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REVIEW

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What's new and what's next for biological and targeted synthetic treatments in psoriatic arthritis?

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ABSTRACT

Introduction: Psoriatic arthritis (PsA) is a chronic arthritis typically associated with cutaneous psoriasis (PsO). Its pathogenesis is connected to an innate and acquired immune response, as well as genetic risk alleles. The extent of immunopathogenic mechanisms and the heterogenicity of clinical manifestation make the identification of patient-targeted therapies a critical issue, and the treatment decision challenging in patients' management.

Areas covered: This review includes a brief overview of biological and small-molecule therapies, focusing on evidence from clinical trials and real-world data that support their use in PsA. We summarize novel and future possible therapeutic strategies, the importance that comorbidities have on selection of therapy and discuss the adverse event of each drug. Relevant papers for up to 1 August 2022 (trials, real-life studies, and reviews) regarding biologics and/or small molecules were summarized.

Expert opinion: In recent years, the treatment of PsA has been revolutionized by new targeted therapies, which offer the opportunity to perform a tailored-tail management, considering risk factors, comorbidities, and the different PsA phenotypes. Growing experience with these new agents allows novel treatment approaches that may improve clinical outcomes for PsA patients, in terms of remission/low disease activity and quality of life.

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Psoriatic arthritis; biological therapies; targeted synthetic treatments; treatment approach

1. Introduction

Psoriatic arthritis (PsA) is a chronic immune mediated inflammatory disease. PsA is a chronic, progressive inflammatory condition characterized by chronic pain and joint damage, frequently associated with skin psoriasis (PsO). PsA carries a significant burden for the individuals affected, who commonly report reduced quality of life, and high socio-economic costs. The clinical manifestations of PsA are highly heterogenic, characterized by peripheral arthritis, enthesitis, dactylitis, axial involvement (spondylitis and sacroiliitis), as well as extra-articular manifestation, such as PsO, onychopathy, inflammatory bowel disease (IBD), and uveitis. Metabolic syndrome, cardiovascular diseases, and psychological comorbidities, such as depression and anxiety, are frequent in PsA when compared to the general population [1,2]. The disease onset is commonly between the third and fourth decades and affects equally men and women with a variable geographical incidence [3]. The clinical presentations and associated comorbidities occur variably in each individual affected by PsA, reflecting the multifaceted underlying pathological mechanisms. PsO and PsA share genetic and environmental risk factors, pathogenesis, and treatments. The strong similarities between the two conditions led to the hypothesis that they are part of the same disease spectrum, defined as psoriatic disease (PsD) [4]. A deeper understanding of PsD pathogenesis has led to a growing number of the immunotherapies available but, despite the advances in the last decades, a significant number of patients with PsA still have not sufficiently controlled disease activity and progression. Therefore, there is the need to better understand the pathogenesis and develop new targeted-therapies, and perfect the treatment choice and patients' management. With this review, we want to provide a summary of the efficacy and safety of the treatments currently available and to provide an overview on the new potential drugs to treat PsA.

2. Pathogenesis of PsA

PsD pathogenesis is complex and yet not fully understood, involving both autoimmunity and autoinflammatory mechanisms [5]. Different genetic and environmental factors (e.g. mechanical strain, gut dysbiosis, lifestyle, obesity, depression) have an important role in the pathogenesis and contribute to an imbalance of the innate and adaptive immune responses that variably targets the joints, skin, and other apparatus.

Both human leukocyte antigen (HLA) and non-HLA genes have been associated with PsA and/or PsO. Among the HLA genes, HLA-B27 is associated with the axial involvement, and HLA-C*0602 associated with PsO and, to a lesser extent, to PsA

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Article highlights

- Currently, the management of PsA is mainly based on the phenotypic presentation of the patients.
- Nevertheless, treatment outcomes for both skin and joints, as well as associated comorbidities, are not achieved in a considerable number of patients, making it necessary to expand the available therapies at disposal.
- p40 IL-23i and IL-17Ai have been used for several years in PsA with good results, and promising data on safety and tolerability are emerging about the use of p19 IL-23i and inhibitors of other isoforms of IL-17, especially IL-17F.
- JAKi represent a class of small molecules capable of interfering at the intracellular level with signaling pathways and which offer the potential to modulate the activity of numerous cytokines implicated in the pathogenesis of PsA simultaneously.
- Among novel therapies, nanobodies seem the most intriguing ones in treating PsA patients.

[6]. Interestingly, different HLA genes, including HLA-B*08, B*27, B*38, and B*39, have been linked to different clinical manifestations in PsA [7]. Genome-wide association studies (GWAS) linked non-HLA genes with PsA pathogenesis, including molecules involved in the immune activation and signaling, such as type I interferons (IFNs), tumor necrosis factor (TNF)-α, and interleukin (IL)-23/IL-17 pathways. For example, IL-23 R, IL-23A (p19), IL-12B (p40), tyrosine kinase 2 (TYK2), TRAF3 Interacting Protein 2 (TRAF3IP2) have been consistently associated with PsA [8,9].

In genetically predisposed individuals, different environmental triggers have a putative role in the onset of PsA, among those biomechanical stress and gut dysbiosis seem particularly relevant [10,11]. Biomechanical stress at articular and periarticular sites (tendons and enthesis) can induce local inflammation in PsA, known as the 'deep Koebner phenomenon' [12]. An unbalanced local immune response can lead to chronic inflammation and to excessive repair processes responsible for the typical disease manifestations, such as enthesitis and local bone formation resulting in enthesophytes and ankylosis [13]. There is growing interest around the role of gut dysbiosis in the pathogenesis of immune mediated inflammatory diseases. Subclinical intestinal inflammation in PsA is highly frequent and likely associated with gut dysbiosis [14,15]. Subclinical gut inflammation has also been associated with peripheral joint disease activity in subjects with SpA [16]. The tissue damage associated with biomechanical stress and gut dysbiosis induces local innate immune responses [17], triggering the production of pro-inflammatory cytokines, including TNF- α and IL-23. The following activation of adaptive immune responses perpetuates the pro-inflammatory loop leading to chronic inflammation [18,19]. The resulting pro-inflammatory milieu induce leukocytes recruitment, angiogenesis, and the production of metalloproteinases, responsible for local inflammation and bone erosions [20–23]. The IL-23/Th17 pathway is primarily involved in the joint, enthesis, skin, and intestinal mucosal immune response providing a link between the genetic predisposition, local mechanical triggers, and systemic pro-inflammatory response. Recently, immune mediated diseases have been elegantly classified based on their molecular signature, and the IL-23/IL-17 immune pathways has been described as the main pathogenic cytokine hub in PsD, shared with SpA and IBD [24]. IL-23 is a pro-inflammatory cytokine that induces the expression IL-17 cytokines, IL-17A, and IL-17 F by resident T cells. IL-23 also induces the expression of other pro-inflammatory cytokines, including TNF- α, IL-22, and IL-21 [25–27], which synergistically contribute to the maturation of IL-17 expressing cells and tissue inflammation [28–30]. TNF-α is another pro-inflammatory cytokine with direct effects on skin, joints, and periarticular structures [31]. Due to the simultaneous and variable involvement of different immune pathways, the interest in blocking simultaneously different pro-inflammatory cytokines has been growing in recent years, with the intent to obtain better control of the disease and to move toward personalized treatment strategies. Inhibitors of common intracellular signaling molecules, i.e. Janus kinases (JAK)/signal transducer and activator of transcription (STAT) molecules, offer this opportunity and have been recently developed to treat rheumatoid arthritis (RA) and PsA. The JAK family includes JAK1, JAK2, JAK3, and TYK2 [32] and leads the intracellular cascade of type I and type II cytokines, including, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-6, IL-12, IL-21, IL-22, IL-23, directly and indirectly involved in the IL-17 and TNF-α immune responses [33,34]. Thus emerges the possibility to interfere with the inflammatory cascade at different levels or to prevent the simultaneous activation of multiple molecules [35–37]. Currently, it is mainly the clinical phenotype of PsD to guide treatment choice (Figure 1) [38], although it is difficult to improve all the signs and symptoms with the use of one drug. Therefore, novel therapeutic strategies are needed for PsA patients.

3. bDMARDs targeting IL-23

In the last few years, several drugs against IL-23/17 axis have been studied and approved. The inhibition of IL-23 is effective in controlling peripheral joint and skin inflammation, as well as the gut domain [39]. This class of drugs appears ineffective on axial disease, emphasizing the recent findings about the uncoupled action of IL-23 and IL-17 in axial-SpA and ankylosing spondylitis (AS), and the hypothesis of a pathogenic role of IL-23 in the initiation of AS but not in maintaining the disease [40]. Ustekinumab (UST), a fully human monoclonal antibody directed against p40 subunit shared by IL-12 and IL-23, primarily inhibits Th-17 differentiation and maturation and it was approved to treat PsA in 2013 [41]. A phase II, double-blind, randomized, placebo-controlled, and crossover study demonstrated a significant improvement in articular and dermatologic involvement in PsA patients, with the achievement of an ACR (American College of Rheumatology) 20 response, HAQ-DI (Health Assessment Questionnaire-Disability Index), DLQI (Dermatology Life Quality Index) at week 12 [42]. Important results were obtained from two phase III, multicenter, double-blind and placebo-controlled studies, which enrolled patients naïve to biologics with moderate-to-severe disease activity nonresponding to nonsteroidal anti-inflammatory drugs (NSAIDs) or csDMARDs (PSUMMIT-1), or who failed to respond to at least one TNFi (PSUMMIT 2) [43,44]. At week 24, there was an improvement in most of PsA domain, including

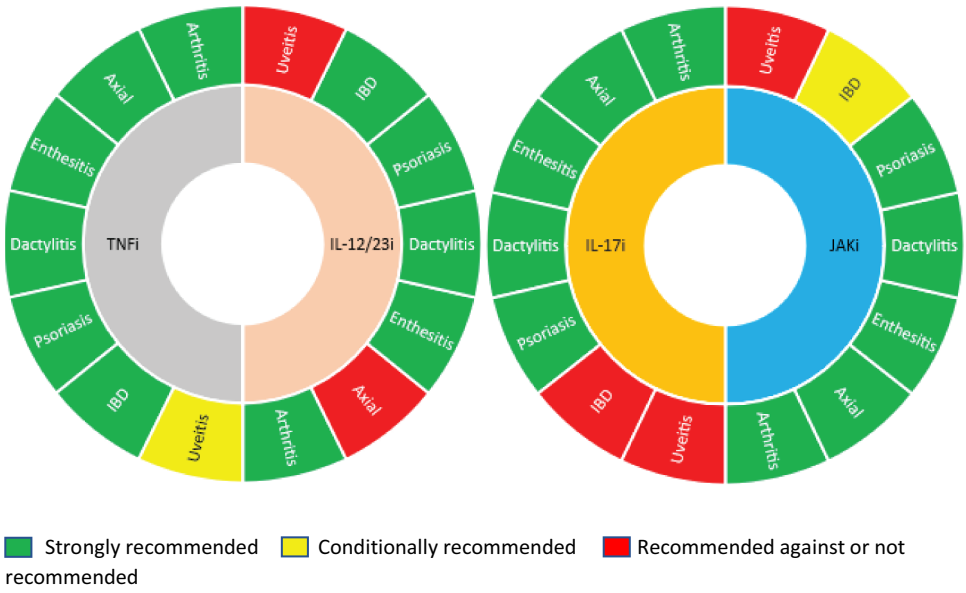

Figure 1. Summary of recommendations for treatment of PsA according to Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [38]. Abbreviations: TNFi, Tumor Necrosis Factor inhibitors; IL-23i, interleukin-23 inhibitors; IL-17i, interleukin-17 inhibitors; JAKi, Janus kinase inhibitors; IBD, inflammatory bowel diseases.

enthesitis and dactylitis; progression of radiographic joint damage was inhibited, mostly in the TNFi naïve group [45]. Moreover, two studies showed that UST was superior to TNFi in resolving the enthesitis and PsO, but not peripheral arthritis [46,47]. The effectiveness of UST was demonstrated in real-world, multicenter study on PsA patients, in particular in skin and peripheral joint domain with a greater response and drug survival in patients with fewer lines of previous bDMARDs [48]. In addition, data from PsAbio, an observational prospective real-world study, suggested a similar response to TNFi and UST in reaching low disease activity (LDA) or minimal disease activity (MDA) after 6 months, with comparable safety outcomes [49]. UST has a good safety profile, as reported in long-term extension studies. The most frequently notified adverse events (AEs) were mild-to-moderate upper respiratory tract infections (URTIs), while the new onset of neoplasms and major cardiovascular events (MACEs) were rare [50].

Guselkumab (GSK) is a human IgG1λ antibody that binds to IL-23 p19 subunit and inhibits IL-23 signaling. Previously approved for the treatment of moderate-to-severe plaque PsO, in 2020 it was approved with or without methotrexate (MTX) for the treatment of PsA in adults with an inadequate response or intolerance to prior csDMARDs therapy. The DISCOVER-1 and DISCOVER-2 trials, which enrolled patients who failed to respond to TNFi or biologic-naïve, respectively, demonstrated significantly better clinical and radiographic outcomes with GSK when compared to placebo. Both skin and axial involvement improved at week 8 with sustained response at week 52 [51,52]. A recent phase IIIb, randomized, controlled study (COSMOS) demonstrated a sustained efficacy of GSK compared to placebo in treating enthesitis, dactylitis, and achieving PsO remission and MDA in patients with inadequate response to TNFi. GSK was also effective in improving fatigue, physical function, and Health-Related Quality of Life (HRQoL) scores [53]. To date, head-to-head trials comparing GSK with other biological therapies are not available; however, a recent network meta-analysis has shown comparable efficacy to anti-IL-17A agents and TNFi in treating arthritis, while offering better cutaneous responses [54]. These studies underline that GSK is a promising treatment option in patients with severe skin involvement, inadequate response to other biologics, or difficult-to-treat PsA. A recent real-world study confirmed Disease Activity in PSoriatic Arthritis (DAPSA) remission or low disease activity (LDA) after 6 months of GSK treatment in 75% of a cohort of 34 PsA patients [55]. GSK has a favorable safety profile with the most common AEs including nasopharyngitis, headache, and URTI. Severe infections, malignancies, and MACEs did not appear to be increased in patients treated with GSK compared to placebo and adalimumab (ADA) [56].

Another IL-23 inhibitor (IL-23i) is Risankizumab (RSK), an antibody that selectively blocks IL-23 by binding to its p19 subunit. RSK was recently approved by the Food and Drug Administration (FDA) for adults with active PsA. The studies KEEPsAKE-1 and KEEPsAKE-2 evaluated its efficacy and safety in adult patients who had responded inadequately or were intolerant to cs- and bDMARDs. These trials showed improvements in the number of swollen and tender joints, as well as enthesitis and dactylitis, with a good safety profile [57,58]. However, there are no current studies evaluating RSK efficacy in real-life PsA patients, unlike on PsO [59].

Tildrakizumab (TLK) is a humanized IgG1κ monoclonal antibody that selectively binds the p19 subunit of IL-23 with high affinity and it is currently approved for the treatment of moderate-to-severe plaque PsO in adult patients who have failed treatment with topical and other systemic therapy [60]. A phase 2b, randomized, double-blind, multidose, placebo-controlled, multicenter study evaluated the efficacy and safety of TLK in PsA. A total of 391 patients were randomized to receive one of the four doses of TLK or placebo. At week 24, a significantly higher proportion of patients receiving any dose

of TLK achieved ACR20 (from 71.4% to 79.5%) versus placebo-treated patients (50.6%), with more responders to TLK 200 mg every 4 weeks (Q4W). Other endpoints were also significantly improved in all TLK groups, such as higher rates of ACR50/70, DAS28-CRP<3.2, and MDA through week 52. On the other hand, TLK was not effective in determining resolution of dactylitis and enthesitis. Most AEs were mild with nasopharyngitis and URTI being the most frequent [61]. Furthermore, ongoing randomized clinical trials are evaluating its efficacy and safety in PsA patients, especially in patients naïve to TNFi [62].

Data on IL-23i are illustrated in Table 1.

4. bDMARDs targeting IL-17

The central role of IL-17 in the immunopathogenesis of PsA justifies the use of IL-17 inhibitors (IL-17i) in all domains of PsD [63]. Interestingly, IL-17 can also be produced independently from IL-23 stimulation at the entheseal site, mainly in the axial enthesis, as well as in the gut epithelium with a role in repair processes and local tissue homeostasis [64]. Thus, the blockade of IL-17 may lead to a paradoxical exacerbation or new onset of IBD, contraindicating their use in IBD patients. Moreover, monoclonal TNFi would be preferred over IL17i for patients with repeated uveitis as there is minimal evidence indicating efficacy of anti-IL-17 therapies in treating uveitis [65]. Finally, women and people with a higher Body Mass Index (BMI) may benefit more from IL-23 inhibition compared to TNF inhibition [66]. A tailored approach currently lacks biological markers; however, the choice toward one mechanism of action or another can be led by the clinical phenotype and individual characteristics.

Secukinumab (SEC), the first IL-17i approved to treat PsA, is a fully human IgG1κ monoclonal antibody that selectively binds to IL-17A with high affinity [67]. The FUTURE trials showed a sustained improvement of arthritis, enthesitis, dactylitis, skin, nail disease, and health status in PsA patients. Interestingly, the sustained response through week 52 was independent of previous treatment with TNFi. Moreover, it was observed an inhibition of structural damage and radiographic progression in patients treated with SEC compared to those receiving placebo [68–70]. In the PREVENT phase III study, SEC successfully improved symptoms in a non-radiographic axial SpA (nr-axSpA) group of patients. Male sex, elevated C-reactive protein, and the evidence of active sacroiliitis on MRI were predictors of good response to treatment [71]. In a head-to-head trial comparing the efficacy and safety of SEC versus ADA in biologic-naïve patients, SEC was not superior to ADA in achieving the primary endpoint of ACR20 response at week 52. However, SEC was associated with a higher treatment retention rate than ADA [72]. Interestingly, a network meta-analysis comparing SEC to other bDMARDs showed that in the mid-long term, TNFi naïve patients treated with SEC were more likely to achieve clinical responses than those receiving infliximab (IFX) [73]. The superiority of SEC compared to UST was similarly shown in a systematic review and in a meta-analysis on TNFi naïve PsA patients; however, it was not confirmed in patients who failed to respond to TNFi [74,75]. One of the first real-world study has suggested the efficacy of SEC in peripheral arthritis in patients who have failed prior TNFi treatment [76]. A recent real-world study has demonstrated an improvement in joint and skin diseases, as well as an enhancement of disease severity in a cohort of about 600 European patients [77]. Additionally, it was demonstrated that SEC was efficacious in daily clinical practice in PsA and AS patients characterized by several comorbidities and/or previous treatment failures. Interestingly, the SEC retention rate was shown to be independent from BMI or sex, suggesting a greater efficacy of SEC in overweight patients and women [78]. Moreover, SEC was demonstrated to be safe in patients with concomitant multiple sclerosis, unlike to TNFi [79]. The safety profile of SEC was investigated in a long-term analysis, in which a low frequency of AEs was described. As expected, considering the important role of Th-17 on skin and mucous defense against fungi and extracellular bacteria, higher cases of candidiasis were compared to placebo [80]. As already mentioned, paradoxical exacerbation or new onset of IBD could be observed during IL-17i treatment. Furthermore, a recent analysis showed no particular warnings on congenital malformations or miscarriages during treatment with SEC, despite these promising preliminary results might require future confirmations [81].

Ixekizumab (IXE), a recombinant IgG4κ monoclonal antibody-binding IL-17A, was tested in two phase III trials. SPIRIT-P1 was a randomized trial versus ADA in PsA patients with inadequate response to csDMARDs and naïve to bDMARDs. SPIRIT-P2 was a trial versus placebo on patients who had an inadequate response to TNFi. These trials showed a superiority of IXE to reach a complete remission of PsO (PASI 100) compared to ADA, as well as a higher improvement of arthritis, physical function, quality-of-life, enthesitis, and dactylitis when compared to placebo [82,83]. IXE was also associated with a reduced structural joint damage and radiographic progression in AS and nr-axSpA patients [84,85]. SPIRIT-P3, conducted on biologic naïve PsA patients, evaluated the efficacy and safety of continuing versus withdrawing IXE in patients who achieved sustained MDA. The results demonstrated that MDA was maintained in patients who continued IXE, while it was lost after IXE withdrawal. However, in these latter, MDA was regained after restarting IXE [86]. The first completed head-to-head trial comparing IXE and ADA (SPIRIT- H2H) was conducted on patients with active PsA and inadequate response to csDMARDs. After 24-weeks of treatment IXE was non-inferior to ADA in reaching an ACR50 response and superior to ADA in achieving a PASI100. Furthermore, significantly more patients achieved DAPSA remission with IXE than ADA, suggesting differences between biologics not only in skin domain [87]. In a real-life clinical setting population, it was observed the achievement of PASI 75/90/100 and BSA, as well as an improvement of DAPSA within the first 6 months from the treatment beginning, with a sustained efficacy during the 12 months follow-up [88,89]. Other real-world experiences and preliminary studies outlined the effectiveness of IXE in PsA patients, also after failure of SEC and TNFi, suggesting the differences between drugs belonging to the same class [90,91]. IXE has

Table 1. IL-23i approved for PsA and ongoing studies.

Drug	Inhibition	Efficacy vs placebo			Efficacy vs ADA	Ref
		Joint	Skin	Other domains		
Ustekinumab (UST)	p40 subunit of IL-12 and IL-23	ACR20, ACR50 and ACR70 responses significantly higher in UST arm ($p < 0.0001$ for all comparisons)	Significantly higher rate of PASI75 response in both UST 45 mg and 90 mg arms ($p < 0.001$ for both comparisons)	Greater improvement in DLQI score and HAQ-DI ($p < 0.001$ for both) Greater improvement in MASES score ($p < 0.01$). Significantly less radiographic progression in PsA modified vdH-S score ($p < 0.001$)	Improvement of SPARCC and MASES index in UST arm compared to TNFi ($p = 0.007$ and $p = 0.022$, respectively)	[42–46]
Guselkumab (GSK)	p19 subunit of IL-23	ACR20 and ACR 50 response higher in both GSK Q4W and Q8W dose regimen 15 mg and 30 mg arms ($p < 0.001$ for all comparisons)	Higher PASI75, PASI90, and PASI100 response rate in both GSK Q4W and Q8W arms ($p < 0.001$ for all comparisons)	Significantly improved the HAQ-DI score, SF-36 PCS score and SF-36 MCS score in both GSK Q4W and Q8W dose regimen ($p < 0.001$ for all comparisons) Improvements in the LEI in GSK Q4W and Q8W dose regimen ($p < 0.001$ and p < 0.0003, respectively) and in dactylitis scores ($p < 0.002$ for all comparisons)	-	[51–53]
Risankizumab (RSK)	p19 subunit of IL-23	ACR20, ACR 50 and ACR70 response significantly higher in RSK group ($p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively)	Significantly higher achievement of PASI90 responses ($p < 0.001$)	Greater decrease of dactylitis and enthesitis ($p < 0.001$ and $p < 0.01$, respectively) Higher improvement of HAQ-DI score, SF-36 PCS score and FACIT-fatigue score ($p < 0.001$, $p < 0.001$ and $p < 0.01$, respectively)	-	[57,58]
Tildrakizumab (TLK)	p19 subunit of IL-23	Higher ACR2/50/70 response in both TLK 200 mg Q4W or Q12 W ($p < 0.05$)	Higher rate of PASI75/90/100 responses in each TLK arm ($p < 0.05$)	-	-	[61]

IL-23i, interleukin-23 inhibitors; PsA, Psoriatic Arthritis; ADA, adalimumab; UST, ustekinumab; GSK, guselkumab; RSK, risankizumab; TLK, tildrakizumab; ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; DLQI, dermatology life quality index, HAQ-DI, health assessment questionnaire-change in disease activity; SF-36, Short-Form 36; MASES, Maastricht ankylosing spondylitis enthesitis score; vdH-S, van der Heijde Score; SPARCC, spondyloarthritis research consortium of Canada scoring system; TNFi, Tumor Necrosis Factor Inhibitors; Q4W, once every 4 weeks; Q8W, once every 8 weeks; Q12 W, once every 12 weeks; SF-36, short form health survey-36; PCS, physical component score; MCS, mental component score; LEI, Leeds Enthesitis Index; FACIT-fatigue score, functional assessment of chronic illness therapy-fatigue score.

a favorable side-effect profile, similar to SEC with more frequent injection site reactions, probably for its higher immunogenicity [92].

Recently, the simultaneous targeting of different cytokines implicated in PsD pathogenesis using bispecific antibodies has been outlined as a new potential alternative to combination therapy, theoretically offering a better disease control and a better safety profile [93]. IL-17A and IL-17 F share structural homology and have a similar biological function. Dual inhibition of IL-17A and IL-17 F can be achieved with bimekizumab (BMK), a IgG1κ humanized monoclonal antibody [94]. In in vitro models, BMK appears to be more potent than SEC and as potent as IXE at inhibiting IL-17A [95]. BMK was recently approved by the European Medicines Agency (EMA) to treat moderate or severe plaque PsO. Two phase 3 trials in PsO patients (BE READY and BE VIVID), demonstrated the superiority of BMK in achieving PASI100 compared to placebo (91% vs 1% of patients) and UST (59% vs 21% of patients) [96,97]. Moreover, BMK was demonstrated to induce a greater skin clearance than ADA (BE SURE trial) [98] and SEC [99]. Given the encouraging results in reducing skin disease activity in PsO patients, BMK was also tested in PsA. In the randomized, double-blind, placebo-controlled, dose-ranging phase 2b clinical trial BE ACTIVE, 206 PsA patients were assigned to receive placebo or four doses of BMK Q4W. After 12 weeks, BMK 16 mg and 160 mg (with or without a 320 mg loading dose) were associated with significant improvements in ACR50 compared with the placebo group. The efficacy was independent to prior TNFi therapy exposure [100]. These results were sustained up to 108 weeks, as demonstrated in the open-label extension study (BE ACTIVE2) [101]. Of note, a sustained improvement in pain and fatigue up to 3 years was observed [102]. Currently, there are other ongoing trials on BMK in PsA patients, evaluating its efficacy and safety vs placebo in the treatment of TNFi inadequate responders (BE COMPLETE) [103], its efficacy and safety vs ADA (BE OPTIMAL) [104], and incidence of AEs (BE VITAL) [105]. In all these trials, AEs were reported more frequently in patients who received BMK than in those who received placebo or another bDMARD. Most AEs were mild or moderate and there was no relation between BMK dose and the incidence or severity of AEs, and did not lead to discontinuation of the drug. The most frequently reported AEs were nasopharyngitis, URTI, and oral candidiasis. No cases of IBD, uveitis, MACEs, or hypersensitivity to BMK were reported [106].

Brodalumab (BRD) is a human IgG2 antibody against IL-17 receptor A (IL-17RA), resulting in the inhibition of the action of IL-17A, IL-17 F, and IL-17E [107]. BRD is approved for the treatment of moderate-to-severe plaque PsO in adult patients who have failed treatment with topical and other systemic therapy [108]. Two phase III multicenter, randomized, double-blind, placebo-controlled clinical trials (AMVISION-1 and AMVISION-2), evaluated its efficacy and safety in patients with active PsA despite prior cs- and bDMARDs therapy. The primary endpoint (ACR20 response) was met with both BRD doses (140 mg and 210 mg Q2W), and the ACR response rate was higher than placebo at week 24. Moreover, a significant ACR50 and ACR70 response, dactylitis, and enthesitis resolution rates, as well as HAQ-DI, CDAI, DAPSA, and PASDAS scores were observed in the BRD cohort [109]. Of note, six cases of suicides were reported in patients receiving BRD, carrying the FDA to insert a specific warning box. However, no direct causal relationship was established between these events and BRD [110]. AEs incidence was similar to other IL-17i, with nasopharyngitis and URTI the most frequent [111]. Finally, a concern associated with all bDMARDs is the increased susceptibility of different forms of neoplasms, although results from a real-life population study showed their safety in PsO patients with a past medical history of malignant cancer, with any worsening or reactivation of cancer [112].

Data on IL-17i are illustrated in Table 2.

5. JAK-inhibitors

Recently, a new class of small molecules, called targeted synthetic DMARDs (tsDMARDs), are carving out a place as important treatment options for different immune-mediated inflammatory diseases. Among them, JAK-inhibitors (JAKi) are able to interfere with the JAK/STAT pathway that regulates the expression of different cytokines that play a key role in the pathogenesis of autoimmune disease [113]. The JAK1/STAT1/STAT3/STAT5 intracellular pathways have been shown to drive the expansion and the activation of IL-17+ and IL-23 R + T helper cells in skin and joints, highlighting their role in the pathogenesis of PsD [114,115].

Tofacitinib (TOF), selective for JAK1 and JAK3, was the first JAKi approved by EMA and FDA to treat PsA patients. Its efficacy was evaluated in two randomized, double-blind, phase III trials conducted on patients with active PsA and an inadequate response to at least one csDMARD and TNFi naïve (OPAL Broaden) or in TNFi insufficient responders (OPAL Beyond), respectively [116,117]. In both trials, ACR20 response rates and improvement in HAQ-DI scores were significantly greater with TOF 5 mg bis in die (BID) and 10 mg BID when compared to placebo. Moreover, the achievement of PASI75 and an amelioration of enthesitis and dactylitis was observed at week 12. Analyzing pooled data from OPAL Broaden and OPAL Beyond trials, a better control of peripheral arthritis, dactylitis, enthesitis, and PsO was registered in both TOF groups than placebo up to 6 months of therapy [118]. Of note, in OPAL Broaden, patients with axial disease showed a halted radiographic progression at month 12, sustained up to 30 months, as shown in the long-term extension study [119]. Notably, OPAL Broaden also included an active control arm in which patients received ADA. Clinical improvements were comparable in the TOF and ADA arms, but there was no planned analysis of noninferiority or superiority of the two treatments. A recent study showed a median time to HAQ-DI and FACIT-F total score improvements of 1 month in patients treated with TOF 5 mg. Moreover, TOF was noninferior to ADA in PASDAS and MDA response, confirming a similar spectrum of efficacy between TOF and ADA [120]. A real-life experience with the aim of analyzing the efficacy of TOF in monotherapy compared to combination therapy has shown an overlapping effectiveness of the two approaches, underlying the strength of JAKi in monotherapy [121]. Furthermore, in a post-hoc

Table 2. IL-17i approved for PsA and ongoing studies.

Drug	Inhibition	Efficacy vs placebo			Efficacy vs ADA	Ref
		Joint	Skin	Other domains		
Secukinumab (SEC)	IL-17A	Higher ACR20/50/70 response in all SEC groups ($p < 0.05$)	Higher rate of PASI 75/90 in all SEC arms ($p = not\ shown$)	Improvement of dactylitis and enthesitis ($p = not\ shown$)	Similar ACR20/50 and PASI 75/100 responses but higher treatment retention rate of SEC than ADA	[68–70,72]
Ixekizumab (IXE)	IL-17A	ACR20, ACR50 and ACR70 responses significantly higher in both IXE Q4W and Q2W 5- arms ($p < 0.001$ for ACR20 and $p < 0.05$ for ACR 50/70)	Significantly greater PASI75/90/100 and NAPSI responses ($p < 0.01$ and $p < 0.001$, respectively)	Improvement of HAQ-DI and SF-36 with IXE Q4W and Q2W ($p < 0.001$ and $p < 0.01$, respectively)	IXE was non-inferior to ADA in reaching ACR50 response and superior to ADA in achieving PASI100 ($p = 0.001$)	[82–84]
Bimekizumab (BMK)	IL-17A, IL-17 F, IL-17A/F heterodimer	ACR50 response significantly higher with BMK 16 mg and 160 mg Q4W ($p < 0.01$ in both groups)	Significantly greater PASI75 responses in all BMK groups ($p < 0.01$ for all groups)	Improvement of HAQ-DI and SF-36 in all BMK groups ($p = not\ shown$)	*Ongoing trial*	[100,104]
Brodalumab (BRD)	IL-17RA	ACR20, ACR50 and ACR70 responses significantly higher ($p < 0.0001$, $p < 0.0001$ and $p < 0.01$, respectively)	Higher rate of PASI 75/90/100 ($p < 0.0001$, $p < 0.0001$ and $p < 0.001$, respectively)	Improvement of dactylitis and enthesitis ($p < 0.001$ and $p < 0.01$, respectively)	-	[109]

IL-17i, interleukin-17 inhibitors; PsA, Psoriatic Arthritis; ADA, adalimumab; SEC, secukinumab; IXE, ixekizumab; BMK, bimekizumab; BRD, brodalumab; ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; NAPSI, nail psoriasis severity index; dermatology life quality index, HAQ-DI, health assessment questionnaire-change in disease activity; SF-36, Short-Form health survey-36; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

analysis of pooled data from OPAL Broaden and OPAL beyond trials, treatment with TOF resulted in lasting improvements in dactylitis, with minimal emergence of new dactylitis up to 6 months [122]. TOF displayed a quite favorable safety profile, consistent with the studies on RA patients. Most AEs were headache, nasopharyngitis, and URTI, and they were similar among the two different diseases, suggesting no specific PsA side effects. The increases in total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), as well as elevations of liver enzyme levels, were more common in TOF treated groups than placebo. However, there was no apparent correlation with increased cardiovascular risk, and the incidence of MACEs was low in all the aforementioned studies, and these data were confirmed in a real-world setting [123]. Finally, the incidence of herpes zoster (HZ) infection was dose-dependent and was higher in Asiatic population. However, vaccination against HZ prior to starting the drug may be considered to prevent the virus reactivation [124].

Upadacitinib (UPA) selectively inhibits JAK1 and has been recently approved in RA, AS, and PsA. Two phase 3, randomized, placebo-controlled trials evaluated efficacy of UPA in adult patients with active PsA which failed to respond to at least one csDMARD (SELECT-PsA 1, which had also an arm of patients receiving ADA) or to at least one bDMARD [125,126]. Both studies demonstrated improvements in PsA domains including peripheral arthritis, enthesitis, dactylitis, PsO, physical function, pain, fatigue, and quality of life, as well as the inhibition of radiographic progression, with similar results between 15 mg and 30 mg daily dose of UPA [127]. In SELCET-PsA 1 trial, by the comparison between UPA and ADA, it was demonstrated the noninferiority of 15 mg and 30-mg doses of UPA to ADA in reaching the ACR20 response at week 12, while only the 30 mg dose was superior. Moreover, both doses of UPA and ADA showed a similar efficacy profile in other domains of PsD, including PsO, enthesitis, physical function, fatigue, and quality of life [128]. The safety findings were consistent with the known safety profile of UPA observed in RA with URTI, nasopharyngitis, and increased creatine phosphokinase (CPK) the most common AEs reported. MACEs and venous thromboembolic events (VTEs) were rare. Rates of HZ and opportunistic infections were higher with UPA than ADA [129].

Also, filgotinib (FLG) is a selective inhibitor of JAK1. Preclinical data showed that FLG prevents JAK1-mediated Th1 and Th2 differentiation, and to a lesser extent Th17 differentiation [130]. Moreover, studies on murine models demonstrated a reduction of inflammatory cytokines and chemokines in a rodent collagen-induced arthritis [131]. A randomized, double-blind, phase 2 trial (EQUATOR), compared the efficacy of FLG 200 mg daily vs placebo in patients with active PsA and an insufficient response or intolerance to at least one csDMARD [132]. FLG showed a significantly better performance than placebo with a greater proportion of patients achieving the primary endpoint of ACR20 response at week 16, as well as ACR50 and ACR70. The trial also found higher improvement of peripheral arthritis, enthesitis, PsO, physical functioning, fatigue, and pain. The safety profile of FLG was similar to other JAKi, with mostly mild or moderate AEs [133]. Nevertheless, there have been concerns regarding testicular toxicity. In fact, preclinical studies in rats and dogs reported that male reproductive organs were affected by FLG, with a reduction of the sperm count and/or cell debris at high doses [134]. Hopefully, the results from the MANTA-Ray testicular safety study will clarify this concern [135].

Data on IL-17i are illustrated in Table 3.

6. Future perspectives

Despite the wide number of available drugs to treat effectively the PsD, some patients do not respond, stop responding over time, or exhibit drug toxicity, leading to drug discontinuation or to combination therapies. Thus, there is still a great need for novel therapeutic options [136]. New drugs targeting the IL-23/IL-17 pathway are emerging and, among these, nanobodies seem promising. Nanobodies are the new generation of recombinant variable domains of heavy-chain-only antibodies, with low molecular weight, excellent solubility and stability, quick clearance from blood and deep tissue penetration. For these properties, nanobodies are considered not only as therapeutic tools but also as drug delivery [137].

Netakimab (NTK) is a humanized IgG1 nanobody that targets IL-17A and is currently registered in Russia for the treatment of moderate-to-severe PsO in adults [138]. PATERA study is an ongoing randomized, placebo-controlled, phase 3 clinical trial that is investigating the efficacy and safety of NTK 120 mg in PsA patients with an inadequate response to csDMARDs or one TNFi. Current available data showed a significantly greater percentage of NTK-treated patients achieving ACR20/50/70 responses, and MDA after 24 weeks. The most frequent AEs (mild to moderate) were lymphopenia, neutropenia, URTI, hypercholesterolemia, ALT increased and hyperbilirubinemia [139]. Moreover, NTK is currently under study in AS patients [140].

Sonelokimab (SLK) is a novel trivalent nanobody built on a C-terminal moiety-binding IL-17A and IL-17 F, a central moiety binding to serum albumin, and an N-terminal moiety that binds specifically to IL-17 F [141]. Its efficacy and safety on patients with moderate-to-severe plaque PsO was evaluated in a phase 2b, randomized, placebo-controlled trial, with SEC as an active comparator. Preliminary results showed that 76.5% of the patients treated with SLK 120 mg (augmented load) achieved the primary endpoint of PASI 90 after 12 weeks. SLK has a favorable safety profile, similar to other IL-17i, with an increased risk of candida infections [142]. Despite the good results on skin domain, there are currently no studies evaluating SLK in PsA patients.

Remtolumab, formerly known as ABT-122, is a dual variable domain immunoglobulin (DVD-Ig) that was built on an ADA backbone adding IL-17A binding domains, resulting in a double bond to TNF and IL-17A in a 1:1 ratio [143]. A phase 2 randomized trial, with ADA as an active comparator, evaluated the efficacy and safety of ABT-122 at two doses (120 mg and 240 mg weekly) in 240 PsA patients with an inadequate response to MTX. After 12 weeks, the efficacy of ABT-122 was superior to placebo, and with ABT-122 240 mg the PASI75 response, ACR50, and ACR70 response rates were superior to the ADA group. However, the ACR20 and PASI90 responses (primary endpoints) were generally similar between

Table 3. JAKi approved for PsA and ongoing studies.

				Efficacy vs placebo				
Drug	Inhibition	Population reclute	Time of evaluation	Joint (ACR20 response)	Skin (PASI75 response)	Other domains (Changes from baseline in LEI or resolution of enthesitis defined as LEI = 0)	Efficacy vs ADA	Ref
Tofacitinib (TOF)	JAK 1/ JAK 3	Adult PsA patients with inadequate response to ≥ 1 TNFi	12 weeks	TOF 5-mg 50.47% vs 33.33% (*p = not shown)* TOF 10-mg 60.58% vs 33.33% (*p = not shown)*	TOF 5-mg 42.68% vs 14.63% (*p = not shown)* TOF 10-mg 44.29% vs 14.63% (*p = not shown)*	TOF 5-mg -0.82 vs −0.43 (*p = not shown)* TOF 10-mg −1.46 vs −0.43 (*p = not shown)*	**ACR20 response** TOF 5-mg 50.47% vs 51.89% (*p = not shown)* TOF 10-mg 60.58% vs 51.89% (*p = not shown)* **PASI75 response** TOF 5-mg 42.68% vs 38.96% (*p = not shown)* TOF 10-mg 44.29% vs 38.96% (*p = not shown)* **Changes from baseline in LEI** TOF 5-mg -0.82 vs −1.10 (*p = not shown)* TOF 10-mg −1.46 vs −1.10 (*p = not shown)*	[118]
Upadacitinib (UPA)	JAK1	Adult PsA patients with inadequate response to ≥ 1 bDMARDs	12 weeks	UPA 15-mg 70.6% vs 36.2% (*p = not shown)* UPA 30-mg 75.8% vs 36.2% (*p = not shown)*	UPA 15-mg 62.6% vs 21.3% (*p = not shown)* UPA 30-mg 62.4% vs 21.3% (*p = not shown)*	UPA 15-mg 53.7% vs 32.4% (*p = not shown)* UPA 30-mg 57.7% vs 32.4% (*p = not shown)*	**ACR20 response** UPA 15-mg 70.6% vs 65.0% (*p = not shown)* UPA 30-mg 75.8% vs 65.0% (*p = not shown)* **PASI75 response** UPA 15-mg 62.6% vs 53.1% (*p = not shown)* UPA 30-mg 62.4% vs 53.1% (*p = not shown)* **LEI = 0** UPA 15-mg 53.7% vs 47.2% (*p = not shown)* UPA 30-mg 57.7% vs 47.2% (*p = not shown)*	[125]
Filgotinib (FLG)	JAK1	Adult PsA patients with inadequate response to ≥ csDMARDs and maximum 1 bDMARDs or tsDMARDs	16 weeks	80% vs 33% (p < 0.0001)	45% vs 15% (p = 0.0034)	−1.8 vs −0.7 (p = 0.03)	-	[132]

JAKi, Janus Kinase Inhibitors; PsA, Psoriatic Arthritis; TOF, tofacitinib, UPA, upadacitinib; FLG, filgotinib; ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; LEI, Leeds Enthesitis Index; TNFi, Tumor Necrosis Factor Inhibitors; bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

Table 4. Main clinical trials evaluating novel agents in PsA patients (sonelokimab and mirikizumab are currently not under study in PsA).

Drug	Mechanism of action	Study Population	Primary endpoint	Time of evaluation	Comparator	Preliminary results	Ref
Netakimab (NTK)	IgG1 nanobody that binds to IL-17A	Adult PsA patients with inadequate response to csDMARDs or one TNFi	ACR20 response	24 weeks	Placebo	82.47% vs 9.28% *(p = not shown)*	[139]
Remtolumab (ABT-122)	DVD-Ig that binds to TNF and IL-17A	Adult PsA patients treated with MTX ≥ 10 mg/week for ≥4 weeks, bDMARDs naïve	ACR20 response	12 weeks	Placebo and ADA	ABT-122 120-mg 64.8% vs 25.0% *(p < 0.001)* vs 68.1% ABT-122 240-mg 75.3% vs 25.0% *(p < 0.001)* vs 68.1%	[144]
Deucravacitinib (DEU)	Oral agent that selectively inhibits TYK2 via an allosteric mechanism by binding to the nonconserved regulatory domain of the kinase	Adult PsA patients with inadequate response to csDMARDs or one TNFi	ACR20 response	16 weeks	Placebo	DEU 6 mg 52.9% vs 31.8% *(p = 0.0134)* DEU 12 mg 62.7% vs 31.8% *(p = 0.0004)*	[151]
Brepocitinib (BRP)	Oral agent that binds to and inhibits the activation of TYK2 and JAK1	Adult PsA patients	ACR20 response	16 weeks	Placebo	brepocitinib-10 mg 64.52% vs 43.28% *(p = not shown)* brepocitinib-30 mg 66.67% vs 43.28% *(p = not shown)* brepocitinib-60 mg 74.58% vs 43.28% *(p = not shown)*	[154]

PsA, Psoriatic Arthritis; ACR, American College of Rheumatology; Ig, Immunoglobulin; DVD-Ig, dual variable domain immunoglobulin; IL-, interleukin; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biologic disease-modifying antirheumatic drugs TNFi, Tumor Necrosis Factor Inhibitors; DVD-Ig, Dual Variable domain-Ig; MTX, methotrexate; ADA, adalimumab; JAK, Janus Kinase; TYK2, Tyrosine Kinase 2.

the ABT-122 and ADA groups. For this reason, the double TNF and IL-17A inhibition path was no longer followed, despite treatment with DVD-Ig seems promising for difficult-to-treat PsA patients [144].

Mirikizumab (MRK) is a humanized IgG4 antibody targeting the p19 subunit of IL-23 [145]. A phase 3 randomized clinical trial (OASIS-1) showed that 64% of the patients treated with MRK 250 mg Q4W achieved PASI90 at 16 weeks versus 6.5% in the placebo arm [146], while the OASIS-2 study showed non-inferiority at week 16 and superiority at week 52 of MRK when compared to SEC [147]. Despite these promising results, there are no current studies evaluating MRK in PsA patients.

Targeting the JAK-STAT system is also an attractive therapeutic mechanism of action due to the simultaneous effect on multiple cytokines. Deucravacitinib (DEU) is a selective TYK2 inhibitor that binds to the regulatory domain (pseudokinase) of TYK2 and induces a conformational change that locks the enzyme in an inactive state, in contrast to the action of other JAKi that bind the active domain of the kinase [148]. DEU is being studied for treatment of PsO, PsA, systemic lupus erythematosus (SLE) and IBD [149]. In a randomized, double-blind, placebo-controlled, phase 2 trial, 267 patients with moderate-to-severe plaque PsO received one of five dosages of DEU or placebo for 12 weeks. After 12 weeks, the percentages of patients with PASI 75, PASI 90, and PASI 100 response were higher in all DEU groups, suggesting that DEU may be a promising therapy [150]. Moreover, DEU was tested in a double-blind, phase 2 trial in which 203 patients with active PsA were randomized to receive placebo, DEU 6 mg daily or 12 mg daily. At 16 weeks, patients in each DEU group achieved higher rates of ACR-20, ACR-50, ACR-70 response, regardless of prior TNFi exposure, BMI, or sex. Moreover, DEU induced an improvement in most of PsA domain, including PsO, enthesitis, and dactylitis. DEU was well tolerated, and the most common AEs (mild to moderate) were URTI, rash, diarrhea, and headache. Changes in laboratory measures were not observed, including hematological parameters and lipid levels, demonstrating its good safety profile due to its selectivity for TYK2 [151]. Further ongoing clinical trials are currently evaluating the efficacy and safety of DEU in PsA patients naïve to bDMARDs or who failed to respond to TNFi [152,153].

Brepocitinib (BRP) can inhibit TYK2 and JAK1 and is currently under study for the treatment of PsA, PsO, atopic dermatitis, and SLE. To date, a phase 2b trial is evaluating BRP efficacy and safety in PsA patients [154].

Data on novel agents are illustrated in Table 4.

7. Expert opinion

Despite the novelties in terms of understanding pathogenesis and the development of new drugs, the management of PsA remains difficult for health-care professionals. Moreover, PsA is a heterogenic condition where multiple systems can be affected, and the response to current treatments is variable between different patients and within the same individual depending on the organ involved. Currently, the clinical management of PsA is based on the evidence from the available clinical trials and the clinical manifestation occurring. Nevertheless, a significant number of patients still do not respond to treatment, which can also lose the efficacy over time.

The advances in understanding the pathogenesis of PsA have shed light on the exploration of new molecular mechanisms that may be targeted by very specific therapies. From

a theoretical point of view, this offers the possibility to stratificate patients according to risk factors, clinical biomarkers, and disease phenotype with a potentially better management of the disease and a lower spectrum of side effects. A growing interest is pointing toward combination therapies with the intention of targeting multiple pathogenic pathways to better control the disease. Several agents in development exert a dual inhibition of different cytokines belonging to the same or different family, such as nanobodies, whose stability, strong affinity in binding antigens, solubility, and size, make them one of the most fascinating next-generation biodrugs. Nanobodies have been extensively studied in the treatment of various forms of cancer and are currently also being evaluated for infectious and inflammatory diseases. The preliminary results are promising, but larger studies are required to test the efficacy and safety of these new agents in real life.

Most of the cited studies have evaluated patients with a long history of PsA and who have undergone already several treatments. Thus, a notable step forward in this field would be to analyze patients with an early diagnosis of PsA and to have serological or histological biomarkers that can strictly direct the choice of pharmacological treatment in a targeted manner. In this way physicians could facilitate the slowing of the progression of PsA and reduce the impact of the disease on daily life activities in these patients.

Furthermore, PsA is associated with the potential development of several comorbidities such as obesity, diabetes, metabolic syndrome, cardiovascular diseases, IBDs, neoplasms, and depression, which require long-term management with consequent cumulative expenses. This economic burden further increases in patients who have a long history of disease, diagnostic delay, and failure of multiple therapies. Therefore, for both clinical and economic aspects, it is not difficult to hypothesize a future in which patients will be early stratified according to their immunophenotype or the presence of histological markers, leading to an ever greater importance of the principle of personalized medicine. However, current reliable biomarkers able to predict the disease evolution and the response to treatment in each person suffering with PsA are still lacking. Further studies are obviously needed to identify a molecular signature that can guide physicians in the most appropriate therapeutic choice, but great progress has been made in recent years and the future seems to be promising.

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