

Unmet needs in psoriatic arthritis, a narrative review

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ABSTRACT

Psoriatic arthritis is a chronic rheumatic disease that poses challenges in its diagnosis, evaluation, and management. The heterogeneity in the manifestations and the absence of definitive diagnosis biomarkers often complicates the process of accurate diagnosis. Furthermore, the involvement of multiple disease domains poses difficulties in assessing disease activity and defining the concept of remission. Despite therapeutic advancements, a subset of patients remains refractory to treatment, leading to the emergence of the concept of "difficult-to-treat" patients and the necessity for novel therapeutic approaches (e.g., drugs with novel mechanisms of action; combinations of treatments). This review addresses key unmet needs in psoriatic arthritis, in terms of diagnosis, classification, evaluation, comorbidities and treatment.

Keywords: Diagnosis, management, psoriatic arthritis, treatment.

Psoriatic arthritis (PsA) is a chronic rheumatic disease found in approximately 30% of individuals with Psoriasis (PsO).¹ PsA shares both genetic and clinical characteristics with other forms of spondyloarthritis (SpA) and is usually placed under the umbrella of SpA. Moll and Wright described several clinical subtypes of PsA in 1973,² including some which are now considered key subtypes: (i) the oligoarticular subtype, affecting four or fewer joints asymmetrically which is the most frequent in clinical practice; (ii) the polyarticular subtype, involving five or more joints and resembling rheumatoid arthritis (RA), often seen in clinical trials; and (iii) the axial subtype, which primarily involves the spine and sacroiliac joints.

Beyond the usual form of peripheral arthritis with psoriasis, patients may present with nail lesions, enthesitis, dactylitis, axial involvement

and extra-musculoskeletal manifestations, such as inflammatory bowel disease (IBD) and uveitis. This heterogeneity in the clinical picture may pose challenges in the diagnosis and management of this disease.

This review addresses key unmet needs in PsA, in terms of diagnosis, classification, evaluation, comorbidities and treatment.

DIAGNOSIS OF PsA

The heterogeneity in the manifestations and the absence of definitive diagnosis biomarkers often complicates the process of accurate diagnosis. There are no diagnostic criteria available. Currently, the Classification Criteria for Psoriatic Arthritis (CASPAR) are widely used in research and are sometimes also applied in clinical practice (Table 1).³

Table 1. CASPAR classification criteria for psoriatic arthritis

Entry criterion: Articular disease (joint, spine or enthesal)	
	Points
1. Evidence of psoriasis <ul style="list-style-type: none"> • Current psoriasis • Personal history of psoriasis • Family history of psoriasis 	2 or 1 or 1
2. Psoriatic nail dystrophy (pitting, onycholysis, hyperkeratosis)	1
3. Negative test result for rheumatoid factor	1
4. Dactylitis <ul style="list-style-type: none"> • Current dactylitis • History of dactylitis 	1 or 1
5. Radiologic evidence of juxta-articular new bone formation	1

Adapted from Taylor et al.³
CASPAR: Currently, the Classification Criteria for Psoriatic Arthritis; PsA: Psoriatic arthritis. To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine or enthesal) and score ≥ 3 points.

An unmet need is represented by the distinction between PsA and other types of rheumatic articular entities, as well as between PsA and PsA *sine psoriase*. This last entity may represent different profiles of patients, such as an individual with typical PsA who has not yet developed skin psoriasis, a patient who might have a hidden form of psoriasis, or a patient who only has a family history of psoriasis. The heterogenous nature of this disease makes it necessary to differentiate PsA from other conditions, such as RA, osteoarthritis (OA), crystal-induced arthritis and other forms of SpA.¹

Rheumatoid arthritis, particularly seronegative RA, poses challenges in distinguishing it from PsA, as it can resemble the polyarticular subtype

of PsA. RA is characterized by proximal and symmetric synovitis in the joints of the hands and feet but respecting the distal interphalangeal joints (Table 2).

Given that around 15% of PsA patients manifests as monoarticular arthritis at the disease onset,⁴ it might be misdiagnosed as gout or pseudogout. Furthermore, uric acid levels may be also elevated in patients with PsA, complicating the differential diagnosis. The involvement of distal phalangeal joints can also be observed in hand OA. One way to distinguish both diseases is the physical examination. PsA is characterized by painful palpation of distal joints with soft swelling, whereas in OA, the swelling is solid and arises from a bony osteophyte. In addition, PsA with distal phalangeal involvement often coincides with

Table 2. Differential diagnosis for peripheral PsA

	Peripheral PsA	Rheumatoid arthritis	Crystal-induced arthritis	Osteoarthritis
Joint distribution	Asymmetric	Symmetric	Asymmetric	Asymmetric
Number of affected joints	Often oligoarticular	Polyarticular	Mono- or oligoarticular	Mono- or oligoarticular
Distal joints involved	Yes	No	Yes	Yes
Elevated CRP levels	Yes	Yes	Yes	No
Elevated acid uric levels	Common	Uncommon	Common	Uncommon
Erosions in radiographs	Yes	Yes	Yes	No

PsA: Psoriatic arthritis; CRP: C-reactive protein.

nail diseases such as pitting or onycholysis, which are absent in OA (Table 2).

Finally, axial spondyloarthritis (axSpA) (and, specifically, radiographic axSpA, previously termed ankylosing spondylitis) is also difficult to differentiate from PsA with axial involvement. For instance, axial involvement in PsA is characterized by an asymmetrical sacroiliitis (or even the absence of sacroiliitis) with an asymmetric distribution of non-marginal syndesmophytes.⁵ Additionally, back pain may be non-inflammatory or even absent. The onset of axial involvement in PsA typically occurs in the fourth decade, contrasting with axSpA, which typically begins later in the second decade of life or early in the third decade. There is currently a considerable debate about the similarities and differences between both entities, and a study is ongoing under the auspices of the expert groups for PsA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, GRAPPA) and axSpA (ASAS).⁶

Several screening tools and questionnaires have been developed for dermatologists to facilitate early detection of patients with PsA in dermatology consultations. Some examples are the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire,⁷ the Psoriasis Epidemiology Screening Tool (PEST),⁸ the Toronto Psoriatic Arthritis Screening (ToPAS)⁹ and the PURE-4.¹⁰ Because their implementation is incomplete, the early screening of PsA remains an unmet need.¹¹

DISEASE ACTIVITY AND EVALUATION

Disease activity and its evaluation represents an important area of difficulties since no consensus exist on the optimal composite index and on the concept of remission.

The Core Domain Set was updated in 2016 by the GRAPPA-Outcome Measures in Rheumatology (OMERACT) PsA working group.^{12,13} A Core Set represents a consensus on elements to be assessed in trials and clinical studies.¹⁴ In the Core (Figure 1) of elements which are mandatory to assess, are situated elements linked to inflammation: peripheral arthritis is combined with enthesitis and dactylitis under the umbrella of musculoskeletal (MSK) disease activity; skin disease and C-reactive protein must also be assessed. Several patient-reported outcomes are also considered mandatory - this includes fatigue (Figure 1). Indeed, the international patient and physician consensus process leading to this Core Set revealed that fatigue and participation were important to >70% of patients, while these were not so important for physicians.^{12,13} Participation and emotional well-being are proposed as strongly recommended but not mandatory domains for measurement, alongside structural damage and costs (Figure 1).

Following on from this, the same working group is currently developing a PsA Core Outcome Measurement Set. In 2018, the endorsement was granted for employing 66/68 swollen and

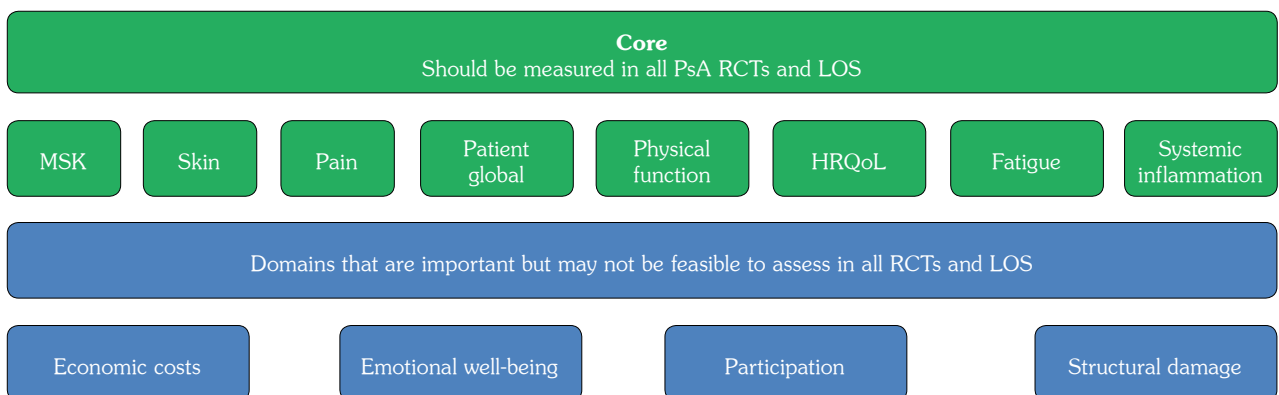


Figure 1. Core Domain Set proposed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and OMERACT in 2016 (adapted from Orbai et al.¹³)

PsA: Psoriatic arthritis; RCTs: Randomised controlled trials; LOS: Longitudinal observational studies; MSK: Musculoskeletal disease activity; HRQoL: Health related quality of life.

tender joint count to assess peripheral joints within the domain of “MSK disease activity”,¹⁵ and provisional endorsement was given to the PsA Impact of Disease 12-item questionnaire (PsAID-12) for measuring the domain of health-related quality of life.¹⁶

Due to the heterogeneity in the clinical manifestations of PsA, assessing its activity requires the utilization of PsA-specific composite instruments that encompass its various domains. Several indices have been proposed (Table 3), each carrying its strengths and limitations.

A recent systematic literature review revealed that data collection across cohorts and registries highly diverge, reflecting the need for international consensus on outcome measures.¹⁷

THE CONCEPT OF REMISSION

Several sets of recommendations address what to aim for in PsA. Both the European Alliance of Associations for Rheumatology (EULAR) and the GRAPPA recommendations for the management

Table 3 Composite indices for evaluating disease activity in PsA

	PsARC	PsAJAI	DAPSA	PASDAS	GRACE	MDA	CPDAI
Physical assessment							
TJC, SJC	+	+	+	+	+	+	+
Enthesitis				+		+	+
Dactylitis				+			+
Skin					+	+	+
Axial disease							+
PROs							
Pain		+	+		+	+	
Patient global assessment	+	+	+	+	+	+	
Physical function							
HAQ		+				+	+
HRQoL							
PsAQoL					+		
SF-36 PCS				+			
Other							
Physician global assessment	+	+		+			
C-reactive protein		+	+	+			

PsA: Psoriatic arthritis; PsARC: Psoriatic arthritis response criteria; PsAJAI: Psoriatic Arthritis Joint Activity Index; DAPSA: Disease activity for psoriatic arthritis; PASDAS: Psoriatic arthritis disease activity score; GRACE: Group for research and assessment of psoriasis and psoriatic arthritis composite exercise; MDA: Minimal disease activity; CPDAI: Composite psoriatic disease activity index; TJC: Tender joint count; SJC: Swollen joint count; PROs: Patient-reported outcomes; HAQ: Health assessment questionnaire; PsAQoL: Psoriatic arthritis quality of life questionnaire; SF-36: Short form-36; PCS: Physical component summary.

Table 4. Most frequent scores used for evaluating disease activity in PsA and their components

	66-68 SJC/TJC	28-28 SJC/TJC	Enthesitis (LEI)	Acute phase reactants	Skin (BSA or PASI)	Pain	Patient global assessment	HAQ
MDA/VLDA	+		+		+	+	+	+
DAPSA	+					+	+	
DAS28		+		+			+	

PsA: Psoriatic arthritis; SJC: Swollen joint count; TJC: Tender joint count; LEI: Leeds enthesitis index; BSA: Body surface area; PASI: Psoriasis area severity index; HAQ: Health assessment questionnaire; MDA: Minimal disease activity; VLDA: Very low disease activity; DAPSA: Disease Activity for Psoriatic Arthritis; DAS28: Disease Activity Score 28.

of PsA state that treatment should be aimed at reaching the target of remission or, alternatively, low disease activity.^{18,19} Nevertheless, there is not an official and consensual definition of this disease state, though the term 'abrogation of inflammation' has been proposed.¹⁸

Another expert group specifically addressed how to define remission. The treat-to-target (T2T) recommendations advise the use of either the Disease Activity Index for Psoriatic Arthritis (DAPSA) or Minimal Disease Activity (MDA) to define remission.²⁰

There is variability in scores used in clinical practice; Disease Activity Score 28 (DAS28) though not developed for PsA, is sometimes (wrongly) used (Table 4).

A cut-off of DAPSA ≤ 4 is used to define remission (DAPSA-REM) and a cutoff of ≤ 14 for low disease activity. The minimal disease activity (MDA)/very low disease activity (VLDA) is a state rather than a score.²¹ It includes tender and swollen joint count, cutaneous involvement, and three patient-reported outcomes (Table 5). A state of MDA (corresponding to low disease activity) requires the fulfilment of five of the seven criteria, while the fulfilment of the seven criteria represented remission (state of VLDA) (Table 5).²²

Remission, although the announced objective, is difficult to reach. In fact, less than a half of the patients reach a target of remission or low disease activity (13-42% for REM and 36-60% for LDA) according to a recent meta-analysis.²³

There is a moderate to poor agreement across the composite measures to evaluate the concept of remission. MDA (reflecting low disease activity) and VLDA (reflecting remission) were found to be the most stringent measures, perhaps due to the mandatory absence of active arthritis, but also enthesitis and psoriasis, and due to Boolean scoring.^{23,24} This contrasts with DAPSA-REM, where the composite score allows residual levels of symptoms.²⁵ It is still unclear at this point in time if the residual symptoms allowed by DAPSA-REM are clinically relevant.

IMAGING

Joint damage is not rare in PsA: more than 50% of patients develop erosions over the first 10 years of disease.¹ The factors known to be associated to radiographic include disease activity (i.e., the number of joint counts), elevated acute-phase reactants, baseline radiographic damage, dactylitis and nail psoriasis.²⁶

Joint radiographs are feasible and cost-effective for assessing and monitoring structural damage (including erosions and new bone formation) in patients with PsA. Although no formal recommendation exists, we suggest performing radiographs of the hands and feet and the affected joints every two years over the first 10 years of PsA. This would allow a precise assessment of the progression of radiographic damage. In addition, radiographs of the sacroiliac joints and spine

Table 5. Definitions of low disease activity and remission in PsA

	Components	Low disease activity	Remission
MDA	Tender joints (≤ 1) Swollen joints (≤ 1) Skin psoriasis (PASI ≤ 1 or BSA ≤ 3) LEI (≤ 1) Pain (≤ 15) Patient global (≤ 20) HAQ (≤ 0.5)	MDA 5/7 criteria	VLDA 7/7 criteria
DAPSA	Tender joints Swollen joints Pain Patient global CRP	DAPSA 5 to ≤ 14	DAPSA remission ≤ 4

PsA: Psoriatic arthritis; MDA: Minimal disease activity; PASI: Psoriasis Area Severity Index; BSA: Body surface area; LEI: Leeds enthesitis index; HAQ: Health Assessment Questionnaire; VLDA: Very low disease activity; DAPSA: Disease Activity for Psoriatic Arthritis; CRP: C-reactive protein.

can be used to evaluate the presence of axial involvement in these patients.

Ultrasound (US) and magnetic resonance imaging (MRI) are more sensitive to detect inflammation. US presents several advantages over MRI, including greater accessibility, reduced overall cost and absence of contraindications. Nonetheless, MRI offers the advantage of accessing sites where US has limited visibility, such as the axial skeleton and all osseous-based pathology. With this increased evidence supporting early treatment of active inflammation, the necessity of incorporating sensitive imaging tools into routine practice has become more imperative than ever.²⁷

Enthesitis is recognized as a typical clinical feature of PsA. Since there is an overlap between enthesal sites and the classic fibromyalgia (FM) points, patients can be misdiagnosed as having FM.²⁸ We demonstrated a strong agreement between the clinical enthesitis score, the Maastrich Ankylosing Spondylitis Enthesitis Score (MASES) and the tender points of the 1990 American College of Rheumatology (ACR) criteria of fibromyalgia and, interestingly, this strong overlap exists also in the subgroup of patients without fibromyalgia. This study raised the question of the specificity of the purely clinical assessment of peripheral enthesitis, suggesting the important role of imaging in the assessment of enthesitis (particularly in case of polyenthesitic presentations without other objective signs of SpA).

Ultrasound offer real-time and dynamic imaging of the entheses sites, also providing information on increased vascularity. A recent study suggested that both psoriatic individuals and patients with PsA exhibit abnormal vascularity at the enthesal level, demonstrating a low sensitivity.²⁹ In the recent EULAR Points to Consider for very early PsA, it is stipulated that the interpretation of imaging abnormalities should be made with caution in particular if there are no concordant clinical findings.¹¹

Furthermore, this study indicated that the range of chronic enthesal changes in healthy subjects overlapped with those of psoriatic individuals and PsA patients, and similar results were reported in a study concerning individuals with FM.³⁰

COMORBIDITIES

Overall comorbidities

Psoriatic arthritis is associated with several comorbidities, defined as the presence or occurrence of any distinct additional entity during the clinical course of a patient with PsA. These comorbidities encompass, among others, obesity and cardiovascular (CV) risk factors (diabetes, hypertension, hyperlipidemia), hepatic steatosis, as well as depression and anxiety.³¹ Moreover, the development of non-alcoholic fatty liver disease (NAFLD) can be associated to the PsA disease. Different studies have described that NAFLD occurs more frequently in PsA patients compared to the general population. Furthermore, there is a close interplay between cardiovascular disease (CVD) and hepatic damage, where dysfunction in adipose tissue, associated with metabolic alterations such as obesity, hypertriglyceridemia, insulin resistance or chronic inflammation, plays a direct role.³²

Cardiovascular comorbidities and mortality

The presence of CV risk factors may contribute to an increased prevalence of CVD, encompassing conditions such as ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and venous thromboembolism. To date, data on the CV mortality in PsA are conflicting.

A study conducted in Canada in 2020 revealed that male patients exhibited better survival rates than females, with a notably elevated mortality observed in younger population.³³ In this study, the primary causes of death included malignancy, acute myocardial infarction, and pneumonia.

Another study in Israel reported an increased mortality of 16%, but only of 2% after adjusting for confounders - considered not clinically relevant. Malignancy also emerged as the leading cause of death (26%) followed by ischemic heart disease (16%).³⁴

A recent nationwide population-based cohort study conducted in Sweden demonstrated an elevated all-cause mortality in PsA with an increase of 11% in mortality compared to the general population over 10 years of follow-up, mainly driven by increased risks in women and

cases with a longer time since diagnosis; CVD and malignancy were the leading causes of death.³⁵

It should be noted that comparing mortality data across studies might be problematic for several reasons. First, studies originate from different centers and geographical areas, with diversity on disease severity, treatments, and access to therapies. Second, studies relying on medical record registries may not accurately define the disease phenotype, since a misclassification may occur between PsA and psoriasis patients. Finally, most studies do not take into account the effect of medications on mortality risk.

In general, recent studies align in suggesting an elevated mortality risk in PsA patients, primarily attributed to the presence of comorbidities, particularly CVD. This should be taken into account when managing patient. Although no specific comorbidity management recommendations have been developed, it seems logical to us to assess CV risk at least every 2-5 years after the age of 40.³⁶

Fibromyalgia and widespread pain

Fibromyalgia and PsA frequently coexist. Both PsO and PsA are linked to obesity and depression which are also closely associated with chronic pain.³⁷ Like FM, the presence of depression can affect pain reporting, while more severe disease increases the risk of developing depression. Additionally, obesity and chronic pain often coexist, with higher body weight leading to increased mechanical stress, which may also play a role in the PsA pathology.

The reported prevalence of concomitant widespread pain syndrome in PsA ranges from 10 to 27%.³⁸ The presence of this comorbid condition in PsA patients may result in higher scores in composite scores and patient-reported outcomes (i.e., DAPSA and Health Assessment Questionnaire [HAQ]), while differences in objective signs of inflammation such as the C-reactive protein and swollen joint count are absent.³⁹

Impact of comorbidities on management

The presence of comorbidities in patients with rheumatic diseases, particularly PsA, pose challenges in managing the rheumatic condition in various ways: contraindications for certain drugs, perpetuation of the inflammation and

treatment non-adherence. The 2021 GRAPPA recommendations propose a table to orient clinicians for treatment choices when faced with specific comorbidities.¹⁹ Nevertheless, managing PsA and its comorbidities remains a challenge.⁴⁰ Indeed, comorbidities and widespread pain contribute to complicated management of patients (what can be term 'difficult to manage').^{41,42} This emphasizes the need to address both inflammatory and non-inflammatory factors for optimal PsA management, with consideration of all comorbidities in therapeutic decision-making.⁴³

TREATMENT

In 2024, there is a wide range of therapeutic options for treating patients with PsA. These include medications targeting various signaling pathways such inhibitors of tumor necrosis factor (TNF), interleukin (IL)-12/23, IL-23, IL-17, JAK/STAT (The Janus kinase/signal transducers and activators of transcription) and phosphodiesterase type 4 (PDE4) signaling

Table 6. Drugs approved in Europe for treating PsA in 2024⁴⁵

Drug	Administration	Inhibition
Infliximab	i.v. or s.c.	TNF
Adalimumab	s.c.	
Golimumab	s.c.	
Certolizumab	s.c.	
Etanercept	s.c.	IL-17A
Secukinumab	s.c.	
Ixekizumab	s.c.	
Bimekizumab	s.c.	IL-17A/F
Abatacept	i.v. or s.c.	CTLA-4
Ustekinumab	s.c.	IL-12/23
Guselkumab	s.c.	IL-23
Risankizumab	s.c.	
Apremilast	Oral	PDE4
Tofacitinib	Oral	JAK
Upadacitinib	Oral	

PsA: Psoriatic arthritis; TNF: Tumor necrosis factor; IL: Interleukin; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PDE4: Phosphodiesterase type 4; JAK: Janus kinases; i.v.: Intravenous; s.c.: Subcutaneous.

pathways (Table 6). EULAR has developed updated recommendations for the management of PsA which include all the currently available treatment options and should help physicians for decision-making.⁴⁴

However, despite this extensive therapeutic arsenal, a considerable number of patients do not achieve low disease activity or remission; and persistence with medications is often limited due to secondary inefficacy. Moreover, recommendations on treatment strategies are scarce.

New drugs are currently being developed. Deucravacitinib (TYK2 inhibitor)⁴⁵ and brepocitinib (TYK2/JAK1i)⁴⁶ have shown promising clinical efficacy in phase 2 trials, with phase 3 trials for deucravacitinib currently in progress. High-affinity (Affibody) molecules represent a new class of small, triple helical, high-affinity protein domains that are well suited for therapeutic development. Affibody molecules are often engineered as fusion proteins with a small albumin-binding domain to prolong plasma half-life and enhance tissue penetration, including increased drug exposure at sites of inflammation. The Affibody technology has been used to identify a novel molecule specifically targeting the inhibition of IL-17A signaling. This molecule, izokibep, was optimized by combining two IL-17A-specific Affibody domains with one albumin-binding domain. Izokibep has demonstrated the ability to selectively bind to and inhibit human IL-17A, showing efficacy in the treatment of moderate-to-severe psoriasis.⁴⁷ In PsA, positive results from the phase 2 PsA trial have been reported,⁴⁸ with phase 3 studies currently underway.

Nevertheless, the costs, the elevated rate of non-responders and the potential undesirable effects of biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), render necessary the development of precision medicine for PsA patients. This approach could help to predict treatment responses to various agents, thereby minimizing adverse events and the necessity for frequent switching of medications.

Precision medicine

Currently, there are no validated biomarkers available to aid in the decision-making process for

facilitating precision medicine in PsA. However, it is unlikely that a single protein will have predictive utility; therefore, combination of biomarkers would prove to be more beneficial.

Genetic polymorphisms in the TNF promoter regions hold significance in predicting treatment response. The TNF α -induced protein 2 gene (TNFAIP3) have been linked to an improvement of quality of life after three months of TNF-inhibitor (TNFi) treatment.⁴⁹ Additionally, IL-17 induces the expression of the TNFAIP3 gene. Interestingly, A20 interacts with IL-17 differently compared to other pathways,⁵⁰ and further research is necessary to determine whether polymorphisms at A20 alter the effectiveness of IL-17 inhibitors compared to TNFi.

Regarding soluble biomarkers, the concentration of serum IL-22 has been recognized as a predictor of DAPSA-REM after one year of IL-17i therapy.⁵¹ On the other hand, Shimauchi et al.⁵² evaluated serum levels of IL-22 and vascular endothelial growth factor (VEGF) and found that both were unable to predict response to treatment with ustekinumab or TNFi. In a prospective substudy, Wagner et al.⁵³ analyzed baseline levels of 92 biomarkers in 100 patients from the GO-REVEAL trial investigating the response of PsA patients to golimumab. Pyridinoline, adiponectin, prostatic acid phosphate, and factor VII were identified as a panel of markers with the potential to predict ACR20 response.

Overall, studies examining biological predictors of response to biologic treatments have been limited in size and have included a mix of patients with both skin psoriasis and PsA. Future research should also explore alternative single-nucleotide polymorphism (SNP) targets, including those related to the IL-23/T helper (Th)17 axis, as well as analysis of synovial biopsies.

Combinations of bDMARDs

As previously mentioned, many patients fail to respond to multiple lines of bDMARDs. Consequently, novel therapeutic strategies involving the simultaneous use of two biologics or a combination of a biologic and a targeted synthetic DMARD (tsDMARDs) with distinct mechanisms of action are being investigated. This approach aims to suppress proinflammatory

activity across various disease domains in PsA,⁵⁴ such as musculoskeletal, cutaneous, or intestinal involvement. An increasing number of case series involving these combination therapies have been reported. A multicenter retrospective study analyzed 14 patients with PsA receiving combined therapy, with five of them also suffering from concomitant inflammatory bowel disease.⁵⁵ The most common class combination consisted of a TNFi plus either an IL-12/23 inhibitor or an IL-17 antagonist, and only one patient experienced a serious adverse event. Another study collected data on 10 patients treated with a total of 15 combinations of TNFi plus IL-12/23, IL-23 or IL-17 inhibitors.⁵⁶ Among these treatments, eight did not result in adverse events, while six were associated with infections of varying severity.

Given the limited understanding of bDMARDs combinations in clinical practice, an ongoing randomized trial is investigating their efficacy in patients with PsA. This study will compare the efficacy and safety of an IL-23 inhibitor (guselkumab) in combination with a TNFi (golimumab), versus guselkumab or golimumab alone in PsA patients who have shown inadequate response to at least one TNFi.

Overall, new data on the efficacy and safety of drug combination are needed, with the requirement of a close communication and collaboration between clinicians in different specialties.

DIFFICULT-TO-TREAT PsA

Psoriatic arthritis is a complex disease, involving multiple tissues and domains. Furthermore, therapeutic decisions and PsA are influenced by the presence of extra-musculoskeletal manifestations and the high prevalence of comorbidities, leading to the avoidance of certain drugs in specific scenarios. Thus, we can say that some patients with PsA are 'difficult to treat'. Currently, both EULAR and GRAPPA are separately addressing the concept of difficult-to-treat (D2T) PsA, based on previous similar work in RA.⁵⁶

In a recent systematic literature review performed by GRAPPA, the definitions found for D2T PsA were variable across the studies: in some cases, this was vaguely described as

multiple treatment attempts, while in others it covered from failure to ≥ 1 TNFi to failures involving ≥ 2 b/tsDMARDs or even extending to ≥ 3 b/tsDMARDs.⁴²

An EULAR survey conducted in 2023 among specialist rheumatologists revealed varied opinions concerning the criteria for defining D2T PsA.⁴⁰ The majority of respondents (34.8%) supported a definition of D2T PsA that involved the failure of at least 2 classes of b/tsDMARDs with a pragmatic definition of truly 'refractory PsA' being preferred, indicating 'failing all available classes of b/tsDMARDs' (74%). About two-thirds (68%) believed that failure to ≥ 1 conventional synthetic (csDMARD) should also be considered.

Beyond previous treatments and targets, the survey highlighted five additional areas as important for consideration in the definition of D2T PsA: radiographic progression and structural changes, axial disease, function, comorbidities and extra-musculoskeletal manifestations.

As more data emerges, there is a need to standardize the definition for D2T and 'difficult to manage' PsA in the coming years. This standardization would facilitate clinical research and the development of treatment pathways for these patients.⁴⁰

Conclusion

In recent years, significant advances have been obtained in the field of PsA; however, several unmet needs remain.

Although the CASPAR criteria have significantly advanced disease classification in the context of studies and trials, diagnostic criteria for clinical practice are still lacking. Additionally, despite the availability of screening questionnaires for dermatologists, their limited implementation may contribute to diagnostic delays, which is not favorable in the context of a potential window of opportunity.

We currently have a better understanding of the different types of PsA and their clinical manifestations. However, further work is needed to enhance the better characterization of PsA, and to distinguish with more certainty enthesitis from FM or widespread pain.

The assessment of PsA disease activity is still difficult due to the involvement of multiple domains. The lack of a single consensual score to assess disease activity complicates the comparison of studies, patient discussions among colleagues, and the establishment of a standardized approach to disease activity assessment. This challenge is further evident in the significant variability observed in achieving remission targets based on different scoring systems. More information is needed on how best to assess patients with PsA, and on how to ensure an acceptable treatment.

Although many treatment options are now available in PsA, there is still an unmet need, as close to half of the patients do not reach a target of remission or low disease activity.⁵⁷ This contributes to ongoing work on D2T PsA, where patients may exhibit resistance to multiple drug types or have comorbidities impacting their management and outcomes. Recent treatment recommendations now integrate all the currently available drugs and modes of action, but new drugs and novel ways of managing patients such as personalized medicine and combination of biologics are being explored.

The next years will bring us more knowledge on these current unmet needs.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017;376:957-70. doi: 10.1056/NEJMra1505557.
- Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55-78. doi: 10.1016/0049-0172(73)90035-8.
- Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665-73. doi: 10.1002/art.21972.
- Kasiem FR, Luime JJ, Vis M, Kok MR, Wervers K, Gerards AH, et al. Lessons learned from clinical phenotypes in early psoriatic arthritis: The real-world Dutch south west early psoriatic arthritis study. *Scand J Rheumatol* 2021;50:124-31. doi: 10.1080/03009742.2020.1803398.
- Lopez-Medina C, Ziade N. Axial Disease in Psoriatic Arthritis: How can we define it, and does it have an impact on treatment? *Mediterr J Rheumatol* 2022;33(Suppl 1):142-9. doi: 10.31138/mjr.33.1.142.
- Poddubnyy D, Baraliakos X, Van den Bosch F, Braun J, Coates LC, Chandran V, et al. Axial Involvement in Psoriatic Arthritis cohort (AXIS): The protocol of a joint project of the Assessment of SpondyloArthritis international Society (ASAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). *Ther Adv Musculoskelet Dis* 2021;13:1759720X211057975. doi: 10.1177/1759720X211057975.
- Dominguez PL, Husni ME, Holt EW, Tyler S, Qureshi AA. Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire. *Arch Dermatol Res* 2009;301:573-9. doi: 10.1007/s00403-009-0981-3.
- Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: The Psoriasis Epidemiology Screening Tool (PEST) questionnaire. *Clin Exp Rheumatol* 2009;27:469-74.
- Gladman DD, Schentag CT, Tom BD, Chandran V, Brockbank J, Rosen C, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: The Toronto Psoriatic Arthritis Screen (ToPAS). *Ann Rheum Dis* 2009;68:497-501. doi: 10.1136/ard.2008.089441.
- Audureau E, Roux F, Lons Danic D, Bagot M, Cantagrel A, Dernis E, et al. Psoriatic arthritis screening by the dermatologist: Development and first validation of the 'PURE-4 scale'. *J Eur Acad Dermatol Venereol* 2018;32:1950-3. doi: 10.1111/jdv.14861.
- Zabotti A, De Marco G, Gossec L, Baraliakos X, Aletaha D, Iagnocco A, et al. EULAR points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to psoriatic arthritis. *Ann Rheum Dis* 2023;82:1162-70. doi: 10.1136/ard-2023-224148.
- Orbai AM, de Wit M, Mease PJ, Callis Duffin K, Elmamoun M, Tillett W, et al. Updating the Psoriatic Arthritis (PsA) core domain set: A report from the PsA workshop at OMERACT 2016. *J Rheumatol* 2017;44:1522-8. doi: 10.3899/jrheum.160904.

13. Orbai AM, de Wit M, Mease P, Shea JA, Gossec L, Leung YY, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Ann Rheum Dis* 2017;76:673-80. doi: 10.1136/annrheumdis-2016-210242.
14. Naye F, Toupin-April K, de Wit M, LeBlanc A, Dubois O, Boonen A, et al. OMERACT Core outcome measurement set for shared decision making in rheumatic and musculoskeletal conditions: A scoping review to identify candidate instruments. *Semin Arthritis Rheum* 2024;65:152344. doi: 10.1016/j.semarthrit.2023.152344.
15. Duarte-García A, Leung YY, Coates LC, Beaton D, Christensen R, Craig ET, et al. Endorsement of the 66/68 joint count for the measurement of musculoskeletal disease activity: OMERACT 2018 psoriatic arthritis workshop report. *J Rheumatol* 2019;46:996-1005. doi: 10.3899/jrheum.181089.
16. Orbai AM, Holland R, Leung YY, Tillett W, Goel N, Christensen R, et al. PsAID12 provisionally endorsed at OMERACT 2018 as core outcome measure to assess psoriatic arthritis-specific health-related quality of life in clinical trials. *J Rheumatol* 2019;46:990-5. doi: 10.3899/jrheum.181077.
17. Aouad K, Moysidou G, Rakotzafiarison A, Fautrel B, Gossec L. Outcome measures used in psoriatic arthritis registries and cohorts: A systematic literature review of 27 registries or 16,183 patients. *Semin Arthritis Rheum* 2021;51:888-94. doi: 10.1016/j.semarthrit.2021.06.008.
18. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700-12. doi: 10.1136/annrheumdis-2020-217159.
19. Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): Updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol* 2022;18:465-79. doi: 10.1038/s41584-022-00798-0.
20. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018;77:3-17. doi: 10.1136/annrheumdis-2017-211734.
21. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: A proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48-53. doi: 10.1136/ard.2008.102053.
22. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res (Hoboken)* 2010;62:965-9. doi: 10.1002/acr.20155.
23. Hagege B, Tan E, Gayraud M, Fautrel B, Gossec L, Mitrovic S. Remission and low disease activity in psoriatic arthritis publications: A systematic literature review with meta-analysis. *Rheumatology (Oxford)* 2020;59:1818-25. doi: 10.1093/rheumatology/keaa030.
24. Gorlier C, Orbai AM, Puyraimond-Zemmour D, Coates LC, Kiltz U, Leung YY, et al. Comparing patient-perceived and physician-perceived remission and low disease activity in psoriatic arthritis: An analysis of 410 patients from 14 countries. *Ann Rheum Dis* 2019;78:201-8. doi: 10.1136/annrheumdis-2018-214140.
25. Coates LC, Lubrano E, Perrotta FM, Emery P, Conaghan PG, Helliwell PS. What should be the primary target of "treat to target" in psoriatic arthritis? *J Rheumatol* 2019;46:38-42. doi: 10.3899/jrheum.180267.
26. Kerschbaumer A, Smolen JS, Dougados M, de Wit M, Primdahl J, McInnes I, et al. Pharmacological treatment of psoriatic arthritis: A systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2020;79:778-86. doi: 10.1136/annrheumdis-2020-217163.
27. Zabotti A, Bandinelli F, Batticciotto A, Scirè CA, Iagnocco A, Sakellariou G; Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology. Musculoskeletal ultrasonography for psoriatic arthritis and psoriasis patients: A systematic literature review. *Rheumatology (Oxford)* 2017;56:1518-32. doi: 10.1093/rheumatology/kex179.
28. Hamitouche F, Lopez-Medina C, Gossec L, Perrot S, Dougados M, Moltó A. Evaluation of the agreement between the ACR 1990 fibromyalgia tender points and an enthesitis score in patients with axial spondyloarthritis. *Rheumatology (Oxford)* 2023;62:2757-64. doi: 10.1093/rheumatology/keac683.
29. Aydin SZ, Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, et al. The link between enthesitis and arthritis in psoriatic arthritis: A switch to a vascular phenotype at insertions may play a role in arthritis development. *Ann Rheum Dis* 2013;72:992-5. doi: 10.1136/annrheumdis-2012-201617.
30. Marchesoni A, De Lucia O, Rotunno L, De Marco G, Manara M. Enthesial power Doppler ultrasonography: A comparison of psoriatic arthritis and fibromyalgia. *J Rheumatol Suppl* 2012;89:29-31. doi: 10.3899/jrheum.120238.
31. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. *Curr Opin Rheumatol* 2015;27:118-26. doi: 10.1097/BOR.0000000000000152.
32. Torosian K, Lal E, Kavanaugh A, Loomba R, Ajmera V, Guma M. Psoriatic disease and non-alcoholic fatty liver disease shared pathogenesis review. *Semin Arthritis Rheum* 2023;59:152165. doi: 10.1016/j.semarthrit.2023.152165.

33. Elalouf O, Muntyanu A, Polachek A, Pereira D, Ye JY, Lee KA, et al. Mortality in psoriatic arthritis: Risk, causes of death, predictors for death. *Semin Arthritis Rheum* 2020;50:571-5. doi: 10.1016/j.semarthrit.2020.04.001.
34. Haddad A, Saliba W, Lavi I, Batheesh A, Kasem S, Gazitt T, et al. The association of psoriatic arthritis with all-cause mortality and leading causes of death in psoriatic arthritis. *J Rheumatol* 2022;49:165-70. doi: 10.3899/jrheum.210159.
35. Exarchou S, Di Giuseppe D, Klingberg E, Sigurdardottir V, Wedrén S, Lindström U, et al. Mortality in patients with psoriatic arthritis in Sweden: A nationwide, population-based cohort study. *Ann Rheum Dis* 2024;83:446-56. doi: 10.1136/ard-2023-224965.
36. Drosos GC, Vedder D, Houben E, Boekel L, Atzeni F, Badreh S, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. *Ann Rheum Dis* 2022;81:768-79. doi: 10.1136/annrheumdis-2021-221733.
37. Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. *Best Pract Res Clin Rheumatol* 2019;33:101423. doi: 10.1016/j.berh.2019.06.005.
38. Duffield SJ, Miller N, Zhao S, Goodson NJ. Concomitant fibromyalgia complicating chronic inflammatory arthritis: A systematic review and meta-analysis. *Rheumatology (Oxford)* 2018;57:1453-60. doi: 10.1093/rheumatology/key112.
39. Brikman S, Furer V, Wollman J, Borok S, Matz H, Polachek A, et al. The effect of the presence of fibromyalgia on common clinical disease activity indices in patients with psoriatic arthritis: A cross-sectional study. *J Rheumatol* 2016;43:1749-54. doi: 10.3899/jrheum.151491.
40. Marzo-Ortega H, Harrison SR, Nagy G, Machado PM, McGonagle DG, Aydin SZ, et al. Time to address the challenge of difficult to treat psoriatic arthritis: Results from an international survey. *Ann Rheum Dis* 2024;83:403-4. doi: 10.1136/ard-2023-225087.
41. Siebert S, Marzo-Ortega H. Difficult-to-treat psoriatic arthritis: Moving out of the rheumatoid arthritis shadow. *Nat Rev Rheumatol* 2024;20:135-6. doi: 10.1038/s41584-024-01083-y.
42. Singla S, Ribeiro A, Torgutalp M, Mease PJ, Proft F. Difficult-to-treat psoriatic arthritis (D2T PsA): A scoping literature review informing a GRAPPA research project. *RMD Open* 2024;10:e003809. doi: 10.1136/rmdopen-2023-003809.
43. Lubrano E, Scriffignano S, Perrotta FM. Difficult to treat and refractory to treatment in psoriatic arthritis. *Rheumatol Ther* 2023;10:1119-25. doi: 10.1007/s40744-023-00574-w.
44. Gossec L, Kerschbaumer A, Ferreira RJO, Aletaha D, Baraliakos X, Bertheussen H, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann Rheum Dis* 2024;ard-2024-225531.
45. Mease PJ, Deodhar AA, van der Heijde D, Behrens F, Kivitz AJ, Neal J, et al. Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. *Ann Rheum Dis* 2022;81:815-22. doi: 10.1136/annrheumdis-2021-221664.
46. Mease P, Helliwell P, Silwinska-Stanczyk P, Miakisz M, Ostor A, Peeva E, et al. Efficacy and safety of the TYK2/JAK1 inhibitor Brepocitinib for active psoriatic arthritis: A phase IIb randomized controlled trial. *Arthritis Rheumatol* 2023;75:1370-80. doi: 10.1002/art.42519.
47. Gerdes S, Staubach P, Dirschka T, Wetzel D, Weirich O, Niesmann J, et al. Izokibep for the treatment of moderate-to-severe plaque psoriasis: A phase II, randomized, placebo-controlled, double-blind, dose-finding multicentre study including long-term treatment. *Br J Dermatol* 2023;189:381-91. doi: 10.1093/bjd/ljad186.
48. Mease P, Taylor P, de Vlam K, Peloso P, Lertratanakul A, Wetzel D, et al. Izokibep demonstrates major disease control on ACR70, PASI100 and enthesitis resolution in patients with active psoriatic arthritis treated through 46 weeks. *Arthritis Rheumatol* 2023;75(suppl 9):1688 [Abstract]
49. Ovejero-Benito MC, Muñoz-Aceituno E, Reolid A, Fisas LH, Llamas-Velasco M, Prieto-Pérez R, et al. Polymorphisms associated with anti-TNF drugs response in patients with psoriasis and psoriatic arthritis. *J Eur Acad Dermatol Venereol* 2019;33:e175-e177. doi: 10.1111/jdv.15431.
50. Garg AV, Gaffen SL. IL-17 signaling and A20: A balancing act. *Cell Cycle* 2013;12:3459-60. doi: 10.4161/cc.26699.
51. Miyagawa I, Nakayamada S, Ueno M, Miyazaki Y, Iwata S, Kubo S, et al. Impact of serum interleukin-22 as a biomarker for the differential use of molecular targeted drugs in psoriatic arthritis: A retrospective study. *Arthritis Res Ther* 2022;24:86. doi: 10.1186/s13075-022-02771-4.
52. Shimauchi T, Hirakawa S, Suzuki T, Yasuma A, Majima Y, Tatsuno K, et al. Serum interleukin-22 and vascular endothelial growth factor serve as sensitive biomarkers but not as predictors of therapeutic response to biologics in patients with psoriasis. *J Dermatol* 2013;40:805-12. doi: 10.1111/1346-8138.12248.
53. Wagner CL, Visvanathan S, Elashoff M, McInnes IB, Mease PJ, Krueger GG, et al. Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. *Ann Rheum Dis* 2013;72:83-8. doi: 10.1136/annrheumdis-2012-201697.
54. Winthrop KL, Mease P, Kerschbaumer A, Voll RE, Breedveld FC, Smolen JS, et al. Unmet need in rheumatology: Reports from the advances in targeted therapies meeting, 2023. *Ann Rheum Dis* 2024;83:409-16. doi: 10.1136/ard-2023-224916.

55. Valero-Martínez C, Urgelles JF, Sallés M, Joven-Ibáñez BE, de Juanes A, Ramírez J, et al. Dual targeted therapy in patients with psoriatic arthritis and spondyloarthritis: A real-world multicenter experience from Spain. *Front Immunol* 2023;14:1283251. doi: 10.3389/fimmu.2023.1283251.
56. Thibodeaux Q, Ly K, Reddy V, Smith MP, Liao W. Dual biologic therapy for recalcitrant psoriasis and psoriatic arthritis. *JAAD Case Rep* 2019;5:928-30. doi: 10.1016/j.jdc.2019.08.015.
57. Nagy G, Roodenrijs NMT, Welsing PM, Kedves M, Hamar A, van der Goes MC, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31-5. doi: 10.1136/annrheumdis-2020-217344.