Unmet needs in psoriatic arthritis, a narrative review

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Title: UNMET NEEDS IN PSORIATIC ARTHRITIS, a narrative review

Running title: Unmet needs in PsA

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Abstract

Psoriatic Arthritis (PsA) 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 PsA, in terms of diagnosis, classification, evaluation, comorbidities and treatment.

Keywords: Psoratic Arthritis, diagnosis, management, treatment

1. Introduction

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: a) the oligoarticular subtype, affecting four or fewer joints asymmetrically which is the most frequent in clinical practice; b) the polyarticular subtype, involving five or more joints and resembling rheumatoid arthritis (RA), often seen in clinical trials; and c) 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.

2. 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 (adapted from Taylor W, et al[3])

Entry criterion: **Articular disease (joint, spine or entheseal)**	
	Points
1. Evidence of psoriasis • 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 • Current dactylitis • History of dactylitis	 1 or 1

5. Radiologic evidence of juxta-articular new bone formation	1

To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine or entheseal) 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 rheumatoid arthritis (RA), osteoarthritis, crystal-induced arthritis and other forms of SpA [1].

RA, 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 osteoarthritis. One way to distinguish both diseases is the physical examination. PsA is characterized by painful palpation of distal joints with soft swelling, whereas in osteoarthritis, the swelling is solid and arises from a bony osteophyte. In addition, PsA with distal phalangeal involvement often coincides with nail diseases such as pitting or onycholysis, which are absent in osteoarthritis (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].

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

CRP: c-reactive protein

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].

3. Disease activity and evaluation

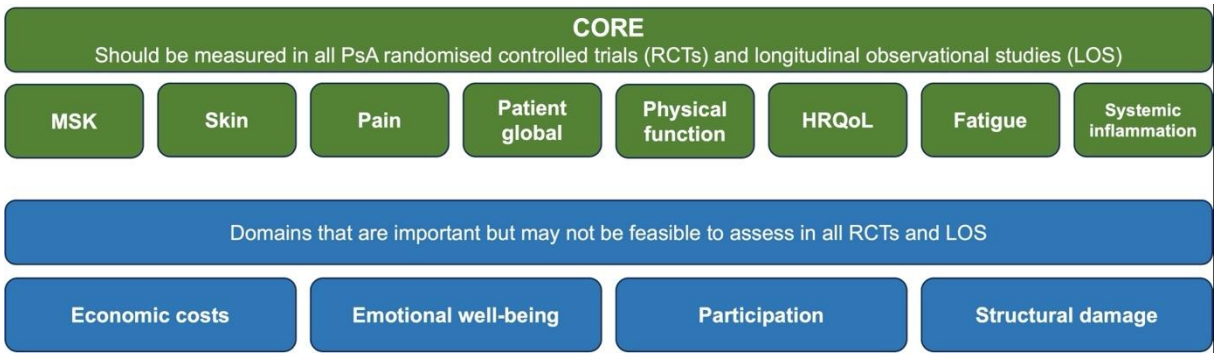
Disease activity and its evaluation represents an important area of difficulties since no consensus exist on the optimal composite index and on the concept of remission.

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 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].

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 AM, et al[13])



HRQoL: Health Related Quality of Life; LOS: longitudinal observational studies; MSK: Musculoskeletal disease activity; RCTs: Randomized Controlled Trials.

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.

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	+	+		+			
CRP		+	+	+			

PsA, psoriatic arthritis; TJC, Tender Joint Count; SJC, Swollen Joint Count; CRP, C-reactive protein; DAPSA, Disease Activity for Psoriatic Arthritis; HAQ: Health Assessment Questionnaire; SF-36: Short Form-36, Physical component; PsAQoL: Psoriatic Arthritis Quality of Life Questionnaire; PsARC, Psoriatic Arthritis Response Criteria; PsAJAI, Psoriatic Arthritis Joint Activity Index; GRACE, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Exercise; PASDAS, Psoriatic Arthritis Disease Activity Score; CPDAI, Composite Psoriatic Disease Activity Index; MDA, minimal disease activity.

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].

4. 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 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; DAS28 though not developed for PsA, is sometimes (wrongly) used (Table 4).

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; TJC, Tender Joint Count; SJC, Swollen Joint Count; DAPSA, Disease Activity for Psoriatic Arthritis; DAS28: Disease Activity Score 28; HAQ: Health Assessment Questionnaire; PASDAS, Psoriatic Arthritis Disease Activity Score; MDA, minimal disease activity; LEI: Leeds Enthesitis Index; BSA: Body Surface Area; PASI: Psoriasis Area Severity Index.

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].

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; DAPSA, Disease Activity for Psoriatic Arthritis; HAQ: Health Assessment Questionnaire; PASDAS, Psoriatic Arthritis Disease Activity Score; MDA, minimal disease activity; LEI: Leeds Enthesitis Index; BSA: Body Surface Area; PASI: Psoriasis Area Severity Index; CRP: c-reactive protein.

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.

5. 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 2 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 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 routing practice has become more imperative than ever [27].

Enthesitis is recognized as a typical clinical feature of PsA. Since there is an overlap between entheseal sites and the classic fibromyalgia points, patients can be misdiagnosed as having fibromyalgia [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 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).

US 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 entheseal 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 entheseal 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].

6. 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 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 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 cardiovascular risk factors may contribute to an increased prevalence of cardiovascular disease (CVD), encompassing conditions such as ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and venous thromboembolism. To date, data on the CV mortality is 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, especially 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 cardiovascular 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 fibromyalgia, 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 HAQ), while differences in objective signs of inflammation such as the CRP 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 withs specific comorbidities [40]. Nevertheless, managing PsA and its comorbidities remains a challenge [41]. Indeed, comorbidities and widespread pain contribute to complicated management of patients (what can be term 'difficult to manage' [42,43]. 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 [44].

7. Treatment

In 2024, there is a wide range of therapeutic options for treating patients with PsA. These include medications targeting various signalling pathways such inhibitors of TNF, IL-12/23, IL-23, IL-17, JAK-STAT and phosphodiesterase type 4 (PDE4) signalling 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 [45].

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.

Table 6. Drugs approved in Europe for treating PsA in 2024 (Gossec L, et al.[45]).

Drug	Administration	Inhibition
Infliximab	i.v. or s.c.	TNF
Adalimumab	s.c.	
Golimumab	s.c.	
Certolizumab	s.c.	
Etanercept	s.c.	
Secukinumab	s.c.	IL-17A
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	

JAK: Janus Kinases; IL: interleukin; i.v.: intravenous; s.c.: subcutaneous;

New drugs are currently being developed. Deucravacitinib (TYK2 inhibitor) [46] and brepocitinib (TYK2/JAK1i) [47] 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 [48]. In PsA, positive results from the phase 2 PsA trial have been reported [49], 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 TNFalpha-induced protein 2 gene (TNFAIP3) have been linked to an improvement of quality of life after 3 months of TNFi treatment [50]. Additionally, IL-17 induces the expression of the TNFAIP3 gene. Interestingly, A20 interacts with IL-17

differently compared to other pathways, [51] 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 1 year of IL-17i therapy [52]. On the other hand, Shimauchi et al. 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 [53]. In a prospective substudy, Wagner et al. analyzed baseline levels of 92 biomarkers in 100 patients from the GO-REVEAL trial investigating the response of PsA patients to golimumab [54]. 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 SNP targets, including those related to the IL-23/Th17 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 [55], 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 5 of them also suffering from concomitant inflammatory bowel disease [56]. The most common class combination consisted of a TNF inhibitor plus either an IL12/23 inhibitor or an IL17 antagonist, and only one patient experienced a serious adverse event. Another study collected data on ten patients treated with a total of fifteen combinations of TNF inhibitors plus IL12/23, IL23 or IL17 inhibitors [57]. 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 TNF inhibitor (golimumab), versus guselkumab or golimumab alone in PsA patients who have shown inadequate response to at least one TNF inhibitor.

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.

8. Difficult-to-treat PsA

PsA 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 [57].

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 tumour necrosis factor inhibitors (TNFi) to failures involving ≥2 b/tsDMARDs or even extending to ≥3 b/tsDMARDs [43].

A EULAR survey conducted in 2023 among specialist rheumatologists revealed varied opinions concerning the criteria for defining D2T PsA [41]. 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 extramusculoskeletal 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 [41].

9. 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 favourable 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 fibromyalgia 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 [58]. 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.

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