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REVIEW ARTICLE

Navigating Psoriatic Arthritis: Treatment Pathways and Patient-Specific Strategies for Improved Outcomes

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Abstract

Psoriatic arthritis (PsA) is a multifaceted chronic immune-mediated disease characterized by joint, skin, nail and entheseal involvement, affecting approximately 0.3–1% of the global population. In recent years, the treatment options for PsA have expanded from traditional nonsteroidal anti-inflammatory drugs and conventional synthetic disease-modifying antirheumatic drugs (DMARDs) to include biologic DMARDs and targeted synthetic DMARDs. Owing to the heterogeneity of the disease and prevalence of comorbidities, the selection and sequence of treatment are often unclear. In this narrative review, we outline the patient journey from diagnosis through various treatment lines, from conventional therapies to bDMARDS and tsDMARDs, and the considerations for treatment sequencing in patients who do not achieve an adequate response. We examine the factors influencing treatment response, such as disease severity, predominant disease domain, comorbidities, genetic variations, pharmacokinetic and immunogenicity issues. We highlight the importance of identifying robust biomarkers to predict response and the need to determine patient-specific factors, including the contribution of inflammatory mechanisms to disease activity, to inform treatment strategies and improve long-term outcomes. Promising results with more recently marketed biologic and targeted synthetic DMARDs, and the use of combination treatment approaches, offer new options for managing treatment-experienced patients.

1 Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated disease characterized by synovio-entheseal inflammation. The disease not only affects the joints but also impacts the skin and other organs, leading to a range of clinical manifestations that can severely impair physical function and psychosocial health [1].

PsA affects approximately 0.3–1% of the global population, and up to 30% of patients with psoriasis [2–4]. The

Key Points

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease that affects up to 1% of the global population.

Treatment options have expanded to include biologic and targeted drugs, but determining the most effective treatment strategy is challenging owing to the complex pathogenesis of the disease involving interactions between various immune system pathways, genetic and environmental factors.

Up to 40% of patients with PsA experience inadequate drug responses. These can be influenced by disease severity, predominant disease domain, comorbidities, genetic variations, pharmacokinetic and immunogenicity issues.

A personalised approach, whereby both the clinical characteristics of the disease and the individual circumstances of the patient are considered, along with the latest results from real-world studies on treatment sequencing and treatment combinations, is key to improving the management of treatment-experienced patients.

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mechanisms underlying the pathogenesis of PsA are complex, involving interactions between genetic predispositions, immune system dysregulation and environmental factors [5]. Advances in understanding the interplay of various immune cells, including T cells, dendritic cells and macrophages, as well as pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-17 (IL-17) and interleukin-23 (IL-23) has led to targeted therapies that specifically block parts of the immune response (Fig. 1).

In recent years, the array of therapeutic options for PsA has expanded significantly. Historically, the management of PsA was limited to non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate. Over the past two decades, the introduction of biologic DMARDs (bDMARDs) and, more recently, targeted synthetic DMARDs (tsDMARDs), including inhibitors of phosphodiesterase 4 (PDE4) and Janus kinase (JAK), has offered the opportunity to tailor treatments to individual patient needs, considering the diverse clinical presentations and disease severities encountered in practice (Table 1).

Owing to the heterogeneity of the disease and prevalence of comorbidities, the selection and sequence of treatment are often unclear. Various consensus articles and reviews have been published to guide the management of PsA, taking predominant disease domains and comorbidities into account [6–8].

The most recent European Alliance of Associations for Rheumatology (EULAR) recommendations and treatment algorithm [9] suggest using NSAIDs as a short-term monotherapy in mild PsA only. Rapid initiation of methotrexate or another csDMARD is recommended for patients with peripheral arthritis. If the treatment target is not achieved, patients should be treated with a tumour necrosis factor (TNF) inhibitor or other bDMARD. bDMARDs targeting interleukin (IL) 12/23p40, IL-23p19, IL-17A and IL-17A/F are considered preferable when there is extensive skin psoriasis. The updated recommendations also propose using tsDMARDS after bDMARD failure or when bDMARDs are unsuitable, taking relevant risk factors into account.

For this narrative review, we performed a literature search in PubMed and Google Scholar, focussing on articles reporting the results of drug switching (change to a drug with the same mechanism of action) and swapping (change between drug classes) strategies to gain insights that could aid the management of PsA in treatment-experienced patients. Cited articles were chosen at the authors' discretion.

Further understanding why patients either fail to respond adequately to therapy or lose their initial response could help guide decisions on next line of treatment. Whilst the use of concepts such as 'difficult to treat' and 'refractory' patients has been proposed to help guide targeted treatment strategies and define patient groups for clinical trials, defining these terms is challenging owing to the complexity and

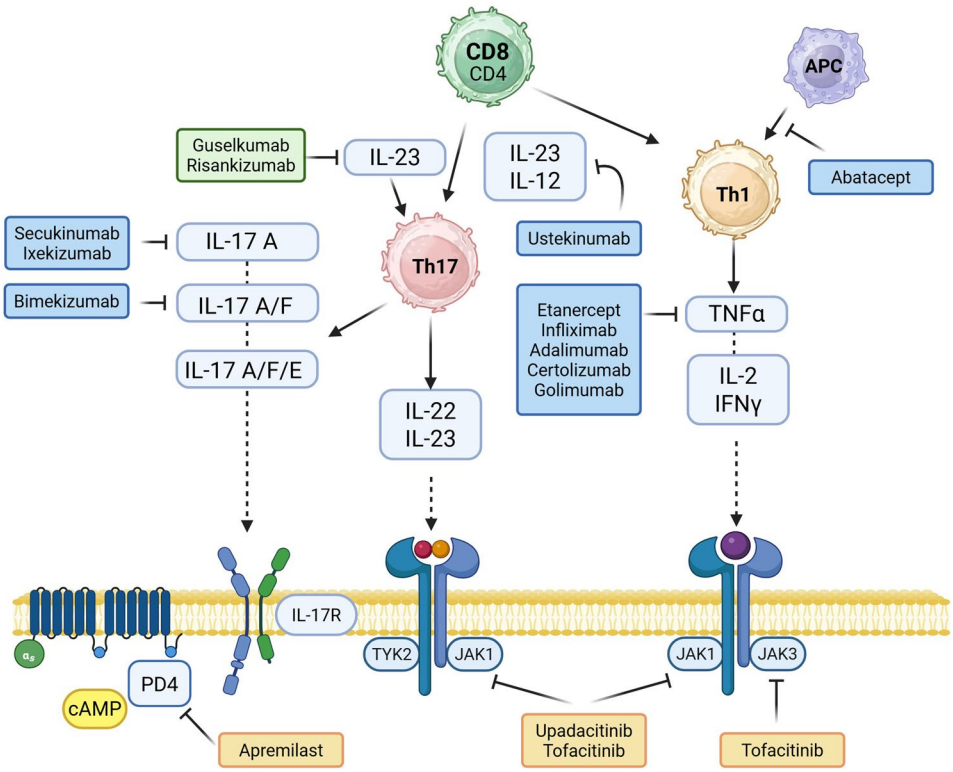

Fig. 1 Main therapeutic targets in psoriatic arthritis. Approved biologic disease-modifying antirheumatic drugs and targeted synthetic disease-modifying antirheumatic drugs inhibit specific pathways in the inflammatory process that contribute to inflammation and pain. Adapted from Azuaga AB. Int J Mol Sci. 2023 Mar 3;24(5):4901. https://doi.org/10.3390/ijms24054901 [126]

heterogeneity of PsA. In this article, we refer to treatment-naïve and treatment-experienced patients. Rather than focussing on the number of previous treatments, we emphasise the importance of identifying the underlying factors contributing to drug discontinuation to inform treatment strategies and improve patients' quality of life.

Table 1 Overview of drugs approved for the treatment of psoriatic arthritis (PsA) and typical points in the patient journey when they might be prescribed based on authors' opinions and current local practice

Drug class	Generic name	Typical prescription point in patient journey
Non-steroidal anti-inflammatory drugs (NSAIDs)	Various	Initial treatment for mild joint symptoms and inflammation
Corticosteroids	Prednisone, methylprednisolone	Short-term relief for flare-ups; local injections may be considered as adjunctive therapy
Conventional synthetic DMARDs (csDMARDs)	Methotrexate	Early in the disease for moderate symptoms; often used in combination with biologics or as a first-line agent
	Leflunomide	Alternative to methotrexate or in combination when response to monotherapy is inadequate
	Sulfasalazine	Used when patients have peripheral arthritis. Less effective for skin lesions
Biologic DMARDs (bDMARDs)	**TNF inhibitors**	
	Adalimumab	Moderate to severe cases; can be first line for severe disease or after failure of at least one csDMARD
	Etanercept	Similar use as adalimumab
	Infliximab	Similar use as other TNF inhibitors
	Certolizumab pegol	Similar use as other TNF inhibitors
	Golimumab	Similar use as other TNF inhibitors
	IL-12/23 inhibitors	
	Ustekinumab	For patients with inadequate response to TNF inhibitors or those who prefer less frequent dosing
	IL-17 inhibitors	
	Secukinumab	Effective for both joint and skin symptoms; used after or in place of TNF inhibitors
	Ixekizumab	Similar use as secukinumab
	Bimekizumab	Inhibits both IL-17A and IL-17F, providing a potentially broader suppression of the inflammatory processes associated with PsA
	IL-23 inhibitors	
	Risankizumab	For patients with inadequate response or intolerance to csDMARDs and other bDMARDs
	Guselkumab	For patients with active psoriatic arthritis, particularly those with an inadequate response to TNF inhibitors
	CTLA-4 inhibitor	
	Abatacept	For patients who have shown intolerance or an inadequate response to TNF inhibitors or other bDMARDs; no effect on psoriasis
Targeted synthetic DMARDs (tsDMARDS)	**PDE4 inhibitors**	
	Apremilast	For patients with moderate disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAKi is appropriate
	JAK inhibitors	
	Tofacitinib	For patients with moderate to severe PsA, particularly those who have had an inadequate response to at least one bDMARD, taking safety considerations into account
	Upadacitinib	Similar use as tofacitinib, with potentially broader anti-inflammatory effects

CTLA-4, cytotoxic T-lymphocyte associated protein 4; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase, PDE4, phosphodiesterase type 4; TNF, tumour necrosis factor

2 The Typical Patient Journey

The presentation of PsA can be quite varied. Typical clinical features are joint symptoms (asymmetric oligoarthritis being the most common one), skin lesions (psoriasis precedes the onset of PsA in 84% of patients), axial involvement, nail changes, enthesitis and dactylitis [2].

Diagnosis of PsA involves a combination of clinical evaluation, imaging studies and laboratory tests to rule out other conditions. Overlapping clinical features with other diseases, such as osteoarthritis or rheumatoid arthritis, make PsA a challenging disease to diagnose, especially in the early stages [10]. Early diagnosis is crucial for starting a prompt therapeutic intervention and could improve clinical outcomes [11], but it is still unclear how early intervention may influence the course of PsA [12–14].

Efforts to characterise the earliest stages of disease have focussed on understanding the psoriasis-to-PsA transition [15]. Understanding the metabolic signature of patients with PsA may reveal pivotal disease mechanisms and the identification of early biomarkers of PsA [16].

Typically, the psoriasis-to-PsA transition takes approximately 10 years [15]. Analyses of the progression from initial skin symptoms to the first signs of PsA have highlighted risk factors such as obesity, nail involvement, family history of PsA and extensive or severe psoriasis. A subclinical stage of PsA has also been identified and is characterized by unexplained arthralgias and/or evidence of enthesosynovial inflammation detected by ultrasound and magnetic resonance imaging (MRI). This subclinical phase usually occurs 1–3 years before the onset of arthritis; such patients are at imminent risk of developing PsA. These insights have paved the way for preventive interventions targeting patients with psoriasis who are at risk of PsA. However, there is still insufficient evidence about what current biological therapies could do at these different stages [17]. Johnson & Johnson is currently conducting a clinical trial to validate the effectiveness of guselkumab in the subclinical stage of PsA [18].

In a consensus statement from the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN), experts in the disease proposed the following three terms to describe patients in pre-clinical stages of PsA: 'at increased risk for PsA' for those having one or more risk factors for progression to PsA, 'psoriasis with asymptomatic synovio-entheseal imaging abnormalities' and 'psoriasis with musculoskeletal symptoms not explained by other diagnosis' [19]. These three stages are similar to those proposed by EULAR [20]. Adopting these terms could help stratify patients for PsA prevention trials. Following diagnosis, the treatment strategy should be based on a shared decision between the patient and healthcare provider and consider the benefit–risk profile of different options [21].

2.1 Treatment Paradigms

PsA treatment should aim to achieve sustained remission, or maintain low disease activity, and prevent structural damage by using a treat-to target approach [9]. A stepwise treatment approach is common, with patients often starting with topical therapies or phototherapy for skin symptoms or NSAIDs and intra-articular steroid injections for joint symptoms. If disease activity persists, systemic treatment with csDMARDs, such as methotrexate, are used. For patients with more severe disease or those who fail to respond to initial therapies, bDMARDs targeting specific inflammatory mediators such as tumour necrosis factor (TNF) or IL inhibitors are recommended [9, 22]. TsDMARDs are usually used as second-line targeted therapy (or third-line DMARDs) but can be administered after a csDMARD if a bDMARD is not appropriate and safety issues are considered.

The updated EULAR recommendations highlight the need to consider extra-musculoskeletal manifestations and comorbidities when making treatment choices. Patients with clinically relevant skin involvement should preferably be given an IL-17A, IL-17A/F, IL-23 or IL-12/23 inhibitor, and those with uveitis, a TNF inhibitor (TNFi)—although the dual IL-17A/F inhibitor bimekizumab has been shown to reduce the incidence of uveitis in patients with axial spondyloarthritis [23]; and those with inflammatory bowel disease a TNFi or an IL-23 inhibitor or IL-12/23 inhibitor or a JAK inhibitor [9]. To date, the choice of drug often rests on the presence of comorbidities, psoriasis severity or cost [8].

Despite the number of treatment options, patients often do not achieve an adequate response, lose response or develop intolerance over time [24, 25].

2.2 Factors Contributing to Treatment Discontinuation and/or Inadequate Response to Treatment

There are many reasons why patients with PsA can have an inadequate response to a first bDMARD. Patients with PsA experience a greater prevalence of cardiometabolic disorders, such as obesity, hypertension, dyslipidemia and diabetes mellitus, which have implications for treatment. Comorbidities can affect the tolerability and efficacy of DMARDs [7] and, thus, should be systematically evaluated and managed in all patients with PsA [26].

Obesity is one of the most prevalent comorbid conditions [27] and has been identified as a risk factor for methotrexate-related liver toxicity [28]. Many studies have observed that the response to TNFi is inferior in obese patients [6, 29, 30]. Interestingly, a better clinical response to the IL-17A inhibitor secukinumab was observed in obese patients compared with normal-weight patients [31]. Furthermore, a Spanish multicentre study showed that, in patients with PsA

and axial spondyloarthritis, the factors associated with lower risk of secukinumab discontinuation were obesity, hypertension and diabetes, highlighting the central role of IL-17A in the pathogenesis of these diseases, which contribute to the immune-mediated inflammation associated with PsA [32, 33]. These data suggest that patients with PsA and cardiometabolic disorders may benefit from an IL-17A-targeted therapy over other interventions.

Modifiable factors such as tobacco use can also affect the response to TNFi. The DANBIO registry showed that, in PsA, smokers had a poorer response to TNFi compared with non-smokers. This was most pronounced in patients treated with infliximab or etanercept [34].

Although gene variants in the NF-κB pathway and TNF-α gene polymorphisms have been associated with worse response to TNFi, further research is required before they can be used to guide treatment selection [35–37].

Other factors that affect treatment response include disease severity and duration, predominant disease domain (which could make targeting specific immune pathways less effective, such as IL-23 inhibitors in axial PsA), drug dose, pharmacokinetic issues and immunogenicity leading to anti-drug antibody formation [8, 38–40]. Previous medication history and inadequate pain management can also lead to poor responses [41]. Additionally, non-adherence to treatment regimens due to socioeconomic factors, medication side effects or psychological barriers should also be considered [37]. Observational studies have shown that female sex is associated with poorer outcomes and lower persistence rates with TNFi, secukinumab, ustekinumab and apremilast [42]. These findings were confirmed in a meta-analysis that highlighted the need to report sex-disaggregated results of randomised controlled trials to better understand sex-related differences in PsA [43].

Real-world studies have shown that the IL-17 inhibitor ixekizumab and the JAK inhibitor tofacitinib have a good retention rate in patients with PsA who are refractory to biologic and targeted synthetic DMARDs, regardless of sex, disease duration, comorbidities (including obesity) or prior line of treatment [44, 45]. This type of study could help rheumatologists to better position bDMARDs and tsDMARDs in PsA treatment schemes.

The multitude of factors that influence treatment response underscores the complexity of PsA and the importance of a personalised approach, whereby both the clinical characteristics of the disease and the individual circumstances of the patient are considered.

Whilst the use of concepts developed for rheumatoid arthritis to describe patients who have failed b/tsDMARDs from two different classes ('difficult to treat' patients), or who remain with disease symptoms after failing to respond to all available b/tsDMARDS (refractory or treatment-resistant patients) is appealing [46, 47], they are difficult to define for patients with PsA and, therefore, of limited utility. A recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) study found that, whilst experts favour the differentiation between 'difficult to treat' and 'complex to manage' patients, there is less than 50% agreement on the specific treatment failure criteria [48]. Both GRAPPA and EULAR are independently working on definitions of 'difficult to treat' PsA, which will help facilitate studies and trials in this area. Further understanding the characteristics of these patients, particularly the contribution of inflammatory mechanisms versus non-inflammatory mechanisms to disease activity, could be particularly useful when deciding on the next line of treatment [49].

In some cases, despite apparent control of the inflammatory process, which is difficult to assess objectively, residual pain persists. To improve the clinical management of these patients, it is important to determine the factors associated with this clinical phenotype. One of the most frequent causes of this therapeutic failure is the presence of pre-existing conditions such as non-inflammatory pain secondary to fibromyalgia. However, sometimes the persistence of pain, despite the reduction of inflammation, may be due to a central hypersensitivity process, not related to concomitant fibromyalgia, but secondary to the disease itself [50–52]. In this case, comorbidities such as depression or insomnia could influence the process. Also, pain catastrophizing, a psychological response to pain, has been recently confirmed as an independent predictor of drug suspension within 2 years in patients with PsA and axial spondyloarthritis [53]. In patients with rheumatoid arthritis, persistent pain can trigger neuroendocrine responses that initiate neurogenic inflammation, amplify the release of cytokines and the JAK/signal transducer and activator of transcription (JAK/STAT) signalling pathway, which has been linked to pathophysiological mechanisms of pain [51, 54]. Clinical trials have reported that JAK inhibitors may be effective in reducing pain regardless of their anti-inflammatory action [55].

As mentioned above, there are no reliable, validated predictors to anticipate how a patient will respond to a specific treatment. This leads to clinical uncertainty, delays in finding the right treatment and potential unnecessary side effects. Currently, artificial intelligence (AI), particularly machine learning (ML), is being used to identify patterns in large volumes of clinical and genomic data. The ML models have the potential to predict response to treatments on the basis of a combination of clinical and biological data. However, they are dependent on the quality of the data used to develop them and misapplication of AI algorithms, which can yield suboptimal recommendations, may hinder treatment selection and negatively impact clinical outcomes. Therefore, careful validation and refinement of these tools are essential to harness their full potential in clinical practice [56].

In the next sections, we focus primarily on people with established PsA. We review advances in identifying

biomarkers of drug response and studies examining the effects of targeted therapies in both treatment-naïve and treatment-experienced patients that could optimise treatment sequencing.

3 Efforts to Identify Biomarkers of Drug Response

Integrating imaging and clinical assessment with biomarker analysis could help to tailor treatments to patients' molecular phenotype. Despite important advances in this area, biomarkers predictive of drug response need further validation before they can be implemented in general clinical practice (Table 2) [57].

Administering bDMARDs according to patients' immunophenotype, on the basis of the proportion of activated T helper 17 (TH17) cells and activated TH1 cells within the CD4 population, has been shown to be more effective than providing standard bDMARD therapy on the basis of their clinical features [58, 59]. These immunophenotypes are currently being prospectively tested and further refined in the OPTIMISE study [60].

There is evidence that genetic variants and histone modifications can affect drug response in patients with PsA [61, 62], with genetic variants in the TNF–TNFR pathway and the NF-kB pathway correlating with TNFi response [63]. Hypothesis-free genome-wide association studies (GWAS) in large well-characterised cohorts are required to validate these variants as genetic biomarkers of drug response.

Proteomic analyses have also identified serum biomarkers and autoantibodies associated with disease activity and treatment response, but they also need to be validated in large-scale studies [64, 65].

Artificial intelligence-based methods are helping to integrate multimodal clinical, imaging and biomarker data and could facilitate the recognition of PsA and prediction of drug response in the not too distant future [66, 67]. Until then, clinical examination and ultrasound and radiographic imaging are crucial to determine structural damage and the extent of inflammatory versus non-inflammatory mechanisms in disease activity [46, 47, 68, 69]. This could help reduce unnecessary exposure to less effective treatments, particularly in treatment-experienced patients.

4 Considerations in Treatment Sequencing

Understanding the rationale for treatment sequencing is important for optimising therapeutic outcomes, especially in patients who have experienced multiple treatment failures. It is not uncommon for patients with PsA to switch or swap medications after 6 months to overcome drug resistance or reduce side effects. However, several studies have shown that minimal disease activity is achieved in as few as 20% of patients, even after switching to a second or third b/tsDMARD, independent of the mechanism of action [70, 71].

Whilst the EULAR recommendation is to swap drugs after a second failure [72], GRAPPA does not offer a recommendation on this issue [7].

Further understanding why treatment-experienced patients may be less likely to achieve treatment targets could change the positioning of newer b/tsDMARDs in the PsA treatment algorithm, as their uptake mostly occurs in treatment-experienced patients [73].

A 15-year real-world study showed that drug switching or swapping were both good treatment options after failure of the first bDMARD [74]. Yet, many studies have shown that patients who experience inadequate response or intolerance to TNFi, often the first-choice biological treatment for PsA, have a higher risk of treatment failure with other types of biologics [41].

Recent results from clinical trials with the IL-23 inhibitor risankizumab and the IL-17A/F inhibitor bimekizumab suggest that they can have durable efficacy in TNFi-experienced patients. The global phase 3 KEEPsAKE 1 and 2 trials showed that, in patients with active PsA who had an inadequate response to $\geq$ 1 csDMARD and/or 1-2 bDMARDs, risankizumab had durable efficacy and was well tolerated through 100 weeks [75, 76]. Bimekizumab treatment also resulted in rapid and sustained responses in patients with PsA previously treated with TNFi [77]. This response was similar to that observed in bDMARD-naïve patients [78], suggesting that failure or intolerance to TNFi does not seem to affect the efficacy of bimekizumab, but further real-world studies will be required to confirm this.

Similarly, trials with the IL-17i ixekizumab and the JAKi tofacitinib showed that they were able to improve symptoms in patients with prior inadequate response to TNFi [79, 80].

Interestingly, a retrospective cohort study of 30,700 treatment-naïve patients with psoriasis and PsA showed that patients starting with TNFi will switch/swap more rapidly and frequently than those who start with anti-IL inhibitors, with those starting with IL-23 inhibitors switching/swapping biological therapy less frequently than those with anti-IL-12/23 and anti-IL-17 (4.9% versus 8.7% and 9.4%, respectively) [81]. These results suggest that, as has been shown for rheumatoid arthritis, TNFi may not necessarily be the best first-choice bDMARD [82].

It is worth noting that biosimilar-to-biosimilar switching is safe. The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have recently released statements supportive of switching to biosimilars, including

Table 2 Selected biomarkers that may help predict drug response in patients with psoriatic arthritis (PsA)

Biomarker category	Specific biomarkers	Potential predictive value for drug response	Relevant drugs	Notes	References
Genetic biomarkers	Various, including polymorphism in HLA genes; TNF-A, FCGR2A, TNFAIP3, TNFR1/TNFR1A/TNFRSF1A, TRAIL-R1/TNFRSF10A, FCGR3A	Correlate with response at various levels of statistical significance	TNFi	Genetic markers may help predict patient's risk profile and quality of life improvements post-treatment	[35–37]
Cellular biomarkers (and related cytokines)	Activated Th17 and Th1, IL-17A, IL-17F, IL-22, IL-6	High levels of Th17 cells may predict poor response to TNFi but better response to IL-17 inhibitors	TNFi, IL-17 inhibitors	Th17 cells drive inflammation in PsA; targeting their cytokines may be effective	[15, 64]
TNF-related biomarkers	TNFα, TNFR1, TNFR2	High serum levels of TNFα have been linked to better responses to TNF inhibitors	TNFi	Differential response may be due to the forms of TNFα (transmembrane versus soluble) targeted by the TNFi	[117]
Other circulating biomarkers	CRP, MMP-3, complement C3	High levels of CRP and MMP-3 are associated with better response to TNFi; lower C3 associated with response to adalimumab and etanercept	TNFi	CRP and MMP-3 are involved in inflammation and joint destruction, C3 in immune response	[15, 64]
Tissue biomarkers	Various including, S100-A8, collagen, annexin A1/2	Proteins predictive of response to TNFi and other biologics	TNFi, other biologics	High-throughput proteomic analysis of synovial tissue can identify response predictors	[15]
Auto-antibodies	Rheumatoid factor, anti-CCP	Low baseline levels may predict better response to treatment.	Various bDMARDs	Presence may indicate a more aggressive disease phenotype and influence treatment choice	[65]

bDMARDs, biologic disease-modifying antirheumatic drug; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; HLA, human leucocyte antigen; FCGR-, Fc gamma receptor; IL, interleukin; MMP, matrix metalloproteinase; Th, T helper; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; TRAIL-R1, TNF-related apoptosis-inducing ligand receptor 1

switching from one biosimilar to another biosimilar of the same reference biologic [83].

5 Combination Treatments

Sometimes, using a combination of therapies can be more effective than a single treatment. If monotherapy fails, introducing an additional medication might provide better control of the disease. In rheumatoid arthritis, there is high-quality evidence supporting combination therapy. The 2022 EULAR recommendations for managing rheumatoid arthritis suggest continuing with methotrexate (or other csDMARDs) when treatment with bDMARDs or a JAK inhibitor is planned [72].

The evidence for using a bDMARD with methotrexate in patients with PsA is less clear [84, 85]. EULAR guidelines on the management of PsA advise to continue methotrexate but to reduce the dose in good responders.

Real-life studies have shown that etanercept combination therapy with csDMARDs did not provide greater improvement on the long-term drug survival [86] and that combining a b/tsDMARD with a csDMARD is associated with lower persistence and worse safety profile compared with monotherapy in PsA [87]. These findings are consistent with clinical trials showing that concomitant methotrexate did not increase the efficacy of ustekinumab, ixekizumab or bimekizumab [79, 88, 89].

Dual targeted therapy (DTT) has emerged as a promising approach in patients with refractory spondyloarthritis and extra-musculoskeletal manifestations or with PsA and extra-musculoskeletal manifestations, but its effectiveness/safety ratio remains unclear. In a recent retrospective analysis of DTT in clinical practice for spondyloarthritis/PsA, the most commonly used combinations were TNFi plus an IL12/23 inhibitor and TNFi plus an IL-17 inhibitor [90]. Major clinical improvement (change in Ankylosing Spondylitis Disease Activity Score with C-reactive protein > 2 or improvement > 85% in Disease Activity in Psoriatic Arthritis) was achieved in 69.4% of cases, and almost 60% reached a low-activity/remission rate. In several case reports, a TNFi in combination with an IL-23 inhibitor has shown good efficacy with acceptable safety in treatment-resistant patients with PsA [91]. Johnson & Johnson are evaluating a fixed-dose combination of guselkumab and golimumab versus either bDMARD alone in PsA patients with inadequate responses to TNFi (NCT05071664). This study replicates one in patients with ulcerative colitis that suggested that the combination of guselkumab plus golimumab combination therapy was more effective than either drug alone [92].

It is worth noting that the development of remtolumab, a TNF and IL-17A targeted dual variable domain immunoglobulin, was discontinued as it showed no difference in efficacy compared with adalimumab after 12 weeks [93].

Further research is required into combination therapies involving tsDMARDs. Evidence to date indicates that the efficacy and safety of tsDMARDs in combination with csDMARDs or bDMARDs seems to be similar [94–96] or lower [97] compared with tsDMARDs monotherapy.

Intriguingly, sequential (or alternating) rather than combination treatment with secukinumab and guselkumab was successful in three patients who had previously shown inadequate responses to monotherapy with TNF inhibitors, secukinumab and guselkumab [98]. Because of overlapping drug half-lives, there is an element of combination therapy in this approach.

6 Expert Opinion on the Drug Pipeline and Optimal Management of Treatment-Experienced Patients

Amongst the molecules that are in clinical development for PsA, eight are bDMARDs, with four in phase II trials and four in phase III trials. Of these, six are IL-17 inhibitors and one is an IL-23 inhibitor. There are also seven tsDMARDs in clinical development: four in phase II and three in phase III trials; six of these are JAK inhibitors, and the seventh is a MAP-kinase-activated kinase 2 inhibitor [99] (Table 3).

Despite the association of PsA with over 100 genetic variants, the drug development pipeline remains largely focussed on a small subset of targets. This narrow focus leaves other potential disease-relevant pathways unexplored, thereby missing opportunities to develop treatments that could be more effective for different subgroups of patients or that could address aspects of the disease not currently well managed by existing therapies.

One of the selective JAK1 inhibitors under investigation is ivarmacitinib. A phase 3 randomised clinical trial in patients with rheumatoid arthritis showed that ivarmacitinib could benefit patients with an inadequate response to csDMARD [100]. Other potential candidates in this class of drugs that are not yet in clinical trials for PsA are peficitinib, solcitinib, abrocitinib, itacitinib and ropsacitinib [101].

Tyrosine kinase 2 (TYK2) inhibitors represent a new class of tsDMARD that is showing promise for the treatment of PsA. TYK2 is a member of the JAK family and mediates IL-23 signalling. An oral, small molecule that inhibits TYK2 allosterically, deucravacitinib, has been approved for the treatment of moderate to severe plaque psoriasis. In a phase II trial, deucravacitinib has shown sustained effectiveness in several domains of PsA, namely

arthritis, enthesitis and dactylitis, and was well tolerated [102]. Significant reductions in IL-23 pathway-associated biomarkers correlated with therapeutic response to deucravacitinib treatment [103]. The results of larger, longer trials are awaited to establish its long- term efficacy and safety in patients with active PsA. Deucravacitinib's high selectivity for TYK2 may avoid the safety issues associated with JAK inhibitors as well as orthosteric TYK2 inhibitors, such as brepocitinib, which has completed phase II trials for PsA and inhibits TYK2 as well as at least one other JAK [104]. Another highly selective, oral, allosteric TYK2 inhibitor, zasocitinib, is being tested in patients with active PsA (NCT05153148), and results at 12 weeks have recently been reported [105].

Future head-to-head comparisons with other targeted agents will be needed to establish the position of these drugs in the management of PsA.

As discussed above, despite advances in reducing the inflammatory burden of psoriatic disease, a proportion of patients continue to experience significant pain. The presence of persistent pain, unrelated to inflammation, has been documented in rheumatoid arthritis patients by using the ratio of number of swollen joints (NSJ) to number of tender joints (NTJ). A ratio below 0.5 was predictive of poor therapeutic response [106]. In the Danish DANBIO registry of patients with PsA who had failed at least one biologic treatment, those with a lower NSJ/NTJ ratio also had a poorer response to treatment [107].

Clinical trials that have included treatment-experienced patients (Table 4) and retrospective studies provide interesting insights into the management of patients who fail to respond to a first biological therapy. Drug adherence rates and patient-specific factors (such as sex [108] and reasons for previous drug discontinuation) need to be considered. A recent study showed that German patients with PsA might persist longer with TNFi and an IL-17 inhibitor than an IL-12/23 inhibitor or JAK inhibitor [109], whilst another study using data from the Danish Rheumatology Registry reported that patients with PsA receiving a first- or second-line IL-17 inhibitor showed similar adherence to therapy [110]. These findings suggest that failure to respond to a first TNFi or IL-17 inhibitor should not preclude switching to another drug with the same mechanism of action. Several studies have shown that swapping rather than switching drugs offers no significant advantage and that failure rates are similar to those in treatment-naïve patients [74, 111]. Thus, decisions on whether to switch or swap should be based on individual patient responses and tolerability.

7 Conclusions

When managing treatment-experienced patients, in addition to reviewing their treatment history, comorbidities and lifestyle factors that can influence treatment response, and their treatment preferences, healthcare providers should try to determine the contribution of inflammatory and non-inflammatory mechanisms to disease activity as this could help inform the most appropriate next line of therapy. Particular attention should be given to patients on biologics with persistent, inflammation-independent pain, one of the most frequently cited reasons for lack of treatment success,

Table 3 Molecules in development for psoriatic arthritis

Drug class	Name	Target	Phase	CT number/status
bDMARDs	Izokibep	IL-17A inhibitor	II	NCT05623345/terminated
	Sonelokimab	L-17A & IL-17F inhibitor	II	NCT05640245/completed
	Vunakizumab	IL-17A inhibitor	II	NCT05055934/completed
	Neihulizumab	PSLG-1 inhibitor	II	NCT02267642/completed
	Netakimab	IL-17A inhibitor	III	NCT03598751/unknown
	Brodalumab	IL-17 receptor inhibitor	III	NCT02024646/completed*
	Tildrakizumab	IL-23 p19 inhibitor	III	NCT04314544/recruiting
tsDMARDs	Brepocitinib	JAK1 inhibitor, TYK2 inhibitor	II	NCT03963401/completed*
	VTX958	TYK2 inhibitor	II	NCT05715125/terminated
	NDI-034858	TYK2 inhibitor	II	NCT05153148/completed*
	Zunsemetinib	MAP-kinase-activated kinase inhibitor	II	NCT05511519/terminated
	Filgotinib	JAK1 inhibitor	III	NCT04115748/terminated*
	Ivarmacitinib	JAK1 inhibitor, STAT3 inhibitor	III	NCT04957550/unknown status
	Deucravacitinib	TYK2 inibitor	III	NCT04908202/active, not recruiting

IL, interleukin; JAK1, Janus kinase 1; MAP kinase, mitogen-activated protein kinase; PSLG-1, P-selectin glycoprotein ligand 1; STAT3, signal transducer and activator of transcription 3; TYK2, tyrosine kinase 2

* With results

Table 4 Clinical trials for psoriatic arthritis (PsA) that include treatment-experienced patients

Trial name	Intervention	Patient population	Primary outcome	Key findings	Clinical trial ID	References
FUTURE5	Secukinumab	PsA patients with inadequate response or intolerance to one or more anti-TNF therapies	ACR20 response at week 16	Secukinumab significantly improved ACR20 response rates compared with placebo	NCT02404350	[118]
MAXIMISE	Secukinumab	PsA patients with active spinal manifestations and previous inadequate response to NSAIDs	ASAS20 response at week 12	Secukinumab significantly improved spinal symptoms in PsA patients compared with placebo	NCT02721966	[119]
SPIRIT-P2	Ixekizumab	PsA patients with prior inadequate response to TNF inhibitors	ACR20 response at week 24	Ixekizumab significantly improved symptoms and inhibited disease progression	NCT02349295	[79]
BE COMPLETE	Bimekizumab	PsA patients with inadequate response to one or two TNF inhibitors	ACR50 response at week 16	Bimekizumab showed significant improvement in ACR50 response rates compared with placebo	NCT03896581	[120]
Keepsake 1 and Keepsake 2	Risankizumab	PsA patients with inadequate response to conventional synthetic DMARDs and/or biologic DMARDs	ACR20 response at week 24	Risankizumab significantly improved ACR20 response rates compared with placebo	NCT03675308 and NCT03671148	[121]
DISCOVER-1	Guselkumab	PsA patients with inadequate response to up to 2 anti-TNF agents	ACR20 response at week 24	Guselkumab showed significant improvement in ACR20 response compared with placebo	NCT03162796	[122]
AFFINITY	Guselkumab and golimumab	PsA patients with inadequate response to 1 or 2 anti-TNF agents	Percentage of participants who achieve minimal disease activity (MDA) at week 24	No results posted	NCT05071664	Not available
PALACE-1-3	Apremilast	PsA patients with prior anti-TNF treatment failure	ACR20 response at week 16	Apremilast showed moderate improvement in ACR20 responses	NCT01172938 NCT01212757 NCT01212770	[123]
OPAL Beyond	Tofacitinib	PsA patients with inadequate response to at least one TNF inhibitor	ACR20 response at month 3	Tofacitinib improved physical function and reduced pain significantly more than placebo	NCT01882439	[80]
SELECT-PsA 1	Upadacitinib	PsA patients with inadequate response to non-biologic DMARDs	ACR20 response at week 12	Upadacitinib showed superior efficacy in achieving ACR20 compared to placebo and adalimumab	NCT03104400	[124]
SELECT-PsA2	Upadacitinib	PsA patients with inadequate response or intolerance to at least 1 biologic DMARDs	ACR20 response at week 12	Upadacitinib showed superior efficacy in achieving ACR20 compared with placebo	NCT03104374	[125]
Efficacy and Safety of Filgotinib	Filgotinib*	PsA patients with prior inadequate response or intolerance to one TNF inhibitor	ACR20 response at week 16	Development program for filgotinib for participants with psoriatic arthritis has been stopped	NCT03320876	Not available

ACR20, American College of Rheumatology response criteria; ASAS20, Ankylosing Spondylitis response criteria; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor

* Not approved for PsA

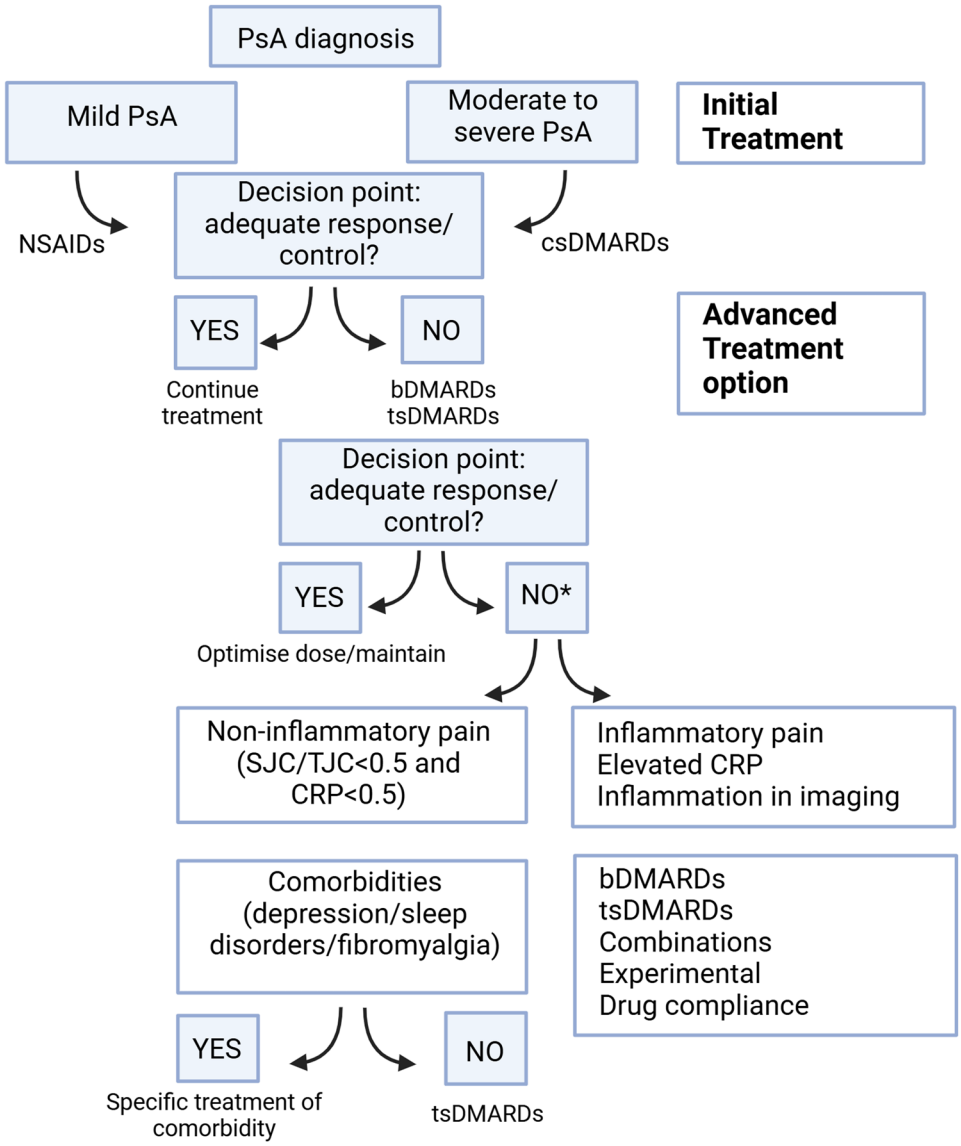

Fig. 2 Treatment of psoriatic arthritis (PsA): Flowchart illustrating the complex decision-making process, from initial diagnosis and NSAID use, progressing through conventional synthetic DMARDs and biological/targeted synthetic DMARDs, including decision points based on patient response and comorbidities (based on authors' opinion). *Both options (non-inflammatory and inflammatory pain) may co-exist; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, corticosteroids and conventional synthetic disease-modifying antirheumatic drug; NSAID, non/steroidal anti-inflammatory drug; SJC/TJC, swollen joint count/tender joint count ratio; tsDMARDs, targeted synthetic disease-modifying antirheumatic drug

as they may benefit from alternative approaches for pain management [112, 113]. One way to detect this group of patients would be by a low NSJ/NTJ ratio, along with normal C-reactive protein levels and moderate or high Disease Activity in Psoriatic Arthritis score. In these cases, the presence of fibromyalgia, pain catastrophising or other comorbidities (depression or sleep disorders) should be ruled out. In cases where these conditions are present, patients may benefit from alternative approaches to pain management, including psychological support [54]. If these conditions are ruled out, treatment with JAK inhibitor could be considered, based on its pain-reducing effects (Fig. 2).

Imaging technologies, in particular musculoskeletal ultrasound, can detect subclinical inflammation, and preliminary evidence suggests that they could be used to identify patients with psoriasis at risk of progression to PsA, predict drug response and potentially guide treatment decisions in refractory patients [114, 115].

It is also important to highlight the role of non-pharmacological approaches, such as physical activity and diet modifications, in the management of patients with PsA. There is growing evidence of the benefits of lifestyle modifications on PsA symptoms and associated comorbidities [9, 116]. Non-pharmacologic approaches could be especially useful for treatment-experienced patients. As the therapeutic landscape for PsA continues to evolve, a better understanding of the biological and clinical nuances of the disease, coupled with a patient-centred approach to treatment, remains crucial for managing this complex condition and improving the quality of life of treatment-experienced patients.

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