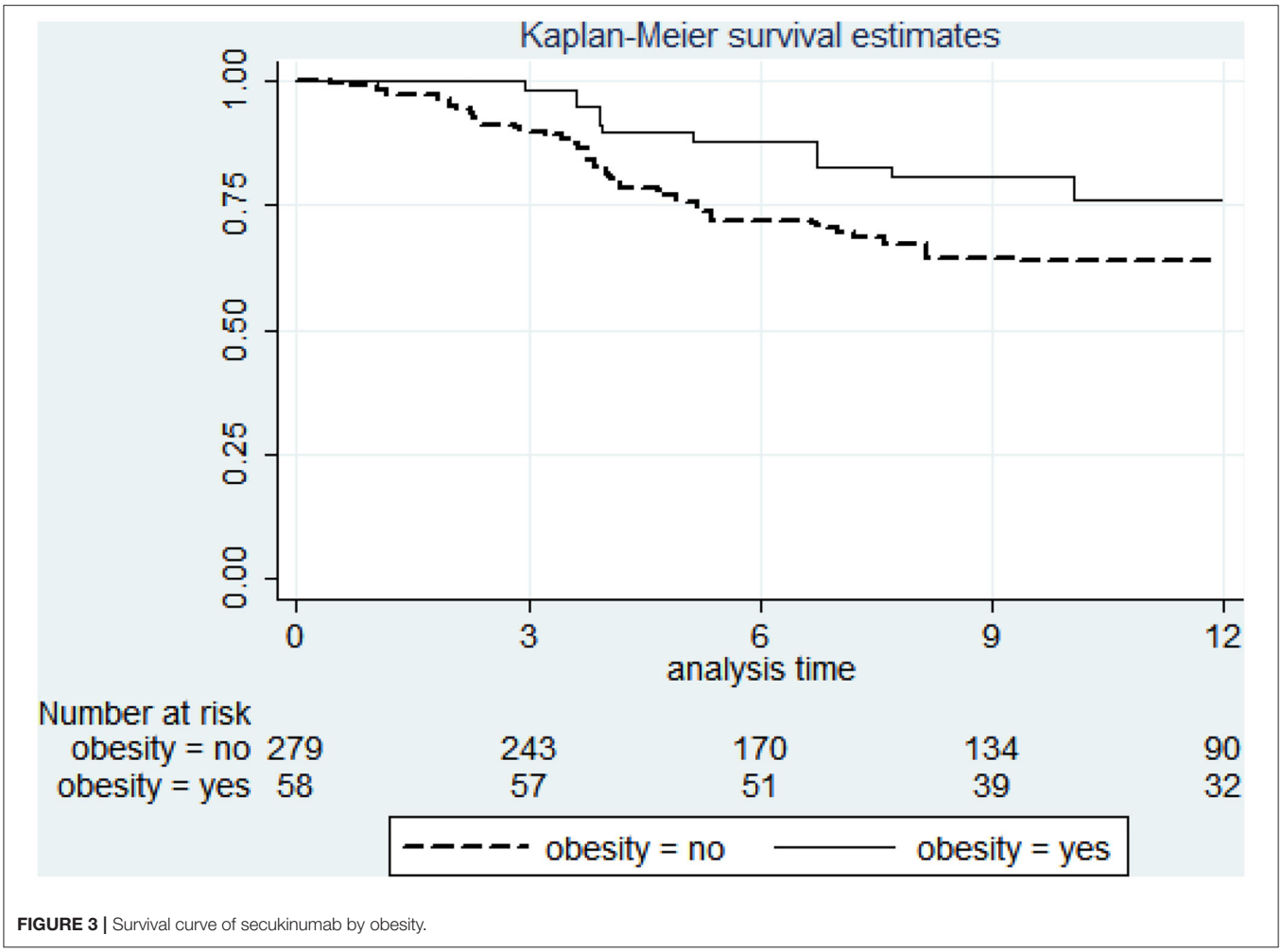

FIGURE 3 | Survival curve of secukinumab by obesity.

to be an efficacious drug irrespective of body weight. PASI 75, PASI 90, and PASI 100 response rates were high across weight quartiles and were maintained through week 52 in the pooled analysis of phase III trials with SEC. Moreover, SEC 300 mg dose demonstrated consistently greater benefit than the 150 mg dose across weight quartiles (40). Data from the CLEAR study showed that SEC 300 mg had a significantly higher efficacy (PASI 90 at week 16) than Ustekinumab 90 mg in patients with a body weight over 100 kg (41). All these data indicate that obesity may be one of the most relevant clinical factors driving the choice of SEC over other drugs in patients with AxSpA and PsA. IL-17 has been associated with insulin resistance and obesity in patients with psoriatic disease (42). Moreover, IL-17-deficient mice are characterized by enhanced insulin sensitivity and increased glucose uptake. In human co-culture experiments, macrophage-derived IL-1β was shown to enhance IL-17 production. Since macrophages do express IL-17 receptors, there might exist a positive and paracrine feedback loop that enhances local visceral adipose tissue inflammation (42). In line with these findings, our study shows that patients with a cardiometabolic inflammatory profile (obesity, diabetes, hypertension, arthritis) show better SEC survival, thus giving IL17 a central role in the pathogenesis of this inflammatory phenotype.

In our study we identified depression as a predictor of poor survival of SEC. According to the EULAR recommendations for the management of PsA and AxSpA, comorbidities such as depression should be considered (43, 44). Depression affects nearly 20% of patients with PsA (45) and SpAs and is associated with increased disease activity (higher BASDAI, ASDAS, DAPSA, and CDAI), worse functional impairment (higher BASFI, BASMI, and PGA), poor prognosis and greater non-adherence (45). Different studies have shown that patients with major depression have overexpressed levels of pro-inflammatory cytokines, acute phase reactants, and chemokines. Thus, IL-6, IL-17, and TNF levels are higher in patients with depression compared with healthy controls. These alterations may partly explain the correlation between higher inflammation, depressive symptoms and pain, the depression-pain syndrome, and the worse impact of the disease reported by patients on PROs (46, 47). Regarding fibromyalgia, although some of our patients met this profile, most of them fell into the category of patients with depression, so this aspect was not assessed independently.

TABLE 3 | Bivariable and multivariable survival analysis.

Characteristic	HR (95% CI)	
	Bivariable	**Multivariable**
Age, per year	1.00 (0.99 - 1.02)	
Male sex	0.77 (0.54 - 1.09)	0.54 (0.38 - 0.78)
Disease duration, per year	0.97 (0.95 - 1.00)	0.97 (0.94 - 1.00)
Biologic order		
First biologic	Ref.	
Second	2.49 (0.97-6.38)	3.62 (1.39-9.44)
Third	2.77 (1.10-6.98)	4.25 (1.66-10.93)
Fourth or more	2.53 (0.99-6.44)	5.09 (1.93-13.44)
csDMARD prior to Sec	0.75 (0.52-1.09)	
Glucocorticoids	2.00 (0.80-1.81)	
Obesity (BMI>30)	0.49 (0.30-0.82)	0.53 (0.30-0.93)
Smoker	1.09 (0.87-1.35)	
Hypertension	0.51 (0.34-0.77)	0.55 (0.35-0.85)
Dyslipidemia	0.87 (0.60-1.27)	
Diabetes	0.29 (0.13-0.63)	0.42 (0.18-0.99)
Cardiovascular disease*	4.63 (0.64-33.39)	
Ischemic heart disease	0.64 (0.26-1.58)	
Depression	2.10 (1.38-3.21)	2.53 (1.61-3.96)
Kidney failure	1.40 (0.56-3.49)	
Hepatic failure	1.09 (0.44-2.68)	

**Myocardial infarction or cerebrovascular event.*

Treatment with biological therapy, mitigating pain and reducing inflammation, may suggest a beneficial effect on the control of depressive symptoms and therefore a better response and increased survival of these therapies in patients with PsA or AxSpA. However, the present study identified depression as a risk factor for reduced survival among patients with PsA or AxSpA treated with SEC (HR 2.52, 95% CI 1.61-3.95 $p = 0.000$). Our results are in line with Danish (48) and British cohort (19) studies which included 1,750 and 566 PsA patients treated with TNFi therapy and with a Canadian cohort of 825 patients with ankylosing spondylitis and PsA (49). In all these cohorts, baseline depression negatively affected the response to TNFi therapy and was correlated with higher baseline disease activity and shorter TNFi persistence. Our study showed similar results of drug retention with an anti-IL17A therapy.

Our study has some limitations, which deserve to be discussed. First, we acknowledge that the sample size was relatively small and that the study was performed within an ethnically homogeneous population being cared for in various centers in north Spain, and therefore, these results may not be generalizable. Second, the collection of data in a retrospective manner may carry a certain risk of bias due to the lack of standardization in data collection. Unfortunately, we did not make a distinction between radiographic and non-radiographic AxSpA. This distinction is relevant because as Lopalco et al. demonstrated, the effectiveness of TNFi seems to be lower in non-radiographic AxSpA patients than in those with radiographic disease (50). The strength of our study is the interest of real clinical practice studies to complement the results of clinical trials, providing valuable data regarding the overall safety, efficacy and survival of a drug in heterogeneous patient populations usually with co-morbidities not registered in RCTs. In addition, data of SEC survival on Spanish population are still scarce.

In conclusion, in this study of real clinical practice, SEC showed a 66% retention rate at 1 year in a population mostly refractory to biological therapy. Treatment persistence has been optimal even in third line treatment, independent of the underlying disease, and obesity does not seem a marker of poor treatment response. The implications of our findings should be replicated in larger cohorts.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical approval for this study was obtained from the Sierrallana Hospital of Torrelavega, Spain (HUC- SEC-2019-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IV, SA, SF, EA, and RQ: study design, data management, analysis, verification, interpretation, and writing. LoC: study design, analysis, interpretation, and writing. JM, LiC, MP, LR, IM, MS, and AB: data management, analysis, and interpretation. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We especially thank Raquel Linge, Agnes Díaz, and Juan Calatayud, for their thoughts and ideas that have enriched the content of this project. Part of this work has been presented as a conference paper with the following reference (51).

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Conflict of Interest: IV consultant of: UCB, Speakers bureau: Novartis, MSD, Lilly, JM Grant/research support from: AbbVie, Pfizer, Janssen, and Celgene, Speakers bureau: Pfizer and Lilly, LR Grant/research support from: Yes, Speakers bureau: Yes, LoC Grant/research support from: Novartis Farmaceutica, SA, Pfizer, S.L.U., Merck Sharp & Dohme España, S.A., Roche Farma, S.A, Sanofi Aventis, AbbVie Spain, S.L.U., and Laboratorios Gebro Pharma, SA (All trhough institution).

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

frontiers in Medicine

ORIGINAL RESEARCH
published: 27 August 2021
doi: 10.3389/fmed.2021.669397

Depression and Endothelial Dysfunction in Psoriatic Arthritis: Is There Any Possible Relationship?

*Enrico De Lorenzis[1,2], Angela Di Giorgio[3], Gerlando Natalello[1], Antonio Nesci[3], Giacomo Tanti[1], Pietro Rubortone[1], Donatella Lucchetti[4], Maria Rosaria Magurano[5], Clara Di Mario[1], Barbara Tolusso[6], Giusy Peluso[6], Angelo Santoliquido[3] and Elisa Gremese[1,6]**

[1] Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2] PhD Program in Biomolecular Medicine - Cycle XXXV, University of Verona, Verona, Italy, [3] Department of Internal Medicine, Angiology Unit, Catholic University of the Sacred Heart, Rome, Italy, [4] Department of Translational Medicine and Surgery, Catholic University of the Sacred Heart, Rome, Italy, [5] Unit of Clinical Psychology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [6] Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

OPEN ACCESS

Edited by:
Piero Ruscitti,
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Reviewed by:
Alen Zabotti,
Università degli Studi di Udine, Italy
Ilenia Pantano,
University of Campania Luigi Vanvitelli, Italy

***Correspondence:**
Elisa Gremese
elisa.gremese@unicatt.it

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: 18 February 2021
Accepted: 02 August 2021
Published: 27 August 2021

Citation:
De Lorenzis E, Di Giorgio A, Natalello G, Nesci A, Tanti G, Rubortone P, Lucchetti D, Magurano MR, Di Mario C, Tolusso B, Peluso G, Santoliquido A and Gremese E (2021) Depression and Endothelial Dysfunction in Psoriatic Arthritis: Is There Any Possible Relationship? Front. Med. 8:669397. doi: 10.3389/fmed.2021.669397

Background: Cardiovascular events (CVEs) are the first cause of death in patients with psoriatic arthritis (PsA). Depression is a recognized risk factor in cardiovascular events and is frequently associated with PsA. Flow-mediated dilatation (FMD) is a widely used method for assessing endothelial dysfunction, a parameter with strong prognostic implications for CVEs. The study aims to explore the relationship between FMD, depressive symptoms and serum cytokines in a cohort of patients with PsA.

Patients and Methods: FMD was assessed in 50 consecutive PsA patients aged between 30 and 75 years without known cerebrovascular and coronary heart disease or diabetes. Depressive symptoms were reported using the related subscale of the Hospital Anxiety and Depression Scale (HDS). Disease features, activity indexes, and adjusted Framingham risk score (aFRS) were calculated. Serum level of IL-6, TNF-α, and IL-17A were also assessed.

Results: In PsA patients (age 50.7 ± 10.2 years, male 42%, disease duration 5.9 ± 3.3 years, Disease Activity in PSoriatic Arthritis (DAPSA) score 14.0 ± 9.4) FMD inversely correlated with the severity of depressive symptoms according to HDS ($\rho = -0.339$, $p = 0.016$), age ($\rho = -0.507$, $p = 0.001$), aFRS (rs $= -0.453$, $p < 0.001$), duration of PsA ($\rho = -0.507$, $p = 0.001$), intensity of pain ($\rho = -0.507$, $p = 0.001$), and DAPSA ($\rho = -0.507$, $p = 0.001$). No statistically significant correlation was found between FMD or HDS and serum cytokines concentrations. HDS predicted FMD in a model adjusted for age, aFRS, PsA duration, and pain intensity ($\beta = -0.271$, $p = 0.008$), with depressive symptoms contributing directly to 6.4% of the variance.

Conclusions: Depressive symptoms correlate with endothelial dysfunction with an exposure-response pattern in our cohort of PsA patients.

Keywords: psoriatic arthritis, depression, flow-mediated dilatation, cardiovascular risk, interleukin-6, tumor necrosis factor-α, interleukin-17

INTRODUCTION

Cardiovascular events (CVEs) are the leading cause of death in patients affected by psoriatic arthritis (PsA), who indeed present an increased rate of myocardial infarction and stroke (1). Nonetheless, current strategies for cardiovascular risk estimation (2) and reduction (3) appear inadequate. Both overt depression and subsyndromal depressive symptoms are currently recognized as independent cardiovascular risk factors comparable with smoking, obesity, hypertension, dyslipidemia, and diabetes (4–6). Depression is often associated with PsA (7) but the effective contribution of mood disorders in the cardiovascular burden of PsA patients is currently unknown.

Endothelial dysfunction (ED) is the inability of an artery to dilate in response to chemical or physical stimuli due to a reduced nitric oxide (NO) availability. ED plays a key role in early atherosclerosis and has the power to predict CVEs such as stroke, myocardial infarction, and cardiovascular death (8) consistently with the antiatherogenic and plaque-stabilizing properties of endothelium-derived NO (9). The ultrasound assessment of flow-mediated dilation (FMD) is a widely used method for assessing the endothelial function and strongly correlates with more invasive measures of the vasomotor responses (10).

Reduced FMD has been reported in both PsA patients (11) and depressed subjects (12) and related mainly to traditional cardiovascular risk factors and systemic inflammation. A dysregulated production of cytokines—particularly interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-17 (IL-17)—could be proposed as a unifying common feature between PsA, depression, and ED, as it plays a key role in the pathogenesis of psoriatic diseases and seems to be associated to mood disorders and impaired endothelial function in non-psoriatic cohorts (13, 14). Alternative or complementary mechanisms including heightened sympathetic arousal with excessive circulating catecholamines, abnormal neurohormonal function, reduced circulating endothelial progenitor cell, abnormal platelet activation, or increased oxidative stress could represent further mechanisms of impairment of vasomotor responses in PsA-depressed patients (15).

The aim of this study is therefore to evaluate the relationship of ED evaluated by FMD with depressive symptoms and serum cytokines in a cohort of PsA patients.

MATERIALS AND METHODS

Study Design and Rheumatological Assessment

The study has a comparative cross-sectional design. The protocol has been approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli-IRCCS (FPG), Rome (Protocol n.0014580/18), and written informed consent was obtained from all participants. Consecutive patients, aged between 30 and 75 years who met classification criteria for psoriatic arthritis (CASPAR) (16) and on stable treatment for at least 3 months were enrolled at the outpatient rheumatology clinic of FPG between October 2018 and March 2019. PsA patients with diabetes, stroke, peripheral arterial disease, or overt coronary heart disease for previous myocardial infarction, coronary bypass surgery or angioplasty, coronary stenosis on angiogram, or evidence of exercise-induced myocardial ischemia, were excluded. Other exclusion criteria were history of neoplasm in the last 5 years, kidney or liver failure, chronic liver infection, drug or alcohol abuse, secondary hypertension, and treatment with antidepressant or corticosteroids.

Duration of PsA, history of peripheral arthritis, axial disease, dactylitis, enthesitis, skin disease and nail disease, pain intensity and patient global assessment (PtGA) on a 10-cm visual analog scale, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were registered. Systemic, cutaneous, and articular examination—including tender and swollen joint count—was performed for all patients. Disease Activity in Psoriatic Arthritis (DAPSA) index and Psoriasis Area Severity Index (PASI) were calculated to assess disease activity. The use of conventional and biologic disease-modifying antirheumatic drugs (DMARDs) was noted.

Assessment of Traditional Cardiovascular Risk Factors

Smoking habit, premature coronary artery disease in first- and second-degree relatives (male aged <55 years and female aged <65 years) and sedentary lifestyle were recorded. Body mass index (BMI) and waist-to-hip ratio (WHR) were recorded as well as proportion of patients with obesity (BMI $\geq$30 kg/m^2) and abdominal obesity (WHR $\geq$0.94 for males and WHR $\geq$0.80 for females) were reported. Baseline resting blood pressure was measured by auscultatory technique, recording the average of three consecutive measures. Total cholesterol, high- (HDL) and low-density (LDL) lipoprotein cholesterol, and triglycerides were assessed before the visit according to standard practice, and atherogenic index of plasma (AIP) and LDL/HDL cholesterol ratio were computed. High-risk lipid profile has been defined as AIP >0.5 or LDL/HDL cholesterol ratio >3.5 in men and >3.0 in women (17). Ongoing treatment for systemic arterial hypertension and dyslipidemia were recorded (18).

Framingham risk score (FRS) (19) was used to estimate the 10 year risk of coronary heart disease death, non-fatal myocardial infarction, coronary insufficiency or angina, fatal or non-fatal ischemic or hemorrhagic stroke, transient ischemic attack, intermittent claudication, and heart failure for each patient according to traditional risk factors. The score was based on the following variables: age, sex, smoking status, total cholesterol, HDL cholesterol, and systolic blood pressure. This prediction model was adjusted for patients with chronic arthritis by a 1.5 multiplier (aFRS) (20). Notably, the age between 30 and 75 years was chosen as inclusion criteria, since FRS is validated in this range.

Assessment of Depressive Symptoms

The presence of depression and the severity of psychological symptoms were evaluated by an experienced psychologist blinded to the other clinical data using the depression subscale of the Hospital Anxiety and Depression Scale (HDS). This scale was chosen because the items do not include somatic symptoms that may be caused by immunosuppressive drugs and extra-articular

physical manifestations of PsA. Although it is not a basis for the clinical diagnosis of depression, a validated cutoff of 8 was used to define patients with significative depressive symptoms, who were referred to as depressed in this paper (21).

Evaluation of Flow-Mediated Dilation

FMD was evaluated within 2 days from the screening visit by an experienced angiologist blinded to other clinical data. All participants were studied in the morning beginning between 8:00 and 9:00 am, fasting, and having avoided alcohol for at least 24 h and caffeine for at least 12 h. Vasoactive and non-steroidal anti-inflammatory medications were withheld for 48 h before the test. Subjects rested supine in a quiet, temperature-controlled environment for 20 min before the exam. The right brachial artery was imaged in the longitudinal plane 2 to 15 cm proximal to the antecubital fossa using a 17–5 MHz linear array transducer connected to an iU22 ultrasound machine (Philips Medical Systems, Monza, Italy). Depth and gain were selected to enable optimal identification of the anterior and posterior intimal interface between lumen and vessel wall on 2D grayscale images. Baseline images were then acquired. Blood flow was measured from the pulsed wave Doppler signal with a 60° insonation angle. After recording baseline values, a sphygmomanometer cuff was applied around the forearm, inflated to 250 mmHg, and left in place for 5 min, causing forearm ischemia and consequent dilation of downstream resistance vessels. Blood flow was measured over the first 15 s after cuff deflation, whereas arterial images were acquired between 60 and 90 s after cuff release (22).

Assessment of Serum Cytokines

Blood samples for soluble biomarkers assays were collected from all enrolled PsA patients soon after FMD evaluation. Sera were collected from blood samples after centrifugation at 3,500 rpm for 15 min and stored at −80°C until the time of analysis. Serum levels of IL-6 were measured by ELISA (R&D Systems, Abingdon, UK) with a sensitivity of the test of 0.7 pg/ml. Serum levels of TNF-α and IL-17A were simultaneously measured by Luminex assay (R&D Systems, Minneapolis, USA) on a Luminex xMAP system (Bio-Plex 200 System, Bio-Rad Laboratories, Hercules, CA). Results were analyzed using a dedicated Bio-Plex Manager software and are expressed in picograms per milliliter.

Statistical Analysis and Sample Size Calculation

Data were analyzed using IBM SPSS Statistics v26.0 (Armonk, NY, USA). Categorical variables were reported as numbers and percentages. Continuous variables were reported as mean ± SD or median and interquartile range (IQR), according to the distribution of the data. Normality of continuous variables was assessed by inspection of Q–Q (quantile-quantile) plots. Variables without Gaussian distribution were normalized using the logarithm transformation, when effective. Linearity of the relationship between continuous variables and the presence of significant outliers were assessed by scatterplot. The relationship between FMD and HDS or other paired continuous variables was explored using Pearson's (ρ) or Spearman's coefficient (r_s) as indicated. The relationship between FMD and natural dichotomous variables was tested by point-biserial correlation (ρ) after ruling out the presence of significant outliers by boxplot and checking the homogeneity of variances by Levene's test. Hierarchical multivariate linear analyses were done with the percentage of FMD as the dependent variable. Variables showing a correlation with FMD were included in the model as predictors. The first block included predictors of FMD shared with general population (traditional cardiovascular risk factors, baseline brachial diameter), in the second block the model was adjusted for potential PsA-related predictors, in the last block HDS was added to the model. HDS was added in the last step in order to estimate the percentage of the total variance of FMD explained by depressive symptoms after controlling for potential confounding variables. Statistical significance of F modification was reported for each step. Independence of residuals was assessed by Durbin-Watson test, multicollinearity was excluded for $\rho < 0.700$ for each couple of predictors. Homoscedasticity and normality of residual distribution were checked by visual inspection of a plot of standardized residuals vs. standardized predicted values and a probability plot, respectively. All tests were two sided. Statistical significance was defined as $p < 0.05$.

Consistent with the available literature, we calculated the minimum sample size based on the occurrence rate of depression (defined by HDS ≥8) of 33% in PsA patients defined by HDS ≥8, and an expected FMD value of 6.5 ± 3.0 in patients with depressed symptoms and 8.5 ± 3.0 in the other PsA patients. The α was set as double-sided 0.05 (5% level of significance), and β was set as 0.2 (90% power). Thus, we set the sample size as $n = 50$ in this study.

RESULTS

Clinical Characteristics of PsA Patients, Serum Cytokines, Traditional Risk Factors for CVEs, and Depressive Symptoms

Fifty consecutive PsA patients were enrolled; the clinical characteristics of the study cohort are summarized in **Table 1** and modifiable and non-modifiable risk factors for cardiovascular diseases in **Table 2**. The patients were treated according to standard of care at the time of the evaluation. Thirty-three patients (46.0%) were treated with conventional synthetic (cs)-DMARDs and specifically 19 with methotrexate, 16 with sulphasalazine, and two with leflunomide. Twenty-two patients (44.0%) were treated with biologic (b)-DMARDs, of whom five in monotherapy. In particular, 18 patients assumed an anti-TNFα, two patients secukinumab, and two ustekinumab. One patient was treated with apremilast.

Four patients (8.0%) were in high disease activity, 19 (38.0%) in moderate disease activity, 20 (40.0%) in low disease activity and 7 (14.0%) in remission according to DAPSA score while under treatment. Twenty (40.0%) patients were depressed according to HDS ≥8 with an average HDS of 6.8 ±3 0.3. Depressed and non-depressed patients did not significantly differ according to disease features and serum levels of IL-6, TNF-α, and IL-17A (**Table 1**).

TABLE 1 | Clinical features of the enrolled PsA patients.

	All patients	HDS ≥ 8	HDS < 8	*p*-Value
N	50	20	30	–
Disease duration (years, mean ± SD)	5.9 ± 3.3	6.4 ± 3.5	5.6 ± 3.2	0.378
Age of onset (years, mean ± SD)	41.1 ± 11.9	40.4 ± 12.1	41.6 ± 12.0	0.732
Peripheral arthritis [*n* (%)]	50 (100.0)	20 (100.0)	30 (100.0)	–
Dactylitis [*n* (%)]	25 (50.0)	11 (55.0)	14 (46.7)	0.564
Enthesitis [*n* (%)]	28 (56.0)	11 (55.0)	17 (56.7)	0.907
Spondylitis [*n* (%)]	11 (22.0)	3 (15.0)	8 (26.7)	0.269
Psoriatic skin disease [*n* (%)]	40 (80.0)	15 (75.0)	25 (83.3)	0.470
Psoriatic nail disease [*n* (%)]	20 (40.0)	10 (50.0)	10 (33.3)	0.239
TJC on 68 joints [median (IQR)]	1.0 (0.0–4.5)	1.5 (0.0–8.8)	1.0 (0.0–2.5)	0.138
SJC on 66 joints [median (IQR)]	0.0 (0.0–2.0)	1.0 (0.0–3.5)	0.0 (0.0–2.0)	0.222
Pain intensity on VAS (cm, mean ± SD)	5.1 ± 2.7	6.2 ± 2.6	4.1 ± 2.8	0.008
PtGA (cm, mean ± SD)	3.6 ± 2.3	4.7 ± 2.3	2.9 ± 2.0	0.004
DAPSA (mean ± SD)	14.0 ± 9.4	18.4 ± 10.5	11.1 ± 7.6	0.007
PASI [median (IQR)]	0.5 (0.0–3.5)	0.6 (0.0–4.2)	0.5 (0.0–3.5)	0.935
HAQ-DI [median (IQR)]	0.889 (0.000–1.120)	0.935 (0.370–1.778)	0.060 (0.000–0.870)	0.001
Conventional DMARDs (%)	32 (64.0)	13 (65.0)	19 (63.3)	0.904
Biologic DMARDs and apremilast [*n* (%)]	23 (46.0)	8 (40.0)	15 (50.0)	0.487
No DMARDs [*n* (%)]	13 (26.0)	5 (25.0)	8 (26.7)	0.895
IL-6 [pg/ml, median (IQR)]	0.21 (0.01–2.08)	0.82 (0.01–2.56)	0.02 (0.01–1.42)	0.165
TNF-α [pg/ml, median (IQR)]	3.52 (2.23–5.57)	3.88 (2.56–5.63)	3.36 (2.22–5.09)	0.442
IL-17A [pg/ml, median (IQR)]	0.01 (0.01–0.24)	0.01 (0.01–0.11)	0.01 (0.01–0.35)	0.760

PsA, psoriatic arthritis; HDS, depression subscale of the Hospital Anxiety and Depression Scale; SD, standard deviation; TJC tender joint count; SJC, swollen joint count; IQR, interquartile range; VAS, visual analog scale; PtGA, patient global assessment; DAPSA, disease activity in psoriatic arthritis; HDA, high disease activity; MDA, moderate disease activity; LDA, low disease activity; PASI, psoriasis area severity index; IL, interleukin; TNF, tumor necrosis factor; DMARDs, disease-modifying antirheumatic drugs.

The median 10 year risk of CVEs according to aFRS was 10.7% (IQR, 7.2–14.5%). Depressed patients were less frequently male (20.0% vs. 56.4%, $p = 0.01$) while they did not differ according to the other recorded cardiovascular risk factors (**Table 2**).

Flow Mediated Dilatation

Single correlations of FMD and HDS with traditional risk factors for CVD and other clinical features are shown in **Supplementary Table 1**. Baseline brachial artery diameter on ultrasound was 3.7 ± 0.7 mm and mean FMD was 7.9% ± 3.6%. There was a statistically significant, negative correlation between endothelial function according to FMD and severity of depressive symptoms according to HDS ($\rho = -0.339$, $p = 0.016$), explaining 11% of the variation in endothelium-dependent vasodilation. The relationship was similar if the cutoff of HDS ≥8 was considered to define depressed patients ($\rho = -0.322$, $p = 0.022$). Regarding traditional risk factors for CVD, there was a statistically significant, strong negative correlation between FMD and age ($\rho = -0.507$, $p = 0.001$) and a moderate negative correlation with aFRS ($r_s = -0.453$, $p < 0.001$) and Log(aFRS) ($\rho = -0.423$, $p = 0.002$). Of notice, aFRS was normalized by log transformation because of the markedly skewed distribution of the data.

There was a statistically significant correlation between gender and HDS ($\rho = -0.320$, $p = 0.024$), with females showing higher depressive scores compared with males (7.7 ± 2.8 vs. 5.5 ± 3.6). As concerns disease characteristics, FMD correlated with PsA disease duration ($\rho = -0.507$, $p = 0.001$), intensity of pain ($\rho = -0.507$, $p = 0.001$), and DAPSA ($\rho = -0.507$, $p = 0.001$) while HDS correlated with TJC on 68 joints ($r_s = 0.312$, $p = 0.028$), the intensity of pain ($\rho = 0.483$, $p < 0.001$) and DAPSA ($\rho = 0.495$, $p < 0.001$) (**Figures 1**, **2**). Notably, there was not a significant correlation between FMD or HDS and serum cytokine concentrations and classic acute-phase reactants.

Multiple regression analyses was carried out to assess the relative contribution of the variables in predicting FMD. Predictors were chosen according to both theoretical importance and statistical significance on bivariate correlation. Since pain intensity and PtGA were both highly correlated with DAPSA ($\rho = 0.821$, $p < 0.001$ and $\rho = 0.791$, $p < 0.001$, respectively) and each other ($\rho = 0.802$, $p < 0.001$), these measures have not been entered simultaneously in the model, to avoid multicollinearity. We decided to use pain intensity in the model since it was included in DAPSA formula and because psychological factors have an established role in the experience of pain. Therefore, hierarchical regression was run to predict FMD, entering as

TABLE 2 | Traditional risk factors for cardiovascular disease.

	All patients	HDS ≥ 8	HDS < 8	*p*-Value
N	50	20	30	–
Age (years, mean ± SD)	50.7 ± 10.2	51.5 ± 11.1	50.1 ± 9.6	0.638
Male sex [*n* (%)]	21 (42.0)	4 (20.0)	17 (56.7)	0.010
Family history of premature CVD [*n* (%)]	13 (26.0)	5 (25.0)	8 (26.7)	0.895
BMI (kg/m^2, mean ± SD)	26.0 ± 4.0	24.7 ± 3.8	26.8 ± 4.0	0.067
Obesity [*n* (%)]	10 (20.0)	3 (15.0)	7 (23.3)	0.365
WHR (mean ± SD)	0.88 ± 0.14	0.92 ± 0.10	0.86 ± 0.16	0.162
Abdominal obesity [*n* (%)]	34 (68.0)	14 (70.0)	20 (66.7)	0.804
Current smokers [*n* (%)]	13 (26.0)	6 (30.0)	7 (23.3)	0.599
Sedentary lifestyle [*n* (%)]	32 (64.0)	12 (60.0)	20 (66.7)	0.630
SBP at the time of the study (mmHg, mean ± SD)	123 ± 16	123 ± 15	123 ± 17	0.818
DBP at the time of the study (mmHg, mean ± SD)	80 ± 11	80 ± 10	81 ± 11	0.815
Antihypertensive treatment [*n* (%)]	18 (36.0)	8 (40.0)	10 (33.3)	0.630
Total cholesterol (mg/dl, mean ± SD)	207 ± 31	207 ± 33	207 ± 31	0.994
HDL-cholesterol (mg/dl, mean ± SD)	63 ± 18	64 ± 22	61 ± 16	0.615
LDL-cholesterol (mg/dl, mean ± SD)	123 ± 33	125 ± 32	122 ± 35	0.783
Triglycerides (mg/dl, mean ± SD)	112 ± 75	101 ± 46	118 ± 87	0.454
Atherogenic index of plasma [median (IQR)]	0.44 (−0.09 to 0.96)	0.49 (−0.10 to 1.00)	0.42 (−0.06 to 0.96)	0.740
Atherogenic index of plasma at risk [*n* (%)]	24 (48.9)	10 (50.0)	14 (46.7)	0.912
LDL/HDL cholesterol ratio (mean ± SD)	2.17 ± 0.97	2.16 ± 0.85	2.18 ± 1.05	0.930
LDL/HDL cholesterol ratio at risk [*n* (%)]	8 (16.0)	3 (15.0)	5 (16.7)	0.599
Lipid-lowering treatment [*n* (%)]	8 (16.0)	3 (15.0)	5 (16.7)	0.599
aFRS [%, median (IQR range)]	10.7 (7.2–14.5)	11.3 (7.2–18.2)	10.8 (8.0–15.2)	0.501

HDS, depression subscale of the Hospital Anxiety and Depression Scale; SD, standard deviation; CVD, cardiovascular disease; BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoproteins; LDL, low-density lipoprotein; IQR, interquartile range.

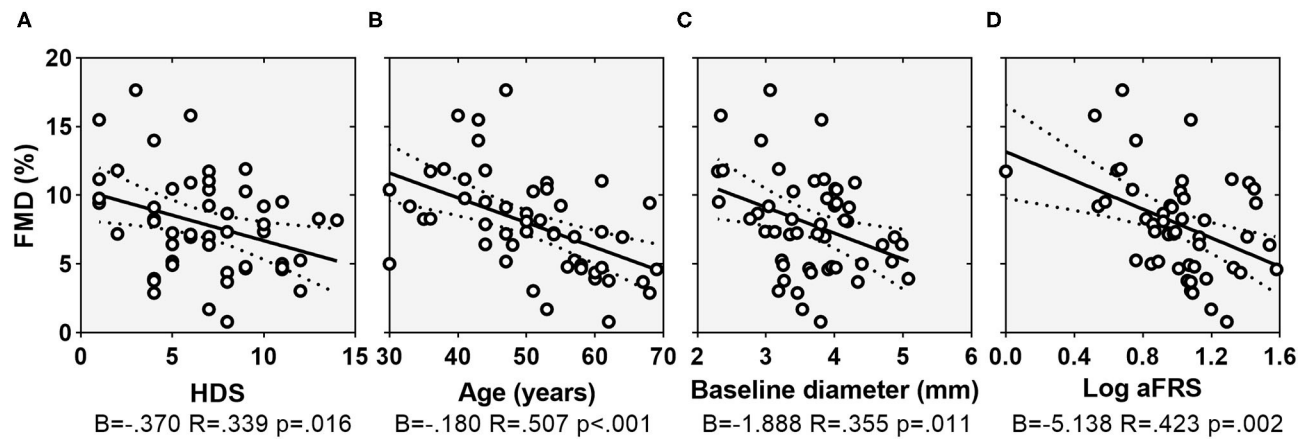

FIGURE 1 | Scatterplots showing the relationship between FMD and HDS **(A)**, age **(B)**, baseline arterial diameter **(C)**, and Log(aFRS) **(D)**. Dotted lines indicate 95% confidence interval. FMD, flow-mediated dilation; HDS, depression subscale of the Hospital Anxiety and Depression Scale; aFRS, adjusted Framingham risk score.

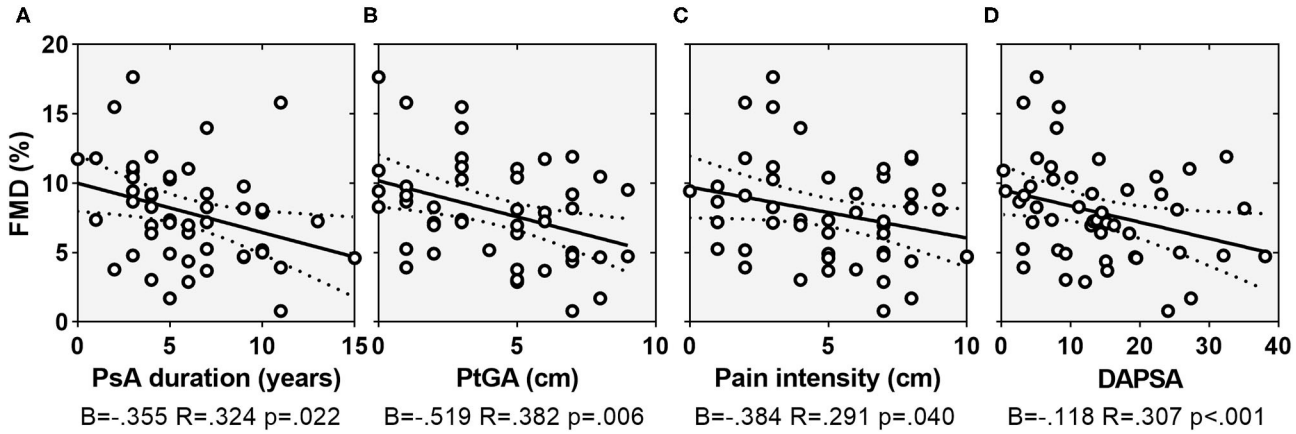

FIGURE 2 | Scatterplots showing the relationship between FMD and PsA duration **(A)**, PtGA **(B)**, pain intensity on VAS **(C)**, and DAPSA **(D)**. Dotted lines indicate 95% confidence interval. FMD, flow-mediated dilation; PsA, psoriatic arthritis; PtGA, patient global assessment; VAS, visual analog scale; DAPSA, disease activity in psoriatic arthritis.

TABLE 3 | Hierarchical linear regression analysis of FMD in patients with PsA.

	Predictors	*B*	CI 95%		*p* (*B*)	*β*	*F* change	*p* (*F* change)	R^2	R^2 change
Step 1	Age	−0.152	−0.261	−0.042	0.008	−0.425	6.88	0.001	0.310	–
	Baseline artery diameter	−1.159	−2.837	0.519	0.171	−0.218				
	Log(aFRS)	−0.482	−5.047	4.084	0.883	−0.040				
Step 2	Age	−0.132	−0.237	−0.025	0.015	−0.370	3.64	0.034	0.408	0.098
	Baseline artery diameter	−0.869	−2.522	0.783	0.295	−0.163				
	Log(aFRS)	−1.087	−5.440	3.266	0.617	−0.089				
	PsA duration	−1.016	−0.431	0.123	0.270	−0.140				
	Pain severity	−0.358	−0.670	−0.045	0.026	−0.271				
Step 3	Age	−0.132	−0.233	−0.032	0.011	−0.372	5.21	0.027	0.472	0.064
	Baseline artery diameter	−1.182	−2.785	0.422	0.145	−0.222				
	Log(aFRS)	−1.016	−5.177	3.146	0.625	−0.084				
	PsA duration	−0.098	−0.368	0.171	0.466	−0.090				
	Pain severity	−0.178	−0.516	0.161	0.295	−0.135				
	HDS	−0.324	−0.610	−0.038	0.027	−0.297				

FMD, flow-mediated dilatation; PsA, psoriatic arthritis; CI, confidence interval; aFRS, adjusted Framingham risk score; PsA, psoriatic arthritis; HDS, depression subscale of the Hospital Anxiety and Depression Scale.

variables age, baseline arterial diameter, and Log(aFRS) in the first step. PsA duration and pain intensity were added in the second step and HDS in the third step. Regression coefficient (R^2)values are reported in **Table 3**. Conventional cardiovascular risk factors (age, aFRS) and baseline arterial diameter accounted for 31.0% of the total FMD ($F = 6.88$, $p < 0.001$) with age independently associated with the endothelial function ($\beta = -0.425$, $p = 0.008$). PsA-related variables in the second step, the explained variance increased up to 40.8% ($F = 3.64$, $p = 0.034$) and pain intensity ($\beta = -0.370$, $p = 0.015$) and age ($\beta = -0.271$, $p = 0.026$) were both significantly associated with the endothelial function in the adjusted model. The inclusion of HDS in the third step contributed to an additional 6.4% of the variance in predicting FMD ($F = 5.21$, $p = 0.027$). It should be noted that at the last step the correlation between FMD and HDS remained significant on multivariate regression analysis ($\beta = -0.297$, $p = 0.027$) suggesting an independent effect of the depressed mood on endothelial function. Age was also significantly associated with FMD ($\beta = -0.372$, $p = 0.011$) in the full-enter model.

DISCUSSION

In the present study, we examined the endothelial function assessed by FMD according to depressed mood and key serum cytokines in a clinically well-characterized cohort of PsA patients. Our main observation was an inverse correlation between endothelial function and severity of depressive symptoms according to HDS, confirmed after adjusting for other relevant

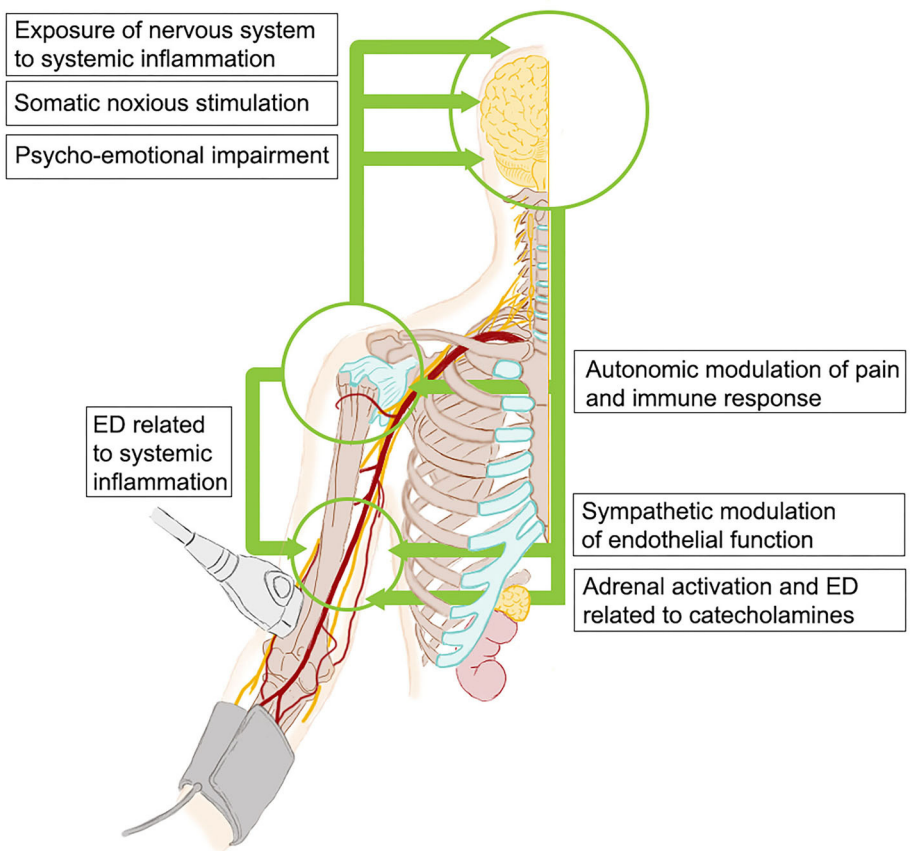

FIGURE 3 | Potential mechanisms of interconnections between neurohormonal system, inflammation, and endothelium in patients with PsA and depressive symptoms. PsA, psoriatic arthritis; ED, endothelial dysfunction.

variables such as age, baseline brachial diameter, traditional cardiovascular risk factors (aFRS), disease duration, and pain severity. In the multivariable linear model, the largest variation of FMD was explained by age and aFRS, as reported in the general non-psoriatic population (23, 24), while disease duration and pain severity were the only disease characteristics that were related to FMD, explaining further 9.8% of its variance. Expanding the hierarchical model, we found that the variation of FMD independently explained by HRS was of 6.4%. Even if this percentage may appear small or clinically irrelevant, it must be emphasized that very small differences in FMD can predict major CVEs (8).

These data allow us to speculate that the gap between predicted and actual incidence of CVEs could be in part explained by a quote of endothelial dysfunction related to an eventual concurrent depressive status. In this perspective, the investigation of depressive symptoms in PsA could contribute to a more accurate stratification of cardiovascular risk, since mood disorders are often under-recognized and under-treated in these patients (25). It should also be noted that mood disorders have a stronger impact on cardiovascular disease burden in women than in men (26) and that depressive symptoms are more frequent in female PsA patients (27). The identification of depressive symptoms may therefore be crucial in female PsA patients that could be mistakenly considered at low risk in premenopausal age. Notably, the relationship between depressive symptoms and FMD showed a linear trend, suggesting that evaluating the depressive status as dichotomous phenomenon (i.e., depressed vs. non-depressed) may eventually be inadequate in the stratification of cardiovascular risk.

Mechanisms of ED in PsA or depression are still unclear, but they are expected to be multiple and overlapping. The crosstalk between central and peripheral nervous system, the inflammatory and autoimmune response, and the cardiovascular system is complex (**Figure 3**), and our current understanding of these interactions is incomplete, particularly in PsA patients. It is well-known that, even if traditional cardiovascular risk factors are frequently reported in PsA and depression, ED and cardiovascular risk are independent of them in both cases (28–30). Systemic inflammation is considered a major actor in ED in PsA and other chronic inflammatory diseases (13), indeed we failed in detecting a correlation between endothelial function and acute-phase reactants or inflammatory molecules (i.e., IL-6, TNF-α, and IL-17A), consistently with previous reports on FMD in PsA patients (11, 28, 30). Interestingly, ED has been related to the cumulative rather than the transient exposure to inflammation (30, 31),

and we consistently found an inverse correlation between FMD and disease duration. Depression itself has also been associated with a sustained state of systemic inflammation and increased concentrations of inflammatory molecules in patients without overt systemic inflammatory diseases (14) and, in this regard, we previously reported that depressive symptoms were independently associated with elevated IL-6 in a larger cohort of unselected PsA patients (32). An alternative or complementary explanation is that other non-inflammatory mechanisms may interfere with endothelial function in these patients. These include deregulation of the hypothalamic-pituitary-adrenal axis with elevated circulating cortisol levels (33, 34) and an imbalance between the sympathetic and parasympathetic systems (35, 36). Such mechanisms might be heightened in PsA-depressed patients. Coherently with this hypothesis, autonomic dysfunction has been reported in PsA patients (37), particularly in association with psychoemotional impairment (38). Notably, we also fund that ED was inversely correlated with pain, that is cross-linked with sympathetic activation (39).

The limitations of the present study include the lack of a control group and the cross-sectional design with the consequent inadequacy to more strongly support the relationship between endothelial dysfunction and depressive symptoms. Moreover, we did not directly measure potential non-inflammatory determinants of ED nor the cumulative exposure to inflammation or depressive mood (40). Lastly, we did not assess the impact of different immunosuppressants on endothelial function since the study was not powered for this aim.

The study has some strengths, too. To the best of our knowledge, this is the first study assessing the relationship between ED and depressive symptoms in patients with PsA. The patients have been thoroughly studied in terms of traditional cardiovascular risk factors, and we applied stringent exclusion criteria in order to limit confounding factors. Patients treated with antidepressants, for example, were excluded from the study because of the effect of antidepressant drugs on endothelial function (41).

CONCLUSIONS

In our cohort of PsA patients, depressive symptoms were related to ED. If validated in longitudinal studies, this evidence would encourage a systematic research of depressive symptoms as a part of a correct assessment of cardiovascular risk in PsA, helping to raise the effectiveness of prevention strategies. The future research agenda should clarify if the choice of both immunosuppressant and antidepressant treatment in PsA could be personalized according to effects on endothelium, as part of cardiovascular prevention strategies.

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 protocol and the template informed consent forms were reviewed and approved by Committee on Research Ethics of Catholic University of the Sacred Heart. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors gave substantial contributions to the conception or design of the work, acquisition, analysis, or interpretation of data, drafting the work or revising it critically for important intellectual content, and final approval of the version published.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.669397/full#supplementary-material

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

frontiers in Medicine

REVIEW
published: 30 August 2021
doi: 10.3389/fmed.2021.735150

Psoriatic Arthritis and Metabolic Syndrome: Is There a Role for Disease Modifying Anti-Rheumatic Drugs?

Fabiola Atzeni[1], Elisabetta Gerratana[1], Ignazio Francesco Masala[2], Sara Bongiovanni[3], Piercarlo Sarzi-Puttini[3†] and Javier Rodríguez-Carrio[4,5†]*

[1] Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina, Messina, Italy, [2] Trauma and Orthopedic Unit, Santissima Trinità Hospital, Cagliari, Italy, [3] Rheumatology Unit, Azienda Socio Sanitaria Territoriale (ASST)-Fatebenefratelli L. Sacco University Hospital, University of Milan, Milan, Italy, [4] Department of Functional Biology, Immunology Area, Faculty of Medicine, University of Oviedo, Oviedo, Spain, [5] Area of Metabolism, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

Although psoriatic arthritis (PsA) primarily leads to joint and skin damage, it is associated with higher prevalence of metabolic syndrome (MetS) and its components, namely hypertension, dyslipidemia, obesity, and type II diabetes. Additionally, chronic inflammation is known to aggravate these cardiometabolic factors, thus explaining the enhanced cardiovascular (CV) morbidity and mortality in RA. Furthermore, emerging evidence suggest that some risk factors can fuel inflammation, thus pointing to a bidirectional crosstalk between inflammation and cardiometabolic factors. Therefore, dampening inflammation by disease-modifying anti-rheumatic drugs (DMARDs) may be thought to ameliorate MetS burden and thus, CV risk and disease severity. In fact, recommendations for PsA management emphasize the need of considering comorbidities to guide the treatment decision process. However, the existing evidence on the impact of approved DMARDs in PsA on MetS and MetS components is far from being optimal, thus representing a major challenge for the clinical setting. Although a beneficial effect of some DMARDs such as methotrexate, TNF inhibitors and some small molecules is clear, no head-to-head studies are published and no evidence is available for other therapeutic approaches such as IL-23 or IL-17 inhibitors. This narrative review summarizes the main evidence related to the effect of DMARDs on MetS outcomes in PsA patients and identify the main limitations, research needs and future perspectives in this scenario.

Keywords: metabolic syndrome, psoriatic arthritis, dyslipidemia, diabetes, hypertension

OPEN ACCESS

Edited by:
Piero Ruscitti,
University of L'Aquila, Italy

Reviewed by:
Prasanta Padhan,
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Fabio Massimo Perrotta,
University of Molise, Italy

****Correspondence:***
Fabiola Atzeni
atzenifabiola@hotmail.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *02 July 2021*
Accepted: *09 August 2021*
Published: *30 August 2021*

Citation:
Atzeni F, Gerratana E, Francesco Masala I, Bongiovanni S, Sarzi-Puttini P and Rodríguez-Carrio J (2021) Psoriatic Arthritis and Metabolic Syndrome: Is There a Role for Disease Modifying Anti-Rheumatic Drugs? Front. Med. 8:735150. doi: 10.3389/fmed.2021.735150

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal and skin disease, associated with psoriasis (PsO). PsA can affect peripheral joints, entheses, and the axial skeleton, and it is characterized by different clinical manifestations and a variable clinical course (1). It affects 10–40% of PsO patients, although in some cases it may occur in the absence of skin manifestations. In most cases, skin manifestations precede arthritis, in 15% of the cases the onset is simultaneous, and in 10–15% of the cases arthritis precedes PsO (2). Moreover, beyond musculoskeletal and skin

manifestations, patients of PsA have a higher prevalence of comorbidities compared to the general population (3), with more than half of PsA patients reporting at least one comorbidity and up to 40% of patients having more than three comorbidities (4). PsA patients exhibit a high prevalence of cardiovascular (CV) risk factors, including the metabolic syndrome (MetS) (5).

METABOLIC SYNDROME

MetS is defined as a constellation of interrelated alterations, which directly increase the risk of CV disease and type II diabetes mellitus (DM) (6). The main components of MetS are: atherogenic dyslipidemia (hypertriglyceridemia, increased Apo-B, low HDLc levels), altered glucose homeostasis, arterial hypertension, and chronic pro-thrombotic and pro-inflammatory state (7, 8). These are all risk factors for developing CV disease, occurring in association with each other more often than expected by chance (6). Although definitions may vary, nowadays the most widely used MetS definition was formulated by the US National Heart, Lung, and Blood Institute (NHLBI) together with the American Heart Association (AHA) (7). In accordance with the NHLBI/AHA criteria, MetS is diagnosed when three or more of the following five criteria are present:

1) Fasting blood glucose level $\geq$100 mg/dl or pharmacological therapy for hyperglycemia.
2) Blood pressure $\geq$130/86 mmHg or pharmacological therapy for hypertension.
3) Triglycerides $\geq$150 mg/dl or pharmacological therapy for hypertriglyceridemia.
4) High-density lipoprotein cholesterol (HDLc) $<$40 mg/dl in men or $<$50 mg/dl in women.
5) Waist circumference $\geq$102 cm in men and $\geq$88 cm in women.

Interestingly, both MetS and its components are significantly over-represented in patients with PsA than in the general population and also compared to PsO and RA patients (9–12). Approximately 24–58% of patients with PsA have MetS, whereas it is only observed in 15–24% of individuals from the general population (5, 11, 13, 14). According to a study conducted in China, the odds ratio of MetS in PsA is 2.68 (95% CI: 1.60–4.50) when compared with the general population (5). A similar picture was observed for MetS prevalence in PsA compared to RA or ankylosing spondylitis populations in an outpatient arthritis clinic cohort [odds ratio (OR): 2.44, 95% confidence interval (CI): 1.48–4.01] (4). Importantly, the MetS components seem to precede the occurrence of PsA by at least 5 years (15), and hyperlipidemia and obesity have been described as risk factors for PsA development (16).

The elevated MetS may account for the elevated CV risk observed in PsA. In fact, patients with PsA have a 55% higher probability of developing CV diseases such as ischemic heart disease, cerebrovascular events or congestive heart failure (17). Moreover, a recent meta-analysis found that PsA patients exhibit increased mortality [relative risk (RR): 1.74, 95% CI: 1.32–2.30], particularly arising from CV disease (RR: 1.84, 95% CI: 1.11–3.06) (18).

The reasons for this increased prevalence of MetS in patients with PsA is an interesting field of research. Actually, recent studies have also associated MetS components with subclinical CV outcomes (19), thus suggesting that attenuating MetS components may lead to a certain degree of CV protection.

Diabetes

The evaluation of the individual components of MetS in PsA patients revealed that the prevalence of DM, as well as the presence of insulin resistance, is higher than in the general population (4). In addition, studies conducted on PsA patients without DM diagnosis at the time of enrollment, have shown that patients with PsA have a greater risk [hazard ratio (HR): 1.4–1.5] of developing type II DM over time compared to the general population (10, 20, 21). Moreover, this risk appears increased in women and in those with higher disease activity (20, 22). In addition to obesity and lifestyle factors, the inflammatory process related to arthritis pathogenesis may also play a key role in the risk of developing type II DM (23, 24). In 2013, a meta-analysis showed that the risk of type II DM was higher in patients with PsA (OR: 2.18; 95% CI: 1.36–3.50) compared to those with PsO (OR: 1.76, 95% CI: 1.59–1.96) (24). In a study using data from the "Consortium of Rheumatology Researchers of North America (CORRONA registry)" the prevalence of type II DM in PsA patients was also found to be higher than in those diagnosed with RA (15 vs. 11%; OR: 1.56, 95% CI: 1.07–2.28) (11).

Of note, the risk of type II DM seems to be related to disease severity in PsA, being positively associated with joint involvement and erythrocyte sedimentation rate (20, 22). Moreover, inflammation seems to trigger insulin resistance (23, 24) in this condition, hence pointing to a potential connection of MetS and inflammatory burden in PsA.

Hypertension

Arterial hypertension (HTN) is another CV risk factor with a higher prevalence in patients with PsO and PsA compared to the general population (4, 25). Data from a large Middle-Eastern PsA cohort reported an increase in the prevalence HTN (OR: 1.51; 95% CI: 1.40–1.6), in addition to that of hyperlipidemia (OR: 1.54; 95% CI: 1.43–1.67), type II DM (OR: 1.48, 95% CI: 1.36–1.61), and obesity (OR: 1.71, 95% CI: 1.58–1.84) (26). In a Spanish monocentric study, the prevalence of HTN was found to be higher in PsA compared to PsO (29 vs. 18%, OR: 1.7, 95% CI: 1.25–2.50) (26). A higher prevalence of HTN in patients with PsA than in patients with PsO was also observed in a cohort study of the University of Toronto (OR: 2.17, 95% CI: 1.22–3.83), after adjusting the data for demographic factors, comorbidity, and pharmacological treatments (9).

In a study obtained using data from the MarketScan claims database, a higher HTN prevalence (19.9 vs. 18.6%) and incidence (79.8 vs. 74.0 per 1,000 patient-years) were observed in PsA when compared to RA (27). Analyzing the prevalence of HTN in patients with PsO, Duan and coworkers observed an elevated prevalence of HTN compared to the general population only in patients with severe psoriatic disease (OR: 1.13, 95% CI: 1.03–1.25), but not in their mild disease counterparts (OR: 1.09, 95%

CI: 0.98–1.22), suggesting that a relationship between HTN and the systemic inflammatory response is also likely (28).

Dyslipidemia

Dyslipidemia is defined as a disorder of lipid metabolism characterized by increased LDL-cholesterol (LDLc) and triglycerides levels, usually associated with decreased HDLc levels.

A higher prevalence of dyslipidemia was observed in PsA compared to both the general population (5, 10, 25, 29). A study from the MarketScan database showed a higher incidence of hyperlipidemia in PsA patients than in controls [incidence risk ratio (IRR): 1.10, 95% CI: 1.04–1.17] (27). A similar picture was observed when compared with PsO patients (4, 26, 30). In fact, dyslipidemia seems to be more prominent in PsA patients with active disease, suggesting a potential link between inflammation and lipid profiles [reviewed in (18)]. However, the study of lipids is challenging in this scenario, since inflammation can lower serum LDLc levels (31, 32), as observed in RA (33). Therefore, hypercholesterolemia as a risk for MetS and CV disease may not apply in systemic diseases and should be interpreted with caution. Moreover, beyond lipoprotein levels, PsA patients exhibit qualitative alterations in their lipid profiles, namely a HDL3 sub-fraction reduction and an increase in most dense LDL sub-fraction, these features being associated with an enhanced atherogenicity activity (34). Furthermore, numerically higher lipoprotein A [Lp(a)] serum levels have been reported in PsA (34). Moreover, dyslipidemia in PsA patients is associated with increased markers of inflammation, such as C-reactive protein (CRP), and with a higher risk of subclinical atherosclerosis (35–37).

Obesity

Obesity is defined as a body mass index (BMI) $\geq$ 30 kg/m^2. Several studies have reported a higher prevalence of obesity in patients with PsA compared to the general population (10, 11, 25, 27, 38, 39), but also compared to patients with PsO (22.68 vs. 16.75%) in a large cohort study from the UK THIN database (40). However, also patients with PsO have a higher incidence of obesity when compared to the general population (OR: 1.66, 95% CI: 1.46–1.89), as demonstrated in a systematic review with pooled data of more than 200,000 PsO patients (41). The prevalence of obesity is also higher in PsA patients than in their RA counterparts (11), as well as in other chronic inflammatory diseases (29). Obesity has been also associated with poor treatments outcomes and decreased rates of remission attainment in PsA patients undergoing TNF inhibitors (42), thus affecting not only the metabolic dimension of the disease but the inflammatory process itself.

Obesity appears to be a significant risk factor for both the development of PsA and PsO, and this risk seems to be weight-dependent, as the risk of developing PsA increases with increasing BMI (43–45). In fact, a British study reported a growing risk RR of developing PsA with increasing BMI: the RR of PsA was 1.09 (0.93–1.28), 1.22 (1.02–1.47), and 1.48 (1.20–1.81) with BMI of 25–29.9, 30.0–34.9, and 35.0 kg/m^2 (44), respectively. Moreover, the risk of PsA in obese patients seems to decrease if the patient undergoes weight loss, as demonstrated by several studies (46, 47). The results of two broad population-based cohort studies also showed a protective effect of bariatric surgery for the development of PsA (HR 0.52, 95% CI 0.33–0.81) (46–48).

MetS AND INFLAMMATION

In addition of an enhanced CV risk, PsA patients with MetS have been reported to exhibit higher disease activity scores. In fact, there is evidence supporting that MetS occurrence is associated with PsA severity (49, 50). The underlying reasons are unclear, but several explanations might (co)exist (**Figure 1**). First, the composite indices to measure PsA activity contain patient reported outcomes (PROs). Obesity may contribute to the joint discomfort referred by patients, thus causing an overestimation of PROs. In addition, obesity, especially visceral obesity (51), is associated with increased CRP. Furthermore, obesity has also been associated with a lower probability of achieving a therapeutic response (52), thus accounting for an enhanced pro-inflammatory milieu as well. The increase in obesity-related PROs and CRP levels may therefore result in a higher score of the composite indices to measure disease activity (53, 54). Of note, the association between MetS and inflammation can be regarded as bi-directional, since elevated inflammation or disease severity has been associated with higher odds of DM occurrence (HR: 1.21, 95% CI: 1.03–1.41; and HR: 1.53, 95% CI: 1.08–2.18, respectively) in a recent cohort study (20), and inflammation is known to trigger impaired glycemic and lipid metabolism, hence contributing to MetS severity.

Of note, although MetS is known to predict CV disease development or subclinical atherosclerosis occurrence in PsA, inflammation has been demonstrated to play a role in shaping this association, probably by accelerating atherosclerosis development or by aggravating MetS burden (55–58). Of note, CV disease prevalence cannot be fully explained by traditional risk factors in RA (39), hence suggesting that other factors such as inflammation may play a significant role.

Mechanistic evidence adds to these findings, since a number of cytokines implicated in the psoriatic and arthritic disease domains can contribute to atherosclerosis and metabolic impairments, including Th1 (TNF, IFNγ, and IL-12) and Th17 cytokines (IL-17, IL-22, IL-23, IL-6, and TNF). These cytokines can act on distant organs, such as liver, skeletal muscle, vascular endothelia, and adipose tissue, thus bridging chronic inflammation, atherogenesis, and metabolic dysfunction leading to CV risk [reviewed in (59)].

Taken together, it is tempting to speculate that a good control of PsA may lead to an amelioration of the underlying inflammatory process thus causing an improvement of the articular and skin outcomes, but also to the MetS burden. In fact, an improvement of MetS components has been associated with reaching the minimal disease activity status in PsA (52, 60, 61), thus consequently suggesting a link between inflammation and reduction of the CV risk (62). Importantly, PsA patients not taking disease modifying anti-rheumatic drugs (DMARDs)

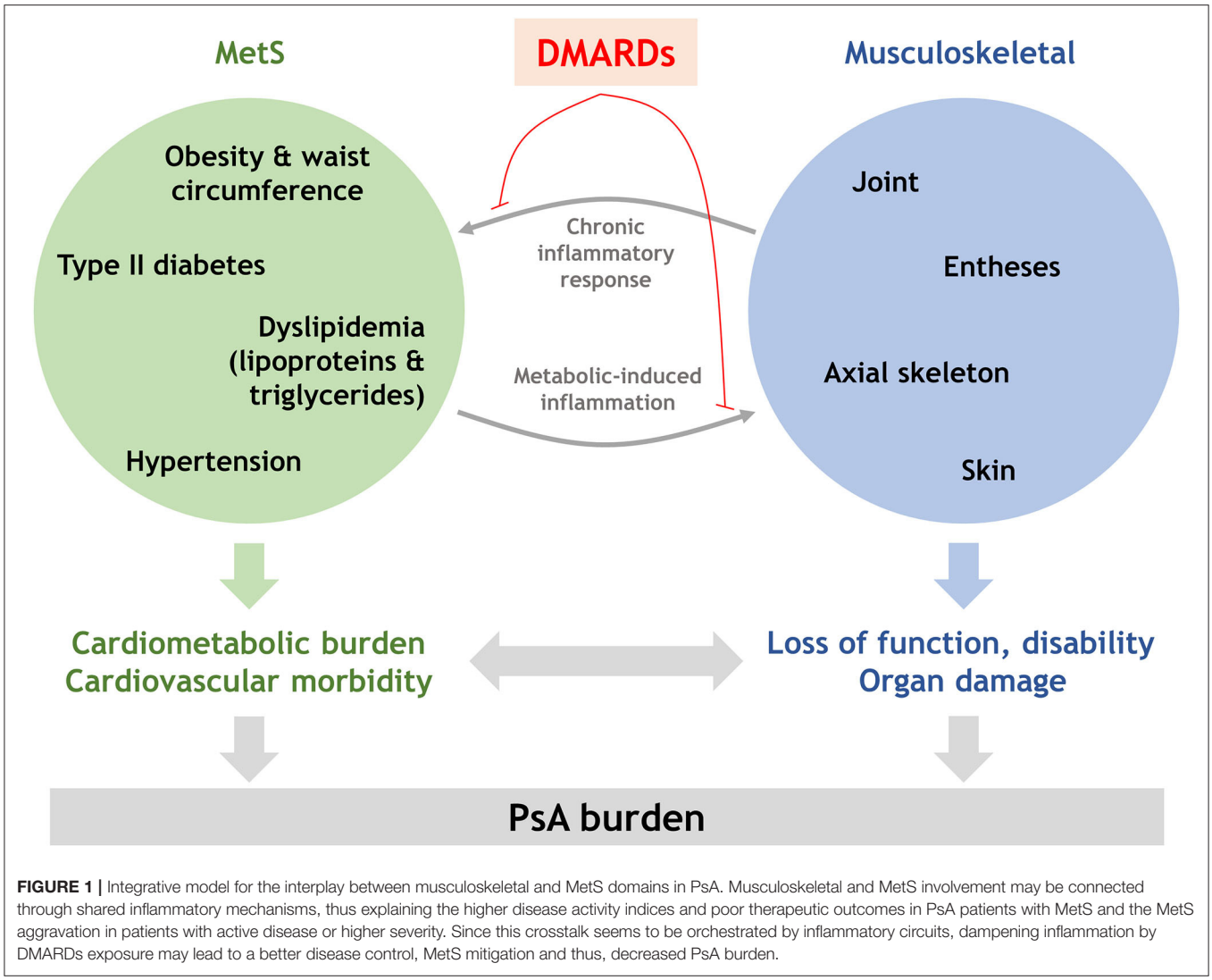

FIGURE 1 | Integrative model for the interplay between musculoskeletal and MetS domains in PsA. Musculoskeletal and MetS involvement may be connected through shared inflammatory mechanisms, thus explaining the higher disease activity indices and poor therapeutic outcomes in PsA patients with MetS and the MetS aggravation in patients with active disease or higher severity. Since this crosstalk seems to be orchestrated by inflammatory circuits, dampening inflammation by DMARDs exposure may lead to a better disease control, MetS mitigation and thus, decreased PsA burden.

were twice as likely to have MetS compared to PsO patients even after adjusting by age, CRP and blood pressure (adjusted OR: 2.09, 95% CI: 0.78–5.59) (19). Similarly, patients not taking DMARDs are more likely to suffer a major adverse CV event (MACE) compared to the general population (HR: 1.24, 95% CI: 1.03–1.49) after adjusting for confounders, and exhibit a numerically higher risk when compared to their DMARD-treated counterparts (HR: 1.08, 95% CI: 1.02–1.15) (40). Furthermore, a recent meta-analysis concluded that systemic therapies, including TNF inhibitors and methotrexate, was associated with a reduction of CV events, although evidence was lower than for RA patients (63). Finally, many studies linked the suppression of inflammation with a favorable impact on subclinical CV surrogate markers (18, 26, 43, 45). Taken together, all these lines of evidence support that DMARDs exposure may ameliorate MetS burden, and thus CV risk, in PsA patients (**Figure 1**).

Therefore, the possible presence of MetS should be seriously taken into account during the therapeutic decision process for PsA. Targeting inflammation with DMARDs may have an important effect in mitigating MetS burden in PsA.

DMARDs AND MetS IN PsA

Conventional DMARDs

Methotrexate

Numerous data exists supporting the role of methotrexate (MTX) in reducing CV risk in patients with chronic inflammatory diseases. The protective effect of MTX is linked to an overall reduction of the inflammatory response. Although most of the studies are derived from RA populations (64), the first data begins to appear also for patients with PsA and associated MetS.

A study assessing the safety of MTX on glucose metabolism in PsA and MetS patients found that glycated hemoglobin in such patients showed no difference before and after 12 weeks of starting treatment. As a result, the use of MTX in this category of patients is safe, having shown no hyperglycemic effects (65). It actually seems to even have a positive effect on

carbohydrate metabolism. In fact, a study observed reduction of glycated hemoglobin after starting MTX treatment in patients with arthritis of about half (∼0.4 units) of what would be obtained with metformin (∼0.8 units). A comparable result was observed after starting treatment with TNF inhibitors (TNFi) (65). The PSARA (Psoriatic Arthritis, Ankylosing Spondylitis, Rheumatoid Arthritis Study) study, aimed at observing the effects on endothelial function of MTX in monotherapy, MTX in combination with TNFi, and TNFi in monotherapy, noted an improvement in endothelial function after 6 months of treatment in all the three treatment groups. However, this improvement was stronger in the group of patients treated with MTX in monotherapy (66).

Biological DMARDs

TNF Inhibitors

The effectiveness of TNFi in patients with MetS is still a subject of debate. Several studies highlight the reduced efficacy of TNFi in obese patients (67, 68). A meta-analysis including 22 studies (for a total of 11,873 patients) conducted by Singh and coworkers showed that obesity was associated with a lower therapeutic response in patients with PsO and PsA (OR: 1.57, 95% CI: 1.30–1.89) (67). A recent study based on the US CORRONA PsA/SpA registry found that the presence of obesity was a strong predictor of failure to achieve remission in PsA (OR: 0.51, 95% CI: 0.32–0.81) (68). By contrast, an Italian study observed that the presence of MetS does not reduce the anti-inflammatory effect of TNFi neither the likelihood of reaching MDA (69). In a separate study, the same study group found out that in patients with MetS and PsA, the carotid intima-media thickness (cIMT) was greater in those treated with other DMARDs than in those undergoing TNFi, thus suggesting that the latter, by reducing inflammation may reduce CV risk in PsA (70). Whether a stronger, general effect on inflammation or a specific role of the TNF pathway was responsible of these findings remain to be elucidated. The efficacy of TNF blockade therapy in reducing or containing subclinical atherosclerosis was confirmed by other studies (71).

However, it is not yet clear whether weight-dependent changes in the dosage of the drug, possible with intravenous golimumab and infliximab, can improve the therapeutic response to TNFi in obese patients (4). Although the efficacy of TNFi may be lower in obese patients than in their non-obese counterparts, some studies have shown a lower risk of developing DM in TNFi-treated patients compared to other non-biological systemic treatments (excluding MTX) (72–74).

Interestingly, the impact of TNFi seems to be associated with a beneficial effect on several MetS components, including, including waist circumference, levels of triglycerides and HDLc as well as blood glucose levels (75). In fact, a clinical trial including 127 patients with PsA and active PsO undergoing TNFi treatment reported an increment in apolipoprotein AI, apolipoprotein B and triglycerides and a decline of Lp(a) after 12 weeks, although the relevance of these findings in terms of CV risk remained unclear (76).

Other Biological Drugs: IL-17 and IL-12/23 Inhibitors

Unfortunately, there is a lack of robust clinical evidence on the role of drugs targeting IL-17 and IL-12/23 on MetS and CV outcomes in PsA. Interestingly, this axis is expected to contribute to the cardiometabolic alterations, at least in PsO (77). A recent prospective study has demonstrated that overweight and obese patients had a better Disease Activity in Psoriatic Arthritis (DAPSA) score compared with their normo-weight counterparts (78), and serum IL-17 seem to correlate BMI, pointing to an association between obesity and IL-17 and thus, a potential better clinical benefit in patients with obesity. This finding was also supported by the fact that obesity was related to a Th17 expansion in adipose and peripheral tissues. However, due to the paradoxical association between IL-17 and CV disease (79, 80), whether IL-17 blockade leads to a more favorable profile and MetS mitigation requires further research.

Concerning IL-12/23 inhibitors, short-term data revealed no increased CV risk in PsO patients (81, 82). Moreover, it has been hypothesized that IL-23 inhibition may be more effective in patients with comorbidities in PsO patients (83). However, a recent *post-hoc* analysis of two clinical trials revealed no differences between PsO patients with and without MetS (84). Nevertheless, no evidence on its impact on MetS components in PsA is available. Due to the functional differences in the IL-23/IL-17 axis across chronic inflammatory conditions (85, 86), and the role of IL-23 in maintaining gut homeostasis and preventing obesity in animal models (87), studies on the effect of IL-23 blockade in metabolic outcomes in PsA patients are warranted.

Small Molecules

Apremilast

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor belonging to the class of oral small molecules. It is indicated for the treatment of PsA and moderate/severe PsO (88). It acts at the intracellular level by modulating the production of pro-inflammatory and anti-inflammatory mediators by PDE4. In addition to fueling inflammatory processes, PDE4 seems to be also involved in lipid and glucose metabolism disorders, liver steatosis, altered lipolysis, and neuroendocrine alterations (89, 90). Therefore, its inhibition may bring benefits on both the inflammatory component at the base of PsO/PsA, as well as on the MetS components.

Inhibition of PDE4 improves liver steatosis, reduces lipid deposition in the liver and consequently improves insulin resistance (89). Apremilast also appears to contribute to counteracting endothelial dysfunction, thus reducing CV risk (91, 92), and to stabilize atherosclerotic plaques, hence blocking its evolution to an unstable, high risk phenotype (93). An interesting study conducted by Mazzilli and coworkers observed a better therapeutic response to apremilast in diabetic patients compared to non-diabetic patients, with a reduction in blood glucose and total- and LDLc levels (94). Based on these findings, apremilast may be an appropriate therapeutic choice in patients with PsO/PsA and MetS (94).

Tofacitinib

Tofacitinib is an oral Janus kinase inhibitor (JAKi) that works interfering with the intracellular signaling pathway of s number of cytokines and inflammatory mediators. It is indicated for the treatment of PsA (95–97). Tofacitinib treatment has been observed to increase LDLc levels (98). Hypercholesterolemia is an important CV risk factor, and for this reason tests have been carried out aimed at assessing the efficacy and safety of tofacitinib in patients with MetS, and in general in those with increased CV risk (98, 99). A *post-hoc* analysis of phase III tofacitinib studies analyzed the efficacy and safety profile of this drug in patients with MetS (99).

Regarding efficacy data, the proportion of patients with MetS reaching endpoints such as ACR20/50/70 and Health Assessment Questionnaire-Disability Index (HAQ-DI) response, as well as resolution of enthesitis and dactilytis, was greater in the tofacitinib group compare to placebo. When comparing patients with and without MetS, similar results were observed except for resolution of dactylitis and HAQ-DI response, which were lower in patients with MetS. Regarding safety data, no differences in the proportion of adverse events were found between tofacitinib and placebo groups, and no new risk factors were identified in tofacitinib-treated presenting MetS at baseline (99). Since patients with MetS are much more likely to develop non-alcoholic fatty liver disease (100), and considering the tofacitinib-induced hyperlipidemia, the hepatic impact of tofacitinib in this subset of patients was analyzed, and no clinically relevant abnormalities were found (99).

Considering the increased CV risk in PsA patients, Dafna and coworkers analyzed changes in lipid profile, risk factors for CV disease occurrence, and incidence of MACE in patients with PsA undergoing treatment with tofacitinib (5 or 10 mg twice a day) in combination with conventional DMARDs (98). Although a 10–15% increase in lipid levels was observed, HDLc was increased in conjunction with other lipids, and no significant changes were observed in the LDLc/HDLc or total cholesterol/HDLc ratios (98). A parallel, significant reduction in CRP levels was also registered (98). Importantly, lipid ratios and CRP levels and blood pressure/hypertension are known CV risk factors in PsA (101–103). Therefore, these findings did not show overall a further increased risk of CV disease after treatment with tofacitinib (98), thus suggesting that these lipid changes do not fully translate into CV disease occurrence. Similar picture has been also observed in RA (32, 104).

UNMET NEEDS, FUTURE PERSPECTIVES AND CONCLUSIONS

Compelling evidence urges the intervention of cardiometabolic risk in PsA patients. Due to the involvement of inflammatory pathways on MetS components, the use of DMARDs may be accompanied by a MetS mitigation. This aligns with the EULAR recommendations of keeping a tight disease control and flare prevention in order to achieve a good CV risk management (105). Overall, the current literature is supportive of a therapeutic effect of approved DMARDs on MetS outcomes in PsA populations. However, the whole picture is far from being clear and the existing evidence is not optimal for a robust therapeutic decision making process in PsA. Of note, DMARDs may be double-edge swords in this scenario. For example, corticosteroids worsen glucose homeostasis, and NSAIDs are associated with an increased CV risk (4). On the contrary, other treatments such as TNFi may decrease the cardiometabolic risk by reducing the underlying inflammatory response in PsA (63, 106). Therefore, the MetS burden may be at the center of the therapeutic decision process, in addition to joint and skin involvement. This is in line with the most recent international recommendations for PsA management, which highlight the relevance of comorbidities to choose the most appropriate drug for each patient and tailor therapeutic approaches in accordance (107–109).

Unfortunately, the evidence on the harmful/beneficial balance effect of the different DMARDs approved for PsA is far from being optimal, and there is a lack of robust evidence to guide these decisions in PsA populations. On the one hand, most of the evidence in terms of CV effects derive from RA and PsO studies. Although similarities between RA and PsA exist (59), significant differences in terms of pathogenesis are present, especially regarding $CD4^+$ T-cell involvement, TNF/IL-17 role and participation of the humoral response. More importantly, traditional CV risk factors are overrepresented in PsA compared to RA populations, although CV disease occurrence seems to be higher in the latter, hence pointing to divergent patterns in the inflammation-cardiometabolic risk connection across diseases. Of note, the levels of evidence of the recommendations for CV risk management in PsA is lower than those of RA (105). Taken together, all these lines of evidence emphasize the need for further, well-conducted PsA-specific studies. In fact, in a complex clinical scenario as PsA, a special attention should be paid to the comorbidity-multimorbidity spectrum (3). Multimorbidity could be a novel driving force in improving the disease management by giving a role for the several conditions potentially coexisting in PsA, shifting from a classical "index disease" model to a "multimorbidity centered" scheme. The role of patient preferences and patient-centric concepts is warranted in this setting.

In addition to better studies and comparative trials with the drugs therein reviewed, there is a clear knowledge gap in terms of the clinical effects on the MetS and its components of the approved drugs targeting the IL-17/IL-23 axis in PsA patients. Individual and head-to-head comparative clinical trials are much awaited due to the clinical benefit of these drugs in joint and skin domains in PsA patients. However, to which extent this clinical benefit translates to MetS, CV or multimorbidity outcomes in PsA patients remain unclear. Similarly, whether these drugs may benefit the general PsA population or specific patient subsets represent an important unmet need in this setting. Additionally, it is important to note that the existing evidence came from pharmaco-epidemiological studies, and thus are inherently affected by allocation and confounding by indication biases, which are a key limitation to establish firm recommendations for clinical practice. The need for better design trials and large registries to address this questions is in the research agenda (104).

Besides the effect of DMARDs on MetS outcomes, PsA patients face important rates of underscreening, underdiagnosis, and undertreatment of CV risk factors, including MetS components [reviewed in (59)]. This poses relevant questions in terms of cardiometabolic risk intervention. First, it may be important to ascertain whether the documented effect of DMARDs in the existing studies may be an underestimation of their actual effect due to poor risk factor conventional treatment (anti-hypertensive, lipid-lowering, oral antidiabetic agents, etc.). Second, it may be key to elucidate if DMARDs plus conventional risk factor conventional treatments show potential synergistic effects or if drug-drug interactions should be considered. Third, whether an optimal management of CV risk factors leads to a better disease control by virtue of the bi-directional crosstalk between cardiometabolic and inflammatory pathways remain to be elucidated.

Finally, the role of lifestyle interventions should be considered in future studies and clinical research. EULAR urges the implementation of lifestyle modifications to dampen CV risk factors. Whether these interventions can add to or modulate the effect of DMARDs on the MetS burden needs to be established. With the advancement of the syndemics framework for complex conditions (110, 111), such an approach must be conceived in this scenario.

AUTHOR CONTRIBUTIONS

FA, EG, IF, SB, and JR-C designed and performed the literature search. FA and JR-C drafted the narrative review and edited the manuscript. All authors read the manuscript, revised it for intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

FUNDING

JR-C was supported by European Union FEDER funds and Fondo de Investigación Sanitaria (PI16/00113) from Instituto de Salud Carlos III (ISCIII).

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

frontiers in Medicine

REVIEW
published: 16 September 2021
doi: 10.3389/fmed.2021.737256

Managing Psoriatic Arthritis With Inflammatory Bowel Disease and/or Uveitis

Alfred Yu Ting Chia[1,2], *Gladys Wei Xin Ang*[2], *Anita Sook Yee Chan*[1,3], *Webber Chan*[4], *Timothy Kit Yeong Chong*[5] *and Ying Ying Leung*[1,5]*

[1] Duke-NUS Medical School, Singapore, Singapore, [2] Translational Immunology Institute, SingHealth Duke-NUS Academic Medical Centre, Duke-NUS Medical School, Singapore, Singapore, [3] Singapore National Eye Center and Singapore Eye Research Center, Singapore, Singapore, [4] Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore, Singapore, [5] Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore

Psoriatic arthritis (PsA) is a chronic inflammatory disease that presents with psoriasis (PsO), peripheral and axial arthropathy. The heterogeneity of disease presentation leads to the term "psoriatic disease (PsD)" which is thought to better encompass the range of clinical manifestations. PsA is associated with several comorbidities such as cardiovascular diseases, metabolic syndrome and other extra-articular manifestations including uveitis, and inflammatory bowel disease (IBD). While novel therapeutics are being developed following advances in our understanding of the pathogenesis of the disease, the diverse combinations of PsA with its various comorbidities still pose a clinical challenge in managing patients with PsA. This article reviews our current understanding of the pathogenesis of PsA and how various pathways in the pathogenesis lead to the two comorbid extra-articular manifestations – uveitis and IBD. We also review current evidence of treatment strategies in managing patients with PsA with comorbidities of uveitis and/or IBD.

Keywords: psoriatic arthritis, uveitis, inflammatory bowel disease, co-morbidity, biologic therapy

OPEN ACCESS

Edited by:
Piero Ruscitti,
University of L'Aquila, Italy

Reviewed by:
Anabela Barcelos,
New University of Lisbon, Portugal
Qiang Xu,
Guangzhou University of Chinese Medicine, China

***Correspondence:**
Ying Ying Leung
katyccc@hotmail.com

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *06 July 2021*
Accepted: *20 August 2021*
Published: *16 September 2021*

Citation:
Chia AYT, Ang GWX, Chan ASY, Chan W, Chong TKY and Leung YY (2021) Managing Psoriatic Arthritis With Inflammatory Bowel Disease and/or Uveitis. Front. Med. 8:737256. doi: 10.3389/fmed.2021.737256

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis (PsO) (1). It belongs to the family of spondyloarthritis (SpA) and the musculoskeletal manifestations include peripheral arthritis, dactylitis, enthesitis, and axial arthropathy. The impact of PsA extends beyond skin and joints to disability, fatigue, anxiety, depression, and poor quality of life (2, 3). PsA is associated with comorbidities such as obesity, metabolic syndrome, insulin resistance, and cardiovascular disease (4). The extra-articular manifestations of PsA include inflammatory bowel disease (IBD) and uveitis (5). In recent years, there are advancements in therapeutic options to treat musculoskeletal manifestations of PsA (6), but research to understand the pathogenesis of extra-articular manifestations and their treatment options is still in infancy. The purpose of this review is to summarize the current understanding of pathogenesis of PsA and the extra-articular manifestations and their treatment options.

EXTRA-ARTICULAR MANIFESTATIONS

IBD

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of IBD. CD is characterized by chronic, patchy granulomatous inflammation with skip lesions, affecting any part of the

gastrointestinal tract, especially the terminal ileum and colon. The inflammation is transmural which can lead to fibrosis, stricture, and fistula. In contrast, UC is characterized by continuous mucosal inflammation extending from the rectum proximally toward the colon. Differentiating these two conditions is important as each has diverse prognoses and differential responses to treatment (7). The clinical presentations of IBD include recurrent abdominal pain, bloody diarrhea, and mucus in the stool. Patients with CD can present with intestinal obstruction, recurrent fistulas, and other perianal findings. Systemic symptoms include fatigue, weight loss, fever, and symptoms of anemia. The standardized mortality ratio for CD ranges from 1.2 to 1.9 times the general population (8). The prognosis of IBD has improved in recent decades due to therapeutic advances.

Amongst patients with IBD, extraintestinal manifestations are common, including musculoskeletal (axial and peripheral arthropathy and arthritis), ocular (uveitis, scleritis and episcleritis), and skin. Inflammatory arthropathies are reported up to 40% of patients with IBD (9). While asymptomatic sacroiliitis may be seen in up to three-quarters of IBD patients, the reported prevalence of seronegative SpA ranges from 18–45%, and ankylosing spondylitis (AS) 3–9.9% (10, 11). Peripheral arthritis is reported in 7–16% of IBD patients. Peripheral arthritis is mainly asymmetrical and oligoarticular, usually acute and occurs during IBD exacerbations, and self-limiting. However, it may also persist for months or years. Its onset usually coincides with or after IBD but may precede IBD. Enthesitis and dactylitis were reported in 2–4% of patients (12).

Amongst patients with SpA, IBD is common (13). Patients with PsO, PsA and AS have a 1–4 fold increased risk of IBD compared to the general population (14–18). Among patients with SpA, 30–42 % have endoscopic (macroscopic) gastrointestinal inflammation (19–22) while 46–58 % have histologic (microscopic) inflammation (20, 21, 23). The presence of macroscopic or microscopic inflammatory lesions poorly correlates with symptoms (19). In patients with axial SpA, the severity of microscopic inflammation was significantly associated with severity of bone marrow edema on magnetic resonance imaging, indicating a link between mucosal inflammation and progressive disease (24).These subclinical gastrointestinal inflammatory lesions may predispose SpA patients to develop IBD, with a lifetime IBD risk of between 4–8% (25–28). Among patients with PsO and PsA, IBD is more common in patients with more severe PsA (29). IBD is also more common in patients with axial-PsA than in those with peripheral-only PsA (30).

Uveitis

Uveitis is the inflammation of the uveal tract of the eye which comprises of the iris, ciliary body, and choroid. Adjacent structures including retina, optic nerve, vitreous, and sclera may also be affected. Clinically, uveitis is categorized anatomically – anterior, intermediate, posterior, or panuveitis (31). There is an increased association of ocular manifestations amongst patients with PsD (32, 33). Other presentations like vitritis, retinal vasculitis, and cystoid macular edema involving the posterior chamber are sight-threatening (34, 35). The prevalence of uveitis increases with disease duration, lifelong prevalence is over 40%. Among patients with SpA, acute anterior uveitis (AAU) is most common (26) and its prevalence varied with the type of SpA: 33% in AS; 37% in IBD-associated arthritis; 26% in reactive arthritis; 25% in PsA; and 13% in undifferentiated SpA (36, 37). In both Asian and Western populations, uveitis is common in patients with severe PsO and those with PsA (38, 39). Uveitis in SpA usually presents with a 'unilateral alternating' pattern, sudden in onset, confined to the anterior chamber, and completely resolves between episodes (40). In contrast, uveitis in PsA is insidious in onset, bilateral with a chronic relapsing course. PsA patients with both uveitis and axial arthropathy tend to be male and HLA-B*27 positive (41, 42). HLA-DR*13 positivity is also associated with uveitis in patients with PsA (43). Uveitis may also precede the development of PsA in patients with PsO (44).

PATHOGENESIS

Pathogenesis of PsA

A combination of genetic and environmental factors contributes to pathogenesis of PsA (**Figure 1**). Genetic component in PsA is strong (45). HLA class I alleles such as HLA-B*27:05:02 haplotype is widely reported to be positively associated with enthesitis, dactylitis, and sacroiliitis while the HLA-B*08:01:01–HLA-C*07:01:01 haplotype is positively associated with joint fusion, deformity and asymmetrical sacroiliitis. In contrast, the B*44:03:01–C*16:01:01 haplotype may be protective against enthesitis (46). Additional HLA haplotypes associated with susceptibility to PsA were HLA-B*38, and HLA-B*39 (47–51). Non-HLA PsA susceptibility loci related to inflammatory pathways have been implicated. IL-23 receptor (*IL-23R*) polymorphisms are associated with risk of PsA (52). Tumor necrosis factor receptor-associated factor 3-interacting protein 2 (*TRAF3IP2*), encoding nuclear factor-κB (NFκB) activator protein 1 (Act1) which is an adaptor protein for interleukin-17 (*IL-17*) receptor (53–55), *IL-23A*, *IL-12B*, and *TYK2* (Tyrosine Kinase 2) are other examples, highlighting the importance of IL-23/IL-17 axis in the pathogenesis of PsA (56).

In a genetically predisposed individual, environmental factors including mechanical stress may trigger enthesitis – a hallmark clinical presentation of SpA including PsA (57, 58). Mechanical stress and trauma release damage-associated molecular patterns (DAMPs), triggering the production of prostaglandin E2 (PGE2) (59) by resident mesenchymal cells, which recruit innate immune cells to perpetuate inflammation. PGE2 also induces T cell secretion of IL-17, a key driver in PsA pathogenesis (58, 60). Innate immune cells such as dendritic cells (DCs), monocytes/macrophages, neutrophils, and innate lymphoid cells (ILCs) corroborate with adaptive immune cells to perpetuate inflammation in PsA (61). Additionally, plasmacytoid dendritic cells (pDCs) infiltrate the synovium to act as antigen presenting cells (APCs), triggering downstream expression of TNF-α, IFN-γ, and IL-2 from CD68+ macrophage-like-synoviocytes that mediate synovial inflammation and bone erosions (62, 63). TNFα synergizes with DCs to activate and polarize Th17 cells (64). In addition to Th17 cells, type 3 innate lymphoid cells (ILCs) (65, 66), mucosal-associated variant T (MAIT) cells (67, 68), and

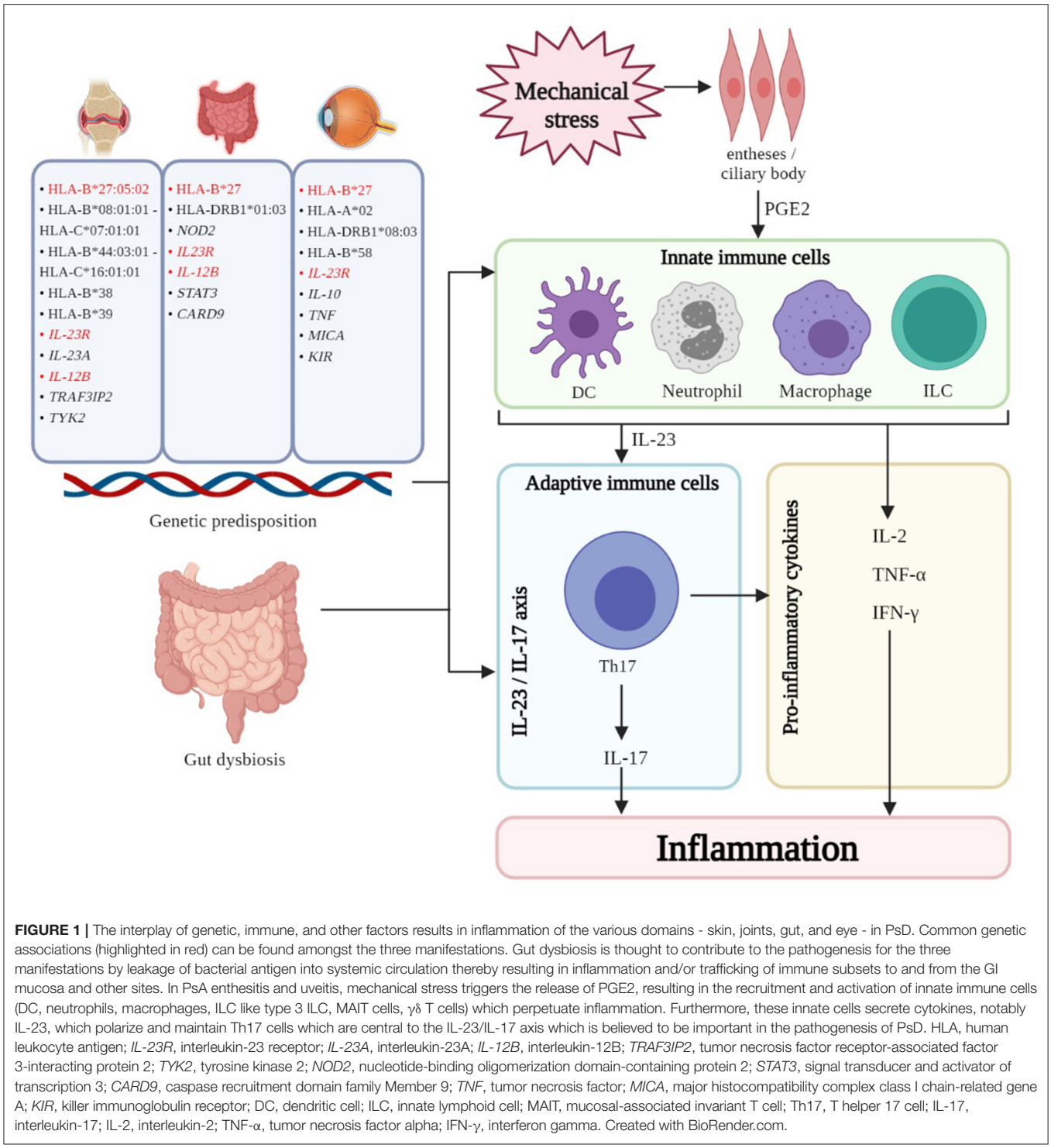

FIGURE 1 | The interplay of genetic, immune, and other factors results in inflammation of the various domains - skin, joints, gut, and eye - in PsD. Common genetic associations (highlighted in red) can be found amongst the three manifestations. Gut dysbiosis is thought to contribute to the pathogenesis for the three manifestations by leakage of bacterial antigen into systemic circulation thereby resulting in inflammation and/or trafficking of immune subsets to and from the GI mucosa and other sites. In PsA enthesitis and uveitis, mechanical stress triggers the release of PGE2, resulting in the recruitment and activation of innate immune cells (DC, neutrophils, macrophages, ILC like type 3 ILC, MAIT cells, γδ T cells) which perpetuate inflammation. Furthermore, these innate cells secrete cytokines, notably IL-23, which polarize and maintain Th17 cells which are central to the IL-23/IL-17 axis which is believed to be important in the pathogenesis of PsD. HLA, human leukocyte antigen; *IL-23R*, interleukin-23 receptor; *IL-23A*, interleukin-23A; *IL-12B*, interleukin-12B; *TRAF3IP2*, tumor necrosis factor receptor-associated factor 3-interacting protein 2; *TYK2*, tyrosine kinase 2; *NOD2*, nucleotide-binding oligomerization domain-containing protein 2; *STAT3*, signal transducer and activator of transcription 3; *CARD9*, caspase recruitment domain family Member 9; *TNF*, tumor necrosis factor; *MICA*, major histocompatibility complex class I chain-related gene A; *KIR*, killer immunoglobulin receptor; DC, dendritic cell; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; Th17, T helper 17 cell; IL-17, interleukin-17; IL-2, interleukin-2; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma. Created with BioRender.com.

γδ T cells (69) are recruited to the synovium and produce IL-17A upon stimulation (70). In short, the IL-23/IL-17 axis is the central driver of inflammation in PsA (71–75).

Pathogenesis of IBD

Genetic predisposition increases the risk of developing IBD amongst patients with PsA and SpA. HLA-B27 is the major HLA associated with IBD risk. 25–78% of patients with AS and IBD are HLA-B27 positive (9, 76, 77). HLA-DRB1*01:03 is also common between AS and IBD (76, 78–80). Non-HLA polymorphisms such as nucleotide-binding oligomerization domain-containing protein 2 (*NOD2)* polymorphisms increase the risk of CD about 4–40 times and is associated with sacroiliitis amongst patients with IBD. NOD2, an intracellular receptor expressed by immune

and intestinal cells, is involved in the activation of NFκB and inducing pro-inflammatory genes in innate immune cells (81–85). *IL-23R* polymorphisms modify susceptibility to IBD, where a loss-of-function mutation may have protective effect against IBD (86). Polymorphisms in genes related to the IL-23/IL-17 axis such as *IL-12B*, signal transducer and activator of transcription 3 (*STAT3*), and caspase recruitment domain family member 9 (*CARD9*) are associated with CD (87). Once again, this highlights the IL-23/IL-17 axis as a major pathogenetic pathway for IBD manifestations in patients with PsA.

The microbiome plays an important role in gastrointestinal health, and dysbiosis of the microbiota is observed in patients with IBD. Microbiota in IBD patients is less diverse compared to healthy controls. Gastrointestinal bacteria may invade the sterile inner colonic adherent mucus layer, disrupt epithelial architecture, and allow leakage of bacterial antigen into the systemic circulation to induce and perpetuate inflammation (88–90). A "gut-joint axis" has been proposed where immune cells traffic between the two domains (91, 92). Fecal microbiota transplantation (FMT) has shown promising results in the treatment of UC in a Cochrane Database systematic review (93). Positive clinical outcomes are associated with higher dosage and delivery of FMT via lower gastrointestinal tract (94), and may be dependent on stool donor (95). However, a recent RCT on FMT in 31 patients with active PsA randomized to FMT vs. sham treatment was not efficacious for arthritis (96). Further study is required.

In patients with IBD, the number of IL-17-secreting MAIT cells (97), was increased in the gastrointestinal tract as compared to the peripheral blood, echoing PsA studies showing depleted MAIT cells in blood, and increased MAIT cells in inflamed synovia and psoriatic skin (67, 68). γδ T cells are found in colonic mucosa and represent around 40% of intraepithelial lymphocytes (98). In contrast to PsA, the presence of γδ T cells appears to be protective and anti-inflammatory in patients with IBD. Different subtypes of γδ T cells may behave differently in different cytokine environments, explaining the diverse observations of γδ T cells in PsA and IBD (99, 100). As with PsA, Th17 cells are major players in IBD (101). The chemokine receptor CCR6 is the main surface marker of the Th17 lineage. CCL20, a ligand for CCR6, is elevated in IBD gut epithelium and likely contributes to recruitment of CCR6+ type 3 ILC, Th17, and dendritic cells (102, 103). Due to high levels of IL-17 and IL-23 in IBD gut epithelia, the IL-23/IL-17 pathway was thought to be a therapeutic target (104–106). However IL-23 inhibition showed efficacy in patients with IBD but IL-17 inhibition lead to disease exacerbation (107). A possible explanation for this paradox is that IL-17 plays a role in maintaining intestinal barrier and microbial defense (108–110).

Pathogenesis of Uveitis

The HLA-B*27 is associated with increased risk of AAU (111), and is a common risk locus for PsA (and other SpA) and uveitis (112). HLA haplotypes such as HLA-A*02 (113), HLA-DRB1*08-03 (114), HLA-B*58 (115) were also associated with development of uveitis. Other non-HLA susceptibility loci are major histocompatibility complex class I chain-related gene A (*MICA*) (116, 117), IL-10 (118), *TNF* (119), killer immunoglobulin receptor (*KIR*) (120), and polymorphisms in *IL-23R*, which all participate in immune response (121). Nonetheless, positive risk polymorphisms do not necessarily translate to uveitis. Other environmental and undiscovered factors are likely required to initiate uveitis in patients with SpA.

The eye is an immunologically privileged organ with a local inhibitory microenvironment, entailing immune ignorance and tolerance to prevent inflammation. The blood-retina barrier and absence of efferent lymphatics reduces exposure of the eye to the circulating immune system (122). In uveitis, infiltration of immune cells into the eye and disrupts the immunologically quiescent environment. However, the trigger of this infiltration is undetermined (123). Some evidence implicates the perturbation of the gut microbiome to SpA-associated uveitis. Animal studies demonstrated trafficking of leucocytes from intestine to eye, supporting the concept of a gut-eye axis (124). Further evidence from retina-specific TCR transgenic mice reared under germ-free conditions showed that the severity of uveitis was reduced in the absence of gut microbiota. This reduction of severity was associated with a reduction in Th17 cells in the lamina propria of the intestine. Reconstitution of gut microbiota increased retina-specific T cell signaling (125). McGonagle *et. al* (2015) proposed that anterior uveal structures are analogous to entheses due to their mechanical and structural roles in lens suspension. The repeated contractions and relaxations of these structures expose them to mechanical stress just like musculoskeletal entheses, thus providing the initial stimuli for inflammation (126). Like entheseal mesenchymal cells in enthesitis, cells in ciliary body express IL-23R, suggesting receptiveness to IL-23 signaling (127). In patients with uveitis, serum IL-17A levels were elevated during active disease (128). Association between Th17 and the development of uveitis has been observed in animal and clinical studies highlighting the importance of the IL-23/IL-17 axis in driving inflammation in PsA and uveitis (129–132). However, clinical trials have yet to demonstrate the efficacy of IL-17 inhibition in uveitis (133).

MANAGEMENT OF EXTRA-ARTICULAR MANIFESTATIONS IN PSA

Therapeutic advances in the last decade for PsA and PsO have improved quality of life of many. The European League Against Rheumatism (EULAR) developed algorithm treatment recommendations for the musculoskeletal manifestations of PsA (134). However, patients who have co-existing non-musculoskeletal manifestations such as IBD and uveitis pose a clinical challenge. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendation guideline highlighted a domain-driven approach focused on peripheral, axial, dactylitis, enthesitis, skin and nails (135, 136). The evidence for optimal treatment options for extra-articular manifestations in PsA is lacking and relies on evidence built in the fields of IBD and uveitis as independent conditions. Regardless of domains, the treatment goals are moving toward achieving low or minimal disease activity. Although some treatment options are common across the different domains, the doses may be different.

TABLE 1 | Therapeutic options and common dosing regimen for PsD and extra-articular manifestations.

Drug class	Agents	Dosage for domains				
		Peripheral arthritis	**Axial arthritis**	**Psoriasis**	**IBD**	**Uveitis**
Corticosteroid		- Intra-articular corticosteroid injection as indicated - Systemic corticosteroid to be avoided	- No indication	- Topical corticosteroid - Systemic corticosteroid to be avoided	- Induction: corticosteroid short tapering course - Maintenance: not indicated	- Corticosteroid eye drops tapering course - Periocular corticosteroid injections or intravitreal implants - Systemic corticosteroid for sight-threatening disease
Immune-modulator	Methotrexate Sulfasalazine Leflunomide Cyclosporin Thiopurines	- MTX 10–25 mg QW, PO - SSZ 500 mg-3g/day, PO - LEF 10–20 mg OM, PO - CyA 2.5-4 mg/kg/day, PO	- Not effective	- MTX 10–25 mg QW, PO - CyA 2.5–5 mg/kg/day, PO	- 5-ASA (UC): 1.5–4.5 g/day, PO - MTX 25 mg QW, SC or IM - SSZ 3–4 g/day, PO - AZA 2.5 mg/kg, PO	- MTX 7.5–20 mg QW, PO - SSZ 3–4 g/day, PO
TNFI	Infliximab	- 5–10 mg/kg loading at W0, 2 and 6, IV - then Q6–8W, IV	- 5–10 mg/kg loading at W0, 2 and 6, IV - then Q6–8W, IV	- 5–10 mg/kg loading at W0, 2 and 6, IV - then Q8W, IV	- Induction (CD/UC): 5–10 mg/kg loading at W0, 2 and 6, IV - Maintenance (CD/UC): 5–10 mg/kg Q8W, IV	Off label use - Induction: 4 to 6 mg/kg at W0, 2, 6, then Q4W until clinical remission, IV - Maintenance: 5 mg/kg Q10–12W, IV
	Adalimumab	- 40 mg Q2W, SC	- 40 mg Q2W, SC	- 40 mg Q2W, SC	- 160 mg or 80 mg at W0, then 80 mg at W2, then 40 mg Q2W, SC	- 40 mg Q2W, SC
	Etanercept	- 50 mg QW to BIW, SC*	- 50 mg QW, SC	- 50 mg BIW for 3 months, - then 50 mg QW, SC*	- 25 mg BIW, SC*	- No indication
	Golimumab	- 50 mg Q4W, SC - Or 100 mg Q4W, SC if BW >100 kg - Alternative IV formulation at 2 mg/kg at W0 and W4, then Q8W	- 50 mg Q4W, SC	Off label use - Not primary approved for Psoriasis	- Induction (CD/UC): 200 mg at W0, then 100 mg at W2 - Maintenance (CD/UC): 100 mg Q4W	- Off label use
	Certolizumab	- 400 mg at W0, 2 and 4, then 200 mg Q2W, SC - 400 mg Q4W, SC can be considered for maintenance	- 400 mg at W0, 2 and 4, then 200 mg Q2W, SC - 400 mg Q4W, SC can be considered for maintenance	- 400 mg Q2W, SC - For BW < 90 kg, can consider 400 mg at W0, 2 and 4, then 200 mg Q2W, SC	- Induction (CD/UC): 400 mg at W0, 2, 4, SC - Maintenance (CD/UC): 400 mg Q4W, SC	- Ongoing phase III trial, promising preliminary data - 400 mg at W0, 2, 4; then 200 mg Q2W
IL-17i	Secukinumab	- Loading 150 mg QW for 5 doses, then monthly, SC - (300 mg if TNFi experienced)	- Loading 150 mg QW for 5 doses, then monthly, SC	- Loading 300 mg QW for 5 doses, then monthly, SC	- (CD) no difference compared to placebo, more adverse events, not indicated	Failure in 3 RCTs - Higher dose is superior to lower doses - No indication
	Ixekizumab	- Loading 160 mg once, then 80 mg monthly, SC	- Loading 160 mg once, then 80 mg monthly, SC	- 160 mg at W0, then 80 mg at W2, 4, 6, 8, 10, and 12, then 80 mg Q4W, SC	- No study, no indication	- No study, no indication

(Continued)

TABLE 1 | Continued

Drug class	Agents	Dosage for domains				
		Peripheral arthritis	**Axial arthritis**	**Psoriasis**	**IBD**	**Uveitis**
IL-12/23i	Ustekinumab	- 45 mg Q4W for 2 doses, then Q12W - 90 mg Q4W for 2 doses, then Q12W if BW>100 kg	- No indication	- 45 mg Q4W for 2 doses, then Q12W - 90 mg Q4W for 2 doses, then Q12W if BW>100 kg	- Induction: single weight-based dose (<55 kg, 260 mg, 55–85 kg, 390 mg, >85 kg 520 mg), IV - Maintenance: 90 mg Q8W, SC	- Ongoing phase 2 trials
IL-23i	Guselkumab	- Loading 100 mg Q4W for 2 doses, then 100 mg Q8W, SC	- No indication	- Loading 100 mg Q4W for 2 doses, then 100 mg Q8W, SC	- Ongoing phase II/III RCTs	- No study, no indication
	Risankizumab	- 150 mg Q4W for 2 doses, then Q12W, SC	- No difference compared to placebo, no indicated	- 150 mg Q4W for 2 doses, then Q12W, SC	- Ongoing phase III studies in CD - Induction (CD): 600 mg or 1200 mg once, IV - Maintenance (CD): 600 mg or 1200 mg Q12W, SC	- No study, no indication
α4β7 integrin inhibitor	Vedolizumab	- No indication	- No indication	- No indication	- Induction (CD/UC): 300 mg at W0, 2, and 6, IV - Maintenance (CD/UC): 300 mg Q8W, IV	- No indication
JAKi	Tofacitinib	- 5 mg BD, PO	- 5 mg BD, PO	- 10 mg BD, PO	- Induction (UC only): 10 mg BD for at least 8 weeks; PO - Maintenance (UC only): then 5 or 10 mg BD, PO - CD: No difference compared to placebo, - No indication	- No study, no indication
	Upadacitinib	- 15 mg OM, PO	- 15 mg OM, PO	- 15 mg OM, PO	- Phase II dose ranging RCT in CD	- No study, no indication

**Less favored due to lower efficacy; not yet approved by authorities; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; BD, two times per day; BIW, twice per week; BW, body weight; CD, Crohn's disease; CyA, cyclosporin A; IL, interleukin; IM, intramuscular; IV, intravenous; OM, daily; PO, per oral; JAKi, Janus kinase inhibitors; LEF, leflunomide; MTX, methotrexate; Q, every; SC, subcutaneous; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitors; UC, ulcerative colitis; W, week.*

We summarize the usual doses used for various domains in **Table 1**.

Therapeutic Goals

The treatment targets for patients with IBD are clinical remission, mucosal healing, and restoring quality of life (137, 138). The importance of mucosal healing defined as restitution of the intestinal lining and regression or disappearance of endoscopic lesions has been emphasized. Achievement of this target is associated with reduced risk of relapse, reduced hospitalization rates, steroid-free remission, and resection-free status (139–141). With medical advancements, the need for bowel resection is substantially reduced (142).

Medical Therapies for CD

Corticosteroids can be used to induce clinical remission. It is given either topically as ileal-release budesonide for active mild-to-moderate CD or systemically for moderate-to-severe CD (132). However, systemic corticosteroid should not be used for maintenance (143, 144). Early initiation of corticosteroid-sparing immunomodulators such as azathioprine (AZA), mercaptopurine or methotrexate (MTX) for maintenance should be considered, although the level of evidence supporting efficacy of these drugs is relatively low (144, 145).

Monoclonal antibody targeting TNFα (TNF inhibitors, TNFi) has become the standard of care for patients with moderate-to-severe, active CD. Infliximab (IFX), adalimumab (ADA), and certolizumab (CZP) have demonstrated efficacy in inducing remission and maintenance in RCTs, and well supported by meta-analyses (146, 147). We summarized the major RCTs supporting the efficacies of TNFi in IBD **Table 2**. In a Cochrane Database Systematic review, CD patients who responded to induction by TNFi were more likely to maintain remission at 52 weeks with TNFi compared to placebo (147). Continued treatment with TNFi reduces surgery and hospitalization for CD (168, 169). Combination therapy of IFX with AZA was more efficacious than either agent alone in achieving response, inducing clinical and histological remission (156), suggesting synergistic effect. TNFi appears to be more effective when given at earlier stage of disease, with higher rates of response and remission, than given at later stage of disease (170, 171). Early escalation to TNFi treatment should be considered for patients with extensive disease and poor prognostic factors (144, 145).

Vedolizumab (VZD) is a monoclonal antibody targeting α4β7 integrin, which reduces lymphocytes trafficking to the gastrointestinal tract by blocking lymphocyte surface α4β7 binding to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1). The efficacies of VZD in induction and maintenance in CD have been demonstrated in the GEMINI-2 (172) and GEMINI-3 trials (173) (**Table 1**). In a meta-analysis involving 1716 patients with CD, VZD was more effective than placebo for inducing clinical remission (RR 1.71 [95% confidence interval, CI: 1.25, 2.34], $p = 0.0008$), and maintaining clinical remission (RR 1.75 (95% CI: 1.25, 2.44), $p < 0.001$).

Ustekinumab (UST) is an antibody targeting the IL-12/23 p40 subunit. The efficacy of UST in inducing remission in CD has been shown in UNITI-1 and UNITI-2 trials in patients with inadequate response to TNFi, and without prior TNFi failure, respectively. Responders from both studies were randomized to the IM-UNITI maintenance study and demonstrated significantly higher clinical remission rates [high dose: 53%, $P = 0.005$; low dose: 49%, $P = 0.04$)] compared to placebo (36%) at week 44 (162). There is no head-to-head study comparing efficacies between TNFi, VZD and UST. The choice of biological treatment is a shared decision between clinician and patient, and according to the individual risk–benefit preferences.

Risankizumab (RZB), an IL-23/p19 inhibitor met the primary remission induction endpoints in CD in two phase III RCTs, ADVANCE (NCT03105128) and MOTIVATE (NCT03104413) (174). Patients in remission from ADVANCE and MOTIVATE were recruited to the Phase III open-label maintenance study, FORTIFY, showing RZB 360 mg every 8 weeks achieved the co-primary endpoints of clinical remission and endoscopic response at 52 weeks (175).

Blocking IL-17, however, has not been effective in CD. In a phase II trial evaluating safety and efficacy of brodalumab (BRO), a monoclonal antibody targeting IL-17 receptor, the primary induction endpoint was not met. The trial was terminated early due to a disproportionate number of cases of worsening CD (160). In a phase II RCT, two doses of 10 mg/kg secukinumab (SEC) given intravenously on days 0 and 22, failed to meet the primary endpoint and had more adverse events compared to placebo (176). However, the use IL-17i is not associated with increased incidence of IBD. Data from the SEC development program pooling 7,355 patients with a cumulative exposure of 16,227 person-years of patients exposed to SEC for PsO, PsA or SpA, no increase in exposure adjusted incidence rates of IBD was observed (15). Similarly, events of IBD remained low in the ixekizumab development program that pooled data from 15 RCTs in PsO and PsA (177).

Phase II RCT results for the Janus kinase inhibitor (JAKi), upadacitinib (UPA), in CD are promising. Endoscopic but not clinical remission increased with dose during the induction period (167). However, in a phase II trial for JAKi, tofacitinib (TOF), no statistically significant differences in clinical responses between TOF and placebo were observed at week 4 (164) (**Table 2**).

Medical Treatment for UC

Oral 5-ASA (5-aminosalicylic acid) is the standard therapy for induction in mild-to-moderately active UC. For those failing 5-ASA or with moderate-to-severe UC, a short 6- to 8-week course of oral corticosteroid is indicated. 5-ASA and thiopurines can be used as maintenance therapy. Like the treatment strategy for CD, early escalation to biologic therapies should be considered for those who failed induction therapy with corticosteroid, or failed maintenance with immunomodulators, and those with poor prognostic factors. TNFi [IFX, ADA, golimumab (GOL)], α4β7 integrin inhibitor (VZD) and IL12/23i (UST) are approved treatments for induction and maintenance of UC (**Table 3**). A combination of TNFi with an immunomodulator is more effective. In the UC-SUCCESS trial, patients treated with IFX and AZA were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving either monotherapy (181).

TABLE 2 | Evidence from major clinical trials for class of therapeutic options for Crohn's disease.

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
TNFi	ADA	CLASSIC I (148)	II	299	Active CD, naïve to TNFi (induction)	- ADA 160/80 mg - Vs. 80/40 mg, - Vs. 40/20 mg at W0, 2, SC	- Clinical remission at W4: ADA 160/80 36% ($p = 0.001$), ADA 80/40 24% ($p = 0.06$), ADA 40/20 18% ($p = 0.036$), Vs. PBO 12% (all comparison vs. PBO).
	ADA	CLASSIC II (149)	II	276	CD achieved induction in CLASSIC I (maintenance)	Patients achieved remission in CLASSIC I were re-randomized ($n = 55$) to - ADA 40 mg QW, SC - Vs. ADA 40 mg Q2W, SC - Vs. PBO - Patients not achieved remission ($n = 209$) received open-labeled ADA 40 mg Q2W, SC	- Clinical remission at W56 for re-randomized ($n = 55$): ADA 40 mg QW 83%, ADA 40 mg Q2W 79% Vs. PBO 44% (all $p < 0.05$ vs. PBO). - Clinical remission at W56 for open labeled patients ($n = 209$): ADA 46%
	ADA	GAIN (150)	III	325	Active CD, TNFi IR (induction)	ADA 160 mg at W0, then 80 mg at W2, SC vs. PBO	- Clinical remission at W4: ADA 21.6% vs. PBO 6.7%, ($p < 0.001$).
	ADA	CHARM (151)	III	854	Active CD despite immunomodulators, non-TNFi IR. All received open labeled induction: ADA 80 mg at W0, 40 mg at W2, SC (maintenance)	Maintenance: - ADA 40 mg Q2W, - vs. 40 mg QW - vs. PBO	- Clinical remission at W26: ADA QW 47% vs. ADA Q2W 40% vs. PBO 17% (all $p < 0.001$ vs. PBO). - Clinical remission at W56: ADA QW 41% vs. ADA Q2W 36% vs. PBO 12%, (all $p < 0.001$ vs. PBO).
	ADA	EXTEND (152)	III	129	Active CD, responded to open labeled ADA induction (160/80 mg at W0, 2, SC) at W4 (maintenance)	Maintenance: - ADA 40 mg QW, SC - vs. 40 mg Q2W, SC - vs. PBO	- Mucosal healing at W12: ADA 27% vs. PBO 13%, ($p = 0.056$). - Clinical remission at W12: ADA 52% vs. PBO 28% ($p = 0.006$) - Mucosal healing at W52: ADA 24% vs. PBO 0% ($p < 0.001$). - Clinical remission at W52: ADA 28% vs. PBO 3% ($p < 0.001$).
	IFX	(153)	II	108	Moderate to severe CD, naïve to TNFi (induction)	- IFX 5 mg/kg, once, IV - vs. IFX 10 mg/kg, once, IV - vs. IFX 20 mg/Kg, once, IV - vs. PBO	- Clinical response W4: IFX 5 mg 81% ($p = 0.33$) vs. 10 mg 50% ($P = 0.26$) vs. 20 mg: 64% ($p = 0.01$) vs. PBO 17%. (all comparison vs. PBO) - Clinical remission W4: IFX (all doses) 33% vs. PBO 4% ($p = 0.005$). - Clinical response W12: IFX (all doses) 41% vs. PBO 12% ($p = 0.008$).

(Continued)

TABLE 2 | Continued

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
	IFX	ACCENT-I (154)	III	573	Active CD, despite immunomodulators naïve to TNFi, all received open-labeled IFX induction, then re-randomized for maintenance (induction and maintenance)	Open-labeled induction (all): IFX 5 mg/kg at W0, IV par Randomized at W2 for maintenance: - IFX 10 mg/kg at W2, 6, then Q8W, IV - Vs. IFX 5 mg/kg at W2, 6, then 5 mg/kg Q8W, IV - Vs. PBO	- Induction: 58% responded to initial IFX at W2. - Clinical remission at W30: IFX10 mg/kg 45% ($p = 0.003$), vs. IFX5 mg/kg 39% ($p = 0.0002$), vs. PBO 21%. (all comparison vs. PBO) - Median time to loss of response at W54: IFX 10 mg/kg >54W ($p = 0.002$), vs. IFX 5 mg/kg 38W ($p = 0.0002$), vs. PBO 19W (all comparison vs. PBO)
	IFX	ACCENT-II (155)	III	282	Fistulating CD, naïve to TNFi (induction and maintenance)	Open-labeled induction (all): IFX 5 mg/kg at W0, 2, 6, IV - Randomized at W14 for maintenance: - IFX 5 mg/kg Q8W, IV - vs. PBO	- Induction: 69% responded to initial IFX at W14. - Time to loss of response: IFX >40W vs. PBO 14W ($p < 0.001$) - Clinical response W54: IFX 36% vs. PBO 19% ($p = 0.009$)
	IFX	SONIC (156)	III	508	Active CD, naïve to immunomodulator and TNFi (induction and maintenance)	IFX 5 mg/kg at W0, 2, 6, then Q8W + AZA 2.5 mg/kg/day - vs. IFX alone - vs. AZA alone	- Corticosteroid-free remission W26: IFX+AZA: 57% ($p = 0.002$ vs. IFX; $p < 0.001$ vs. PBO), vs. IFX alone: 44% ($p = 0.006$ vs. AZA), vs. AZA alone: 30%. - Mucosal healing W26: IFX+AZA 44% ($p = 0.06$ vs IFX; $p = <0.001$ vs. AZA), vs. IFX alone 30% ($p = 0.02$ vs. AZA), vs. AZA alone: 17%.
	CZP	PRECiSE I (157)	III	662	Active CD, 17% concomitant corticosteroid and immunomodulators, 28% prior TNFi (induction)	- CZP 400 mg at W0, 2, 4, then Q4W, SC - vs. PBO	- Clinical response at W6: CZP 35% vs. PBO 27%, ($p = 0.02$); - Clinical response at both W6 and W26: CZP 23% vs. PBO 16%, ($p = 0.02$) - Remission at W6: CZP 14% vs. PBO 10% ($p = 0.17$) - Remission at both W6 and W26: CZP 22% vs. PBO 17% ($p = 0.07$)
		PRECiSE II (158)	III	428	Active CD, 24% concomitant corticosteroid and immunomodulators, 15% prior TNFi (maintenance)	Open-labeled induction ($n = 668$): CZP 400 mg at W0, 2, 4, SC Patient with clinical response were randomized at W6 for maintenance ($n = 428$): - CZP 400 mg Q4W, SC - vs. PBO	- Clinical response at induction (W6): 64% - Clinical remission at W26: CZP 48% vs. PBO 29% ($p < 0.001$).

(Continued)

TABLE 2 | Continued

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
	CZP	WELCOME (159)	III	539	Active CD, TNFi IR (maintenance)	Open-labeled induction ($n = 539$): CZP 400 mg at W0, 2, 4, SC - Patient with clinical response were randomized at W6 for open-labeled maintenance ($n = 329$): - CZP 400 mg Q2W, SC - vs. CZP 400 mg Q4W, SC - vs. PBO	- Clinical response at induction (W6): 62% - Clinical response at W26: CZP Q2W 37% vs. CZP Q4W 40% ($p = 0.55$). - Clinical remission at W26: CZP Q2W 30% vs. CZP Q4W 29% ($p = 0.81$).
IL-17i	BRO	(160)	II	130	Active CD (induction)	BRO 210 mg vs. 350 mg vs. 700 mg Q4W for 4W, SC vs. PBO	- Early termination due to worsening CD in active treatment groups, $n = 130$ analyzed at termination - Clinical response at W6: BRO 210 mg 16% vs. 350 mg 27% vs. 700 mg 15% vs. PBO 13%. - Clinical remission at W6: BRO 210 mg 3% vs. 350 mg 15% vs. 700 mg 9% vs. PBO 13%.
	UST	CERTIFI (161)	IIb		Active CD, TNFi IR (induction and maintenance)	Induction W0-8 ($n = 539$): - UST 1, 3, 6 mg/kg, SC - vs. PBO - Maintenance 8–36W (re-randomized at W8): - UST 90 mg at W8 and 16, SC - vs. PBO	- Clinical remission at W6 (induction): UST6 mg/kg 39.7% vs. PBO 23.5% ($p = 0.005$) NS for other UST doses Maintenance for those responded to induction, $n = 145$ - Clinical response at W22: UST 69.4% vs. PBO 42.5% ($p < 0.05$) - Clinical remission at W22: UST 42% vs. PBO 27% ($p < 0.05$)
IL-12/23i	UST	IM-UNITI (162)	III	397	UNITI-1: active CD, TNFi IR ($n = 741$). UNITI-2: active CD, immunomodulator IR ($n = 628$). IM-UNITI: Who had clinical response in UNITI-1 and 2 ($n = 397$)	Induction W0-8 (UNITI-1 or 2): - UST 130 mg, SC - vs. UST 6 mg/kg, SC - vs. PBO - Maintenance W8-44: - UST 90 mg/8W, SC - vs. UST 90 mg/12W, SC - vs. PBO	Induction: Clinical remission at W8: - UNITI-1 UST 6 mg/kg 38% ($p < 0.001$) vs. UST 130 mg 34% ($p = 0.001$) vs. PBO 20% (all comparison vs. PBO) - UNITI-2 UST 6 mg/kg 58% ($p < 0.001$) vs. UST 130 mg: 47% ($p = 0.001$) vs. PBO 32% (all comparison vs. PBO) Maintenance (IM-UNITI) - Clinical response: UST 90 mg Q8W 59% ($p = 0.02$) vs. UST 90 mg Q12W 58% ($p = 0.03$) vs. PBO 44% (all comparison vs. PBO) - Clinical remission UST 90 mg Q8W 53% ($p = 0.02$) vs. UST 90 mg Q12W 49% ($p = 0.03$) vs. PBO 36% (all comparison vs. PBO)

(Continued)

TABLE 2 | Continued

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
IL-23i	RZB	(163)	II	121	Active CD, TNFi IR (induction)	- RZB 600 mg Q4W - vs. RZB 200 mg Q4W - vs. PBO	- Clinical response at W12: RZD 600 mg 42% ($p = 0.0366$) vs. RZD 200 mg 37% (p = NS) vs. PBO 21% (all comparison vs. PBO) - Clinical remission at W12: RZD 600 mg 37% ($p = 0.025$) vs. RZD 200 mg: 24% (p = NS) vs. PBO 15% ($p = 0.049$) (all comparison vs. PBO)
JAKi	TOF	(164)	II	139	Active CD (induction)	TOF 15, 5, 5 mg BD, PO vs. PBO	- Clinical response W4: TOF 15 mg 46% ($p = 0.467$) vs. 5 mg 58% ($p = 0.466$) vs. 5 mg: 36% ($p \geq 0.999$) vs. PBO 47% (all comparison vs. PBO). - Clinical remission at W4: TOF 15 mg 14% ($p = 0.540$) vs. 5 mg 24% ($p = 0.776$) vs. 5 mg 31% ($p = 0.417$) vs. PBO 21% (all comparison vs. PBO).
	TOF	(165)	IIb	280 (induction) 180 (maintenance)	Active CD, % prior TNFi (induction and maintenance)	Induction 0-8W ($n = 280$) - TOF 10 mg BD, PO - vs. TOF 5 mg BD, PO - vs. PBO - Maintenance 8–26W for those responded to TOF induction ($n = 180$): - TOF 10 mg BD, PO - vs. TOF 5 mg BD, PO - vs. PBO	- Clinical remission at W8 (induction): TOF 10 mg 43% ($p = 0.392$) vs. TOF 5 mg 44% ($p = 0.325$) vs. PBO 36.7% (all comparison vs. PBO). - Clinical remission at W26 (maintenance): TOF 10 mg 56% ($p = 0.13$) vs. TOF 5 mg 40% (p = NS) vs. PBO 38.1%. (all comparison vs. PBO).
	FIL	FITZROY (166)	II	174	Active CD, 27% prior bowel resection, 58% prior TNFi (induction)	FIL 200 mg/day, PO vs. PBO	- Clinical remission at W10: - FIL 47% vs. PBO 36.7%. ($p = 0.0077$)
	UPA	CELEST (167)	II	220	Active CD (induction and maintenance)	Induction W0-16: UPD 3, 6, 12, 24 mg BD or 24 mg/day vs. PBO Maintenance W16-52: UPD 3, 6, 12, 24 mg BD or 24 mg/day No PBO control	- Clinical remission at W16: UPA 3 mg 13% (NS) vs. 6 mg 27% ($p < 0.1$ vs. PBO) vs. 12 mg 11% (NS) vs. 24 mg: 22% (NS) vs. 24 mg/day 14% (NS) vs. PBO 11%. (all comparison vs. PBO) - Endoscopic remission at W16: - UPA 3 mg 10% ($p < 0.1$) vs. 6 mg 8% (NS) vs. 12 mg 8% ($p < 0.1$) vs. 24 mg 22% ($p < 0.01$) vs. 24 mg/day 14% ($p < 0.05$) vs. PBO 0%. (all comparison vs. PBO). - Maintenance: Efficacy was maintained for most endpoints through week 52

ADA, adalimumab; AZA, azathioprine; BD, Twice daily; BRO, brodalumab; BW, Body weight; CD, Crohn's Disease; CZP, certolizumab; FIL, filgotinib; Gp, Group; IFX, infliximab; IL, Interleukin; i, inhibitor; IR, inadequate responder; IV, intravenous; JAKi, Janus kinase inhibitor; NS, not statistically significant; PBO, placebo; Q, every; RCT, Randomized control trial; RZB, risankizumab; TNF, tumor necrosis factor; inhibitor; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; vs., versus; W, week; yr, year.

In a head-to-head study (VARSITY) comparing TNFi and VZD in patients with moderate-to-severe UC, 769 patients with moderate-to-severe active UC were randomized to receive VDZ or ADA (185). Only 26% of patients in either group were on concomitant immunomodulators. At week 52, a higher percentage of patients achieved clinical remission (31.3 vs. 22.5%; $P = 0.006$), and endoscopic improvement (39.7 vs. 27.7%; $P < 0.001$) in VDZ compared to ADA group. Whilst corticosteroid-free clinical remission occurred at a higher rate in the group receiving ADA compared to VDZ (21.8 vs. 12.6%; difference, −9.3 percentage points; 95% CI, −18.9 to 0.4). Despite a slight superiority of VDZ over ADA, more data are pending for consistency and class effect. The choice of biologics is, again, a shared decision between between clinician and patient.

Due to the ineffectiveness of IL-17i for CD, there have not been trials for their use in UC. As for IL-23i, there is an ongoing phase II/III trial of RZB for UC (NCT03398148).

In contrast to CD, the JAKi, TOF, was approved for use in moderate-to-severe UC based on three pivotal phase III OCTAVE studies, showing a significantly greater percentage of clinical remission at week 8 for induction, and remission at week 52 for maintenance in TOF compared to placebo group (186). UPA met the clinical remission, endoscopic improvement and histological improvement endpoints in a phase III induction trial for moderate-to-severe UC (187).

Medical Treatment for Uveitis

Prompt control of inflammation using topical corticosteroid is the first-line treatment for anterior uveitis in SpA. Typically, prednisolone acetate 1% eye drops are used as for severe AAU while milder corticosteroids such as dexamethasone 0.1% may be used for maintenance. A mydriatic drug is often prescribed together to reduce the development of posterior synechia and reduce pain from ciliary body spasm. Periocular corticosteroid injections or intravitreal implants can be used for more chronic cases. Adverse effects of corticosteroid in the eyes include cataract and ocular hypertension in up to 30% of patients. Oral corticosteroids may be used for acute management of severe and sight-threatening posterior uveitis such as vasculitis and cystoid macular edema, however, immunotherapy should be considered early in these cases to reduce recurrences (188). Traditional immunomodulators such as sulfasalazine (SSZ) and MTX may be tried although few data have supported their efficacy. Monoclonal antibody-TNFi including IFX, ADA, GOL and CZP are considered as effective treatment options for both acute flares and reducing recurrences of AAU (189). We summarize the major RCTs of therapeutic options for uveitis in **Table 4**. In a *post-hoc* analysis pooling data from four RCTs with TNFi in AS, the frequency of AAU flares was substantially lower among IFX or etanercept (ETN) treated than placebo treated patients. Lower frequency of AAU flares was seen in the open-labeled extension phase compared to the placebo phase of the trial (TNFi: 6.8 flares per 100 patient-years compared to PBO: 15.6 per 100 patient-years, $p = 0.01$) (198). ADA is the only TNFi licensed for treatment of non-infectious uveitis in adult following favorable results in 2 phase III RCTs. In the VISUAL I study, patients with active non-infectious intermediate, posterior uveitis or panuveitis were randomized to receive ADA or placebo after a prednisolone burst (60 mg) with tapering course. Patients treated with ADA were less likely than those treated with placebo to have treatment failure (hazard ratio, HR, 0.50; 95% CI, 0.36 to 0.70; $P < 0.001$). The VISUAL II study recruited 226 patients with inactive, non-infectious intermediate, posterior, or panuveitis controlled by 10–35 mg/day of prednisone were randomized to ADA vs. placebo. All patients underwent a mandatory prednisolone tapering to 0 mg by week 19. The time to treatment failure was significantly longer in ADA compared to placebo arm (median >18 months vs. 8.3 months; HR 0.57, 95% CI 0.39–0.84; $p = 0.004$) (191). ADA is also licensed for juvenile idiopathic arthritis-related uveitis. In an open-label study in 93 AS patients with history of uveitis, GOL reduced uveitis flares compared to patients' historical control 12-month prior to initiation of GOL (192). There is an ongoing phase III 96-week open-label study for CZP in 115 patients with axial SpA and recurrent uveitis. In the 48-week interim analysis of 85 patients, uveitis flares were substantially reduced during the CZP treated period compared to the historical rates (64.0 and 31.5% respectively) (193). The use of ETN in the management of uveitis has diminished in favor of other TNFi because of its weaker ability in preventing flares.

Despite implicated in the pathogenesis of uveitis, inhibiting IL-17A was not effective for uveitis. In three RCTs, SEC failed to meet the primary efficacy endpoints (194). In another RCT comparing three doses of SEC, statistical higher response rates and remission on day 57 for the high dose regimen (30 mg/kg intravenously Q2W for 4 doses) was seen compared to the other two lower dose regimens, suggesting a higher dose intravenous regimen may be required to deliver SEC in therapeutic concentrations (195). Results are awaiting for two trials using UST in active sight-threatening uveitis (STAR) (196) and Behçet uveitis (STELABEC) (197), which may provide insight for its potential use in PsA related uveitis.

Minimal data exist for use of JAKi in uveitis. One phase 2 RCT evaluating filgotinib (FIL) in patients with active non-infectious uveitis (NCT03207815) is ongoing.

MANAGEMENT OF PSA WITH CONSIDERATION OF EXTRA-ARTICULAR MANIFESTATIONS

Given the heterogeneity in manifestations, enhanced collaboration between disciplines are required to deliver optimal care for PsD (199). While collaborations between rheumatologists and dermatologists are increasing (200), collaborations with gastroenterologists and ophthalmologists have traditionally been weaker. Apart from setting up combined clinics, collaborations between disciplines can take other forms as determined by needs and circumstances of different institutions. Minimally, identifying key stakeholders specializing in the care of PsA patients and keeping them in close communication over the management plan is essential. These collaborations serve both clinical and educational needs. Close collaboration between the various disciplines will help in early diagnosis of the various manifestations, providing expert advice on choice of

TABLE 3 | Evidence from clinical trials for class of therapeutic options for ulcerative colitis.

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
TNFi (mAb)	ADA	Ultra 1 (178)	III	186	Active UC, despite corticosteroid and/or immunomodulators (induction)	- ADA 160 mg at W0, 80 mg at W2, 40 mg at W4 and 6, SC - Vs. ADA 80 mg at W0 and 2, 40 mg at W4 and 6, SC - Vs. PBO	- Clinical remission at W8: ADA160/80 18.5% ($p = 0.031$ vs. PBO) vs. ADA 80/40 10.0% ($p = 0.833$ vs. PBO) vs. 9.2% PBO
	ADA	Ultra 2 (179)	III	494	Active UC, despite corticosteroid and/or immunomodulators 40% prior TNFi (induction and maintenance)	- ADA 160 mg at W0, 80 mg at W2, and then 40 mg Q2W, SC - Vs. PBO	- Clinical remission at W8: - ADA 16.5% vs PBO 9.3% ($p = 0.019$) - Clinical remission at W52 ADA 17.3% vs PBO 8.5% ($p = 0.004$) - Better response in TNFi naïve patients
	IFX	ACT I (180)	III	364	Active UC despite corticosteroid and/or thiopurines (induction and maintenance)	- IFX 5 mg or 10 mg/kg at W0, 2, 6, 14, 22, 30, 38, and 46, IV - Vs. PBO	- At W8, higher clinical response in IFX groups: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO: 61.5% vs. 69.4% vs. 37.2%, (all $p < 0.001$ compared to PBO). - At W8, higher clinical remission in IFX groups: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO: 32% vs. 38.8% vs. 14.9%, (all $p < 0.001$ compared to PBO). - Remission rate at W54: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO (34.4% vs. 34.7% vs. 16.5%), (all $p =$ 0.001 compared to PBO).
	IFX	ACT II (180)	III	364	Active UC despite corticosteroid and/or thiopurines and 5-ASA (induction and maintenance)	- IFX 5 mg or 10 mg/kg at W0, 2, 6, 14, and 22, IV - Vs. PBO	- At W8, higher clinical response in IFX groups: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO: 69.2% vs. 64.5% vs. 29.3%, (all $p < 0.001$ compared to PBO). - At W8, higher clinical remission in IFX groups: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO: 27.5% vs. 33.9% vs. 5.7%, (all $p < 0.002$ compared to PBO). - Remission rate at W30: IFX 10 mg/kg vs. IFX 5 mg/kg vs. PBO: 35.8% vs. 25.6% vs. 10.6%, all $p = 0.001$ compared to PBO.

(Continued)

TABLE 3 | Continued

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
	IFX	US-SUCCESS (181)	III	239 (planned 600)	Active UC (induction)	- IFX 5 mg/kg at weeks 0, 2, 6, and 14, IV + AZA 2.5 mg/kg/day, PO - Vs. IFX alone - Vs. AZA alone	- Study terminated early before enrolment target (intermittent IFX regimen raised concern for injection site reaction in another study) - Corticosteroid-free remission at W16: IFX+AZA 39.7% vs. IFX alone 22.1% (p = 0.017) vs. AZA alone 23.7% (p = 0.032). - Mucosal healing at W16: IFX+AZA 62.8% vs. IFX alone 54.6% (p = 0.295) vs. AZA alone 36.8% (p = 0.001).
	GOL	PURSUIT -SC (182)	III	761	Active UC despite corticosteroid and/or immunomodulators (induction)	- GOL 400 mg at W0, then 200 mg at W2, SC - Vs. GOL 200 mg at W0, then 100 mg at W2, SC - Vs PBO	- Clinical response at W6: GOL 400/200 54.9% vs. GOL 200/100 51% vs. PBO 30.3% (all $p < 0.001$ vs. PBO) - Clinical remission at W6: GOL 400/200 17.9% vs. GOL 200/100 17.8% vs. PBO 6.4% (all $p < 0.001$ vs. PBO) - Mucosal healing at W6: GOL 400/200 45.1% vs. GOL 200/100 42.3% (p = 0.0014 vs. PCB) vs. PBO 28.7% (all $p < 0.001$ vs. PBO)
	GOL	PURSUIT -MAINTENANCE (183)	III	464	UC patients responded to GOL induction (maintenance)	- GOL 100 mg Q4W, SC - Vs. GOL 50 mg Q4W, SC - Vs. PBO	- Clinical response maintained at 54W: GOL100 49.7% (p = 0.01) vs. GOL50 47% ($p < 0.001$) vs. 31.2% PBO (all comparison vs. PBO) - Clinical remission at both W30 and W54: GOL100 27.8% (p = 0.004) vs. GOL50 23.2% (NS) vs. 15.6% PBO (all comparison vs. PBO) - Mucosal healing at both W30 and W54: GOL100 42.4% (p = 0.002) vs. GOL50 41.7% (p = 0.011) vs. 26.6% PBO (all comparison vs. PBO)
α4β7 integrin inhibitor	VDL	GERMIN I (184)	III	Induction = 886 Maintenance = 373	- Induction: active UC despite corticosteroid and/or immunomodulators (48.2% prior TNFi) maintenance: patients responded to induction phase	- VDL 300 mg Q4W, IV - Vs. VDL 300 mg Q8W, IV - Vs. PBO - (both induction and maintenance)	- Induction phase at W6: ○ Clinical response: VDL 47% vs. PBO 25.5%, $p < 0.001$ ○ Clinical remission: VDL 16.9% vs. PBO 5.4%, p = 0.001 ○ Mucosal healing: VDL 40.9% vs. 24.8%, p = 0.001 - Maintenance phase at W52: ○ Clinical remission: VDLQ4 44.8% vs. VDLQ8 41.8% vs. PBO 15.9% (all $p <$ 0.001 vs. PBO)

(Continued)

TABLE 3 | Continued

Class of drug	Agent	Trial acronyms	RCT Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
							○ Mucosal healing: VDLQ4 56% vs. VDLQ8 51.6% vs. PBO 19.8% (all $p <$ 0.001 vs. PBO)
	VDL vs. ADA	VARSITY (185)	III	769	- Active UC despite corticosteroid, or immunomodulators (Non TNFi failure) - 21% Prior TNFi exposure - 26% concomitant immunomodulators	- VDL 300 mg W0, 2, 6, 14, 22, 30, 38, and 46, IV - ADA 40 mg 160 mg at W0, 80 mg at W2, then 40 mg Q2W till W50, SC	- Clinical response at W52: VDL 31.3% vs. ADA 22.5%, $p = 0.006$ - Endoscopic improvement at W52: VDL39.7% vs. ADA 27.7%; $P < 0.001$. - Corticosteroid-free remission at W52: VDL 12.6% vs. ADA 21.8%, NS
JAKi	TOF	OCTAVE Induction-1 (186)	III	598	Active UC despite immunomodulators/ TNFi 74% TNFi failure	- TOF 10 mg BD, PO - Vs. PBO	- Clinical remission at W8: TOF 18.5% vs. PBO 8.2%, $p = 0.007$ - Mucosal healing at W8: TOF 31.3% vs. 15.6%, $p < 0.001$
		OCTAVE Induction-2 (186)	III	541	- Active UC despite immunomodulators/ TNFi - 70% TNFi failure	TOF 10 mg BD, PO - Vs. PBO	- Clinical remission at W8: TOF 16.6% vs. PBO 3.6%, $p < 0.001$ - Mucosal healing at W8: TOF 28.4% vs. 11.6%, $p < 0.001$
		OCTAVE -Sustain (186)	III	593	- Patients who has a clinical response in OCTAVE 1 and 2	- TOF 10 mg BD, PO - Vs. TOF 5 mg BD, PO - Vs. PBO	- Clinical remission at W52: TOF10 40.6% vs. TOF5 34.3% vs. PBO 11.1%, (all $p < 0.001$ vs. PBO) - Mucosal healing at W52: TOF10 45.7% vs. TOF5 37.4% vs. PBO 13.1%, (all $p < 0.001$ vs. PBO)
	UPA	AbbVie UPA UC development program	III	>1300	NCT02819635, NCT03653026, NCT03006068	No details yet	- Preliminary: met primary endpoints of clinical response, remission, endoscopic improvement, and response - No detail yet

ADA, adalimumab; AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; AZA, azathioprine; BD, twice daily; CI, confidence interval; CZP, certolizumab; GOL, golimumab; Gp, group; HR, hazard ratio; IFX, infliximab; IR, incidence rate ratio; IV, intravenous; JAKi, Janus kinase inhibitor; M, month; PO, per oral; Q, every; NS, not statistically significant; PBO, placebo; SC, subcutaneous; SEC, secukinumab; TNFi, tumor necrosis factor inhibitor; TOF, tofacitinib; UPA, upadacitinib; VDL, vedolizumab; Vs., versus; W, week; Yr, year.

TABLE 4 | Evidence from clinical trials for class of therapeutic options for uveitis.

Class of drug	Agent	Trial acronyms	Trial Phase	Sample size	Patient population	Treatment vs. comparison	Outcomes
TNFi	ADA	VISUAL-1 (190)	RCT, III	217	Active non-infectious intermediate uveitis, posterior uveitis, or panuveitis despite corticosteroid	- ADA loading 80 mg, then 40 mg Q2W, SC - Vs. PBO	- FU: till 80w or pre-specified events of treatment failure is reached. - Longer median time to treatment failure, ADA vs PBO (24w vs. 13w) - ADA less likely than PBO group to have treatment failure (HR 0.50; 95% CI: 0.36-0.70; $P < 0.001$).
	ADA	VISUAL-2 (191)	RCT, III	229	Inactive, non-infectious intermediate, posterior, or panuveitis requiring prednisolone for maintenance	- ADA loading 80 mg, then 40 mg Q2W, SC - Vs. PBO	- FU: till 80w or at treatment failure event - Long time to treatment failure, ADA vs PBO (10.2m vs. 4.8m) - ADA less likely than PBO group to have treatment failure (HR 0.57; 95% CI: 0.39-.84; $P = 0.004$).
	GOL	GO-EASY (192)	Open label, non-randomized	93	- AS patients (55% TNFi-naive, 27% history of uveitis)	All: GOL 50 mg monthly - VS. historical control (flare rates in previous yr)	- Lower risk of uveitis flare in GOL vs. historical rates (2.2 vs. 11.1 per 100 patient-years, rate-ratio 0.20, 95% CI 0.04–0.91).
	CZP	(Abstract only) (193)	Open label, non-randomized, IV	115 enrolled (85 in interim analysis)	Active axSpA, HLAB27 positive, having history of recurrent uveitis	- All: 400 mg at W0, 2, 4, then 200 mg Q2W till W96 - Vs. historical control	- Interim analysis of 85 patients completed W48 - Few flares CZP vs. historical rates (Poisson-adjusted IR: 0.2 vs 1.5, $p < 0.001$).
IL-17i	SEC	3 RCTs: SHIELD, INSURE, ENDURE (194)	RCT, III	274	Behçet's uveitis = 118 (SHIELD) Active non-infectious active uveitis = 31 (INSURE) Inactive non-infectious uveitis = 125 (ENDURE)	- Varies dosing: - SEC loading (150 mg or 300 mg), then Q2W-Q4W - Vs. PBO	- SHIELD: completed, primary endpoint not met - INSURE: terminated early - ENDURE: completed, planned analysis dropped - No statistically significant differences in uveitis flares, SEC vs. PBO in all 3 RCTs
	SEC	(195)	II	37	Active non-infectious intermediate uveitis, posterior uveitis, or panuveitis, requiring corticosteroid sparing therapy	- SEC 30 mg/kg Q4W, IV for 2 doses, (Group 1) - Vs. SEC 10 mg/kg Q2W, IV for 4 doses, (Gp 2) - Vs. SEC 300 mg Q2W, SC for 4 doses, (Gp 3)	- Higher response rate in higher dose compared to lower dose regimen on day 57. - Responder rates (Gp 1: 72.7% vs. Gp2: 61.5% vs. Gp3: 33.3%, statistically significant Gp 1 vs. Gp3) - Remission rates (Gp1: 27.3% and Gp2: 38.5% vs. Gp3: 16.7%, NS)
IL-12/23i	UST	STAR (196)	II	8 enrolled	Active sight-threatening active intermediate uveitis, posterior uveitis, or panuveitis	- 90 mg, SC at W0,4 and 8 vs 260-520 mg (weight-based dose), IV at W0 then 90 mg, SC at W8	- Completed, awaiting analysis and publication of results
	UST	STELABEC-2 (197)	II	16	Active posterior uveitis and/or panuveitis and/or retinal vasculitis in patients with Behçet's disease	- 90 mg, SC at W0, W4, and W16. Patients with response will receive 90 mg, SC at W28 and W40	- Ongoing

ADA, adalimumab; AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; CI, confidence interval; CZP, certolizumab; GOL, golimumab; Gp, group; HR, hazard ratio; IR, incidence rate ratio; IV, intravenous; M, month; Q, every; NS, not statistically significant; PBO, placebo; SC, subcutaneous; SEC, secukinumab; TNFi, tumor necrosis factor inhibitor; UST, ustekinumab; Vs., versus; W, week; Yr, year.

therapeutics to create a patient-centric, individualized care plan for the heterogeneous manifestations. Often, the therapeutics will need to cover multiple domains, but the predominant domain should drive the therapeutic option of choice in the shared decision-making process.

For severe IBD in the setting of PsA with peripheral manifestations, traditional immunomodulators can be considered for maintenance. TNFi (monoclonal antibodies) is a better option for patients with axial arthropathy. UST is effective for IBD but is less effective on peripheral arthritis as compared to TNFi or IL-17i, and ineffective for axial arthropathy. While IL-17i is an effective treatment for both peripheral and axial arthropathy, and probably does not increase the risk of IBD, it is not recommended for patients with underlying active IBD, due to its possibility of exacerbating pre-existing disease. IL-23i may be promising for IBD but its use requires caution in patients with predominant axial arthropathy. JAKi is effective for UC, peripheral and axial arthropathy, but may exacerbate CD. VDZ is effective for both CD and UC but has no indication for all other manifestations in PsA. With these considerations, TNFi (monoclonal antibodies) with or without concomitant immunosuppressants would be the best option for PsA patients with IBD. IBD is a chronic relapsing condition, and often requires higher doses of TNFi for induction than arthritis alone. Collaboration between rheumatologist and gastroenterologist is invaluable to ensure the optimal choice of treatment regimen.

Uveitis can be serious and sight threatening. Patients with symptoms of possible uveitis should have access to ophthalmology care promptly and given appropriate treatment for uveitis. Uveitis can arise even when arthritis is under control; it may manifest either suddenly or insidiously. It is important that patients are educated to be aware of the symptoms of uveitis and seek appropriate care when the needs arise. Care models like enquiry hotline, early referral or walk-in ophthalmology clinics are examples that may facilitate early diagnosis. For subsequent management, collaboration between rheumatologist and ophthalmologist is essential to ensure regular assessment of response to therapy and to modify management accordingly. If uveitis fails to respond to topical corticosteroids, or fails to be weaned, or is severe at the onset, an escalation to either conventional immunomodulators or biological agents should be considered. The use of systemic corticosteroid is best avoided, given the risk of severe PsO flare upon its withdrawal. For patients with peripheral musculoskeletal manifestations (peripheral arthritis, enthesitis and dactylitis), MTX, SSZ or leflunomide (LEF) can be tried for maintenance, but an early escalation to TNFi (monoclonal antibodies) should be considered if these options fail. Traditional immunomodulators are not effective for axial arthropathy, thus for patients with active axial arthropathy TNFi (monoclonal antibodies) would be a good choice. Some patients may require higher or more frequent doses of TNFi especially for severe uveitis, highlighting again the importance of collaboration between rheumatologist and ophthalmologist for drug titration. IL-17i is an effective treatment for axial arthropathy, but SEC may not be effective for AAU at standard dose, and more data is still needed to inform the use of other IL-17i.

All in all, detailed considerations of all domains and extra-articular manifestations are necessary to formulate the best therapeutic option. Multi-disciplinary collaborative care models are advocated for optimal care for patients with PsA, and especially so for those who present with co-morbidities.

AUTHOR CONTRIBUTIONS

AlC and YL conceptualized the project. AlC, TC, and YL collected relevant data for review and drafted the manuscript. AnC, WC, GA, and YL critically appraised the content of manuscript. All authors approved the final version of manuscript.

FUNDING

YL was supported by the National Medical Research Council, Singapore (NMRC/CSA-Inv/0022/2017). The funding sources had no role in the views expressed in this review.

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frontiers in Medicine

REVIEW
published: 22 September 2021
doi: 10.3389/fmed.2021.737573

Hyperuricemia in Psoriatic Arthritis: Epidemiology, Pathophysiology, and Clinical Implications

Cesare Tripolino[1], *Jacopo Ciaffi*[2], *Piero Ruscitti*[3], *Roberto Giacomelli*[4], *Riccardo Meliconi*[2,5] *and Francesco Ursini*[2,5]*

[1] Geriatric Medicine Unit, Department of Medical Functional Area, "San Giovanni di Dio" Hospital, Crotone, Italy, [2] Medicine and Rheumatology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Ortopedico Rizzoli (IOR), Bologna, Italy, [3] Rheumatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [4] Unit of Allergology, Immunology, Rheumatology, Department of Medicine, Università Campus Bio-Medico Di Roma, Rome, Italy, [5] Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum University of Bologna, Bologna, Italy

Psoriatic arthritis (PsA) represents the articular component of the systemic psoriatic disease and the extra-cutaneous disorder most frequently found in patients with psoriasis. Besides the articular involvement, PsA is associated with several metabolic abnormalities such as insulin resistance, hypertension, diabetes and hyperuricemia. Uric acid is the final product of purine metabolism and the etiological substrate of gout. Accumulating evidence highlights the emerging role of hyperuricemia as a major cardiovascular risk factor. Moreover, different studies evaluated the interplay between hyperuricemia and psoriatic disease, suggesting that individuals affected by psoriasis or PsA might present higher serum levels of uric acid and that hyperuricemia might affect severity of clinical manifestations and degree of inflammation in PsA patients. In this review, we focus on the bidirectional relationship between uric acid and PsA, analyzing how uric acid may be involved in the pathogenesis of psoriasis/PsA and how clinical manifestations of PsA and inflammatory mediators are affected by uric acid concentrations. Finally, the effects of anti-rheumatic drugs on uric acid levels and the potential benefit of urate-lowering therapies on psoriasis and PsA were summarized.

Keywords: uric acid, gout, psoriasis, psoriatic arthritis, inflammation, cardiovascular

OPEN ACCESS

Edited by:
João Eurico Fonseca, University of Lisbon, Portugal

Reviewed by:
Filipa Farinha, University College London, United Kingdom
Prasanta Padhan, Kalinga Institute of Medical Sciences (KIMS), India

***Correspondence:**
Francesco Ursini
francesco.ursini2@unibo.it

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *07 July 2021*
Accepted: *27 August 2021*
Published: *22 September 2021*

Citation:
Tripolino C, Ciaffi J, Ruscitti P, Giacomelli R, Meliconi R and Ursini F (2021) Hyperuricemia in Psoriatic Arthritis: Epidemiology, Pathophysiology, and Clinical Implications. Front. Med. 8:737573. doi: 10.3389/fmed.2021.737573

INTRODUCTION

Psoriatic arthritis (PsA) represents the articular component of a complex clinical entity now recognized as "psoriatic disease." Musculoskeletal involvement is reported in 20% of patients with psoriasis (Pso) (1) and encompasses a wide spectrum of manifestations including enthesitis, dactylitis, peripheral arthritis, and axial disease. Discrete clinical phenotypes (asymmetric oligoarthritis, symmetrical polyarthritis, distal interphalangeal joints arthritis, arthritis mutilans, spondylitis) have been historically identified although, in clinical practice, they frequently intersect each other (2). Beyond the joint involvement, PsA is burdened by a high prevalence of cardiometabolic comorbidities such as obesity, hyperlipidemia, diabetes, hypertension and hyperuricemia (3).

Uric acid (UA) is the end-product of purine metabolism. Recently, serum uric acid (SUA) gained popularity since an association with cardiovascular mortality and morbidity has been demonstrated (4). A number of studies investigated the interplay between hyperuricemia and Pso/PsA suggesting

that subjects with these disorders also show higher levels of SUA or increased prevalence of hyperuricemia (5–21). The mechanisms behind these findings are not completely understood. Hyperuricemia was hypothesized to be a consequence of the accelerated cutaneous cells turnover observed in Pso or an epiphenomenon secondary to the metabolic disorders observed in Pso/PsA.

In the present review, we summarize the available literature regarding the association between Pso/PsA and hyperuricemia focusing on epidemiology, pathophysiology, and clinical implications.

Literature review was limited to published primary research, including basic science, cohort studies, intervention and observational trials, and review articles indexed in PubMed.

The following search terms were used: "psoriasis" OR "psoriatic arthritis" AND "urate" OR "uric acid" OR "monosodium urate" OR "gout" OR "urate-lowering agent." The search was limited to articles written in English, with no date restriction. Title and abstract screening of all retrieved studies published up to 1st June 2021 was performed by two of the authors (CT and JC). Eligible articles proceeded to full-text assessment. As the intent of the review was narrative, inclusion was based on relevance, as deemed so by the authors, to one of the 5 subcategories of interest: (1) pathophysiology of uric acid in psoriasis and psoriatic arthritis, (2) uric acid levels in psoriasis and psoriatic arthritis, (3) uric acid levels and cardiovascular comorbidities in psoriatic arthritis, (4) effects of anti-rheumatic drugs on serum uric acid levels in psoriatic arthritis, and (5) effects of urate-lowering agents on serum inflammatory mediators.

URIC ACID METABOLISM AND BIOLOGICAL FUNCTIONS: A BRIEF OVERVIEW

UA is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen derived from the exogenous and endogenous purine metabolism. Liver and gut, but also muscles, lungs, kidneys and the vascular endothelium represent the main sites of UA production. Normal SUA values range from 1.5 to 6.0 mg/dL in adult females and from 2.5 to 7.0 mg/dL in adult males (22, 23). Urate homeostasis is maintained by a finely regulated balance between production and excretion. Although kidneys are the main responsible for UA excretion (65–75% of UA elimination), also intestine plays a relevant role in UA metabolism (25–35% of UA elimination). Kidneys and intestine exert these activities through the presence of urate transporters on their surface. The primary urate transporters are urate transporter 1 (URAT1), located on the apical surface of proximal tubular cells, glucose transporter 9 (GLUT9), located on the basolateral membrane of the proximal tubule, and ATP-binding cassette subfamily G member 2 (ABCG2), located on both intestinal and renal cells surface (24). On the other hand, organic anion transporters (OAT1, OAT2, and OAT3) at the basolateral membrane, sodium-dependent phosphate cotransporters (NPT1 and NPT4) and multidrug resistance protein-4 (MRP4) at the apical membrane, mediate urate secretion. URAT 1, GLUT 9 and OAT4 are responsible for the tubular urate reabsorption (25).

Raised levels of serum UA derive from increased production, impaired elimination, or a combination of the two. With progress in understanding the pathogenesis, some authors proposed a new classification of hyperuricemia: renal overload type (including overproduction and reduced extra-renal excretion) and renal underexcretion type (26). Neoplastic diseases, Pso, obesity, alcohol consumption, and genetic disorders belong to the first group, whereas kidney disease, diuretics, and immunosuppressant agents are included in the second one (27).

UA formation involves a series of biochemical reactions that lead to the degradation of adenosine and guanosine. As first step, adenosine monophosphate is converted to inosine by a deaminase that removes an amino-group creating the inosine monophosphate. Afterward, it is transformed in inosine by a nucleotidase. Instead, guanine monophosphate is transformed in guanosine by the nucleotidase. Subsequently, an enzyme called purine nucleoside phosphorylase converts inosine and guanosine into hypoxanthine and guanine. The intervention of xanthine-oxidase will transform hypoxanthine in xanthine, whereas the guanine deaminase will convert guanine in xanthine. Finally, xanthine oxidase oxidizes xanthine, forming the uric acid molecule (23). Historically known as the causative agent of gout, uric acid has gained increased popularity in the last years for its double-faced nature as a risk and protective factor in various settings (28).

Uric Acid as Protective Factor

SUA has a strong antioxidant effect and metal-chelating properties (22, 29), acting as a scavenger of plasma nitrogen radicals and reactive oxygen species, thus reducing the production of peroxynitrite (29, 30).

Furthermore, UA plays an important function as immune-stimulating agent especially in innate immune responses and type 2 immune responses (31, 32). Studies suggest that UA acts as a damage-associated molecular pattern after transformation in crystals of monosodium urate (33, 34). In this form it activates dendritic cells and enhances the innate immune system, behaving as an endogenous adjuvant (35, 36). Urate in its crystallin shape is phagocytized by monocytes or neutrophils causing the generation of pro-inflammatory cytokines such as IL-1. Furthermore, the internalization of UA crystals by leukocytes leads to production of free radicals, release of cathepsin B and activation of inflammasome (37, 38).

Interestingly, higher SUA levels have been hypothesized to play a protective role in the development of some neurological disorders such as dementia, multiple sclerosis, Alzheimer's disease and Parkinson's disease (39–42). In a recent meta-analysis involving 5,575 participants, Zhou et al. demonstrated a significant inverse association between SUA and Alzheimer's disease or Parkinson's disease (43). Moreover, the authors found a linear dose-response relationship between UA values and risk of dementia. In a retrospective analysis involving 1,166 subjects with ischemic stroke, higher UA levels proved a significant protective role in preventing negative neurological outcomes in male patients (44). The reasons behind these findings are not fully

elucidated but it has been speculated that the antioxidant and metal-chelating properties of UA exert a neuro-protective effect on brain function and cognitive decline (45).

Uric Acid as Risk Factor

Besides these beneficial effects, UA is also associated with several cardiovascular disorders (46). In the development of atherosclerotic lesions, UA up-regulates inflammatory signal pathways and promotes the pro-inflammatory response of M1 macrophages inhibiting the anti-inflammatory response of M2 (47). Moreover, hyperuricemia leads to development and progression of atherosclerosis through endothelial dysfunction. Intracellular UA reduces nitric oxide bioavailability impairing the activity of endothelial nitric oxide synthase and nitric oxide production (48). A role of UA has also been postulated in insulin resistance. Intracellular UA increases reactive oxygen species (ROS), which in turn cause β-cell apoptosis. Furthermore, due to the stimulation of inducible NO synthase (iNOS) gene expression, UA favors nitric oxide overproduction that leads to β-cell dysfunction and apoptosis and reduces glucose-stimulated insulin secretion (49).

Hyperuricemia is implicated in the development of hypertension and chronic kidney disease. UA activates the renin-angiotensin system and inhibits nitric oxide synthesis, promoting endothelial dysfunction, sodium reabsorption and proliferation of vascular smooth muscle cells. Moreover, uric acid triggers systemic inflammation and secretion of pro-inflammatory cytokines leading to increased extracellular fluid volume and vascular resistances, worsening systemic hypertension. Similarly, increased UA levels cause vascular and tubulointerstitial alterations that facilitate development and progression of chronic kidney disease (50).

However, a direct cause-effect relationship between hyperuricemia and chronic kidney disease or cardiovascular disease has not been definitely determined since hyperuricemia is often associated with other cardiovascular risk factors such as obesity, metabolic syndrome and hypertension, which might contribute to cardiovascular morbidity. In 2017, Li et al. (46) conducted a review of systematic reviews, meta-analyses and Mendelian randomization studies, analyzing the correlation between UA and 136 unique health outcomes. The authors concluded that a definitive association exists only between UA and nephrolithiasis, whereas the link with conditions such as heart failure, hypertension, impaired fasting glucose or diabetes, chronic kidney disease and coronary heart disease was deemed highly suggestive.

PATHOPHYSIOLOGY OF URIC ACID IN PSORIASIS AND PSORIATIC ARTHRITIS

The mechanisms behind hyperuricemia in Pso/PsA are still not fully elucidated and in part can only be hypothesized. High levels of SUA could be the consequence of an increased production, a reduced excretion or a combination of these factors (**Figure 1**).

It is plausible that, in the course of PsA, all these mechanisms contribute, favoring the development of hyperuricemia. It is also possible to distinguish *direct causes* of increased uric acid, related to the pathogenetic features of PsA, and *indirect causes*, linked to comorbidities or pharmacological treatment.

One of the recognized mechanisms leading to hyperuricemia in PsA is the increased cellular turnover characterizing this disorder (51). Indeed, the hyperproliferation of keratinocytes leads to accelerated nucleic acid catabolism and enhanced UA synthesis. However, hyperuricemia might also derive from an increased UA production in the liver. The overwhelming cytokines production in PsA, in particular IL-17, can affect the liver, leading to hepatic complications such as non-alcoholic fatty liver disease (52). Previous investigations found lower hepatic ATP production in hepatic steatosis (53, 54) that in turn causes increased production of UA from the hepatocytes (55).

Additional conceivable mechanisms might be related to the reduced renal and extra-renal clearance. Although the kidney represents the main actor of uric acid excretion, also other organs such as the intestine contribute to its balance. BCRP/ABCG2 is located at the apical membrane of small intestinal epithelial cells and it is involved in the UA secretion from blood into the intestinal lumen (56). A proportion of PsA patients might present evidence of clinical or microscopic inflammatory bowel disease, which might reduce the levels of these transporters and consequently impair UA homeostasis (57–59).

Hyperuricemia may be the consequence of the metabolic comorbidities associated with PsA: obesity, hypertension, insulin resistance or diabetes (60). In obese individuals, hyperuricemia is the result of both impaired excretion and overproduction of UA (61). In hyperlipidemia, the major mechanism causing hyperuricemia is the altered lipid metabolism. Indeed, the increased production of triglycerides lessens the expression of OAT1 in the kidney, leading to a reduced excretion of UA (25).

Again, the mechanism of overproduction of UA during insulin resistance states lies in the increased fatty acid synthesis in the liver that causes *de novo* purine synthesis and accelerated UA production (61–63). Furthermore, insulin stimulates the renal UA transporters leading to hyperuricemia (64).

Beyond the mechanisms underlying hyperuricemia, an intricate interplay between Pso, PsA and UA has been recognized (**Figure 2**), to the point that some authors proposed the term "psout" (65).

Indeed, it seems that UA could initiate and progress the alterations of PsA. The first observation about this issue dates back to 1981 when Goldman (19) found a high prevalence of urate crystals in samples of Pso plaques.

In a retrospective study, Oliverio et al. (66) analyzed the synovial fluid of patients with various articular disorder such as rheumatoid arthritis, osteoarthritis, gout, and PsA. The results of this investigation demonstrated a higher prevalence of urate crystals in PsA patients. Furthermore, the injection of urate crystals *in vivo* leads to the production of Th17 cells and Th17-related inflammatory cyto-chemokines, such as IL-17, one of the main mediators in the pathogenesis of PsA (67).

Urate crystals are able to stimulate human keratinocytes to produce several inflammatory cytokines and chemokines, in particular IL-1α and IL-1β, involved not only in gouty flares but also in the pathogenesis of PsA (68). Moreover,

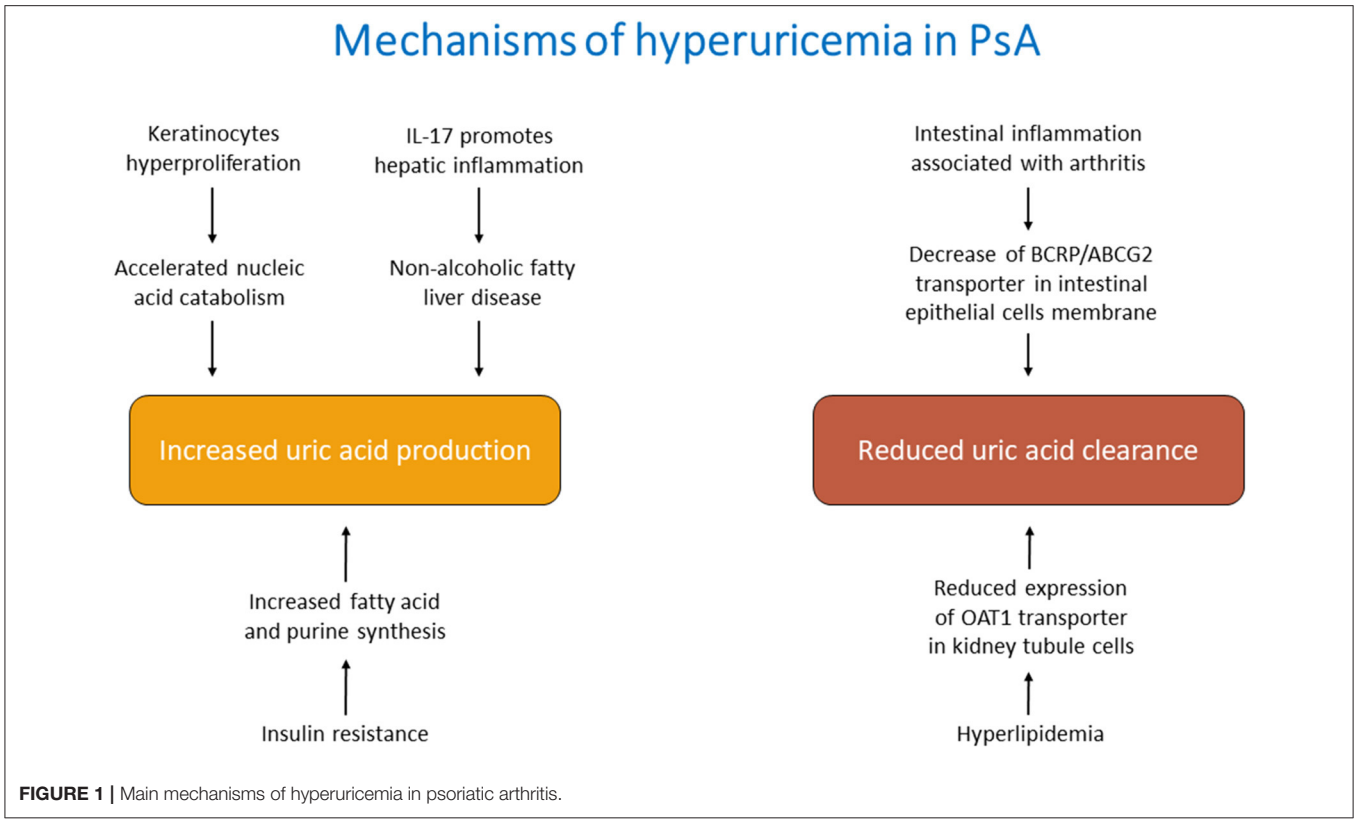

FIGURE 1 | Main mechanisms of hyperuricemia in psoriatic arthritis.

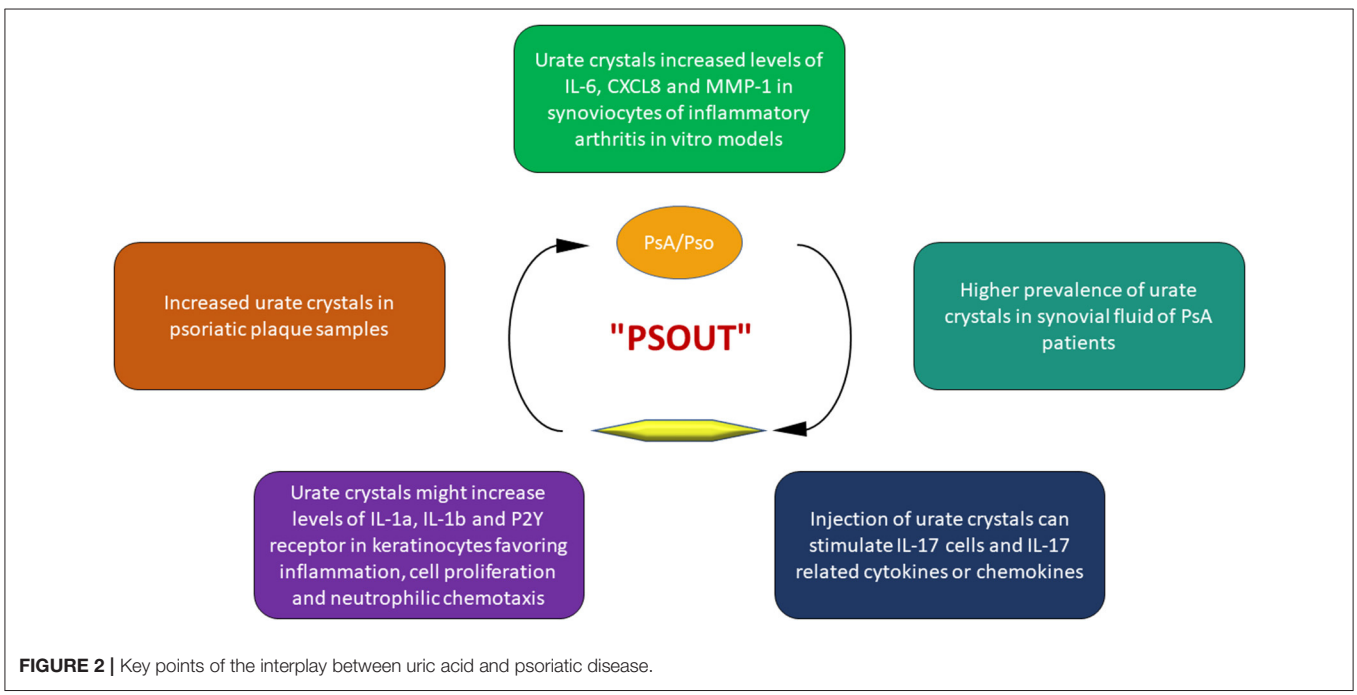

FIGURE 2 | Key points of the interplay between uric acid and psoriatic disease.

UA increases the expression of purinergic receptors P2Y on keratinocytes, stimulating cell proliferation (69), and promoting the production of IL-8/CXCL8, promoting neutrophil chemotaxis (70, 71). Finally, *in vitro* studies on synoviocytes from healthy and rheumatoid arthritis subjects, demonstrated that monosodium urate crystals were able to increase the production of inflammatory mediators such as IL-6, CXCL8 and matrix metalloproteinase-1 (72, 73).

Taken together, these evidences suggest that hyperuricemia doesn't represent a simple epiphenomenon in the course of PsA, but may play an important role in its development and progression.

URIC ACID LEVELS IN PSORIASIS AND PSORIATIC ARTHRITIS

A summary of the included studies is reported in **Table 1**. The association between Pso and hyperuricemia was first described in a pioneering article by Hermann in 1930. Among 140 Pso patients, 31% had raised SUA levels (5). These data were further confirmed in early subsequent research, showing a prevalence of hyperuricemia of 30–50% in Pso (6, 7), while more recent estimates reported a figure of 15% (8). Other studies investigated mean levels of SUA rather than prevalence of hyperuricemia, confirming that Pso patients present significantly higher SUA concentrations than non-Pso controls (9, 10, 12, 15).

In a meta-analysis, Li et al. (13) identified a remarkable difference in SUA levels between subjects with Pso and controls (mean difference 0.89 mg/dl, 95% CI 0.05–1.73, $p = 0.04$). Interestingly, this difference was more evident in the subgroups of Western Europe, whereas it was not significant in the subgroups from East Asia or Middle East.

In a population-based study involving 11,282 participants (14), the authors found that patients with Pso were at increased risk of having hyperuricemia compared with subjects without Pso (OR =1.37; p =0.04). Moreover, participants with Pso were more likely to develop gout (OR =1.83; $p < 0.05$) but both associations were no longer significant after adjustment for confounding factors.

However, contrasting results have been reported in literature. For instance, in a case-control study, Scott et al. (74) didn't find any significant difference in SUA levels between Pso patients, subjects with contact dermatitis and healthy individuals.

Additionally, other studies explored the relationship between UA and extent of cutaneous involvement in Pso. A cross-sectional study on 198 Pso patients found that SUA levels increased proportionally to the extent of cutaneous involvement in both genders and, in a multiple logistic regression model with hyperuricemia as dependent variable, PASI (Psoriasis Area Severity Index) score was a significant predictor (OR = 1.10; $p = 0.03$) (11). Similarly, Gisondi et al. (12) found that Pso patients with PASI score ≥10 exhibited higher SUA levels than subjects with less extensive skin disease. In a subsequent study (75), the same author found a prevalence of hyperuricemia of 20% in Pso patients, with higher SUA levels in obese individuals and no significant correlation with PASI. Furthermore, in a study by Ataseven et al. (76), PASI was weakly correlated with SUA ($r = 0.27$; $p = 0.046$). Conversely, in two cross-sectional studies (15, 16), SUA levels were not associated with the cutaneous extent of Pso. A *post-hoc* analysis of pooled data from three phase 3 trials with secukinumab, an IL-17A inhibitor, showed a statistically significant, although modest, association between the degree of skin involvement and SUA ($R^2 = 0.014$; $p < 0.0001$). After 12 weeks of treatment, improvement in PASI score resulted in a decrease of SUA values ($R^2 = 0.014$; $p < 0.0001$ univariately) (77). Finally, in a large population-based study on 39,111 patients with incident gout and 39,111 matched controls, the former had increased hazard ratios for developing Pso (HR =1.53, 95% CI 1.37–1.74; $p < 0.05$) and, in turn, Pso increased the risk of having incident gout (OR =1.32) (78).

Similar to Pso, the prevalence of hyperuricemia has been reported to be increased also in PsA, with estimates of 13.5% in men and 5% in women described by Lambert and Wright (79) and of 21% reported by Bruce et al. (80). Interestingly, in the latter study, no association between PASI and SUA was observed. In a multi-center, cross-sectional observational study of 160 Asian PsA patients, Lai et al. (82) found a prevalence of hyperuricemia of 31% and a significant correlation between hyperuricemia and PASI score ($p = 0.05$) or Body Surface Area ($p = 0.04$). Similar estimates were provided by AlJohani et al. (83) who described hyperuricemia in 31% of PsA patients in a prospective study. Moreover, compared to a normouricemic PsA control group, hyperuricemic patients had higher PASI scores ($p = 0.006$).

In a retrospective case–control study aimed to determine factors associated with development of PsA in subjects with psoriasis (84), hyperuricemia was a significant predictor after correcting for possible confounders ($OR = 4.18$; $p < 0.01$), thus suggesting that elevated SUA might represent a risk factor for the development of PsA in subjects with Pso.

However, not only the association between Pso or PsA and hyperuricemia has been investigated, but also the correlation between Pso or PsA and gout. In particular, in the subgroup of participants with confirmed Pso of a large, prospective population-based study (81), the multivariate-adjusted HR for gout were 2.72 (95% CI: 1.75, 4.25) in men and 1.40 (95% CI: 0.90, 2.19) in women. Interestingly, the risk of incident gout was substantially elevated in patients with Pso and concomitant PsA (HR = 4.95, 95% CI 2.72–9.01) and it was similar in males and females.

Furthermore, a case-control study in Taiwan (20) analyzed data of 114623 patients with gout compared with 114623 control subjects. Prevalence of Pso (1.6 vs. 1.1%; $p < 0.0001$) and PsA (0.3 vs. 0.1%; $p < 0.0001$) was higher in patients with gout than in controls. In multiple logistic regression analysis, gout was significantly associated with Pso (OR 1.30, 95% CI 1.20–1.42; $p < 0.001$) and PsA (OR 2.50, 95% CI 1.95–3.22; $p < 0.001$).

Finally, in a large retrospective observational study (21) including 14898 PsA patients, the risk for gout was significantly higher (incidence rate = 1.28 vs. 0.66; HR = 2.03; 95% CI 1.75–2.36) compared with the group of 35037 matched controls.

The association between Pso, PsA, and SUA levels has attracted the attention of researches since the first decades of 20th century (6, 7, 17–19). The reason behind this finding is not completely understood but probably the keratinocyte hyper-proliferation and increased cell turnover lead to enhanced catabolism of purines resulting in raised SUA. Furthermore, concomitant metabolic disorders such as metabolic syndrome, diabetes or obesity might contribute to the elevated UA levels observed in subjects with Pso. Over the years, a large number of studies has explored this topic, but the often-conflicting results don't allow to draw definitive conclusions.

TABLE 1 | Characteristics of studies included in the evaluation of the association between serum uric acid levels and psoriasis or psoriatic arthritis.

Author	Study design	Sample description	Outcome of interest	Main findings
Baumann and Jillson (5)	Cross-sectional	140 patients with Pso or PsA	Prevalence of hyperuricemia	Hyperuricemia was present in 44 (31.4%) Pso patients, most often in those with PsA.
Eisen and Seegmiller (6)	Cross-sectional	38 Pso patients (18 males, 20 females)	Prevalence of hyperuricemia	Hyperuricemia was present in 19 (50%) Pso patients.
Steinberg et al. (7)	Cross-sectional	167 Pso patients (98 males, 69 females)	Prevalence of hyperuricemia	Hyperuricemia was present in 47 (48%) of male patients and in 19 (27%) of female patients.
Kamiya et al. (8)	Retrospective cohort	15,287 Pso patients (9,989 males, 5,298 females)	Prevalence of hyperuricemia	Hyperuricemia was present in 15.1% of patients (19.1% of males and in 6.3% of females).
Scott and Stodell (74)	Prospective cohort	41 Pso patients, 41 contact dermatitis, 41 healthy	Difference in SUA levels	No significant difference between the three groups nor associations between SUA and Pso extent.
Alpsoy et al. (9)	Prospective cohort	60 Pso patients and 50 healthy controls	Difference in SUA levels	Mean SUA concentration was significantly higher in Pso than in controls.
Isha et al. (10)	Prospective cohort	25 Pso patients, 25 healthy controls, 25 patients with skin disorders other than PSo	Difference in SUA levels	Mean SUA concentration was significantly higher in Pso than in the other two groups.
Kwon et al. (11)	Retrospective cross-sectional	198 Pso patients	Difference in SUA levels between Pso patients and general population. Assess correlation between Pso characteristics and SUA levels.	No difference in SUA levels between Pso patients and general population. Significant correlation between SUA levels and PASI ($p < 0.05$). Significantly higher PASI in hyperuricemic group than in normouricemic group. PASI was an independent risk factors for hyperuricaemia ($OR = 1.10$; $p = 0.03$).
Gisondi et al. (12)	Prospective cohort	119 Pso patients and 119 healthy controls	Prevalence of hyperuricemia and difference in SUA levels.	Higher SUA levels in Pso patients independently of gender). Asymptomatic hyperuricemia was found in 19% of Pso patients compared with 7% of controls ($p < 0.001$). Pso patients with PASI score $\geq$10 had higher SUA levels than patients PASI <10. Pso was the strongest predictor of hyperuricemia ($OR = 3.20$; $p < 0.01$) independently of other variables.
Gisondi (75)	Prospective cohort	338 Pso patients	Assessment of characterics of Pso patients.	Hyperuricemia was present in 20%. SUA levels were higher in obese patients than in non-obese. SUA levels were not significantly correlated with PASI.
Ataseven et al. (76)	Prospective cohort	56 Pso patients and 33 healthy controls	Prevalence of hyperuricemia and assessment of characteristics of Pso patients.	No difference in SUA levels between groups. In Pso patients PASI showed a significant positive correlation with SUA ($r = 0.27$; $p = 0.046$).
Li et al. (13)	Meta-analysis	Total of 1,644 Pso patients and 27,393 controls	Association berween Pso and SUA levels.	SUA levels significantly higher in Pso patients than in controls. In the studies considering presence of hyperuricemia as a dichotomous variable, significantly higher prevalence in Pso patients than in controls (pooled RR = 2.18; 95% CI 1.29–3.68; $p = 0.004$).
Lai and Yew (14)	Population-based cross-sectional study	297 patients with Pso and 1,493 patients with hyperuricemia in a cohort of 11,282	Risk of hyperuricemia in Pso patients compared with controls.	Patients with Pso were at an increased risk of having hyperuricaemia (OR = 1.37; 95% CI 1.01–1.86; $P = 0.04$). The association was not significant after adjusting for confounders in multivariate regression analysis. No association between Pso severity and risk of hyperuricemia.

(Continued)

TABLE 1 | Continued

Author	Study design	Sample description	Outcome of interest	Main findings
Solak et al. (15)	Case-control study	199 Pso patients and 54 healthy controls.	To compare SUA levels between Pso patients and general population.	SUA levels higher in patients with Pso compared to healthy controls. SUA levels did not correlate with the cutaneous extent of Pso.
Dehlin et al. (77)	*Post-hoc* analysis of randomized control trials	1,042 patients with Pso and 204 with PsA.	To determine the impact of Pso activity on SUA levels.	The degree of skin involvement showed a statistically significant, although modest, association with SUA levels ($R^2 = 0.014$; $p < 0.0001$) at baseline. After 12 weeks of treatment, improvement in PASI score resulted in a decrease of SUA levels ($R^2 = 0.014$; $p < 0.0001$ univariately).
Kuo et al. (78)	Case-control study	39,111 patients with incident gout and 39,111 controls	To determine the burden of comorbidities in patients with gout at diagnosis and the risk of developing new comorbidities post diagnosis.	Patients with gout had increased hazard ratios for Pso (HR =1.53, 95% CI 1.37–1.74; $p < 0.05$). Pso, in turn, increased the risk of having incident gout (OR = 1.32).
Lambert and Wright (79)	Cross-sectional observational	115 patients with PsA (52 men, 63 women)	To determine the prevalence of hyperuricemia in PsA.	Hyperuricemia was present in 7 (13.5%) men and 3 (5%) women. After comparing PsA patients with and without hyperuricemia, no differences in terms of disease activity or Pso extent were found.
Bruce et al. (80)	Prospective cohort	265 PsA patients	To determine the prevalence of hyperuricemia in PsA and to determine the influence of skin involvement on SUA levels.	The authors found an incidence of hyperuricemia close to 21%, while incidence of gout was 0.8%. No association between PASI score and SUA.
Merola et al. (81)	Prospective population-based study	27,751 men and 71,059 women	To determine the risk of gout in Pso.	In the subgroup analysis of participants with self-reported Pso, the multivariate-adjusted HR for gout were 1.79 (95% CI 1.30–2.47) in men and 1.63 (95% CI 1.17–2.27) in women. The multivariate HR were higher among men (HR = 2.72, 95% CI: 1.75, 4.25) than in women (HR = 1.40, 95% CI: 0.90, 2.19) with confirmed Pso. Patients with Pso and concomitant PsA had a high risk of incident gout (HR = 4.95, 95% CI 2.72–9.01).
Lai et al. (82)	Cross-sectional observational study	160 PsA patients	Hyperuricemia in PsA patients	Hyperuricemia was present in 31% of patients. In simple correlation analysis, hyperuricemia was associated with PASI score ($p = 0.05$) and Body Surface Area ($p = 0.04$).
AlJohani et al. (83)	Prospective cohort study	318 hyperuricemic PsA patients and 318 normouricemic PsA patients	Investigate the prevalence and characteristics of psoriatic patients with hyperuricemia and to determine the adverse effect of hyperuricemia on outcomes	Huperuricemic patients had longer disease duration of PsA ($p < 0.001$) and Pso ($p < 0.001$) and higher PASI scores ($p = 0.006$). Multivariate analysis showed an association between persistent hyperuricemia and disease duration of PsA (OR 1.073, 95% CI 1.028–1.113).
Tsuruta et al. (84)	Retrospective cohort study	55 subjects with PsA and 276 with Pso	To determine factors associated with development of PsA in subjects with Pso	Hyperuricemia was significantly more prevalent in patients with Pso and PsA than in the group with only Pso (22 vs. 9%; $p = 0.01$). In multiple logistic regression, hyperuricemia was a strong predictor of PsA development (OR = 4.18; $p < 0.01$).
Hu et al. (20)	Population-based case-control study	114,623 patients with gout compared with 114,623 subjects without gout	Investigate association between Pso, PsA, and gout	Higher prevalence of Pso (1.6 vs. 1.1%; $p < 0.0001$) and PsA (0.3 vs. 0.1%; $p < 0.0001$) in patients with gout than in controls. In multiple logistic regression, gout was significantly associated with Pso (OR 1.30, 95% CI 1.20–1.42; $p < 0.001$) and PsA (OR 2.50, 95% CI 1.95–3.22; $p < 0.001$).

(Continued)

TABLE 1 | Continued

Author	Study design	Sample description	Outcome of interest	Main findings
Kaine et al. (21)	Retrospective observational	14,898 PsA patients and 35,037 matched controls	To investigate frequency and incidence of comorbidities in adult patients with newly diagnosed PsA	PsA patients showed a higher risk for gout (incidence rate = 1.28 vs. 0.66; HR = 2.03; 95% CI 1.75–2.36) compared with the control group.

PASI, psoriasis area severity index; PsA, psoriatic arthritis; Pso, psoriasis; SUA, serum uric acid.

URIC ACID LEVELS AND CARDIOVASCULAR COMORBIDITIES IN PSORIATIC ARTHRITIS

The cardiovascular consequences of hyperuricemia in PsA subjects were investigated by Gonzalez-Gay in a small observational study (85). To this purpose, 52 PsA patients without cardiovascular disease underwent clinical assessment with the aim to determine whether SUA was associated with ultrasound measures of subclinical atherosclerosis. Six individuals (11%) had hyperuricemia (defined as SUA >7 mg/dl) and were found to have a carotid intima-media thickness (IMT) greater than normo-uricemic patients (0.89 ± 0.20 vs. 0.67 ± 0.16 mm; $p = 0.01$). Furthermore, raised SUA levels were a risk factor for increased carotid IMT ($OR = 2.66$; $p = 0.03$) and for carotid plaques ($OR = 1.85$; $p = 0.05$). However, these results should be interpreted with caution. Patients with hyperuricemia also had higher levels of serum creatinine, glucose, total cholesterol, and triglycerides. The authors tried to analyse the relationship between hyperuricemia and carotid IMT adjusting for these variables, but the small number of patients limited the analysis.

Similar results were obtained by Ibrahim et al. (86) comparing PsA patients with high SUA levels to those with normal values. The former had a significant increase in carotid IMT, presence of carotid plaques and impairment of flow-mediated dilation (FMD) ($p < 0.001$). In correlation analysis, SUA was positively associated with carotid IMT in PsA patients ($r = 0.71$; $p < 0.001$), with disease activity scores such as DAS-28 ($r = 0.91$; $p < 0.001$), and with PASI ($r = 0.85$; $p < 0.001$) and disease duration ($r = 0.89$; $p < 0.001$). Furthermore, a significant negative correlation with FMD of the brachial artery ($r = -0.63$; $p < 0.001$) was found.

EFFECTS OF ANTI-RHEUMATIC DRUGS ON SERUM URIC ACID LEVELS IN PSORIATIC ARTHRITIS

On the basis of the described association between PsA and UA, it can be hypothesized that the treatment with anti-rheumatic drugs could lower SUA levels. Some researchers had tested this hypothesis with conflicting results.

In a retrospective study, Wang et al. (87) explored this topic in a population of 99 patients with moderate to severe Pso treated with secukinumab for 24 weeks. Overall, after 24 weeks of treatment, patients showed significantly lower UA values compared to the baseline. Similar results were obtained in a *post-hoc* analysis of pooled data from three phase 3 studies with secukinumab (FIXTURE, ERASURE and SCULPTURE trials) in a population of patients with moderate to severe Pso (88). The total population was composed of 3,010 patients. After 52 weeks of treatment, UA levels were significantly reduced and cutaneous Pso had improved.

Unlike these reports, Karataş et al. (89) did not find significant differences in SUA levels after 6 months of follow-up in a small population of 36 patients (30 diagnosed with ankylosing spondylitis and 6 with PsA) receiving treatment with secukinumab.

Hasikova et al. (90) investigated the effect of TNF inhibitors on SUA levels in a population of patients with systemic autoimmune rheumatic diseases (rheumatoid arthritis, PsA, ankylosing spondylitis). Interestingly, after 3 months of treatments, the authors observed a significant increase in UA levels along with a reduction of inflammatory cytokines.

EFFECTS OF URATE-LOWERING AGENTS ON SERUM INFLAMMATORY MEDIATORS

From the above, it appears that subjects with Pso or PsA have a higher prevalence of hyperuricemia compared with the healthy population but another relevant point to explore is the effect of urate-lowering drugs on systemic inflammation.

In 1981, Goldman evaluated (19) this topic in a group of Pso patients treated with allopurinol. This study showed marked improvement of skin lesions in most cases, confirming the results of previous studies (91, 92). In more recent years, researchers investigated the effects of urate-lowering drugs on cytokines in patients with other inflammatory diseases such as colitis or gout (93, 94). Luis-Rodríguez et al. (95) determined the levels of serum CRP, TNF-α and IL-6 and assessed the mRNA expression of TNF-α and IL-6 in white blood cells of hyperuricemic patients and in subjects with normal SUA. The former had raised CRP and mRNA expression levels of both IL-6 and TNF-a ($p < 0.001$). Similar results were obtained also in multiple regression analysis. Finally, the inflammatory profile of a subgroup of 18 subjects was determined at baseline and after 6 months of treatment with allopurinol. The therapy decreased mRNA expression of TNF-α and IL-6 respectively by 23% and 52% ($p < 0.001$). Furthermore, a significant association was found between variations in SUA and changes in serum TNF-a ($r = -0.62$; $p < 0.01$) or IL-6 ($r = -0.51$; $p < 0.05$).

In a randomized, double-blind, placebo-controlled pilot study, Huang et al. (96) explored the effects of febuxostat on

serum inflammatory markers such as IL-6, IL-17, and TNF-α in 156 Chinese patients with gout and hyperuricemia. Variables were measured at the baseline and at 2, 4, 8, 12, 16, and 24 weeks. After 8 weeks, treatment with febuxostat led to reduction of serum levels of IL-6, IL-17, and TNF-α by 38, 40, and 22%, respectively. The reduction in serum concentrations of pro-inflammatory cytokines correlated with the reduction of SUA levels.

In a similar study, Hao et al. (97) compared the effects of febuxostat and allopurinol in reducing serum levels of IL-1, IL-4, IL-6, IL-8, TNF-α, and cyclooxygenase-2 (COX-2) in 80 patients with gout, after 1 week and 3 months of treatment. Both treatments led to a significantly reduction of inflammatory cytokines, but febuxostat showed a more pronounced effect ($p < 0.05$). Furthermore, febuxostat led to marked reduction of cyclooxygenase-2 compared to allopurinol ($p < 0.001$).

The anti-inflammatory effects of urate-lowering agents were also studied in mice with induced colitis. The authors demonstrated that treatment with febuxostat led to a significant reduction of TNF-α, IL-1β, IL-6, and IFN-γ levels. In particular, it was observed a reduced expression of NF-kB in intestinal mucosa after treatment (98, 99). Finally, allopurinol was also used in the treatment of experimental autoimmune uveitis and it was shown to be more effective than prednisolone in suppressing the inflammatory reaction (100).

CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

PsA is a chronic systemic inflammatory disorder extending far beyond the involvement of skin and joints. This review dealt with the interplay between hyperuricemia and Pso/PsA, summarizing current knowledge on the topic and providing hints for future research. Analyzing the available literature, several issues regarding the mechanisms behind the association between UA and inflammation in Pso/PsA remain unresolved. Which factors contribute to hyperuricemia in Pso/PSA besides increased cellular turnover? What is the role of the kidney in this alteration? To what extent extra-renal organs, such as the intestine, are involved? Could the systemic inflammatory milieu stimulate UA production or hamper its secretion/excretion? Finally, could we still consider PsA and gout as two distinct entities or do they rather represent two facets of the same disease?

Current knowledge doesn't allow to draw firm conclusions about these points and future investigations are needed to shed new lights on this intricate field.

AUTHOR CONTRIBUTIONS

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

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frontiers in Medicine

REVIEW
published: 23 September 2021
doi: 10.3389/fmed.2021.737079

Extra-Articular Manifestations and Comorbidities in Psoriatic Disease: A Journey Into the Immunologic Crosstalk

Lucia Novelli[1†], *Ennio Lubrano*[2†], *Vincenzo Venerito*[3], *Fabio Massimo Perrotta*[2], *Francesca Marando*[1], *Giacomo Curradi*[1] *and Florenzo Iannone*[3*]

[1] *Medical Department, AbbVie srl, Rome, Italy,* [2] *Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy,* [3] *Rheumatology Unit—Department of Emergency and Organ Transplantations, University of Bari "Aldo Moro", Bari, Italy*

Psoriatic arthritis (PsA) is a chronic inflammatory disease primarily affecting peripheral and axial joints, with the possible presence of extra-articular manifestations (EAMs), such as psoriasis, uveitis, and inflammatory bowel disease. Recently, the concept of psoriatic disease (PsD) has been proposed to define a systemic condition encompassing, in addition to joints and EAMs, some comorbidities (e.g., metabolic syndrome, type II diabetes, hypertension) that can affect the disease outcome and the achievement of remission. EAMs and comorbidities in PsA share common immunopathogenic pathways linked to the systemic inflammation of this disease; these involve a broad variety of immune cells and cytokines. Currently, various therapeutics are available targeting different cytokines and molecules implicated in the inflammatory response of this condition; however, despite an improvement in the management of PsA, comprehensive disease control is often not achievable. There is, therefore, a big gap to fill especially in terms of comorbidities and EAMs management. In this review, we summarize the clinical aspects of the main comorbidities and EAMs in PsA, and we focus on the immunopathologic features they share with the articular manifestations. Moreover, we discuss the effect of a diverse immunomodulation and the current unmet needs in PsD.

Keywords: psoriatic arthritis, psoriatic disease, comorbidities, extra-articular manifestations, systemic inflammation, immunomodulation

OPEN ACCESS

Edited by:
Piero Ruscitti,
University of L'Aquila, Italy

Reviewed by:
Cheng-De Yang,
Shanghai Jiao Tong University, China
Prasanta Padhan,
Kalinga Institute of Medical Sciences (KIMS), India

***Correspondence:**
Florenzo Iannone
florenzo.iannone@uniba.it

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *06 July 2021*
Accepted: *26 August 2021*
Published: *23 September 2021*

Citation:
Novelli L, Lubrano E, Venerito V, Perrotta FM, Marando F, Curradi G and Iannone F (2021) Extra-Articular Manifestations and Comorbidities in Psoriatic Disease: A Journey Into the Immunologic Crosstalk. Front. Med. 8:737079. doi: 10.3389/fmed.2021.737079

INTRODUCTION

Psoriatic arthritis (PsA) is a common chronic inflammatory disease characterized by the association of arthritis and psoriasis, first identified by Verna Wright and his colleagues as a distinct and peculiar condition belonging to the group of spondyloarthritis (SpA) (1). Immune dysregulation, with altered cytokines expression and cellular phenotypes is responsible of the typical clinical features of PsA, which involve peripheral joints and the axial skeleton, with the onset of peripheral arthritis and spondylitis (2). In addition to these characteristic musculoskeletal manifestations, patients with PsA can often suffer from extra-articular manifestations (EAMs), which are genetically and immunologically correlated to these features and include psoriasis; inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn disease (CD); and uveitis (3).

Moreover, other concomitant or subsequent diseases, globally called comorbidities, can develop in these patients. These conditions are highly prevalent among patients with PsA and can be due to shared genetic/immunologic risk factors, chronic inflammation, the consequences of its treatment, and reduced physical function and activity (**Table 1**) (4). In recent years, the concept of psoriatic disease (PsD) emerged among the rheumatologic community, defining PsA as a systemic disease encompassing EAMs and comorbidities other than skin and joint involvement (13). This concept was developed as an attempt to explain more fully the complexity of this disease. The presence of EAMs and comorbidities strongly affects disease burden, often correlating with a poorer outcome, worse quality of life, reduced physical function, and poor response to treatments (14). Moreover, EAMs and comorbidities should drive therapeutic choices, and finding the correct balance between disease control, global efficacy, contraindications, and side effects is still a challenge and an unmet medical need, despite the various therapeutics currently available. Herein, we discuss the concept of PsD, reviewing the main PsA comorbidities and EAMs and focusing on some of their shared immunopathologic features and the effect of their modulation in clinical practice.

THE CONCEPT OF PSORIATIC DISEASE

Since the first descriptions of clinical manifestations, PsA appeared to be a multifaceted disease; in 2006, the term PsD was proposed by Scarpa and colleagues to emphasize the clinical and pathogenetic heterogeneity of PsA (13). PsD represents a heterogeneous, chronic, inflammatory disease with a wide spectrum of phenotypical manifestations that can occur only at joint level or in combination with several cutaneous, periarticular EAMs and different comorbidities, (15) which share key cytokines pathways (**Figure 1**). In this context, patients with PsA may have different clinical phenotypes and presentations, and physicians may need to treat patients in whom several coexisting conditions could be present (16).

PSORIATIC ARTHRITIS EXTRA-ARTICULAR MANIFESTATIONS

Psoriasis

Psoriasis (PsO) is the most common non-musculoskeletal organ involvement in PsA. Approximately one-third of patients with PsO develops PsA over time. The incidence rate of PsA in different psoriasis cohorts is between 1.3 and 3.5% per annum (5, 17), with skin involvement preceding arthritis by an average of 7 years (17). PsA mainly develops in patients with an established diagnosis of PsO; indeed, PsO seems to occur after the onset of arthritis only in 15% of PsA cases. Simultaneous onset of PsA and PsO occurs in about 15% of patients, who tend to experience combined flares of both articular and skin involvement (17, 18). This makes PsO the most readily identifiable marker that confers risk of arthritis. Moreover, a recent study found that PsO is more common in PsA patients with axial involvement as well as other EAMs (e.g., uveitis and IBDs) (19). Different clinical subsets of PsO exist, such as plaque psoriasis, nail psoriasis, scalp psoriasis, palmoplantar psoriasis, and inverse or intertriginous psoriasis with distinct morphologic phenotype (5, 20, 21). In particular, nail, scalp and inverse psoriasis has been associated with an increased risk of PsA (5, 22).

For many years, PsO has been considered a classical Th1-mediated disease, with a central role of interleukin (IL−2) and interferon (IFNγ); subsequently, other populations of T-helper cells and their cytokines have been identified as major drivers in PsO development (23). First tumor necrosis factor (TNF) and then IL-17 and IL-12/IL-23 pathways have been recognized as key pathogenic circuits in PsO, acting in synergy for the inflammatory cascade. The currently embraced pathogenic model for PsO suggests a trigger event, leading to the release of autoantigens from skin cells (e.g., LL37), which promote dendritic cell activation, with the consequent release of IL-12 and IL-23. These cytokines activate Th1, Th17, and Th22 cells, which produce IFNγ, TNF, IL-17, IL-22, contributing to the pro-inflammatory cytokines' milieu, to which keratinocytes respond (24). These cytokines also play a major role in PsA articular manifestations and, from a genetic standpoint, several cytokines' genes associated with PsO are also associated with PsA (25). However, gene expression patterns in skin and synovium are distinct, showing a stronger IL-17 gene signature in skin and more equivalent TNF and IFNγ gene signatures in both skin and synovium (26). This might explain why treating skin and joints with the same cytokine target may show different grades of efficacy. In the last 20 years, therapeutics that directly target these cytokines (e.g., TNF or IL-17 inhibitors) completely revolutionized PsO treatment, allowing the complete clearing of psoriasis in a number of patients; however, the latter drugs account for PsA disease control only in ≤50% of patients (17). Some patients, for example, might experience diminished response to anti-TNF drugs over time or develop a paradoxical exacerbation of PsO (27); similar cases of paradoxical psoriasis have been reported for secukinumab (anti–IL-17 monoclonal antibody) and ustekinumab (IL-12/23 inhibitor) (28, 29). In recent years, new therapeutics have been developed that offer additional options and a more tailored approach for patients with PsO, some of which are selective cytokines inhibitors, such as guselkumab, risankizumab, and tildrakizumab. These new biological drugs selectively target IL-23, acting upstream in the inflammatory cascade and eventually reducing the production of IL-17 (30). Janus kinase (JAK) inhibitors are new oral small molecules targeting the JAK/signal transducers and activators

Abbreviations: AMP, adenosine monophosphate; AU, anterior uveitis; cAMP, cyclic adenosine monophosphate; CD, Crohn disease; CNS, central nervous system; CRP, C-reactive protein; CS, central sensitization; DAPSA, Disease Activity in PsA Index; DM, diabetes mellitus; DMARD, disease-modifying anti-rheumatic drug; DVT, deep venous thrombotic; EAM, extra-articular manifestation; FM, fibromyalgia; HAQ-DI, Health Assessment Questionnaire Disability Index; HDL, high-density lipoprotein; HR, hazard ratio; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; JAK, Janus kinase; LDL, low-density lipoprotein; MACE, major cardiovascular event; OP, osteoporosis; PDE4, phosphodiesterase-4; PsA, psoriatic arthritis; PsAID-12, 12-item PsA Impact of Disease Questionnaire; PsD, psoriatic disease; PsO, psoriasis; RA, rheumatoid arthritis; RANK, receptor activator of nuclear factor kappa-B; SpA, spondyloarthritis; STAT, signal transducers and activators of transcription; TNF, tumor necrosis factor; TYK2, tyrosine kinase 2; UC, ulcerative colitis.

TABLE 1 | Prevalence of comorbidities and EAMs in PsA.

Comorbidity	EAM	Prevalence, %	References
CV disease	Psoriasis	19; 7–40	(4, 5)
Metabolic syndrome	IBD	29; 0–29	(3, 4)
Diabetes	Uveitis	6-20; 2–25	(3, 6)
Fibromyalgia	–	17.8–54	(7)
Depression	–	9–22	(8)
Anxiety	–	15–30	(8)
Osteoporosis	–	1.4–68.8	(9–12)

CV, cardiovascular; EAM, extra-articular manifestation; IBD, inflammatory bowel disease; PsA, psoriatic arthritis.

of transcription (STAT) pathway. Several cytokines, transmit their signals via this pathway, with multiple effects on different cells (31), playing a role in different PsA manifestations, including EAMs and comorbidities (**Figure 2**). The JAK family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2); inhibition of each of these molecules can interrupt specific STAT-dependent signaling pathways. JAK-dependent cytokines directly and indirectly mediate the inflammatory response in PsO, (IFNγ, IL-12, IL-23 and TNF, IL-17 respectively), thus, a JAK-inhibition acts broader and more upstream in the inflammatory cascade compared with a selective cytokine-inhibition (32). Upadacitinib, a selective JAK1 inhibitor approved for PsA, has shown good results in treating PsO in PsA clinical trials, with 75% improvement in the Psoriasis Area Severity Index achieved (PASI75) even in 52.3% of patients for whom biologic treatment had failed (33). Tofacitinib, a pan-JAK inhibitor (inhibits JAK1/JAK2/JAK3 and to a lesser extent TyK2) has been approved for PsA, and baricitinib, a JAK1/2 selective inhibitor, is being studied as possible treatment for PsO (34). Finally, a selective inhibitor of TYK2 is also under investigation for PsO and PsA[1, 2].

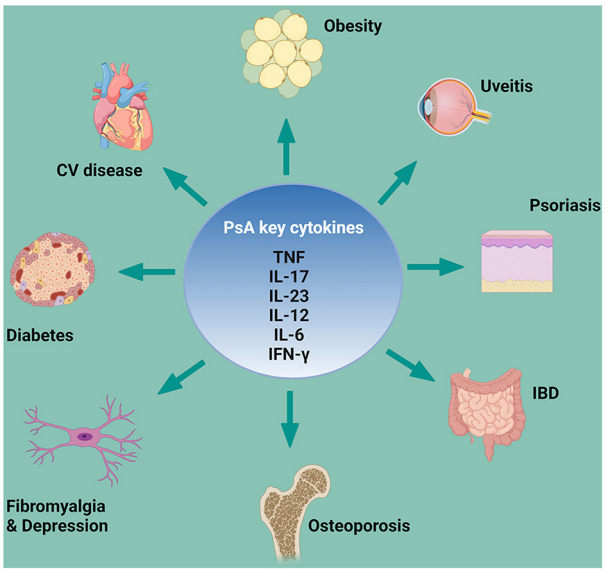

FIGURE 1 | PsA key cytokines involved in comorbidities and EAMs pathogenesis. CV, cardiovascular; EAM, extra-articular manifestation; IBD, inflammatory bowel disease; IFN-γ, interferon; IL, interleukin; PsA, psoriatic arthritis; TNF, tumor necrosis factor. *Created with Biorender.com*.

Inflammatory Bowel Diseases

Crohn's disease (CD) and UC, both IBDs, may occur in patients with PsO and PsA (35). Several studies reported the prevalence of IBD in patients with PsA, ranging from 0 to 20% (3). In a recent meta-analysis, the pooled estimate was 3.3%, although there was major asymmetry on the funnel plot, suggestive of bias (3). An Italian joint consensus by expert rheumatologists, gastroenterologists, and dermatologists has recently defined a core set of red flags for a multidisciplinary referral. Symptoms defined as major criteria for referral to gastroenterologists were bleeding, chronic abdominal pain, perianal fistula or abscess, chronic diarrhea, and nocturnal symptoms. Additionally, authors defined a set of minor criteria, including oral aphtosis, anemia, family history of IBD, weight loss, and fever, underlining the need for at least three of the latter for specialist referral. However, it should be considered that patients with PsO and PsA have a higher risk of developing IBD and that some patients with PsO may have subclinical IBD. To date there is a lack of studies examining the effect of IBD on longitudinal patient-reported outcomes and clinimetrics. The 2019 European Congress of Rheumatology (EULAR 2019) recommendations for PsA treatment (35) therefore advocated a tailored approach, focusing on both musculoskeletal and non-musculoskeletal involvements if present. From a pathogenic standpoint, PsA and IBD seem to share multiple mechanisms.

The interest of the scientific community in a pathogenic link between gut microbiome dysbiosis and PsA (and SpA in general) development has grown in the last few years. Disruption of the normal gut microbiota homeostasis led to systemic inflammation, with a central role of IL-23 in this process, in both SpA and IBD (36). IL-23 behavior, in the context of IBD, is extremely complex because it acts on multiple cells of the innate and adaptive immune systems. Preclinical data in murine models of colitis highlighted the importance of this cytokine in IBD (37); several anti–IL-23p19–specific antibodies, including

[1]Available online at: https://clinicaltrials.gov/ct2/show/NCT04772079?term=deucravacitinib&draw=2&rank=3.
[2]Available online at: https://clinicaltrials.gov/ct2/show/NCT03881059.

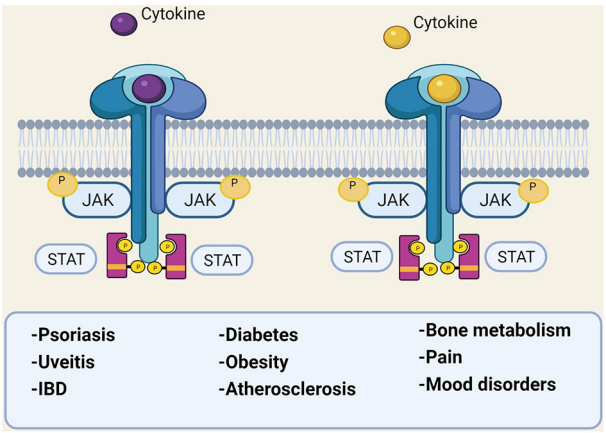

FIGURE 2 | The JAK/STAT pathway involvement in different diseases. IBD, inflammatory bowel disease; JAK, Janus kinase; P, phosphate; STAT, signal transducer and activator of transcription. *Created with Biorender.com*.

risankizumab, brazikumab, mirikizumab, and guselkumab, have been or are currently under evaluation in clinical trials in CD and, in some cases, UC (38). Several cytokines sustain and amplify the chronic inflammatory response in IBD, although with different patterns among CD and UC, and many of them are shared by PsA and IBD pathogenesis, with a largely similar therapeutic approach (39). TNF is a crucial cytokine in this context and is considered the main driver of intestinal tissue inflammation; in the last two decades, different TNF blockers have been developed, most of which have been successfully used in IBD and in enteropathic SpA. Still, some patients do not respond to anti-TNF agents or response is lost after one year, mainly because of drug immunogenicity (40). Moreover, anti-TNF inhibitor etanercept is ineffective for IBD (41), and patients with PsA treated with the etanercept had a significant increase in the risk of developing CD [adjusted HR, 2.0 (95% CI, 0.8–2.2)] or UC [2.0 (1.5–2.8)] (42).

CD is mostly a Th1-driven disease compared with UC. This leads to increased levels of IL-12, which acts in synergy with IL-23 and TNF in sustaining the inflammatory response with multiple downstream pathways, including regulation of pro-inflammatory Th17 cells (43). IL-12 and IL-23 share the p40 subunit, which is the target of ustekinumab, a monoclonal antibody approved for CD and also efficient in PsO and peripheral PsA (38). The discovery of the IL-23/Th17 pathways in IBD boosted intensive research aimed at the development of new therapeutics against these targets; unfortunately, both preclinical data and clinical trials showed a paradoxical worsening of the intestinal disease with anti–IL-17 blockage (44). The Janus of the IL-23 and IL-17 neutralization has been recently explained: anti–IL-23 antibodies reduce Th17, improving inflammation, whereas the blockage of IL-17 affects tissue homeostasis repair, impairing intestinal wall integrity and thus exacerbating the disease (45). These negative results have been largely disappointing, especially in the light of a missing option for patients with enteropathic SpA, whose treatment is often more challenging and requires a tighter, tailored, and multidisciplinary approach (46). Similar to PsA, most of the cytokines involved in IBD signal trough the JAK/STAT pathway and multiple clinical trials have recently been initiated to investigate the efficacy of different JAK inhibitors in CD and UC. Indeed, JAK inhibition in these clinical conditions may block multiple cytokines at the same time. Tofacitinib was the first small molecule to be approved for UC, but it was not effective in CD (47, 48). Filgotinib and upadacitinib (the latter of which is already approved for PsA)[3] are two selective JAK1 inhibitors currently under investigation in phase III clinical trials for CD and UC[4, 5, 6, 7]. These new promising therapeutics might have the advantage of being effective in multiple overlapping clinical conditions, as in the case of enteropathic SpA.

Uveitis

Ophthalmic manifestations are estimated to occur in 10% of patients with PsO and 31% of patients with PsA (3, 49). Uveitis is the most frequent inflammatory eye involvement. In literature, the prevalence of uveitis is reported to affect between 2 and 25% of patients with PsA (3) and, in a recent meta-analysis of 21 studies, the pooled estimate of uveitis was 3.2% (3). The wide range of prevalence reported in PsA may be explained by the variable sets of classification criteria used for patient selection and the different time of follow-up. Nevertheless, the analysis reported high heterogeneity in analyzed studies and a high risk of bias. Anterior uveitis (AU) is the most frequent clinical phenotype of uveitis in PsA. The reported prevalence of AU ranges from 2 to 25% of cases, and it is more frequently observed in patients with axial PsA or who are HLA-B27–positive (50). The involvement of the anterior chamber prompted Bridgewood et al. (51) to speculate that connective tissue of uveal structures might be conceptually similar to a musculoskeletal enthesis. Indeed, elastin and type IV collagen compose the structure of tendons of the ciliary muscle and IL-23R–positive resident cells have also been recently detected in the ciliary body of mice (51, 52). AU is a potentially vision-impairing condition if not treated. Patients often complain of ocular pain, photophobia, tearing, marked eye redness and, in more severe cases, vision blurring due to abundant inflammatory precipitate in the anterior chamber (53, 54). Although the most common type of uveitis is recurrent AU, it does not appear to follow a "unilateral alternating" pattern of ankylosing spondylitis and both eyes can be affected simultaneously. In an Italian study comparing the frequency of uveitis in PsA with other SpA, PsA uveitis had a more insidious onset, was more frequently bilateral (38 vs. 7%) and posterior (44 vs. 17%) and lasted longer (31 vs. 6%) (55). In a large Italian cross-sectional study involving 278 patients with uveitis (n.418

[3]Available online at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-rinvoq-ii-04ii-05_en.pdf.
[4]Available online at: https://www.clinicaltrials.gov/ct2/show/NCT02914600?term=filgotinib&cond=crohn$+$disease&draw=2&rank=1.
[5]Available online at: https://www.clinicaltrials.gov/ct2/show/results/NCT02914522?term=filgotinib&cond=Ulcerative$+$Colitis&draw=2&rank=2.
[6]Available online at: https://www.clinicaltrials.gov/ct2/show/NCT03653026?term=upadacitinib&cond=Ulcerative$+$Colitis&draw=2&rank=1.
[7]Available online at: https://www.clinicaltrials.gov/ct2/show/NCT03345836?term=upadacitinib&cond=Crohn$+$Disease&draw=2&rank=1.

eyes) who were referred to a rheumatologist in two tertiary care centers, Lopalco et al. (56) reported that AU (63.6%) with a chronic course (71.4%) and bilateral involvement (57.1%) was the most frequent phenotype. Nevertheless, the authors also showed that chronic posterior uveitis (42.8%) with bilateral involvement (66.7%) was likely to occur.

Acute AU has a strong genetic component, and most of the identified susceptibility genes belong to various immunologic pathways that are also common in SpA, including PsA. Besides HLA-B27, other genes involving TNF, IL-17, and IL-23 pathways have been identified for uveitis (57), emphasizing the major role of inflammation in this disease. Studies from animal models revealed a role for both innate and adaptive immunity, in line with SpA pathogenesis (58). Moreover, as with synovial fluid from inflamed joints, several pro-inflammatory cytokines can be found in the aqueous humor in case of uveitis, including TNF, IFNγ, IL-17, IL-22, IL-23 (59). Thus, it is not surprising that biological therapies played a role in the treatment of this disease in the last few years; with their immunomodulatory properties and a more selective immunosuppression, these drugs reduce the need for topical corticosteroids, lowering the risk of elevated intraocular pressure and vision loss (60). Anti-TNF drugs, such as infliximab and adalimumab, can successfully control uveitis flares, whereas etanercept can promote a paradoxical uveitis. The reason for this paradoxical effect is unknown, but it may be linked to a drug-induced cytokine imbalance (61). Other TNF inhibitors, such as golimumab and certolizumab pegol, showed promising results (62, 63), but to date, only adalimumab is indicated for uveitis treatment. Genetic studies and mice models revealed a possible involvement of the IL-23/IL-17 axis as well (64), thus modulation of this pathway may represent a future therapeutic option for this condition. Ustekinumab showed efficacy in some case reports, (65, 66) and a phase II clinical trial has been recently completed[8]. The JAK/STAT pathway is also being studied in uveitis because of its role in cytokines signaling. Topical tofacitinib showed symptom improvement in an experimental model of autoimmune uveitis (67), and phase II clinical trials are currently ongoing to test tofacitinib[9] and filgotinib in this disease[10].

PSORIATIC ARTHRITIS COMORBIDITIES

Cardiovascular Disease, Metabolic Syndrome, and Diabetes

Among the different comorbid conditions that could be present in PsA, cardiometabolic disease is the most prevalent, with an important effect on disease burden and outcomes. A recent work analyzed the incidence of new comorbidities per 100 person-years in PsA patients and controls. Compared with controls, patients with PsA had a higher incidence rate of autoimmune disease, cardiovascular disease, fatigue, eczema, obesity/overweight, depression, anxiety, smoking, cancer, diabetes, alcohol use, osteoporosis, uveitis, and liver disease (68). Furthermore, observational studies showed an increased risk (43%) of cardiovascular diseases in patients with PsA, with higher morbidity risks for myocardial infarction, cerebrovascular diseases, and heart failure compared with the general population (69). Of note, the rates of coronary artery disease hospitalizations were significantly higher in patients with PsA than in controls (primary diagnosis, 0.8 vs. 0.5%; non-primary diagnosis, 3.2 vs. 2.2%; $P < 0.001$ for both) (68). Other studies confirmed the increased incidence of cardiovascular diseases in patients with PsA [incidence rate, 9.4 (95% CI, 6.5–13.5)], and even reports coming from administrative data showed higher risk of cardiovascular disorders (incidence rate, 6.5 vs. 5.8 compared with controls) and a higher risk of specific cardiovascular disorders (hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, peripheral vascular disease) (70). All these factors were associated with increased all-cause mortality and, of note, higher cardiovascular mortality rate seemed to be related to the polyarticular pattern, high disease activity, and severity (69). Among cardiovascular risk factors, a recent meta-analysis showed that hypertension is the most prevalent comorbidity in patients with PsA (present in ∼39% of patients), followed by hyperlipidemia, diabetes, and obesity (71, 72). Regarding obesity, studies have also suggested that weight gain may be a consequence of the systemic inflammatory state or that obesity may lead to more weight on the joints, altered mechanics, and repetitive micro-trauma, which could represent a trigger for entheseal and synovial inflammation (73). Moreover, obesity is a negative predictor for response to treatment; in particular, response to anti-TNF could be impaired, with higher risk to not achieve the minimal disease activity in obese patients with PsA (74–76). Finally, among the different comorbidities present in patients with PsA, insulin resistance and diabetes mellitus (DM) appeared to be of peculiar interest. DM appears to be more prevalent in patients with PsA compared with general population, with an estimated prevalence of ranging from 6.1 to 20.2%. Moreover, DM seems to be more frequent in patients with PsA vs. patients with only PsO. Clinical factors associated to the development of DM were recently explored: in a large cohort study, tender joint count and erythrocyte sedimentation rate were deemed the predictor factors associated with the development of DM. These results are in keeping with the concept that disease activity is an important driver, suggesting how elevated inflammatory burden may lead to a higher risk of developing DM (6). Indeed, a robust body of evidence indicates a strong bond between the metabolic and the immune system, and alterations in this complex network, may lead to chronic diseases, including diabetes and obesity (77). For example, IL-6, a cytokine renowned for its pro-inflammatory role, is associated with central obesity, hypertension, and insulin resistance. Moreover, it promotes C-reactive protein (CRP) production (78). Additionally, there is a chronic and low-grade state of inflammation called *metaflammation*, described in obesity and type 2 DM, involving the adipose tissue and other tissues (79). As previously discussed, in patients with PsA,

[8]Available online at: https://clinicaltrials.gov/ct2/show/results/NCT02911116.

[9]Available online at: https://clinicaltrials.gov/ct2/show/results/NCT03580343?term=tofacitinib&cond=Uveitis&draw=2&rank=1.

[10]Available online at: https://clinicaltrials.gov/ct2/show/NCT03207815?term=filgotinib&cond=Uveitis&draw=2&rank=1.

the presence of inflammation is associated with an increase in traditional cardiovascular risk factors, such as a higher body mass index, hypertension, high sugar levels, insulin resistance, and dyslipidemia (80). Intensive research in this field brought to light multiple results supporting the hypothesis that the association between PsA and metabolic syndrome might be due to shared inflammatory pathways (81).

Role of Cytokines

Increasing evidence has established that PsO, PsA, and atherosclerosis involve the same T-cell–mediated inflammatory pathways, specifically T-helper 1 and T-helper 17 cascades (82), with release of several pro-inflammatory cytokines (e.g., INFγ and TNF), which are involved in the initiation and progression of atherosclerotic plaques in the systemic vasculature. Chronic inflammation in both PsA and atherosclerosis promotes increased production of adipokines and pro-inflammatory cytokines (e.g., TNF) with consequent insulin resistance and endothelial dysfunction (83). Indeed, it has been demonstrated that anti-TNF therapy improves insulin resistance (84). Presence of inflammation also influences lipoprotein levels, and patients with PsA have been shown to have several lipid alterations, including oxidized lipoproteins, which are markers of atherosclerosis. Anti-TNF therapies can increase total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and Apo B levels in patients with PsA and rheumatoid arthritis (RA) without changing the atherogenic index (84). According to some authors, these data suggest normalization with suppression of inflammation; to others, these results might be interpreted with caution despite the reduced cardiovascular risk reported in cohorts of patients treated with anti-TNF (85). Patients with PsA receiving disease-modifying anti-rheumatic drugs (DMARDs) showed a lower cardiovascular risk when compared with those not receiving these medications, and anti-TNF treatment seems to be associated with a reduced progression of subclinical atherosclerosis in these patients (86, 87). TNF is not the only cytokine involved in cardiovascular comorbidity: data from animal models and human studies highlighted the pro-atherogenic role of IL-17 on vascular inflammation, acting in synergy with TNF and IL-6 (88). IL-17 is involved in endothelial dysfunction, hypertension, plaque progression and destabilization, stroke, and myocardial infarction. However, it also seems to have anti-atherogenic effects, and low serum levels of IL-17 have been associated with a higher risk of cardiovascular relapses in patients with coronary artery disease (89). TNF and IL-17 can also inhibit the autophosphorylation of the insulin receptor, thus inducing insulin resistance and suppressing the expression of GLUT4 (90). Another link between PsA and DM can be found in adipokines, a group of cytokines secreted by adipose tissue. Adiponectin is an adipokine with anti-inflammatory, insulin-sensitizing, and anti-atherogenic properties, but whose secretion is decreased by pro-inflammatory cytokines (such as TNF, IL-1β, and IL-6). Some studies have shown that in inflammatory diseases such as PsA, adiponectin levels are decreased, with a potential effect on the metabolic status of patients. Of note, it has been demonstrated that biologic drugs, such as anti-TNF, may increase adiponectin levels, leading to a possible improvement of metabolic aspects in PsA (91, 92). IL-17 also links inflammation with insulin resistance and adipocytes dysfunction; for instance, there is a reciprocal regulation between the pro-inflammatory adipokine leptin and IL-17. In mice models with systemic inflammation and insulin resistance, there is accumulation of IL-6/IL-17 co-expressing T cells in the adipose tissue; these cells enhance leptin production, which eventually acts in synergy with IL-6 and IL-17 to promote Th17 differentiation. This complex network drives local and systemic insulin resistance, and, in fact, IL-17 neutralization improves glucose uptake (93). Moreover, clinical studies in patients with inflammatory arthritis and type II DM demonstrated that anti–IL-17 (and anti–IL-12/23) therapies do not seem to have an influence on body weight and do not increase the risk of DM manifestations (88).

Signal Transduction Pathways

Phosphodiesterase-4 (PDE4) is a phosphodiesterase that hydrolyzes cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP). This molecule can be found in keratinocytes and immune cells and is involved in several cytokines' pathways implicated in inflammation. A small molecule targeting PDE4 (apremilast) has been used for the last few years to treat PsO and PsA. Besides inflammatory diseases, derangement of the PDE4-cAMP signaling is relevant in the development of metabolic disorders. In fact, patients with PsA treated with this anti-PDE4 molecule seem to have a better lipid and glucose profile (94). Most of the pro-inflammatory cytokines involved in PsA pathogenesis signal through the JAK/STAT pathway, and a growing body of evidence points to involvement of this pathway in DM and obesity. It has been shown that through activation of the JAK/STAT pathway insulin signal can be decreased, and data have demonstrated that oxidative stress and inflammation work together to induce insulin resistance with JAK performing a central role (95). The β-pancreatic cells respond to insulin, growth factors and cytokines that are JAK/STAT dependent, and this pathway could be involved in both type I and type II DM. In DM mice models (non-obese diabetic [NOD] mice) treatment with a JAK1/JAK2 inhibitor can reverse the disease (96). However, the role of JAK/STAT proteins in metabolism is highly dependent on the context and the cell type. Impairment of JAK/STAT signaling can lead to various metabolic alterations or protection from obesity and insulin resistance. Knock-out mice for JAK3 or TYK2 have been shown to be prone to obesity and insulin-resistance (97, 98). In contrast with these data from animal studies, an *in vitro* study showed that tofacitinib induced "browning" in human adipocytes through IFN suppression (99), in which the increase in the number of brown adipocytes in the adipose tissue has been shown to prevent obesity and improve type II DM. This study opened the path of new area of research, involving JAK inhibitors as possible therapeutic options for obesity (99). Concerning the cardiovascular risk, the effect of JAK inhibitors showed contrasting results. JAK/STAT signaling pathway seems to be deeply involved in atherosclerosis, regulating scavenger receptors

involved in LDL uptake (100), and is involved in NOX-dependent oxidative stress in human aortic smooth muscle cells (101). In randomized controlled trials and real-world studies in patients affected by RA, the use of JAK inhibitors tofacitinib, baricitinib, and upadacitinib increased levels of total cholesterol, HDL, and LDL in the first four weeks of therapy and then plateaued, with lack of changes in the atherogenic index (102, 103). *In vitro* studies have shown that this was associated with release of cholesterol from macrophages by reverse cholesterol transport, and, in line with these observations, tofacitinib was shown to ameliorate atherosclerosis in mice models (104). Moreover, in patients with RA treated with upadacitinib, a significantly higher efflux of cholesterol from macrophages was observed, and this was associated with increased HDLs and reduction of CRP (105). Some real-world studies reported increased major cardiovascular events (MACE) and deep venous thrombotic (DVT) events in patients treated with tofacitinib (especially at higher dose) and baricitinib (106) whereas other studies did not support these findings (107, 108). Currently, it is not possible to establish if this increased risk is related to specific direct and indirect cytokine blockade, to chemical structure and/or pharmacologic and toxicologic properties of specific JAK inhibitors, to the presence of concomitant diseases, or other factors (e.g., genetic mutations). The pathophysiological process that eventually leads to blood clot formation, involves the recruitment of a broad variety of immune cells, chemokines, and cytokines, with an inflammatory response that impairs endothelial function and activates the coagulation cascade (109). Inhibition of the JAK/STAT pathway modulates the inflammatory response and, thus, should reduce the prothrombotic risk. According to some authors, JAK-inhibition specificity matters; when a pro-inflammatory and anti-thrombotic pathway is blocked, other pathways can still transmit pro-thrombotic signals, thus, these complications might not be considered a class drug effect (110). The genetic background of patients could also play a big role, especially in terms of age-dependent JAK mutations (110). A good case in point is the mutation V617F in the JAK2 gene, which enhances its function, resulting in an increased risk of thrombotic events. This mutation is frequent among patients affected by myeloproliferative neoplasms, and ruxolitinib (a JAK1/JAK2 inhibitor) is a recommended second-line treatment for the prevention of thrombosis in these patients (111). Another aspect to take into account, is the patients' clinical response to therapy; to the best of our knowledge, there are contrasting data in the literature regarding a correlation between incomplete disease control and increased MACE/DVT events in patients with inflammatory arthritis treated with tofacitinib: a recently published cohort study from Sweden demonstrated a strong association between disease activity and the risk of venous thrombotic events in patients with RA (112); in contrast, a *post hoc* analysis of a phase III trial of tofacitinib in patients with RA, did not find any association between disease activity and the MACE risk, but it revealed a trend toward an association between elevated erythrocyte sedimentation rate following tofacitinib treatment with an increased risk of future MACE, and this was explained as possibly a form of failure to respond to treatment (113). Thus, the persistence of inflammation, together with other predisposing factors, may contribute to the development of these events in certain individuals.

Osteoporosis

In PsA, bone involvement is quite complex because it involves not only bone loss but also new bone formation. According to some studies, prevalence of osteoporosis (OP) in patients with PsA is similar to the general population (114). However, other studies have shown that OP is found very frequently in PsA, ranging from between 1.4 and 68.8% of patients (9–12), but its likelihood depends on the site of measurement, the arthritic subset, the sex of the patient, and other factors (e.g., menopausal state) (115). Moreover, the use of glucocorticoids are also a contributing factor, although to a lesser extent than RA, requiring a different type of OP management compared with the general population (114). OP is associated with an increased risk of fractures and, according to a study form Pedreira et al. prevalence of fractures seems higher in patients with PsA versus PsO and controls, despite no differences in bone mineral density in the three groups (116). This finding highlights the concept that not only bone density but also bone quality matters when dealing with increased fracture risk (115). The role of the immune system in bone quality and bone metabolism is well established and led to the development of an intriguing field of research called osteoimmunology (117). Bone undergoes continuous remodeling thanks to a delicate but dynamic balance between osteoclasts and osteoblasts. The immune cells and the neuro-endocrine system regulate these cells, answering to physiological/mechanical stress, and dysregulation of this network leads to various bone diseases, including bone damage in inflammatory arthritis and OP (118). Several studies described the role of inflammation in OP pathogenesis as involving both the innate and the adaptive immune systems. Moreover, the presence of a low-grade, chronic, systemic, inflammatory state, associated with aging, has been linked to age-related diseases, including OP (119). Cytokines involved in PsA pathogenesis have an effect on bone cell activity with possible inhibitory or stimulatory stimuli on osteoclasts and osteoblasts. TNF, IL-6, and IL-1, for example, exert stimulatory activity toward osteoclasts and inhibitory activity toward osteoblasts (119). Given the activity of these inflammatory cytokines on bone cells, the high prevalence of OP in a systemic chronic inflammatory disease such as PsA is not surprising. IL-12 and IL-23, involved in PsA, are also critical to inflammation-induced bone resorption. Specifically, IL-23 upregulates the receptor activator of nuclear factor kappa-B (RANK) on preosteoclasts and induces Th17 cells to produce IL-17 (120). IL-17, one of PsA signature cytokines, promotes bone resorption via RANK ligand upregulation (121). Indeed, Th17 cells have been found to be highly increased in blood and tissues of patients with OP (72). PsA and OP often share another risk factor that is tightly connected to inflammation: vitamin D deficiency. A possibility of crosstalk between vitamin D and IL-33, a cytokine involved both in PsA and OP, has recently been suggested (122). Vitamin D and IL-33 under some conditions act in synergy and under other conditions modulate each other. For instance, they both have a protective effect on bone resorption, whereas in inflammatory conditions, vitamin D

deficiency and IL-33 upregulation boost each other (123). The relationship between inflammation and bone loss suggests that, in light of their immunomodulatory properties, biologic drugs can reduce OP and fracture risk (124). Most of research on this topic focuses on the role of anti-TNF drugs, and several of these studies demonstrated a role of these therapeutics in bone loss reduction in patients with inflammatory arthritis (125, 126), although other studies did not completely confirm these data (127). The effect of TNF-blockade on fracture risk specifically still needs to be fully elucidated. Indeed, a recent article by Manara and Sinigaglia concluded that there is little evidence of a clinically relevant effect of TNF-inhibitors on this, especially considering the conflicting results published in literature (125). Similarly, the effect of IL-17 and IL-23 blockade on bone loss is still not completely clear. Animal studies support a bone protective effect of anti-IL-23 and anti-IL-17 antibodies, preventing bone loss (128, 129). However, clinical studies, especially in the context of inflammatory arthritis, are missing. Most of these cytokines control bone homeostasis via JAK/STAT proteins (130) in a tightly regulated way in physiologic conditions. In cases of inflammation, pathologic activation of this pathway can eventually lead to OP, bone erosions, and other bone disorders. Therefore, inhibition of this pathway, which exerts a positive effect on prevention of bone erosions (131), may have a similar effect on bone density (132, 133). In fact, recently published papers indicated that JAK/STAT inhibition induces osteoanabolic effects in mice models and *in vitro* studies (134, 135).

Mood Disorders

Current evidence suggests that patients with PsA have a significantly worse quality of life compared with patients experiencing other rheumatic diseases (136). This may be due to the additive effect of PsO on chronic pain, limitations in physical functioning and work abilities, extreme fatigue, and emotional and social impairment. Such a detrimental effect on quality of life would also entail depression and anxiety in patients with PsA (7, 8). Indeed, according to a recent meta-analysis, the prevalence of depression in patients with PsA ranges from 9 to 22%, and the prevalence of anxiety between 15 and 30%, which is higher than in the general population (137). Anxiety and depression in PsA are more likely to affect patients who are female, unemployed, and with high disease activity (8). The 2019 EULAR recommendations (35) emphasized that comorbidities should be taken into account in the management of PsA, highlighting that anxiety and depression are among the most common ones in such patients. This is particularly important in planning a treat-to-target strategy because the presence of comorbid depression and anxiety has recently been shown to reduce the likelihood of achieving disease remission, according to the American College of Rheumatology/European League Against Rheumatism Boolean and Disease Activity Index for PsA Norwegian-DMARD prospective cohort (138). There is rising evidence that an inflammatory process might be also behind these diseases. Specifically, IL-6 might have a negative effect on mood, and it has been shown to be a predictor of higher severity and chronicity of depression (139). Moreover, elevated levels of CRP and TNF have been found in patients with depression and have been associated with higher symptoms severity (139). There is evidence that neuroinflammation also plays a role in depression, with increased pro-inflammatory cytokines in the brain and activation of microglia cells (140). Anti-inflammatory treatment has been shown to improve symptoms of depression according to different studies (141). However, contrasting evidence has been shown regarding the effect of treatment with conventional synthetic and biological DMARDs on psychological disorders. One study demonstrated a reduction in prevalence of depression and anxiety with etanercept treatment (142), but these findings are at high risk of bias because of insufficient data on sampling, response rates, and statistical analysis. According to a recent meta-analysis (137), the overall effect of PsA treatment on depression and anxiety remained unclear. Lastly, patients treated with a PDE4 inhibitor for PsA and PsO showed increased frequency of depression or suicidal behavior in clinical studies (143).

Fibromyalgia

Fibromyalgia (FM) is a chronic syndrome characterized by pain and tenderness, sleep disturbance, fatigue, cognitive dysfunction, and background emotional distress. It sometimes presents as a comorbidity with another disease or condition (144). FM is the clinical expression of stress-related neurobiological responses that lead to increased reactivity in several sensory neural systems, particularly those in the musculoskeletal system. In most patients with comorbid FM, such responses may be related to the burden of having a chronic illness. This includes the symptoms of the disease; the effect on general health; the need for tests, drugs, and treatments; disability; loss of quality of life; and changes in social and work roles (144). In the general population, the prevalence of FM varies, according to classification criteria, between 2 and 8%. These rates increase significantly when FM manifests as comorbidity, particularly in rheumatic diseases, with FM symptoms often merging with those of the underlying condition. Data from retrospective cohorts show that the prevalence of classified FM in patients with PsA according to 2016 American College of Rheumatology criteria is higher, ranging from 17.8 to 64% (7, 145–147). FM can either interfere with the patient's perception of disease activity or alter physicians' clinimetrics. Indeed, patients with FM frequently experience widespread pain that can be mistaken for arthralgia or enthesitis. Comorbid FM is known to amplify the perception of pain and fatigue in patients with PsA and therefore, negatively affects self-reported assessment of disease activity. Furthermore, coexistent FM can make the therapeutic strategy for PsA challenging hampering the global clinical effectiveness of therapies and misleading doctors in their choices. In general, patients with PsA with FM are more likely to be female with polyarticular phenotype and high disease activity score, whichever index is adopted (145–147). Elsawy et al. and Ulutatar et al. (146, 147) report that patients with PsA with comorbid FM show a significant increase in disease activity scores that incorporate measurements of pain and tenderness compared with patients without FM. These include standard instruments such as the Disease Activity in PsA Index (DAPSA), Tender Joint Count, Leeds Enthesitis Index, and Disease Activity Score on 28 Joints (148). Furthermore, patients

with PsA with FM had significantly poorer sleep quality, greater fatigue, and lower quality of life (146, 147). Of note, the FM PsA group had also a significantly higher body mass index, which is another factor potentially influencing clinical response to treatment (17). Patients with PsA with FM receiving biologic treatments may also have a significantly lower response rate than those without FM at all time points in terms of both DAPSA remission and minimal disease activity (145). Interestingly, the time to discontinuation of the first and second biologic drugs was also far shorter in patients with PsA with versus without FM, with the FM diagnosis doubling the risk of discontinuing treatment (145).

Fibromyalgia may also affect patient-reported outcomes, such as the Health Assessment Questionnaire Disability Index (HAQ-DI) and the 12-item PsA Impact of Disease Questionnaire (PsAID-12). Several authors agree that patients with FM PsA have higher (worse) HAQ-DI scores than those without PsA (145, 147). The presence of a coexisting FM might also influence PsAID-12 interpretation (149). Fibromyalgia has long been considered a non-inflammatory rheumatic disease, but multiple recent studies have brought to light the possible role of inflammation in FM pathogenesis (150). Immunologic alterations are added to genetic, hormonal, environmental, and neural factors and can contribute to the development of an inflammatory state (151). Interestingly, a very recent genetic study investigated the gene expression profile in patients with FM, finding that most of modulated genes belonged to the IL-17 pathway and to the type I IFN signatures, suggesting an autoimmune component for this disease (152). These data corroborate the findings of increased serum levels of pro-inflammatory cytokines, such as IL-1, IL-6 and IL-17, found in patients with FM (153). All of these cytokines are known to be involved in the neuroinflammation contributing to pain also found in inflammatory arthritis, including PsA. For example, IL-1 induces sensory neural sensitization to pain, probably trough tyrosine kinases (154); IL-6 is released by hepatocytes during pain stimuli and by neurons and glial cells and has been associated to hyperalgesia, depression, fatigue and sympathetic nervous system activation (153); and IL-17 modulates pain by increasing nociceptor excitability (155). This has empowered the idea of targeting pro-inflammatory cytokines as a potential therapy for FM; however there are no data currently available in the literature on the possible use of biological drugs in this condition. A key mechanism behind FM and chronic pain is believed to be central sensitization (CS). CS is a phenomenon of synaptic plasticity and increased neuronal responsiveness involving the central nervous system (CNS) (156). CS is typically characterized by activation of glia cells and astrocytes with release of cytokines and chemokines, and accumulating evidence suggests that this neuroinflammation process promotes chronic widespread pain in the body via CS (156). Activation of glia cells and astrocytes in neuroinflammation occurs via activation of the intracellular JAK/STAT signaling pathway (157); this pathway has a pleiotropic effect in the context of CNS, being involved in the regulation of multiple neural functions (158). Several pre-clinical data described the role of this pathway in amplification of pro-inflammatory cytokines implicated in neuropathic pain (154), and the new generation of JAK inhibitors demonstrated rapid pain relief (159). Given the role of this pathway and their dependent and independent cytokines in CS, it is possible to speculate a positive effect of JAK inhibitors on central chronic pain and, thus, FM symptoms, although further studies are needed to demonstrate this hypothesis.

CONCLUSIONS

Psoriatic arthritis is a multifaceted disease encompassing different domains and is associated with several comorbidities that must be considered in the clinical management of patients. The systemic inflammation involved in the musculoskeletal domain plays a major role in EAMs and comorbidities. Current available immunomodulatory treatments can have a multilayered, *yin and yang* effect, which underscores the need for therapies with a more comprehensive disease target.

AUTHOR CONTRIBUTIONS

LN: conceived the work, reviewed the literature, and wrote the manuscript. EL, FI, VV, and FP: reviewed the literature and wrote the manuscript. FM and GC: critically contribute to the idea development, reviewed, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

AbbVie participated in the design of the project, as well as in interpretation of the data, review, and approval of the publication.

ACKNOWLEDGMENTS

We would like to thank Ralph Lippe and Erin Blondell from AbbVie for their critical suggestions and support.

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Conflict of Interest: FM, LN, and GC, are AbbVie employees and may own AbbVie stocks/options. FI has received consultancy fees and/or speaker honoraria from Actelion, Pfizer, AbbVie, Janssen, Celgene, Novartis, MSD, BMS, UCB, Sobi, Roche, Sanofi outside this work.

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

frontiers in Medicine

MINI REVIEW
published: 08 October 2021
doi: 10.3389/fmed.2021.742713

Update on Cardiovascular Risk and Obesity in Psoriatic Arthritis

Julio Ramírez, Ana Belén Azuaga-Piñango, Raquel Celis and Juan D. Cañete*

Arthritis Unit, Department of Rheumatology, Hospital Clínic, Barcelona, Spain

PsA is characterized by a high prevalence of cardiovascular (CV) comorbidities. Recognizing these comorbidities is critical due to their influence on the quality of life and the choice of therapy. Imaging techniques also play an important role in the evaluation of the CV risk in psoriatic disease, improving the prediction of CV events when combined with clinical scores as a predictive tool. Meta-analyses point to a significant reduction in the incidence of CV events associated with the suppression of inflammatory activity when using systemic therapies. Consequently, the mortality rate in PsA patients has fallen in the last 40 years and is now similar to that of the general population, including cardiovascular causes. Obesity is an especially relevant CV comorbidity in patients with psoriatic disease, most of whom are overweight/obese. Body mass index (BMI) is a risk factor for PsA and a causal relationship with psoriasis has been demonstrated by Mendelian randomized studies. The study of fat distribution shows that patients with psoriasis are characterized by visceral fat accumulation, which correlates with CV risk measurements. These findings suggest that approaches to the prevention and treatment of psoriatic disease might come from targeting adiposity levels, in addition to the immune pathways. Weight loss treatment with low energy diets in patients with PsA has been associated with significant improvements in disease activity. Novel strategies using a multimorbidity approach, focused more on patients outcomes, are necessary to better address comorbidities, improve clinical outcomes and the quality of life of patients with psoriatic disease.

Keywords: psoriatic arthritis, comorbidities, obesity, cardiovascular risk, psoriasis

OPEN ACCESS

Edited by:
Ilenia Pantano,
University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Arti Mahto,
King's College Hospital NHS Foundation Trust, United Kingdom
Marco Fornaro,
University of Bari Aldo Moro, Italy

****Correspondence:***
Julio Ramírez
julramga@gmail.com

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *16 July 2021*
Accepted: *13 September 2021*
Published: *08 October 2021*

Citation:
Ramírez J, Azuaga-Piñango AB, Celis R and Cañete JD (2021) Update on Cardiovascular Risk and Obesity in Psoriatic Arthritis. Front. Med. 8:742713. doi: 10.3389/fmed.2021.742713

INTRODUCTION

Psoriatic arthritis (PsA) is one of the most common chronic inflammatory conditions, with a prevalence of 0.3–1% in the general population (1). PsA affects up to 30% of patients with psoriasis and leads to severe physical limitations and disability (2). In addition to skin and joint involvement, PsA is characterized by a high prevalence of comorbidities. More than half of PsA patients have $\geq$1 comorbidity (3), which have a significant negative impact on the quality of life. Recognizing and addressing comorbidities are critical to safely and effectively treating PsA patients as they often have implications not only for physical function and the quality of life but also the choice of therapy. For instance, obesity, hypertension, and a Charlson comorbidity index >1 are prognostic factors for worse treatment outcomes (4).

Despite advances in PsA therapy over the past 20 years, current outcomes are far from those achieved in psoriasis. The traditional approach to comorbidities is a part of the problem, as they are not considered in disease activity indexes, despite influencing inflammatory parameters such

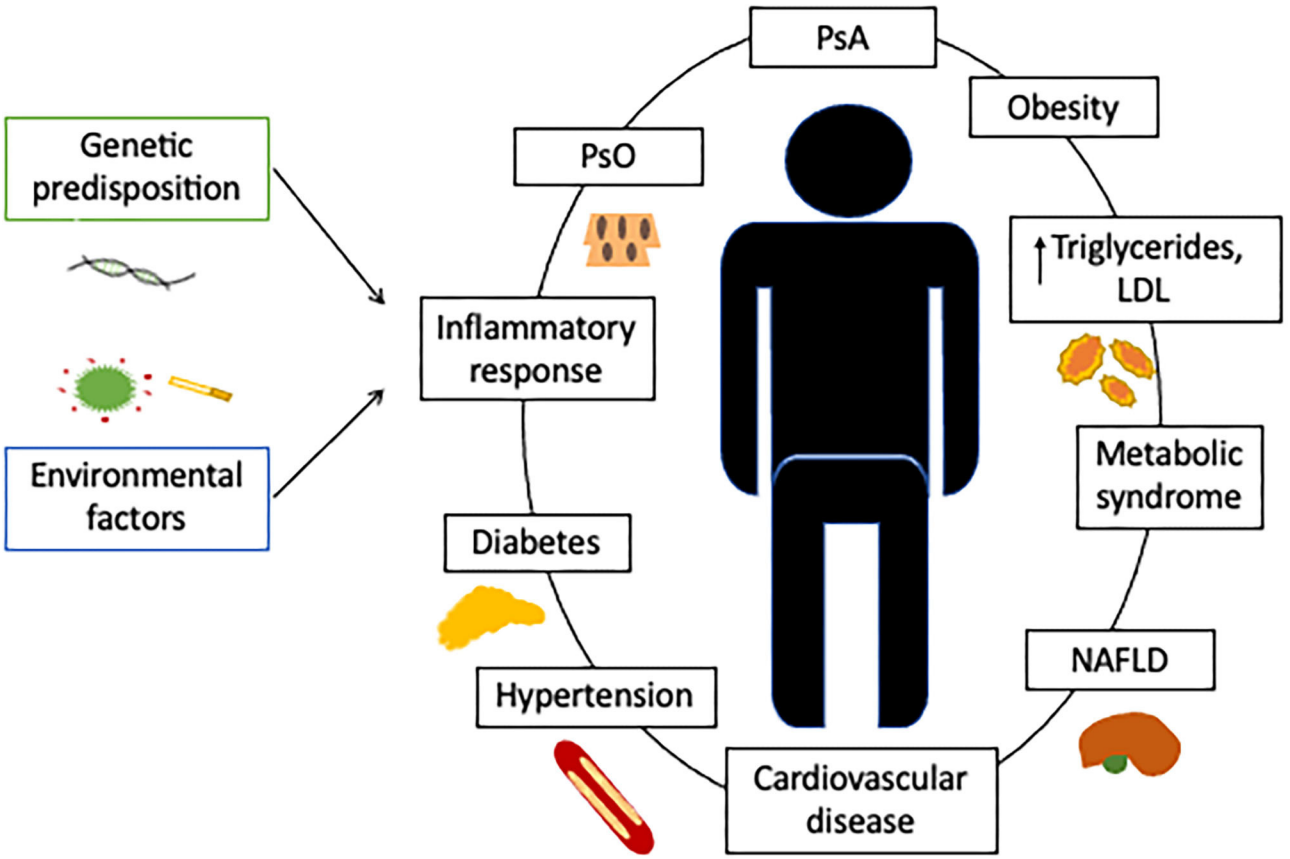

FIGURE 1 | Cardiovascular comorbidities in patients with psoriatic arthritis. Although PsA can be associated with a higher prevalence of cardiovascular risk factors, these conditions do not fully account for the greater incidence of cardiovascular events. Associated factors, such as chronic systemic inflammation, a predisposing genetic background, or the baseline treatment, must contribute to the higher cardiovascular risk. Comorbidity is defined as the existence of any additional entity during the clinical course of a patient who has the index disease under study, such as PsA. In the comorbidity concept, the management and treatment are primarily focused on the index disease and the effect quantified by evaluating the disease activity. In the multimorbidity concept, the patient is of central concern and all coexisting diseases are of equal importance with interactions between each other. In the multimorbidity concept, the management and treatment focus on the patient and effectiveness is quantified by overall indicators such as quality of life or physical function (5). This new approach compels us to tackle with PsA patients from a multidisciplinary perspective. PsO, psoriasis; PsA, psoriathic arthritis; LDL, Low-density lipoprotein; NAFLD, Nonalcoholic fatty liver disease.

as C-reactive protein (CRP) and subjective scores (pain and general assessment). In contrast, the multimorbidity approach treats the patient as the central concern and all coexisting diseases and their interactions are of equal importance. In this model, management and treatment are focused on the patient and effectiveness is quantified by overall indicators such as the quality of life and physical function (5) (**Figure 1**).

Abbreviations: bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C-recative protein; CT, computerized tomography; CV, cardiovascular; DMARDs, disease-modifying antirheumatic drugs; DXA, dual energy X-ray absorptiometry; IL, interleukin; MACE, major adverse cardiovascular events; MRI, magnetic resonance imaging; PsA, psoriatic Arthritis; RA, rheumatoid arthritis; SMR, standardized mortality ratio; TNFi, tumor necrosis factor-alpha inhibitor.

PREVALENCE OF CARDIOVASCULAR COMORBIDITIES IN PSORIATIC ARTHRITIS

The prevalence of comorbidities associated with cardiovascular (CV) risk, such as hypertension or hyperlipidemia in PsA, varies geographically. Extensive data from American cohorts show that almost half of PsA patients have hypertension or hyperlipidemia and up to 20% have diabetes mellitus, while the prevalence of chronic ischemic heart disease is >11% (6). The rate of comorbidities, especially those related to CV risk, are lower in European countries, as recently shown in a Mediterranean cohort, where the prevalence of hypertension, hyperlipidemia and chronic ischemic heart disease were 39, 19.1, and 5.5%, respectively (7), suggesting marked geographic differences. A diverse genetic background and different diets

are hypothetical explanations. Additional data from retrospective Taiwanese cohorts found an association between psoriasis and cerebrovascular disease [Hazard Ratio (HR) 1.27 (95% CI 1.05-1.52) for ischemic stroke (8) and HR 1.28 (95% CI 1.16–1.41)] for general cerebrovascular disease (9). Moreover, a cross-sectional study from Japan found an association with coronary heart disease [Odds ratio (OR) 1.27 (95% CI 1.01–1.58)] in patients with psoriasis (1197) vs. Hospital-based population (113,065) (10), demonstrating a higher CV risk also in Asian population.

CARDIOVASCULAR COMORBIDITIES, HOSPITALIZATION, AND MORTALITY IN PSORIATIC ARTHRITIS

Studies on all-cause mortality revealed mixed results, in part due to differences in PsA definition, patient population, disease duration, study design and therapy. In general, earlier cohorts showed an increased mortality compared with more recent studies (11, 12). In a Canadian PsA cohort with nearly 40 years of follow-up, the major causes of death included malignant neoplasms and acute myocardial infarction, but no disease was above the rate in the general population (13). A longitudinal cohort study performed in the United Kingdom evaluated the cause-specific mortality in patients with PsA compared with the general population and RA patients, finding that suicide (HR 3.03), but not CV (HR 1.09, 95% CI 0.91–1.32) deaths were elevated in PsA patients (14). In contrast, the results of another British study cohort of severe PsA receiving tumor necrosis factor inhibitors (TNFi) from 2002 to 2012 showed that all-cause mortality was increased (Standardized Mortality Ratio [SMR] 1.56; 95% CI 1.12–2.11). Death from malignancy did not increase, but death from coronary heart disease was higher than in the general population (SMR 2.42; 95% CI: 1.11–4.59) (15).

A retrospective US-based claims study with nearly 15,000 PsA patients and 35,037 matched controls found that PsA patients had higher incidence rates of CV disorders (hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease and peripheral vascular disease) and a higher rate of hospitalization due to CV disease than controls (general CV diagnosis: 14.4 vs. 9.4%, $p < 0.05$; coronary disease as primary diagnosis: 0.8 vs. 0.5%, $p < 0.001$) (16), although mortality rates were not analyzed.

SUBCLINICAL ATHEROSCLEROSIS IN PSORIATIC ARTHRITIS

In addition to a higher incidence of CV risk factors, up to half of PsA patients have imaging evidence of atherosclerosis without traditional CV risk factors (12, 17). The relationship between subclinical atherosclerosis and PsA is complex, and traditional risk factors may not entirely explain the accelerated atherosclerotic process in these patients. Other mechanisms (i.e., inflammatory and immunological) have been proposed to explain the relationship between PsA and atherosclerosis. Chronic inflammation, which accelerates the atherosclerotic process, is believed to contribute to this increased risk (18, 19). Accordingly, suppression of inflammatory activity using treat-to-target strategies has a protective effect against plaque progression and atherosclerosis, as has been shown in rheumatoid arthritis (RA), psoriasis and PsA studies (20). In a recent study in 101 patients with PsA, achieving sustained minimal disease activity had a protective effect against plaque progression, as evaluated with carotid ultrasound, a finding independent of biologic disease-modifying anti-rheumatic drugs (bDMARDs) use, suggesting that controlling disease activity may be useful in improving the CV risk in these patients (21). Accelerated coronary plaque formation in PsA patients, particularly mixed plaques, was found on 64-slice coronary CT angiography. This accelerated process was independent of metabolic disease, suggesting disease activity and PsA severity may predict the burden of coronary plaque better than traditional risk factors (22). Taken together, imaging techniques play an important role in the evaluation of CV risk in psoriatic disease. The burden of carotid atherosclerosis, as estimated by carotid ultrasound, can improve the prediction of CV events, when combined with the Framingham risk score as a predictive tool (23).

GLOBAL CARDIOVASCULAR RISK IN IMMUNO-MEDIATED DISEASES

It is known that RA patients have a higher incidence of major cardiovascular events (MACE) and a higher mortality rate than the general population. However, it is not clear whether the CV risk is also higher in psoriatic disease. The prevalence of traditional CV risk factors is higher in psoriatic disease but it is unclear whether this leads to excess mortality and whether PsA should be considered an independent risk factor for CV events such as RA or systemic lupus erythematosus (24, 25).

A British population-based study of MACE in immune-mediated diseases identified psoriatic disease as an independent risk factor for MACE, including myocardial infarction and stroke, although this was only significant in psoriasis and PsA patients not prescribed a disease-modifying anti-rheumatic drug (DMARD). The odds of MACE in RA patients were 39 and 58% higher than in the general population in DMARD and non-DMARD-treated RA patients, respectively (26).

Taking all the evidence into account, RA should be included in the SCORE scale as an independent factor for CV events. Psoriatic disease should be considered as having the same risk as RA, especially psoriatic disease with severe skin involvement (26). PsA, mild skin psoriasis and inflammatory bowel disease should be probably placed on a lower level, with a hypothetically-lower risk of CV events (24, 25) (**Figure 2**), although the evidence is not clear on this point.

CARDIOVASCULAR RISK MODIFICATION WITH SYSTEMIC THERAPIES IN PSORIATIC DISEASE

Meta-analyses show a significant reduction in the incidence of CV events associated with suppression of inflammatory activity using conventional DMARDs (RR 0.72, 95% CI 0.57–0.91 for

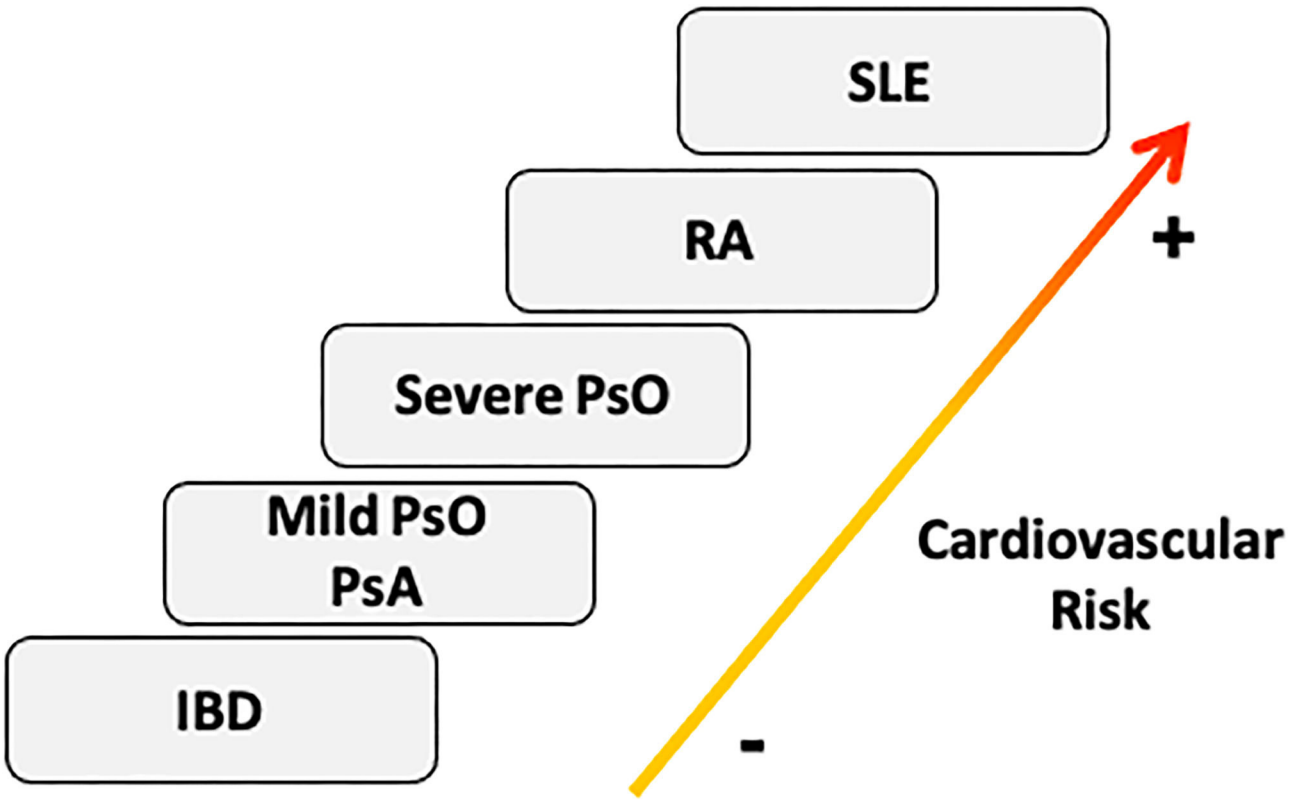

FIGURE 2 | Cardiovascular risk stratification in Immunomediated diseases. According to the prevalence of cardiovascular risk factors and the incidence of cardiovascular events, we should consider SLE as the IMID with highest cardiovascular risk burden, followed by RA, PsO, PsA, and IBD (20). The severity of skin involvement could be essential to classify the cardiovascular profile of psoriatic disease (21). IBD, inflammatory bowel disease; PsA, psoriatic Arthritis; PsO, Psoriasis; RA, Rheumatoid Arthritis; SLE, systemic lupus erythematosus.

methotrexate) or TNFi (RR 0.70, 95%CI 0.54–0.90) in PsA (27). The use of TNFi in RA was shown to reduce the risk of MACE over 8 years (28). Although there is increasing evidence that TNFi may be associated with a reduced risk of CV disease in patients with PsA, data on other biologic treatments are largely lacking.

A large study of 60,028 patients with psoriasis or PsA found no overall differential risk of incident atrial fibrillation and a composite CV endpoint of MI, stroke, and coronary revascularization associated with the use of ustekinumab (interleukin [IL]-12/IL-23 inhibitor) vs. TNFi (29). Ustekinumab has been shown to reduce systemic and vascular inflammation measured using ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) in patients with moderate to severe psoriasis achieving a PASI 75 response (30).

Given the efficacy of secukinumab and other anti-IL17 agents on the skin and musculoskeletal manifestations of psoriatic disease (31–34) and the lack of data on the effect of anti-IL17 on CV risk markers in psoriasis, the CARIMA (Evaluation of cardiovascular risk markers in psoriatic patients treated with secukinumab) study was designed to explore the effects of secukinumab on CV risk markers in patients with psoriasis. Flow-mediated dilation (FMD), a measure of endothelium-dependent control of vascular tone, was assessed as a parameter of vascular endothelial function and an early predictor of the CV prognosis. After one year of therapy, there was a 2% (p=0.002) improvement in FMD with 300 mg of secukinumab with no proatherogenic vessel wall changes or alterations in CV markers, indicating that IL17 inhibition might have a beneficial effect on the CV risk by improving the endothelial function of patients with plaque psoriasis (35). Whether this protective effect might also be seen in PsA remains unclear.

INCREASED WEIGHT/BODY MASS INDEX AND OBESITY IN PSORIATIC ARTHRITIS

Obesity is a major health problem worldwide and one of the biggest public health challenges to emerge in recent decades (36). A high proportion of patients with PsA are overweight (BMI >25) or obese (BMI>30) (37). An analysis of the CORRONA (Consortium of Rheumatology Researchers of North America) database found patients with PsA were a mean of 7.7 Kg heavier than patients with RA. Comparing the BMI in PsA (n = 5

644), psoriasis ($n = 5\ 448$), RA ($n = 5\ 350$), and the general population, the percentages with obesity were 37, 29, 27, and 18% respectively and the odds of obesity were 61% higher for patients with PsA (38).

Obesity is an independent factor for not achieving a therapeutic response in patients with psoriasis and PsA. A reduction in the clinical response has been found, especially for TNFi therapy, as shown by several studies and a recent meta-analysis (39), which found the odds of failing with TNFi therapy were almost two-fold higher for both psoriasis and PsA patients with obesity.

OBESITY AS A RISK FACTOR FOR PSORIASIS AND PSORIATIC ARTHRITIS

Association between higher BMI and psoriasis has been shown by many observational studies (40). Recently, mendelian randomized analyses have provided evidence that a higher BMI increases the odds of psoriasis by 9% per 1 unit increase in BMI, but not the other way around (41). This implies that excess adiposity is part of the reason for some individuals developing psoriasis. Leptin can increase keratinocyte proliferation and proinflammatory protein secretion, which are characteristic of psoriasis (42), while the secretion of adiponectin, which is putatively anti-inflammatory (43), is reduced in obese persons. The skin of obese individuals shows features of impaired barrier function (44), while impairment in lymphatic function may delay the clearance of inflammatory mediators (45). Although further detailed study is required, these findings suggest that approaches to the prevention and treatment of psoriasis might include targeting adiposity levels, in addition to immune pathways in the skin. Although these results imply that such interventions may be effective in the prevention of psoriasis, it has not be determined whether would be effective in improving the disease course after onset.

Obesity could also be a key factor in the transition from skin psoriasis to PsA. Several studies suggest obesity is a risk factor for both psoriasis and PsA. A cohort study by Love et al., which was conducted using an electronic database of medical records representative of the general UK population, with a 15-year time horizon, found the incidence rates of PsA increased in tandem with BMI, both in the 75,395 people with psoriasis and in the general population (almost 2 million) (46). Li et al. analyzed information on BMI, weight change and measures of central obesity in participants in the US Nurse Health Study II (89,049 women) with a 14-year time horizon and found that BMI was monotonically associated with an increased risk of incident PsA. Moreover, there was a graded positive association between weight change from 18 years of age onwards and measures of central obesity, and the risk of PsA. A similar association was found in participants developing psoriasis during the follow-up (47). These studies offer valuable new information on the link between obesity and PsA and provide a potential opportunity to reduce the occurrence of PsA by encouraging a reduction in weight, a modifiable risk factor (48).

FAT MASS DISTRIBUTION IN PSORIATIC DISEASE

Another important issue is the way that fat mass is distributed in the body. Studies on adiposity in PsA and psoriasis generally refer to anthropometric measurements such as BMI, but this does not accurately reflect the visceral fat mass. Using dual energy X-ray absorptiometry (DXA), Toussirot et al. studied body composition and fat distribution (android and visceral fat) in patients with psoriasis and PsA. They found that patients with psoriasis are characterized by visceral fat accumulation, whereas the amount of fat in this region did not differ between PsA patients and controls. Furthermore, visceral adiposity in psoriasis correlated with CV risk measurements, such as SCORE (49).

Magnetic resonance imaging (MRI) may be the most accurate method of measuring the body composition. On MRI, PsA patients showed significantly greater visceral adipose tissue volume and liver fat percentage compared with matched metabolic disease-free controls, whereas the thigh muscle volume was lower. The authors concluded that body fat distribution in PsA is more in keeping with the pattern observed in type 2 diabetes and is more closely associated with cardiometabolic disease (50). These data support the need for a greater emphasis on weight loss in PsA management.

WEIGHT LOSS INTERVENTIONS AS PART OF THERAPEUTIC STRATEGIES IN PSORIATIC ARTHRITIS

The concept of losing weight as an effective measure to improve outcomes in PsA has recently been tested. In 41 patients with PsA and obesity, weight loss treatment with very-low energy diets (640 Kcal/day for 12–16 weeks, followed by a structured reintroduction of an energy-restricted diet) resulted in a median weight loss of 18.6% and was associated with significant improvement in disease activity in the joints, entheses and skin at 6 months. Greater weight loss resulted in improvements in a dose-response manner. The treatment was effective, safe and well tolerated. In addition, an association between higher BMI and increased disease activity at baseline was demonstrated (51). After two years follow up, some PsA patients regained weight, but disease activity outcomes were maintained, and the number of patients with minimal disease activity increased from 28.2% at baseline to 45.7% at 24 months. The weight loss was also associated with improved levels of serum lipids, glucose and urate and antihypertensive treatment was reduced or stopped in several patients during the follow up (52). These results support the findings of previous studies showing better responses to TNFi and greater odds of achieving minimal disease activity after a 5% weight loss (53). Taken together, it seems that active weight loss strategies could be a choice in every PsA patient with overweight/obesity.

Whereas, TNFi are less effective in obese patients, new therapeutic options, such as ustekinumab 90 mg, seem to achieve the same clinical response regardless of the patient's weight, as shown in the *post-hoc* analysis of the PSUMMIT trials in PsA (54).

Similarly, secukinumab seems efficacious irrespective of body weight in psoriasis clinical trials, especially at a dose of 300 mg (55). Pooled analysis of clinical trials of tofacitinib in PsA show higher efficacy than placebo at month 3 across all baseline BMI categories. However, like TNFi, reduced efficacy was generally observed in tofacitinib-treated and placebo-treated patients with baseline BMI $\geq$ 35 compared with patients in the other baseline BMI categories (56).

The reason why TNFi and JAK inhibitors have reduced effectiveness in patients with obesity compared with other drugs are unclear; however, pharmacokinetic properties, the volume of distribution and lipophilicity may be contributing factors (57).

Accordingly, current guidelines for the treatment of PsA recommend weight loss in overweight and obese patients to potentially improve pharmacologic responses (58, 59).

DISCUSSION

Psoriasis and PsA are strongly associated with obesity and CV risk factors. Obesity increases the risk of psoriasis and PsA and is associated with greater disease activity, poorer treatment response and a lower chance of achieving minimal disease activity. Patients with PsA also have an increased risk of CV disease. Chronic inflammation, which accelerates the atherosclerotic process, in combination with a higher prevalence of CV risk factors is believed to contribute to this increased risk. Direct interventions with systemic therapies decrease inflammatory activity and potentially reduce the incidence of CV events.

There is an urgent need to improve the primary and secondary prevention of CV disease in patients with psoriasis and PsA. Lifestyle changes should be actively encouraged; risk stratification should be adjusted in patients with psoriasis and PsA; and correct pharmaceutical interventions should be introduced, and their effectiveness monitored. Physicians caring for patients with psoriasis and/or PsA should play an active role in achieving these goals in collaboration with general practitioners and cardiologists.

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

We thank David Buss for editorial assistance.

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frontiers in Medicine

BRIEF RESEARCH REPORT
published: 01 November 2021
doi: 10.3389/fmed.2021.748262

Prevalence of Depressive Symptoms in Patients With Psoriatic Arthritis: Have Numbers Changed During the COVID-19 Pandemic?

Matthias Englbrecht[1], Peter Bartz-Bazzanella[2], Cay von der Decken[3], Georg Gauler[4], Patrick Wurth[4], Peer Aries[5], Kirsten Karberg[6], Christoph Kuhn[7], Florian Schuch[8], Susanna Späthling-Mestekemper[9], Wolfgang Vorbrüggen[10], Jörg Wendler[8], Martin Welcker[11] and Stefan Kleinert[8,12]*

[1] Freelance Data Scientist, Eckental, Germany, [2] Medizinisches Versorgungszentrum Stolberg, Stolberg, Germany, [3] Klinik für Internistische Rheumatologie, Rhein-Maas-Klinikum, Würselen, Germany, [4] Rheumatologische Schwerpunktpraxis, Osnabrück, Germany, [5] Rheumatologie im Struenseehaus, Hamburg, Germany, [6] Praxis für Rheumatologie und Innere Medizin, Berlin, Germany, [7] Praxis für Rheumatologie, Karlsruhe, Germany, [8] Praxisgemeinschaft Rheumatologie-Nephrologie, Erlangen, Germany, [9] Rheumatologist in Group Practice, Munich, Germany, [10] Verein zur Förderung der Rheumatologie eV, Würselen, Germany, [11] Medizinisches Versorgungszentrum für Rheumatologie Dr M Welcker GmbH, Planegg, Germany, [12] Medizinische Klinik 3, Rheumatology/Immunology, Universitätsklinik Würzburg, Würzburg, Germany

This longitudinal analysis compares the prevalence of depressive symptoms in patients with psoriatic arthritis in the context of the COVID-19 pandemic. Data from a national patient register in Germany were analyzed regarding the Patient Health Questionnaire 2 (PHQ-2) to identify cases suspicious for depression at two time points, i.e., before and during the COVID-19 pandemic. Only patients with complete concurrent information on the Disease Activity in Psoriatic Arthritis Score (DAPSA) were included in the analysis. The frequency of depressive symptoms in psoriatic arthritis patients during the COVID-19 pandemic did not differ from the prevalence rates measured before. In addition, prevalence rates for depressive symptoms did not differ when stratifying the patient sample for DAPSA levels of disease activity measured before the pandemic. These results were confirmed further in a sensitivity analysis, limiting the second PHQ-2 assessment to lockdown periods only. However, longitudinal data on the prevalence of depressive symptoms in patients with rheumatic diseases, in general, and psoriatic arthritis, in particular, are scarce in the context of the COVID-19 pandemic. For a sensible comparison of prevalence rates for depressive symptoms in the future, underlying SARS-CoV-2 infection rates and resulting local healthcare disruptions need to be taken into account, besides the potential use of different depression screening tools to evaluate resulting numbers sensibly and draw corresponding conclusions for patient care.

Keywords: arthritis, psoriatic arthritis, depressive symptoms, COVID-19, SARS-CoV-2, depression

OPEN ACCESS

Edited by:
Piero Ruscitti,
University of L'Aquila, Italy

Reviewed by:
Vincenzo Venerito,
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Debanjali Sinha,
Institute of Neurosciences Kolkata (I-NK), India
Gianluca Bagnato,
University of Messina, Italy

****Correspondence:***
Matthias Englbrecht
pmanagement@statscoach.de

Specialty section:
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

Received: *27 July 2021*
Accepted: *08 October 2021*
Published: *01 November 2021*

Citation:
Englbrecht M, Bartz-Bazzanella P, von der Decken C, Gauler G, Wurth P, Aries P, Karberg K, Kuhn C, Schuch F, Späthling-Mestekemper S, Vorbrüggen W, Wendler J, Welcker M and Kleinert S (2021) Prevalence of Depressive Symptoms in Patients With Psoriatic Arthritis: Have Numbers Changed During the COVID-19 Pandemic? Front. Med. 8:748262. doi: 10.3389/fmed.2021.748262

INTRODUCTION

Depression is acknowledged as frequent comorbidity in inflammatory arthritis (1–4). Psoriatic arthritis (PsA) is one of the diseases summarized under the "inflammatory arthritis" label, with reported prevalence rates for depression of about 13–20% (1, 2). PsA is found in 0.1–1% of the general population and is particularly frequent in patients with psoriasis (∼20%) involving the skin, nails, joints, and entheses (5). PsA patients typically face a combination of dermal and musculoskeletal symptoms impacting the health-related quality of life and social life, resulting in everyday minor and major challenges. Accordingly, recommendations for rheumatologists and dermatologists to screen and manage PsA patients regarding the underlying risk of depression were developed (6). However, regular depression screening has not been implemented into routine rheumatology care yet to help identify patients needing professional mental healthcare support. While depression screening still needed broader implementation into rheumatology care, another challenge occurred in December 2019 caused by a new coronavirus strain (SARS-CoV-2), later referred to as COVID-19. With its global spread and despite the successful initial containment of the first SARS-CoV-2 cases in late January 2020, the first wave eventually hit Germany in early March 2020, resulting in a first national shutdown by March 22nd. The temporal unavailability of face masks further stressed the situation for healthcare professionals and patients in Germany. Although resident rheumatologists and hospitals had taken quick action to refine sanitation and hygiene protocols to reduce SARS-CoV-2 infection risk for staff and patients as far as possible, many routine consultations had to be canceled and postponed. Similar and even more severe disruptive changes in rheumatology care were reported among patients with rheumatic and musculoskeletal diseases in the United States and other European countries (7, 8). In a corresponding qualitative analysis of reported perceptions given by patients referring to the pandemic, the following key themes were identified: emotions in response to the pandemic, perceptions of risks from immunosuppressive medications, protective measures to reduce risk of SARS-CoV-2 infection, and disruptions in accessing rheumatic disease medications (7). Given underlying health concerns, PsA patients perceived SARS-CoV-2 as a larger threat to their health than patients with psoriasis, whereas patients on biologics were more concerned about SARS-CoV-2 and potential outcomes of a SARS-CoV-2 infection (9). Importantly, if health concerns remain unaddressed over a longer time, disregarded feelings of helplessness may lead to depression. Systematic reviews and meta-analyses have consequently reported a high prevalence of depression in the general population, in (front-line) healthcare professionals, and patients diagnosed with SARS-CoV-2 during the pandemic (10–14). However, longitudinal data on this topic are scarce and, thus, little is known about whether the prevalence of depressive symptoms in PsA patients has increased during the COVID-19 pandemic. This retrospective analysis of PsA patient data aims to add some information to this gap and addresses whether depressive symptoms were more frequent during the COVID-19 pandemic than they were before.

METHODS

Patient Sample and Setting

Routine clinical data from patients with an established diagnosis of PsA coming from eight centers in Germany participating in the RheumaDatenRhePort (RHADAR) register were included. RHADAR is a real-world longitudinal register for adult patients with rheumatic diseases in Germany. After informed consent, patients' pseudonymized data are added to the database. For this report, patients having consented until March 31st, 2021, were part of the data analysis. Further details on the RHADAR register can be found elsewhere (15). Symptoms of depression were assessed using the Patient Health Questionnaire-2 (PHQ-2), a brief two-item depression screening tool, which had previously been validated in patients with rheumatoid arthritis, demonstrating good sensitivity and specificity (16, 17). The PHQ-2 sum score ranges from 0 (best) to 6 (worst), with scores $\geq$ 3 indicating depressive symptomatology. The RHADAR database was queried for patients who had had a first PHQ-2 assessment in the 12 months preceding the confirmation of the first SARS-CoV-2 cases in Germany (T1: January to December 2019, first SARS-CoV-2 cases in Germany: January 27th 2020) and had another assessment during the pandemic, i.e., after the first national lockdown taking effect on March 22nd 2020 (T2). If multiple PHQ-2 assessments for T1 were available, the first of them was chosen. The second assessment was supposed to be including PsA patients whose appointments had previously been postponed to cover changes in affective mood, resulting from potential healthcare disrupting effects. In addition, all patients included had to have an assessment of the Disease Activity in Psoriatic Arthritis Score (DAPSA) corresponding to each PHQ-2 assessment (18). Additional sample characteristics include information on sex, age, disease duration, the Hannover Functional Ability Questionnaire (HFAQ) as a measure of physical functioning, which is equivalent to the Health Assessment Questionnaire Disability Index (HAQ-DI), the Body Surface Area (BSA) for skin involvement, and anti-rheumatic treatment, aggregated by drug class (19). Besides the RHADAR inclusion criteria and the mandatory availability of data on PHQ-2 and DAPSA before and during the SARS-CoV-2 pandemic, no further inclusion or exclusion criteria were applied.

Statistical Data Analysis and Analysis Software

Descriptive characteristics of quantitative variables are presented as mean ± standard deviation and as absolute frequencies (per cent) for nominal data if not stated otherwise. Data on prescribed medication were aggregated into the following drug classes: conventional-, targeted synthetic-, and biological disease-modifying anti-rheumatic drugs (cDMARDs, tsDMARDs, bDMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids (GCs). Due to combination therapies, the reported total number of prescriptions may exceed the sample size. Missing values were not imputed to preserve the original information of the available raw data. Differences in the prevalence of symptoms of depression and the prescription

frequencies of aggregated standard anti-rheumatic therapies for PsA were investigated by McNemar's tests for paired nominal data, including Yate's correction for continuity. PHQ-2 sum scores were dichotomized using a sum score cutoff ≥ 3, which is the standard threshold to identify cases suspicious for depression. For both time points, before and during the pandemic, the frequencies of the dichotomized PHQ-2 scores were compared. In a subsequent step, this analysis was repeated, stratified for DAPSA levels of disease activity, i.e., ≤ 4 for remission, >4 and ≤ 14 for low disease activity, >14 and ≤ 28 for moderate disease activity and >28 for high disease activity (20). The stratified PHQ-2 analysis as well as the analysis of drug class-specific prescription frequencies were adjusted for multiple comparisons using Bonferroni-Holm correction to control type I error probability. Inferential test results include test coefficient, *p*-value and effect size, i.e., odds ratios with corresponding 95% confidence intervals. McNemar test-related odds ratios were calculated from the division of the off-diagonal cells in the respective contingency table (**Supplementary File**). An additional sensitivity analysis regarding PHQ-2-related outcomes was conducted to investigate whether the choice of the T2 assessment impacted the results. For this analysis, only patients with a second PHQ-2 assessment during lockdown periods were included. The data analysis was conducted using R (version 4.1.0.) and RStudio IDE (version 1.4.1103) (21, 22). $P \leq 0.05$ were considered statistically significant in cases with no multiple testing adjustment.

RESULTS

Description of the Patient Sample

Eighty-nine PsA patients with 48 female patients (53.93%) and 41 male patients (46.07%) were included in the analysis. On average, patients were 54.16 ± 11.66 years of age and had a disease duration of 9.33 ± 9.02 years at T1. Mean T1 DAPSA was 10.38 ± 14.56, suggesting patients had low disease activity on average, whereas the subgroup analysis revealed the following distribution across DAPSA categories: 38 (42.70%) remission, 31 (34.83%) low disease activity, 12 (13.48%) moderate disease activity, and 8 (8.99%) high disease activity. Mean DAPSA at T2 was 7.91 ± 10.31, whereas DAPSA confidence intervals for both time points indicated comparable disease activity (**Table 1**). With potential scores ranging from 0 (worst) to 100 (best), average HFAQ-scores showed mild impairment of physical functioning at both time points (T1: 80.83 ± 21.77, T2: 82.51 ± 20.30). Further descriptive information is presented in **Table 1**.

At T1, cDMARDs were the most frequent drug ($n = 57$, 64.04%), followed by NSAIDs ($n = 45$, 50.56%), bDMARDs ($n = 35$, 39.33%), GCs ($n = 15$, 16.85%), and tsDMARDs ($n = 1$, 1.12%). Complete data on anti-rheumatic medication was available for 88 (98.88%) patients at T1 and 85 (95.51%) patients at T2. Except for GCs [$\chi^2_{(1)} = 7.11$, $p = 0.008$], which were prescribed less frequent at T2 than at T1, prescription frequencies between the time points of interest did not differ (see section 1 of **Supplementary File** for further information). The corresponding odds ratio for GCs could not be calculated as division by 0, given by the contingency table, is undefined. However, the change in the prescription frequency of GCs remained significant after multiple testing adjustments (critical $p_{adj} = 0.01$). Importantly, our results did indicate that neither cDMARDS [$\chi^2_{(1)} = 0.36$, $p = 0.55$, 95%$CI_{OR} = 0.17–1.95$] nor bDMARDs [$\chi^2_{(1)} = 0$, $p = 1.0$, 95%$CI_{OR} = 0.14–7.10$] were prescribed more or less often during the pandemic than before.

Prevalence of Depressive Symptoms

PHQ-2 frequency analysis showed that the majority of the patients in our sample had a PHQ-2 sum score ≤ 2, which is below the cutpoint for an indication of depressive symptoms at both time points (T1: $n = 74$, 83.15%; T2: $n = 76$, 85.39%). A total of 15 (T1) and 13 (T2) patients were found to show depressive symptomatology. Accordingly, the prevalence of symptoms of depression, identified by a PHQ-2 sum score ≥ 3, was 16.85% at T1, and 14.61% at T2, respectively. The corresponding inferential McNemar analysis did not reveal any significant changes regarding depressive symptoms when comparing data from before SARS-CoV-2 to data during the pandemic [$\chi^2_{(1)} = 0.06$, $p = 0.803$, 95%$CI_{OR} = 0.48–3.45$]. Corresponding frequency data even suggested a slight (although non-significant) decrease in prevalence rates. When PHQ-2 data were stratified for DAPSA levels of disease activity, each of the resulting four categories did not indicate any significant changes in prevalence rates for depressive symptoms. With *p*-values ranging from 0.617 to 1.000 and 95% odds ratio confidence intervals encompassing 1, prevalence rates seemed equal over time irrespective of the DAPSA stratification for disease activity. Further details on PHQ-2 test results are shown in **Tables 2**, **3**; contingency tables are shown in section 2 of the **Supplementary File**. The sensitivity analysis reduced longitudinal comparisons only to those patients that had their second assessment during one of the two national lockdowns. The corresponding results confirmed the previous findings, again, suggesting prevalence rates for depressive symptoms before and during the SARS-CoV-2 pandemic to be comparable in our sample [$\chi^2_{(1)} = 0.25$, $p = 0.617$, 95%$CI_{OR} = 0.31–28.84$; $\chi^2_{(1)} = 1.50$, $p = 0.221$, 95%$CI_{OR} = 0.58–42.80$; see section 3 of the **Supplementary File** for corresponding contingency tables].

DISCUSSION

Regarding the prevalence of depressive symptoms identified by the PHQ-2, our results align with the numbers given by recent systematic reviews in PsA (1, 2). Surprisingly, the results of our data analysis suggest depressive symptoms not to occur more often during the SARS-CoV-2 pandemic compared to the 2019 data for patients having completed a depression screening at both time points. Except for GCs, that were prescribed less frequent at T2, our findings showed that anti-rheumatic medication remained unchanged in the vast majority of our sample. Thus, switches of anti-rheumatic medication do not seem to be a reason for the stable prevalence rates. With the help of a sensitivity analysis regarding the choice of the T2 time point, we were also able to show that results remained unchanged when limiting the second assessment to lockdown periods only. However, given the challenges the healthcare system and rheumatologists

TABLE 1 | Descriptive sample characteristics before and during the SARS-CoV-2 pandemic.

	N (valid)	% (valid)	*N* (NA)	% (NA)	Mean	Lower bound 95%CI	Upper bound 95%CI	SD
T1								
Age	89	100.00	0	0.00	54.16	51.74	56.58	11.66
Disease duration (years)	89	100.00	0	0.00	9.33	7.45	11.20	9.02
DAPSA	89	100.00	0	0.00	10.38	7.36	13.41	14.56
TJC (DAPSA)	89	100.00	0	0.00	3.03	1.29	4.77	8.38
SJC (DAPSA)	89	100.00	0	0.00	1.24	0.39	2.08	4.05
NRS Disease Activity (DAPSA)	89	100.00	0	0.00	2.84	2.27	3.41	2.75
NRS Pain (DAPSA)	89	100.00	0	0.00	2.63	2.09	3.17	2.61
CRP	89	100.00	0	0.00	0.64	0.36	0.92	1.35
BSA	29	32.58	60	67.42	0.45	0.12	0.78	0.91
HFAQ	86	96.63	3	3.37	80.83	76.22	85.43	21.77
T2								
Age	89	100.00	0	0.00	55.27	52.85	57.69	11.63
Disease duration	89	100.00	0	0.00	10.44	8.56	12.32	9.06
DAPSA	89	100.00	0	0.00	7.91	5.77	10.05	10.31
TJC (DAPSA)	89	100.00	0	0.00	1.96	0.56	3.35	6.70
SJC (DAPSA)	89	100.00	0	0.00	0.76	0.29	1.24	2.29
NRS Disease Activity (DAPSA)	89	100.00	0	0.00	2.35	1.90	2.79	2.14
NRS Pain (DAPSA)	89	100.00	0	0.00	2.38	1.90	2.87	2.34
CRP	89	100.00	0	0.00	0.46	0.34	0.58	0.58
BSA	16	17.98	73	82.02	0.75	0.29	1.21	0.93
HFAQ	86	96.63	3	3.37	82.51	78.22	86.80	20.30

CI, confidence interval; SD, standard deviation; DAPSA, Disease Activity Psoriatic Arthritis Score; TJC, Tender Joint Count (68 joints); SJC, swollen joint count (66 joints); NRS, Numerical Rating Scale; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; BSA, Body Surface Area; HFAQ, Hannover Functional Ability Questionnaire. T1, January—December 2019; T2, March 22nd 2020–March 31st 2021.

TABLE 2 | Frequency distribution of PHQ-2 sum scores before and during the SARS-CoV-2 pandemic ($n_{total} = 89$).

	T1			T2		
PHQ-2	***n***	**%**	**% (cumulative)**	***n***	**%**	**% (cumulative)**
0	39	43.82	43.82	41	46.07	46.07
1	12	13.48	57.30	11	12.36	58.43
2	23	25.84	83.15	24	26.97	85.39
3	4	4.49	87.64	3	3.37	88.76
4	6	6.74	94.38	6	6.74	95.51
5	1	1.12	95.51	2	2.25	97.75
6	4	4.49	100.00	2	2.25	100.00
≥ 3	**15**	**16.85**	**–**	**13**	**14.61**	

T1, January–December 2019; T2, March 22nd 2020–March 31st 2021. Bold values represent column sums for n and % in the rows with a PHQ-2 score of 3 or higher, i.e., PHQ-2 scores of 3, 4, 5, and 6.

were facing, particularly during the first national lockdown, the corresponding sample sizes were smaller (T2: first lockdown: $n = 18$, T2: second lockdown: $n = 50$). A post-lockdown study confirmed a similar prevalence in patients with inflammatory arthritis and gave a plausible explanation of why depressive symptoms might not occur more frequently during the SARS-CoV-2 pandemic (23). According to Ciaffi et al., patients with inflammatory arthritis showed higher resilience scores than study participants from the general population—independent of the patients' age or disease duration (23). Resilience is a psychological construct implying resistance to environmental risk experiences or overcoming stress or adversity (24). The authors of the study above hypothesize whether higher resilience might result from the necessity for patients to adapt to everyday hassle resulting from inflammatory arthritis, in turn, training their abilities to cope more effectively in challenging situations

TABLE 3 | McNemar tests for dichotomized PHQ-2 scores for the total sample and stratified by initial DAPSA levels at the first assessment before and during the SARS-CoV-2 pandemic.

Matched sample comparison	*n*	χ^2	df	*p*-value	OR	Lower bound 95%CI	Upper bound 95%CI
Total sample	89	0.06	1	0.803	1.286	0.479	3.452
DAPSA—REM (T1)	38	0.25	1	0.617	0.333	0.035	3.205
DAPSA—LDA (T1)	31	0.00	1	1.000	1.000	0.141	7.099
DAPSA—MDA (T1)	12	0.25	1	0.617	3.000	0.312	28.842
DAPSA—HDA (T1)	8	0.25	1	0.617	3.000	0.312	28.842

df, degrees of freedom; OR, odds ratio (effect size); CI, confidence interval; DAPSA, Disease Activity Psoriatic Arthritis Score; REM, Remission (DAPSA ≤ 4); LDA, low disease activity (DAPSA > 4 and ≤ 14); MDA, moderate disease activity (DAPSA >14 and ≤ 28); HDA, high disease activity (DAPSA > 28).

than individuals in the general population (23). Adding to these findings, another study in the U.S. general population revealed that getting outside more often, exercising more often, sleeping better, praying more often, and perceiving social support from friends, family, and significant others were also related to higher resilience (25). Though we did not measure these characteristics, an additional positive effect of these factors seems conceivable in PsA patients, too. However, in contrast to our findings, a multi-national European study including 1,800 patients with rheumatic and musculoskeletal diseases reported a proportion of 45.9% of the participants at risk of depression during the COVID-19 pandemic (8). These results suggest that prevalence rates of depressive symptoms could be more than double the numbers according to our findings. Several reasons may serve as conceivable explanation of this difference: Firstly, the study mentioned above had a different sample composition, including only 9.1% of PsA patients and were given a different depression screening questionnaire returning two outcome categories for depressive symptoms, which were conflated for the analysis (borderline cases and cases suspicious for depression). The PHQ-2 in our analysis returns a single category for depressive symptoms and has no borderline category. These factors make a direct comparison of results difficult and can lead to considerably different prevalence rates. Secondly, the national healthcare systems across Europe are structured differently and were stressed to an individually different degree during the COVID-19 pandemic, depending on the local rate of infection on the one hand and available healthcare resources on the other. The study by Garrido-Cumbrera et al. included participants from several countries such as Spain, Portugal, France, Italy, or the UK which all had peak 7-day case rates per 100.000 that were twice as high as the numbers in Germany, at least (26). Corresponding limited healthcare resources including considerable disruptions having an impact on the availability of necessary (pain-related) medication and patient care are another feasible explanation for the higher prevalence rates of depressive symptoms found in these countries. The implications from this comparison are important to understand the generalizability of the results coming from our analysis. A mere cross-country comparison of numbers reflecting the occurrence of depressive symptoms in the context of the COVID-19 pandemic does not match the complexity of the issue. Data on prevalence rates of depressive symptoms during COVID-19 need to be interpreted in the context of the impact the pandemic had on the availability of healthcare resources in each region or country of interest. For our analysis, we have chosen longitudinal PHQ-2 data from PsA patients including DAPSA as common measure of disease activity in PsA. However, information on psoriatic skin involvement by BSA were only available for a less than a third of the total patient sample. This might reflect rheumatologists' reluctance for an exact skin documentation, limiting comparability to other PsA samples investigating a similar research question to the musculoskeletal component and the more general visual analog scale for patient-reported global assessment. Furthermore, with including 89 patients with sufficient PHQ-2 and DAPSA documentation, our sample might not be generalizable to other countries or patient samples. Baseline PHQ-2 values preceding the T1 assessment were not included in the manuscript given that we felt that a period of 12 months preceding the COVID-19 pandemic for definition of the T1 assessment was sufficient. Regarding DAPSA, the patients in our sample seemed to have milder disease than the norming sample that was used to define DAPSA levels of disease activity by a quartile split (20). This finding may result from the majority of centers contributing data to the RHADAR register being resident rheumatologists adding patients with lower disease activity to the database than hospitals potentially would. However, since we were able to demonstrate, that the prevalence of depressive symptoms remained similar across DAPSA categories and is independent from the choice of timing for the second assessment as well, we consider our results reliable given similar numbers from previous large-scale systematic reviews. Given comparable results regarding 95% confidence intervals of mean PHQ-2 scores of database patients with a single PHQ-2 assessment at T1 (i.e., patients who were not included into the analysis) and the patient sample presented, we assume that patients with a single PHQ-2 assessment at T1 did not show higher depressiveness on average than the patients included into the analysis of this manuscript (95%CI only T1: 1.44–1.68, 95%CI patient sample: 1.04–1.72). Hence, a potential selection bias resulting from a mandatory T1 and T2 documentation as inclusion criterion is unlikely. Unfortunately, longitudinal data for comparing the prevalence of depressive symptoms before and during SARS-CoV-2 are scarce in rheumatology, yet and, thus, would merit further, preferably large-scale data input leading to improved insights of what kind of circumstances still

can be handled by improved resilience capabilities of patients with rheumatic disorders and at which point even these might not suffice to bolster challenges such as those resulting from the pandemic.

In conclusion, our analysis showed similar prevalence rates of depressive symptoms before and during SARS-CoV-2 in PsA patients in Germany, irrespective of the patients' DAPSA category or the timing of the during COVID-19 assessment. To the best of our knowledge, this is the first longitudinal investigation of depressive symptoms in patients with PsA during the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The raw data for this analysis are not openly available given the patients' consent, allowing for the publication of aggregated data only. However, information on aggregated raw data is given in the contingency tables of the **Supplementary Material**. Requests to access these datasets should be directed to pmanagement@statscoach.de.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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

FUNDING

This study was funded by the RHADAR GbR (A Network of Rheumatologists), Bahnhofstr. 32, 82152 Planegg, Germany. RHADAR GbR received honoraria from UCB Pharma GmbH, Sandoz Deutschland/Hexal AG, Lilly GmbH, and Galapagos Biopharma Germany GmbH, and research support from Novartis Pharma GmbH. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

ACKNOWLEDGMENTS

We would like to thank Nils Körber (by Nils Körber and Joachim Elgas GbR, Erlangen) who developed RheumaDok and the RHADAR database. We would also like to thank all the rheumatological specialist assistants supporting the clinical documentation in the participating centers.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.748262/full#supplementary-material

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Conflict of Interest: WV, CD, SK, PB-B, CK, KK, SS-M, PA, and MW are members of RheumaDatenRhePort GbR. RHADAR GbR received honoraria from UCB Pharma GmbH, Sandoz Deutschland/Hexal AG, Lilly GmbH, and Galapagos Biopharma Germany GmbH, and research support from Novartis Pharma GmbH. ME received remunerations from RheumaDatenRhePort GbR for statistical data analyses and consultation for previous projects.

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

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