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REVIEW

An Update for the Clinician on Biologics for the Treatment of Psoriatic Arthritis

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Abstract: Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy typically associated with psoriasis (PsO). The pathogenesis is strictly related to the association among the presence of genetic risk alleles and innate and acquired immune response with dramatic consequences on bone remodeling. Clinically, PsA patients may present heterogenicity of articular and periarticular manifestations that may be associated with the presence of comorbidities making treatment decision challenging in patients management. The identification of patient-targeted therapies is still a critical issue. Actually, several biological and synthetic drugs are promising in terms of efficacy and safety profile. National and international treatment recommendations support clinicians in the decision of the best treatment, although they may have limits basically related to updates and different outcomes included in the clinical studies evaluated. The aim of this narrative review is therefore to give guidance for clinicians for PsA patients treatment. For this purpose, we evaluated evidence on biological therapies efficacy used for PsA treatment. Specifically, we reviewed data on biological therapies, Janus kinases (JAK) inhibitors, and drugs with a new mechanism of action that are part of the treatment pipeline. The concept of "switching" and "swapping" is also described, as well as data concerning special populations such as pregnant women and elderly patients.

Keywords: psoriatic arthritis, biological therapies, TNF-inhibitors, JAK-inhibitors, phosphodiesterase-4, tofacitinib, tsDMARDs

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis typically associated with psoriasis (PsO) occurring in nearly 30% of patients affected by PsO.[1] PsA is characterized by inflammation at joints, tendons, and enthesal levels making the articular involvement extremely diversified.[1] The clinical heterogeneity of PsA, as well as the frequent presence and association with several comorbidities, make the treatment choice challenging for rheumatologists.[2] Recent evidence suggests a complex interplay between genetic predisposition and innate and acquired immune response.[2,3]

In the 1990s, findings based on the immunopathogenesis of the disease have led to the development of biological drugs directed against pathogenetic targets, such as Tumor Necrosis Factor (TNF).[4] TNF is a pleiotropic cytokine which regulates several inflammatory reactions and immune functions through the control of cellular processes and plays a central role in the pathogenesis of PsA.[5] TNF-inhibitors (TNF-i) drugs [Infliximab (IFX), Etanercept (ETA), Adalimumab (ADA), Golimumab (GOL) and Certolizumab Pegol (CZT)], have opened new therapeutic

horizons in PsA, proving to be effective in the control of the signs/symptoms of inflammation, in improving the quality-of-life and the functional outcome, in inhibiting the progression of the structural damage in the peripheral joints, and in presenting a good safety profile.[5,8] Recently, advances in the role of Interleukin (IL)-23 and IL-17 in PsA pathogenesis and in particular in the pathogenesis of enthesitis and dactylitis, support the use of drugs that have these two cytokines as targets.[9] In addition, research has also focused on bone remodeling in PsA, demonstrating the interplay between IL-23 and IL-17 and osteoblasts and osteoclasts in both erosions and osteoproductive lesions.[10] Currently, histologic features of PsA synovitis also support the relevance of an autoimmune pathway of the disease.[2] However, drugs such as rituximab (RTX) typically used for autoimmune diseases such as rheumatoid arthritis (RA) were only partially effective in PsA treatment. On the contrary, targeted-synthetic DMARDs (tsDMARDs) drugs, approved for RA as Janus kinases inhibitors (JAKi), were demonstrated to be effective for PsA treatment, making the treatment armamentarium richer and the treatment decision intriguing.[11] In order to clarify the different therapeutic options for PsA, guidelines help in identification of the best treatment based on the clinical predominant manifestation. International and National Guidelines suggest to start with the use of conventional DMARDs (csDMARDs) and in cases of inadequate response, contraindication, or intolerance to at least one DMARD, treatment with biological DMARDs (bDMARDs) such as TNFi or anti-IL17 and anti-IL23 therapies [ustekinumab (UST), secukinumab (SEC) or ixekizumab (IXE)] should be considered.[12,13] However, management of PsA patients with special conditions, such as the elderly, pregnancy, or those with several comorbidities, is still a challenge. Relevant suggestions emerged also from registries and real-life data, which may improve our knowledge in bDMARDs use.[14] To date, the position of JAKi and the place of future drugs that will come on the market is still unknown.

The overarching aim of this narrative review was to give guidance for clinicians for PsA patients treatment and to focus on significant insights on potential new therapeutic targets. First of all, we performed a description of the main disease characteristics, both articular and periarticular, as well as the systemic inflammatory involvement as extra-articular manifestations and comorbidities. Then, we described the main studies demonstrating TNFi efficacy and the efficacy of different mechanisms of

action. We also dedicated a section to tsDMARDs, even if they are not considered biologics, but they may have the same place in the treatment armamentarium as bDMARDs. We conclude with a discussion based on our opinion on PsA management as guidance for clinicians.

Clinical Manifestations and Comorbidities

Clinical features of PsA are included in a systemic disease defined as Systemic Psoriatic Disease (SysPsD), highlighting its systemic nature characterized by joints involvement, enthesitis, dactylitis, psoriasis (PsO), and a wide spectrum of extra-cutaneous and -articular manifestations.[2] PsA has an extensive variety of clinical presentations, ranging from single "sausage" digits to arthritis mutilans. The classic description of articular involvement, by Moll and Wright in 1973, was based on the main articular site involved, and portrayed five clinical subtypes, described as: axial PsA, symmetrical polyarthritis, asymmetrical oligoarthritis, distal interphalangeal (DIP) arthritis, and arthritis mutilans.[15] Patterns may change during time or occur in a combined manner; in particular, DIP arthritis and polyarthritis may overlap with axial disease, leading to the forewritten extension of variety of PsA.[16,17] PsA is characterized by a general inflammatory state responsible for associated comorbidities and systemic manifestations, including cardiovascular (CV) disease, diabetes mellitus II (DM), obesity, metabolic syndrome (MetS), uveitis, inflammatory bowel disease (IBD), liver inflammation, osteoporosis, emotional, and psychological symptoms.[18,] More than half of patients with PsA have at least one comorbidity.[21] The prevalence of clinical features and comorbidities are summarized in Table 1. Cardiovascular diseases (CVD) are the leading cause of death in PsA patients, who present a 43% increased risk of CVD over the general population.[22] CV risk appears as an independent risk factor for major adverse cardiovascular events (MACE), although an increased rate of CV events in PsA patients correlate also with the presence of traditional CV risk factors (ie, diabetes, hypertension, obesity, dyslipidemia, and metabolic syndrome).[22,26] Ocular pathologies related to SysPsD include: conjunctivitis, episcleritis, scleritis, keratitis, macular edema, glaucoma, and cataract.[27] However, acute anterior uveitis is the most frequent manifestation.[27,29] SysPsD is also associated with IBD, assuming a gut–joint–skin axis.[30,31] Recent data have shown patients presenting PsA or PsO have 4-fold increased risk of developing IBD.[30] In addition, Scarpa

Table 1 Prevalence of Comorbidities in PsA Patients

	Clinical Manifestation	Prevalence	References
Cardiovascular	MACE	30–37.1%	22,24,25
	Hypertension	37–50%	22
	Obesity	60%	22
	DM II	10–20%	23
	MetS	27–38%	24
	Hyperlipidemia	20.7%	26
Ocular	Acute anterior uveitis	7–20%	27,29
Gastrointestinal	Crohn's disease	5–7%	30,32
	Ulcerative colitis		
	NAFLD	20–28%	20,22
Mental health diseases	Anxiety	24.4–36.6%	33
	Depression	9.6–22.2%	33
Urogenital tract	Urethritis, prostatitis	<1%	20
Kidney	CKD	16%	20
Bone	Osteoporosis	3.50%	20
Lung	COPD, apical pulmonary fibrosis	1.05%	36

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DMII, type 2 diabetes; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; PsA, psoriatic arthritis.

et al[32] found microscopic changes in all PsA patients of their study's population and none of them presented macroscopic mucosal changes or IBD symptoms. Anxiety and depression are common pathologies among SysPsD patients.[20] These disorders have a great impact on QoL patients, lowering their pain threshold and reducing adherence to therapies.[33,34] Little evidence has been reported on any pulmonary diseases, but evidence supports that PsA patients present a tendency to develop drug-related lung fibrosis, especially in those treated with methotrexate (MTX) or TNFi.[35,36] As deducible, PsA represents a significant health issue having a profound impact on QoL: chronic pain together with the effects on bones and cartilages led to a limitation in physical functioning and work abilities, extreme fatigue, and emotional and social impairment.[37] The systemic nature of this disease and the high presence of comorbidities make the treatment choice a task for rheumatologists.

Biological DMARDs

In recent years, extensive research has showed the pathophysiologic basis of rheumatic diseases, combined with the biopharmaceutical developments, leading to the introduction of biotechnological drugs.[38] These agents target specific components of the immune system that are essential for the generation and maintenance of the pathogenetic process.[3,9] Their appearance on the therapeutic scene has considerably changed the approach to PsA treatment.

TNF-Inhibitors

TNFi were the first bDMARDs approved, through the progressive improvement in knowledge on TNFα actions in the pathogenesis of PsA. Indeed, TNFα is a key mediator of acute inflammation in PsA, activating pro-inflammatory genes transcription, cytokines secretion, and overexpression of macrophages and other immune cells, thus promoting and perpetuating unbalanced inflammation and articular damage.[39] One of the first studies demonstrating TNFi efficacy in modifying synovial cell populations and infiltrates in PsA dates back to 2001, when Baeten et al[40,41] showed a reduction of vascularity and inflammatory cell populations following IFX treatment. TNFi have been approved for PsA patients since the 2000s.[3] Evidence of their efficacy in treating both PsO and PsA is available from numerous randomized controlled trials (RCTs), being significantly more effective than placebo in improving American College of Rheumatology 20% (ACR20) response rates, PsA Response Criteria (PsARC), and Psoriasis Area Severity Index (PASI).[42,46] An improvement in nail disease, dactylitis, and enthesitis, as well as a significant inhibition of radiographic progression were also detected.[3] TNFi are

also considered a first-line option for the treatment of axial disease in PsA, despite most of data being based on literature from Ankylosing Spondylitis (AS) and axial spondyloarthritis.[47] Data concerning head-to-head efficacy are still lacking, but all the drugs in the TNFi group have been indirectly compared to each other, demonstrating similar outcomes and safety profiles.[3] With regard to the latter, data on oncologic and infection risk in PsA patients treated with TNFi was derived from RCTs and RCTs-metanalyses, demonstrating a safety profile comparable to the control/placebo.[48] A large metanalysis on ADA has recently shown that the overall rate of malignancy for PsA patients treated was similar to those as expected from the general population.[49] Real-life studies and Registries have confirmed these data.[50,55]

With regard to infections, RCTs and observational studies reported a good safety profile of TNFi. However, even if well tolerated, TNFi are associated with an increased infective risk, including opportunistic infections. Monoclonal antibodies, in particular IFX, seem to be responsible for the increased risk of these infections.[56] Several recommendations for screening infections before initiating TNFi have been proposed. Latent, acute, and chronic infections represent a contraindication to use a biological therapy. In cases of Latent tuberculosis infection, anti-tubercular prophylaxis is recommended. Furthermore, HBV and HCV virological follow-up should be considered during TNFi treatment. Finally, patients who are at high risk of varicella zoster (HZ) reactivation would benefit from a second vaccination in adulthood when receiving TNFi.[57] In recent years, biosimilars for IFX, ETA, and ADA have become available and their licensing studies showed similar pharmacodynamics, pharmacokinetics, and efficacy to the reference product.[43,45] Their advantages are mainly related to economic saving.

Biological DMARDs Other Than TNFi

Although TNFi therapy remains central in the management of PsA, new insights into its pathogenesis led to identification of new therapeutic targets, including IL-12, IL-23, and IL-17. The IL-17 signaling pathway plays a relevant role in the pathogenesis of PsA. This proinflammatory cytokine is richly expressed in psoriatic skin lesions and in the synovial fluid of patients[9] and can induce activation and proliferation of keratinocytes and endothelial cells.[58] On the other side, IL-23 has been shown to play an important role in the polarization of CD4+ T-cells to become IL-17 producers.[59] In the last few years, therapeutic agents targeting the IL-23/IL17 axis have been studied for the treatment of PsA.

Ustekinumab (UST), a fully human monoclonal antibody directed against IL-12/23, was the first of these novel targeted therapies to be approved for the treatment of PsA in 2013.[60] UST showed consistent and sustained clinical efficacy in active PsA.[61] Efficacy and safety of UST has been evaluated in two Phase III trials, which enrolled patients TNFi naïve with moderate-to-severe disease that failed NSAIDs or synthetic DMARDs (PSUMMIT-1), or had failed to ≥1 TNFi (PSUMMIT 2).[62,63] Results clearly demonstrated the effectiveness of UST, right from the first month, in treating most domains of disease, including dactylitis and enthesitis. However, clinical outcomes were better for the TNFi naïve group compared with the TNFi exposed group.[64] Integrated data analysis results indicated that there was a significant and persistent inhibition of radiographic progression in UST treated patients, supporting the role of IL-23 in the radiographic damage of PsA.[64] A prospective randomized-controlled open-label study, ECLIPSA, showed that UST achieved superior responses as compared to TNFi regarding enthesitis and psoriatic skin disease, but not for peripheral arthritis.[65] These results are confirmed by our direct experience: patients who have previously experienced TNFi without a significant improvement in skin disease and enthesis involvement showed a significant response to UST.[14] The best data demonstrating ongoing safety of UST is reported in the 5-year PHOENIX long-term extensions. The most commonly reported adverse events (AEs) were nasopharyngitis, upper respiratory tract infection (URTI), headache, and arthralgia, with similar rates between doses (45 mg and 90 mg).[66]

Novel antibodies directed against the p19 subunit of IL-23 have been developed. Risankizumab (RSK), tildrakizumab (TLK), and Guselkumab (GSK) have been approved for the treatment of moderate-to severe plaque PsO, but they appear to be effective also in PsA.[67,69] Results from two phase III clinical trials, DISCOVER-1 and DISCOVER-2, confirmed its possible role as a therapeutic option for PsA. In DISCOVER-1, which involved patients who were either biologic-naïve or had previously been treated with up to two TNFi, the improvement in peripheral arthritis at week 24 was significantly higher among patients treated with GSK than among those given placebo. DISCOVER-2 was larger than DISCOVER-1 and involved only patients naïve to biologic therapies, giving similarly promising results. The effectiveness of GSK was also demonstrated on dactylitis

and enthesitis in the two studies.[69] Overall, GSK seems to have a favorable safety profile: phase III trials VOYAGE 1 and VOYAGE 2 have found the most common AEs to include nasopharyngitis, headache, and URTI. Serious infection, malignancy, and MACE do not appear to be increased in patients treated with GSK compared to placebo and ADA.[70] Recent clinical trials evaluating the efficacy of UST and other anti-IL23 agents, such as RSK, in AS were performed, but they had surprisingly negative outcomes. These results make anti-IL23 appear to be ineffective on long-standing axial disease, such as AS, even if there is a possibility that UST and RSK might have been under-dosed in these trials or that they should be used in early phases of spondyloarthritis (SpA).[71] A prospective, single-arm, open-label, proof-of-concept trial, the TOPAS, was conducted to evaluate UST efficacy and safety in AS patients who were naïve to biologic therapies. The results showed that UST improved all continuous parameters related to disease activity at week 24, with 65% of patients reaching the primary outcome of a 40% improvement in disease activity according to the Assessment of Spondyloarthritis International Society (ASAS) and 55% reaching a 50% improvement of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[72] Moreover, there was a substantial (41% and 31% for the sacroiliac joints and for the spine, respectively) reduction of active inflammation as detected by MRI in the entire group. Despite the clear limitations of the study, as its open-label design and small sample size, an important indication of the possible therapeutic efficacy of UST in active AS was received.[72] In order to explain the conflicting results from therapeutic trials, it has been speculated that IL-23 might have a pathogenic role in the initiation of AS (or axial SpA) but not in maintaining established disease.[71]

Secukinumab (SEC) is a fully human monoclonal antibody that selectively binds to IL-17A, approved for the treatment of active PsA since 2015. The efficacy and safety of SEC in PsA were assessed for the first time in a randomized, double-blind, placebo-controlled Phase II clinical trial. The results achieved in terms of reduction of disease activity and lowering of acute phase reactant led to the design of the FUTURE trials.[73] According to their results, SEC greatly improved clinical responses regarding arthritis, enthesitis, dactylitis, skin, and nail disease compared to the placebo group, with a comparable safety profile associated with a significant reduction in radiographic progression of structural joint damage relative to placebo.[73,75] Another recent phase III RCT, the FUTURE

5, showed an improvement of clinical and radiographic response in PsA patients related to the placebo group.[75] In the absence of RCTs data, matching-adjusted indirect comparison can estimate the comparative effectiveness of TNFi and SEC in TNFi naïve PsA patients. One of them showed that TNFi naïve patients have a similar probability of achieving clinical responses with subcutaneous SEC or intravenous IFX in the short-term, while in the mid- to long-term patients receiving SEC were more likely to achieve clinical responses than those receiving IFX.[76] Furthermore, data from systematic review and meta-analysis shown as SEC appears to be superior to UST in TNFi naïve but not in TNFi experienced PsA patients.[77,78] Recently, we demonstrated that SEC was efficacious in daily clinical practice in patients affected by PsA and AS characterized by several comorbidities and/or previous treatment failures. Moreover, the SEC retention rate was not influenced by Body Mass Index (BMI) or gender, supporting that another mechanism of action other than TNFi may be effective in overweight patients and in women.[79] In a recent long-term safety analysis, SEC was associated with a generally low frequency of AEs, with higher incidence of URTI. As expected with IL-17 inhibition, cases of candidiasis were observed given that Th-17 cells play an important role in skin and mucous host defense, particularly against fungi and extracellular bacteria.[80] Lower incidence of serious AE and opportunistic infections, comparable between doses of 150 mg or 300 mg, was reported. Neutropenia is an important adverse effect that must be considered when administering SEC to patients, possibly attributed to the effect of IL-17 on granulopoiesis. Anyway, no cases of Grade 3 or 4 neutropenia were reported, and no clinically significant AEs were associated with the development of neutropenia. Grade 1 or 3 neutropenia were registered but it resolved during the time in all cases and no patients discontinued treatment due to neutropenia. Discontinuations due to IBD onset or exacerbation were low but it is important to emphasize that the risk of IBD in this analysis could be different from that observed in the real-world, as patients with active IBD were excluded from all clinical trials.[81] Additionally, a recent analysis did not assess any evidence for increased rates of adverse pregnancy outcomes with SEC. However, the analysis was limited by a sizable amount of missing outcome data and relatively short exposure to SEC.[82]

Ixekizumab (IXE) is a recombinant monoclonal antibody that binds IL-17A with high affinity. Its efficacy in PsA was assessed in two phase III trials (SPIRIT-P1,

SPIRIT-P2). In SPIRIT-P1 PsA patients with inadequate response to csDMARDs and naïve to biologic therapies were randomized to receive IXE and ADA. At week 12, IXE achieved complete remission of PsO in more patients than ADA, while the effect on joints and nail psoriasis was comparable between the two biologics.[83] A long-term extension of the SPIRIT-P1 study showed a sustained improvement in joints, skin, physical function, and quality-of-life over 52 weeks of IXE treatment. Moreover, the radiographic progression was minimal, particularly in patients who maintained IXE from week 0 to 52.[84] In SPIRIT-P2, patients who had an inadequate response to TNFi were randomized to receive IXE versus placebo, with a significant improvement of signs and symptoms of active PsO at week 24 in the first group.[85] Both SPIRIT-P1 and SPIRIT-P2 showed that IXE significantly improved dactylitis and enthesitis, despite statistical significance not being reached when compared with placebo at week 24 for all endpoints, likely due to the small number of patients who exhibited these peri-articular features. Of note, the efficacy of the IXE groups was similar regardless of use of concomitant csDMARDs, particularly MTX. SPIRIT-P3 evaluated the efficacy and safety of continuing versus withdrawing IXE in PsA patients naïve to other biologics and who achieved sustained minimal disease activity (MDA) on IXE. The results demonstrated that patients lost MDA after IXE withdrawal, but regained it with IXE re-treatment, while MDA was preserved in patients who continued IXE therapy.[86] In our experience, a high proportion of PsA patients at 6 months achieved a skin clearance that was maintained over time and a low disease activity of arthritis was reached rapidly within the first 6 months of treatment, with a sustained efficacy during the 12 months follow-up period.[87,88] Recently, SPIRIT-H2H was the first completed head-to-head trial comparing IXE and ADA in patients with active PsA and inadequate response to csDMARDs. The 24-week efficacy data from this study demonstrated that IXE was superior to ADA in simultaneously leading to an ACR50 and PASI100 response, was non-inferior to ADA for achieving ACR50, and was superior to ADA for achieving PASI100. Furthermore, significantly more patients achieved Disease Activity in PSoriatic Arthritis (DAPSA) remission with IXE than ADA, suggesting that skin changes were not the only domain contributing to differences between biologics.[89]

The side-effect profile for IXE was quite favorable and consistent with the studies on psoriasis.[90] The majority of

AE were mild and URTI were the most prevalent. Injection site reactions were predominantly mild but more frequent with IXE than SEC, probably for the lower immunogenicity of SEC. Recurrent chronic candidiasis has been reported in individuals with rare genetic defects in the IL-17 pathway and no cases of invasive or opportunistic fungal infections were reported. Grade 1 and Grade 2 neutropenia were noted with higher frequency with IXE, but no case of Grade 3 or Grade 4. No cases of IBD have been reported in the SPIRIT-P1 (including an extension period to week 52) or SPIRIT-P2 studies. Because of the potential protective role of IL-17A in the gut epithelium, vigilance is required when abdominal symptoms develop after the initiation of IXE.[91]

Pooled meta-analysis was conducted by Mourad et al[78] identifying RCTs evaluating the efficacy of TNF-i, anti-IL12 /23 (UST), and anti-IL17 (SEC, IXE) in treating PsA and conducting a meta-analysis of these agents for treatment of dactylitis and enthesitis. Their results showed that TNF-i and IL inhibitors brought dactylitis to a significant resolution at week 24, with pooled risk ratios (RR) versus placebo of 2.57 (95% CI=1.36–4.84) and 1.88 (95% CI=1.33–2.65) respectively. For resolution of enthesitis at week 24, RR for TNF-i was 1.93 (95% CI=1.33–2.79) versus 1.95 (95% CI=1.60–2.38) for IL inhibitors. According to these results, TNF-i demonstrated the same efficacy of IL inhibitors in treating the two PsA manifestations.[92]

The meta-analysis of Wu et al[92] instead included RCTs evaluating the efficacy of SEC, UST, and IXE in achieving ACR20 and ACR50 over placebo. The rank probabilities based on the network meta-analysis were summarized for each treatment in order to obtain a surface under the cumulative ranking curve (SUCRA): the higher the SUCRA was, the more effective was considered each treatment. SEC showed a SUCRA of 96.42% according to ACR20, compared to the 38.61% of UST and the 50.84% of IXE. According to these results, SEC seems to be the most efficacious short-term treatment for peripheral PsA, although the authors pointed out several limitations of the study. SEC and IXE were also tested in patients with AS, and the clinical outcomes have clearly shown their superiority over placebo.[71]

Brodalumab (BRD) is a human anti-IL17 receptor A monoclonal antibody that inhibits IL-17A, IL-17F, and IL-17E. In two phase III clinical trials, AMVISION-1 and AMVISION-2, patients with active PsA despite prior DMARDs therapy, including biologics, were enrolled and randomized to receive placebo and BRD.[71] At week 24,

a higher rate of patients treated with BRD achieved a significant articular response compared to placebo. These results confirmed that BRD delivers consistent and clinically meaningful improvements in PsA.[93] Current evidence suggests a similar safety profile for BRD compared to other IL-17 antagonists, with the most common adverse events represented by nasopharyngitis, URTI, and candidiasis. The US Food and Drug Administration (FDA) issued a warning after six patients treated with BRD across four clinical trials committed suicide, although no causal relationship was identified.[94]

Bimekizumab (BMK) is a humanized monoclonal antibody that selectively binds to and neutralizes both IL-17A and IL-17F. The BE ACTIVE randomized, double-blind, placebo-controlled phase IIb study showed that BMK was associated with significant improvement in joint involvement compared with placebo, with an acceptable safety profile.[95] Although the results are promising, larger studies are required to better characterize the efficacy and safety profile of both BRD and BMK in the treatment of PsA.[95] The safety profile of BMK was consistent with previous reports, with no apparent relationship between dose and treatment-emergent adverse events.[95]

According to the 2015 updated European League Against Rheumatism (EULAR) recommendations for the management of PsA, anti-IL17 and anti-IL12/IL23 biologic agents are indicated as a second-line biologic therapy for PsA treatment after the failure of one or more TNFi, or as a first-line in case they were contraindicated. This preference given to the TNFi is based on the longer duration of experience with these drugs and the largest amount of long-term efficacy and safety data available. However, in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations published in the same year, TNFi, anti-IL12/23, and anti-IL-17 are included in the same therapeutic step and their use as first or second-line biologic therapy depends on their effectiveness on the dominant PsA manifestations.[13] For clinician guidance, UST is preferred in patients with predominance of PsO, enthesitis and with a concomitant gastrointestinal involvement, such as Crohn's disease, while we give a leading role to SEC in patients with PsO and/or axial PsA. Both therapeutic strategies have shown positive results in patients naïve to biologic therapies, and in patients with comorbidities. Characteristics such as female gender and high BMI may influence SEC indication. These elements lead us to consider the IL inhibitors as a first-line therapeutic option in selected cases. In contrast, monoclonal TNFi would be preferred over anti-IL17 therapy for patients with repeated uveitis as there is minimal evidence indicating anti-IL-17 therapies in effectively treating uveitis. The main randomized clinical trials available for bDMARDs in PsA are summarized in Table 2.

Targeted Synthetic DMARDs

Recent advances provide support that dysfunction of signaling pathways involving the phosphodiesterase 4 (PDE4) enzyme and the kinase (JAK)-signal family pathway play an important role in the complex pathogenesis of PsA.[96,97] PDE4, an enzyme belonging to phosphodiesterases, is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP) into AMP. PDE4 inhibition produces increased cAMP levels in immune and non-immune cells, altering the expression of downstream cascades and modifying inflammatory responses.[98,99] Apremilast (APR) is an oral small molecule that inhibits intracellular PDE4 approved in March 2014 for the treatment of adult patients with PsO and active PsA.[100] The efficacy and safety of APR were firstly demonstrated in four Phase III, placebo-controlled studies (PALACE 1, 2, 3, and 4). The PALACE 1, 2, and 3 enrolled PsA patients who were previously treated with cs- and/or bDMARDs, PALACE 4 evaluated APR monotherapy in csDMARD-naïve and biological-naïve populations.[101,106] In all clinical trials, APR significantly improved PsA signs and symptoms, including enthesitis, dactylitis, PsO, physical function, and Patient-Reported Outcomes (PROs), and response was maintained up to 5 years. Among PsO patients with involvement of ≥3% of the body surface area (BSA) at baseline, cutaneous symptoms improved with apremilast treatment.[106] The efficacy of APR was observed regardless of prior biologic experience or concomitant DMARD use, although apremilast was early efficacious in biologic-naïve patients.[104,105] However, the time to onset of therapeutic effect has not been reported before week 16.[98] A recent phase IIIB study, the Apremilast Monotherapy in a Clinical Trial of BIologic-NaïVE Patients With Psoriatic Arthritis (ACTIVE), showed that in biological-naïve PsA patients, onset of effect with APR was observed at week 2 and continued through week 52.[107] Of interest, weight loss was observed at 52 weeks, suggesting that APR could have a positive impact on obesity and metabolic syndrome.[108] To date, there is no evidence to demonstrate an impact of APR on structural disease progression: the results from PALACE analysis indicated significant improvements in the

Table 2 Therapeutic Indications and Main Clinical Trials on Biologic DMARDs Evaluated and Ongoing for PsA Treatment

bDMARD	EMA/FDA-Approved Therapeutic Indications	Dosage; Administration Route	Clinical Trials in PsA	Study Size	Follow-Up Period
Etanercept	Plaque PsO in patients >4 years old Adults with PsA Adult and juvenile RA AS	50 mg weekly in a single administration or in two 25-mg doses; SC	Phase III (PRESTA)[42] Phase IV (EDUCATE)[194] Phase IV (REPArE)[195] Observational study (ADEQUATE)[196]	752 participants 1122 participants 110 participants 1534 participants	24 weeks 24 weeks 24 months 12 months
Adalimumab	PsO PsA AS RA	40 mg biweekly; SC	Phase III (ADEPT)[43] Phase III (STEREO)[197] Phase III (ACCLAIM)[198] Observational Study (ProAct)[199] Phase IV (CONTROL)[200]	313 participants 442 participants 127 participants 5940 participants 246 participants	24 weeks 12 weeks 12 weeks 5 years 4 years
Infliximab	PsO PsA RA AS UC CD	5 mg/kg at 2 and 6 weeks after the first infusion, then every 8 weeks; IV	Phase III (IMPACT and IMPACT II)[44] Open Label Study (RESPOND)[201]	104 participants 200 participants 115 participants	1 year 54 weeks 16 weeks
Golimumab	PsA RA AS UC	50 mg every 4 weeks; SC	Phase III (GO-REVEAL)[45] Observational study (GO-NICE)[202] Phase IIIb (GO-DACT)[203] Phase III (GOLMEPsA) *[204]	407 participants 1458 participants 44 participants 88 participants	5 years 24 months 24 weeks 24 months
Certolizumab-Pegol	Plaque PsO PsA RA AS CD	200 mg biweekly; SC	Phase III (RAPID-PsA)[46] Phase I (CRADLE)[205]	368 participants 17 participants	24 weeks 14/28 days
Ustekinumab	Plaque PsO in patients >12 years old Adults with PsA	45 mg (for body weight of <100 kg) or 90 mg (for body weight of ≥100 kg) at 0, 4, and 12 weeks, then every 12 weeks; SC	Phase III (PSUMMIT-1, PSUMMIT-2)[62,64]	615 participants, 312 participants	52 weeks 60 weeks
Risankizumab	PsO	150 mg in two 75-mg doses at 0 and 4 weeks, then every 12 weeks; SC	Phase II (Mease et al)[67]	172 participants	16 weeks
Tildrakizumab	PsO	100 mg at 0 and 4 weeks, then 100 mg every 12 weeks; a 200 mg dose can be used for body weight >90 kg or for severe PsO; SC	Phase IIb (Mease et al)[68]	391 participants	52 weeks

(*Continued*)

Table 2 (Continued).

bDMARD	EMA/FDA-Approved Therapeutic Indications	Dosage; Administration Route	Clinical Trials in PsA	Study Size	Follow-Up Period
Guselkumab	Plaque PsO Under investigation for PsA	100 mg at 0 and 4 weeks, then every 8 weeks; SC	Phase III (DISCOVER-1, DISCOVER-2)[69]	381 participants, 741 participants	24 weeks 100 weeks
Secukinumab	Plaque PsO PsA AS	150 mg (in bDMARDs naïve PsA patients) or 300 mg in two 150-mg doses (in PsA patients who had failure at least one bDMARD), weekly from 0 to 4 weeks, then monthly; SC	Phase III (FUTURE1, FUTURE2, FUTURE3, FUTURE4, FUTURE5)[73,75] Phase IIIb (EXCEED1)[206]	606 participants, 397 participants, 64 participants, 341 participants, 997 participants 854 participants	2 years 24 weeks 24 weeks 24 weeks 100 weeks 50 weeks
Ixekizumab	Plaque PsO PsA	160 mg in two 80-mg doses at week 0, then 80 mg biweekly for 12 weeks, then 80 mg every 4 weeks; SC 160 mg in two 80-mg doses at week 0, then 80 mg every 4 weeks; SC	Phase III (SPIRIT-P1, SPIRIT-P2, SPIRIT-P3)[83,86] Phase IV (SPIRIT H2H)[89]	417 participants, 363 participants, 394 participants, 566 participants	24 weeks 24 weeks 104 weeks 52 weeks
Brodalumab	Plaque PsO Under investigation for PsA	210 mg at 0, 1, and 2 weeks, then 210 mg biweekly; SC	Phase III (AMVISION-1, AMVISION-2)[93]	478 participants, 484 participants	24 weeks, 24 weeks
Bimekizumab	Under investigation for plaque PsO Under investigation for PsA	Proposed dosage: 320 mg every 4 weeks; SC	Phase IIb (BE ACTIVE)[95]	184 participants	24 weeks

Note: *Recruitment status.
Abbreviations: AS, ankylosing spondylitis; bDMARD, biologic disease-modifying antirheumatic drugs; CD, Crohn's disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; Ig, immunoglobulin; IL, interleukin; IV, intravenous; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis.

numbers of swollen and tender joints over 5 years of treatment, that may have been associated with inhibition of disease progression.[104] Nevertheless data from real life studies have recently evidenced that APR is able to induce an early and sustained improvement on ultrasonographic inflammatory status at articular and peri-articular level.[109] As other PDE4 inhibitors, APR showed generally an acceptable safety profile.[110] The most common reported AEs were diarrhea, nausea, headache, and URTI. The gastrointestinal side-effects generally occurred within the first month of treatment and subsequently subsided.[108] While the overall incidence of depression reported was low (≤1.8%), it is nevertheless recommended that the risks and benefits of APR should be carefully weighed

prior to initiating therapy in patients with a history of depression and/or suicidal thoughts or behavior.[106,108] Marked laboratory abnormalities were infrequent, returning to baseline with continued treatment, and no laboratory monitoring is required in patients receiving APR.[106,108] Further, the pharmacokinetics of APR are not influenced by mild or moderate impairment of hepatic and renal function. However, dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/mm).[106,108] Importantly, there is no interaction with methotrexate, frequently used in patients with PsA and plaque PsO.[111]

The good safety profile makes APR a convenient option for PsA treatment, especially in patients with high

risk of infections, comorbidities, comedication, or with several contraindications including recent history of malignancies.[99] Despite this, lack of data from head-to-head trials comparing APR with cs- or bDMARDs agents makes it difficult to place this small molecule in the treatment of PsO and PsA. An indirect comparison with csDMARD has shown more effectiveness of APR, in addition to the benefit of not requiring routine therapeutic drug monitoring. On the contrary, the efficacy of APR is lower than it would be anticipated with biologic therapies as ADA.[98] Another indirect comparison indicates that APR, SEC, and UST may have similar efficacy in patients with PsA and an inadequate response to TNFi.[112] GRAPPA guidelines strongly recommended bDMARDs and APR in patients with peripheral arthritis and an inadequate response to csDMARDs.[113] EULAR guidelines also advise us to consider APR in patients with peripheral arthritis who prefer an orally administered therapy.[114]

Emerging studies investigated the potential role of JAK/STAT (Signal Transducers and Activators of Transcription) signaling pathway in the pathogenesis of several inflammatory diseases. JAKs activation leads to translocation of STAT proteins into the nucleus, regulating the transcription of pro-inflammatory gene involved in inflammatory and autoimmune disease.[115] The tyrosine kinases of the JAK family include four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Following their success in RA, JAKi are emerging as a promising therapeutic option for PsO and PsA. The rationale for using JAKi to treat PsA relies on the central role of cytokines in its pathogenesis. Most of the cytokines involved in PsA pathogenesis, directly or indirectly, are regulated through the JAK-STAT pathway, although JAKs cannot transmit signals provided by IL-1, IL-8 TGFβ, MCSF, and IL-17. Moreover, several studies have shown JAK1 and JAK3 dependent pathway activation in cultured cells from psoriasis skin and synovial/joint tissue, higher than in healthy controls or blood derived samples.[116] In this context, targeting all JAKs or different JAK combinations by small-molecule inhibitors is considered a relevant strategy.[117] Tofacitinib is an oral inhibitor of JAK1 and JAK-3, but can have some functions on JAK2 as well at higher doses. It was approved for use in combination with MTX in moderate-to-severe active adult PsA who have an inadequate response or intolerance to previous csDMARDs therapy.[11] The therapeutic efficacy of tofacitinib has been evaluated in two randomized, multicentric, double-blind, placebo-controlled phase III trials, which enrolled patients with active PsA and either an inadequate response to ≥1 csDMARD and TNFi-naïve (OPAL Broaden), or an inadequate response to ≥1 TNFi (OPAL Beyond).[118,119] Primary endpoints (ACR20 response and change from baseline in Health Assessment Questionnaire-Disability Index [HAQ-DI] at month 3) showed significant improvement in patients receiving tofacitinib 5 or 10 mg twice daily vs placebo. Of note, patients on tofacitinib showed an early improvement (2 weeks) from baseline in ACR20 response.[119] Significant improvements in HAQ-DI, tender and swollen joints, PsO, enthesitis, and dactylitis vs placebo were observed for both tofacitinib doses at month 3, with the effects being maintained up to 6 months.[120] Nevertheless, tofacitinib 10 mg BID was more effective in the treatment of moderate-to-severe plaque type psoriasis compared to the 5 mg BID dosage, as reported also in a dermatology trial.[121,122] Post hoc analysis conducted by Strand et al[123,124] showed significant improvement, exceeding placebo, across a range of PROs, proving that tofacitinib not only treats signs and symptoms of PsA but can also improve patient function and quality-of-life. In particular, patients treated with tofacitinib had greater improvement in PROs, fatigue, and quality-of-life. Previous studies have shown that tofacitinib inhibits TNF and IL-6-induced osteoclastogenesis and bone destruction, mediated by receptor activator of nuclear factor kappa-B ligand (RANKL), as well as STAT-activated proteins associated with progressive and destructive joint disease.[125,127] Moreover, it was speculated that elevated C-reactive Protein (CRP) levels at baseline reflect the systemic inflammation state and could be related with joint destruction in PsA.[128] Recently, post hoc analysis of the OPAL Broaden study was conducted for evaluating the effect of baseline risk factors on radiographic progression in enrolled patients. At month 12, >90% of the patients across the tofacitinib groups met the criteria for radiographic non-progression in the joints. However, minimal changes in radiographic outcomes regardless of CRP levels were observed.[129] The effect of tofacitinib on RANKL and IL-22 may have an important role in this context, particularly regarding bone loss, but larger and longer studies are required.[129] The safety profile and AE related to the use of JAKi have also been evaluated. AE were higher in tofacitinib 10 mg compared to 5 mg and the most common were nasopharyngitis, URTI, headache, and gastrointestinal disorders (diarrhea, nausea, vomiting, constipation). Data taken from RA and ulcerative colitis trials identified increased venous thromboembolic events and

pulmonary embolisms in patients treated with tofacitinib, but large observational studies are needed to accurately quantify thromboembolic risks attributable to JAKi.[130,131] Of interest for the side-effect profile of tofacitinib, reactivation of endogenous HZ was observed and vaccination against HZ prior to starting the drug may be considered.[116] In OPAL trials, an increase from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) was reported, as well as elevations of aspartate and alanine aminotransferase concentrations of three or more times the upper limit of the normal range.[99] The association of tofacitinib with lipid lowering agents, such as statins, may increase the safety of JAKs, but additional attention to the hepatic enzymes would be recommended.[99] Tofacitinib is an oral drug with fast onset of action and a short half-life. In PsA, the dosage is 5 mg administered BID but a reduction (5 mg once a day) is recommended in patients with moderate/severe renal or hepatic impairment and in patients receiving drugs inhibiting CYP2C19 and/or CYP3A4. Contraindications to the use of tofacitinib are represented by severe hepatic disfunction, serious or opportunistic infections, active tuberculosis (TB), and it should not be initiated in patients with a low level of hemoglobin (<9 g/dL), low absolute leucocyte count (<750 cells/mm^3), or low neutrophil count (<1000 cells/mm^3). Cautious use of tofacitinib is advised in elderly patients and patients with malignancy history, chronic liver and lung disease, diabetes, and increased risk of GI perforations.[99]

Other JAK-i, some more specific for JAK1 (eg, upadacitinib, filgotinib, baricitinib), are currently being tested for the treatment of PsA in Phase 2 or Phase 3 clinical trials. EQUATOR is the first clinical trial to investigate a selective JAK1 inhibitor for the treatment of PsA.[132] This phase II study explored the effect of filgotinib on patients with active PsA and an insufficient response or intolerance to at least one csDMARD. Data from EQUATOR demonstrated an improvement of disease activity and physical functioning in a PsA population treated with Filgotinib 200 mg once-daily compared to placebo. Particularly, the primary endpoint (ACR20 response at week 16) was achieved in the greater proportion of patients, with measurable improvements in disease activity after 1 week of treatment. ACR50 and ACR70 responses at Week 16 were also significantly higher for filgotinib compared with placebo. The study also found greater improvement of peripheral arthritis, enthesitis, and PsO as measured by MDA and PASI 75, and showed a beneficial effect on physical functioning, fatigue and pain,

with significant improvements in psoriatic arthritis related pain intensity at week 1 and in HAQ-DI at week 2.[132,133] These results are consistent with the previously observed rapid onset of action reported in the DARWIN1 and DARWIN2 trials of filgotinib in RA and are probably of interest to prospective patients.[132,133] Filgotinib was well tolerated and safety-related outcomes were similar to placebo. In the EQUATOR study only one case of fatal pneumonia and of uncomplicated HZ in the filgotinib treatment group were reported, with no case to VTE, PE, malignancies, gastrointestinal perforations, or opportunistic infections/active TB.[134] These findings suggest that selective inhibition of JAK1 might theoretically provide an improved safety profile compared with less selective JAKi.[132] Upadacitinib, a JAK1 inhibitor approved for treatment of moderate-to-severe RA, is under study in two PsA Phase 3 RCTs. The first trial (SELECT-PsA 1) compared the efficacy and safety of upadacitinib with placebo and ADA in adult patients with active PsA who have had an inadequate response to at least one csDMARD;[135] the second one (SELECT-PsA 2) comparing upadacitinib to placebo in PsA patients with inadequate response to at least one bDMARD.[136] The results of both trials showed that upadacitinib, at a dosage of 15 mg or 30 mg once daily, achieved noninferiority compared with ADA and statistically significant ACR responses at week 12 vs placebo. Upadacitinib was also associated with improvements of HAQ-DI at week 12, PASI at week 16, and MDA at week 24. Moreover, both doses of upadacitinib showed inhibition of radiographic progression. As regard to safety, more information comes from RA studies.[137,140] Preliminary data from SELECT-PsA1 and 2 suggest a low incidence of serious infections and cardiovascular events, but the trial's long-term extension is still blinded in order to investigate the long-term safety and tolerability.[135] Although further research is necessary, the advent of newer mode of action therapies has provided additional choice for clinicians who can choose optimal therapies based on their efficacy for different musculoskeletal and skin manifestations and their side-effect profile. Main randomized clinical trials available for tsDMARDs in PsA are summarized in Table 3.

Emerging Biological Therapies for PsA

Many treatment options are now available for PsA management considering all its clinical subtypes and comorbidities.[1] However some patients have an inadequate response or

Table 3 Therapeutical Indications and Main Clinical Trials on Targeted Synthetic DMARDs Treatment for PsA

tsDMARD	FDA/EMA-Approved Therapeutic Indications	Dosage; Administration Route	Clinical Trials in PsA	Study Size	Follow-Up Period
Apremilast	PsA and inadequate response intolerance to a prior DMARDs PsO Adult patients with oral ulcers associated with Behçet Disease who are candidates for systemic therapy	30 mg BID orally; 30 mg once-daily in severe renal impairment and in patients receiving CYP3A4 or CYP2C19 inhibitors.	Phase III (PALACE1,2,3,4)[102,106108] Phase IIIB (ACTIVE)[107] Phase IV (FOREMOST)**[207] Observational (PREVAIL)**[208] Observational (LAPIS-PsA) ***[209]	504, 488, 505, 527 participants 219 participants 330 participants 120 participants 526 participants	24, 24, 24, 52 weeks 104 weeks 24 weeks 6 months 100 weeks
Tofacitinib	PsA RA UC	5 mg BID orally; 5 mg once-daily in moderate severe renal or hepatic impairment	Phase III (OPAL Broaden, OPAL Beyond, OPAL BALANCE)[118,119,210] Open label RCT (PsOLSET-BD)[211]	422 participants 395 participants 686 participants 61 participants	12 months 6 months 48 months 6 months
Upadacitinib	RA Not yet approved for PsA	Not yet approved for PsA	Phase III (SELECT PsA 1 and 2) ***[135,136]	1705 participants, 642 participants	24 weeks 24 weeks
Filgotinib	Under investigation for adult with moderate to severe RA Not yet approved for PsA	200 mg once-daily orally*	Phase II (EQUATOR)[132] Phase III (PENGUIN 1 and 2) **[212,213]	131 participants 854 participants, 390 participants	20 weeks 24 weeks 24 weeks

Notes: *Clinical trial in progress. **Recruitment status. ***Active, not recruiting.
Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drugs; EMA, European Medicines Agency; FDA, Food And Drug Administration; JAK, Janus kinase; BID, twice daily; PDE4, phosphodiesterase 4; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; UC, ulcerative colitis.

a relative contraindication to first-line biologic therapy,[141] advocating the development of novel medications with different mechanisms of action, such as T-cell modulators and anti-CD20.

Abatacept has been recently introduced as a therapeutic option for treating PsA patients with an inadequate response to DMARDs who do not require additional systemic therapy for PsO lesions.[142,143] This drug is a cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4)–Ig human fusion protein that inhibits naïve T-cell activation, and prevents the co-stimulatory binding between CD28 and CD80/CD86. Back in 1999, a role of CTLA4 in the pathogenesis of psoriasis was suggested; a study on patients with stable plaque psoriasis conducted by Abrams et al[144] reported a reduction of intralesional T-cells following Abatacept administration, correlated with reductions in epidermal proliferation, epidermal thickness, reversion of keratinocyte maturational abnormalities, and clinical improvement of PsO. Most recently, Mease et al[145] evaluated its efficacy and safety in 170 PsA patients, in a 6-month, double-blind,

placebo-controlled phase II trial, with less than 50% of participants reaching the ACR20 at 6 months, with a high response in TNFi naïve patients. Abatacept-treated patients also achieved a trend of improvement on additional measures of arthritis severity (ACR50 and ACR70), PsO severity, magnetic resonance imaging (MRI) scores, physical function, and quality-of-life. Following these results, in 2017 Mease et al[146] conducted a Phase III RCT (ASTRAEA), in which 424 PsA patients with inadequate response to DMARDs (including TNFi) were randomized to receive a weekly subcutaneous 125 mg dose of abatacept or placebo for 24 weeks. Less than 40% of patients treated with abatacept achieved the ACR20 as a primary endpoint. High ACR20 responses were seen in a TNFi-naïve subpopulation and in those with baseline-elevated CRP. Resolution of enthesitis and dactylitis in the abatacept group compared to the placebo-one was seen.[146] The efficacy of abatacept was sustained through the follow-up period. Modest results were observed in skin manifestation. Another study by Szentpetery et al[147] randomized 15 TNFi-naïve PsA patients

to receive intravenous abatacept or placebo with the aim to assess changes in immunohistochemical expression markers of synovial and skin inflammation, clinical outcomes, and MRI scores. Results reported EULAR responses in 90% of patients at 6 months, PASI50 response in 30% of cases, significant reduction in synovitis on MRI and synovial biopsies, and a decrease of expression of CD4+ Foxp3+ T-cells in synovial lymphoid follicles.[147] Nowadays there are no clinical trials evaluated the efficacy of abatacept on axial-PsA, but a case report by Olivieri et al[148] and a clinical study on AS patients by Lekpa et al,[149] suggest a higher response in HLA-B27 negative women with no-radiological sacroiliitis. It is possible to assume that abatacept is a promising agent for the immunotherapy of PsA. However, stratification of patients and head-to-head comparisons among old and new biologics are still required for fully establishing his exact role in the management of PsA.[150] Analysing PsA trials, there is an overall low risk of infection. The risk of opportunistic infections was higher in patients with additional comorbidities, including a history of tobacco use and chronic obstructive pulmonary disease (COPD) as well as recent use of high-dose glucocorticoids. Most of the long-term data of abatacept are derived from RA trials. Pneumonia, bronchitis, and urinary tract infections have been some of the most reported serious infections. Most recommend TB screening prior to treatment initiation, although there is no clear risk of TB infection with abatacept. Moreover, Abatacept should be used with caution in patients with history of recurrent infections, COPD, active pregnancy, or malignancy. Interestingly, data from RA patients estimate the development of treatment-related PSO at an incidence rate of <0.6 in those treated with abatacept.[142]

Rituximab (RTX) is an immunosuppressive drug used in autoimmune diseases such as RA, granulomatosis with polyangiitis, microscopic polyangiitis, and systemic lupus erythematosus.[151] In an open-label study, 30% of PsA patients treated with RTX achieved the ACR20 response with another 30% achieving the PASI50, with a high improvement in TNFi-naïve patients.[152] In a prospective study by Jimenez-Boj et al,[153] nine patients with PsA and 14 with RA received rituximab. In PsA patients, the Disease Activity Score (DAS) 28 improved from 6.2 to 4.9 (medians), HAQ was reduced from 1.5 to 1.0, and the Disease Activity Index for psoriatic arthritis was reduced from 52.0 to 32.5. All these improvements were statistically significant. In conclusion, in all these exploratory studies RTX exhibited efficacy in PsA patients with long-standing disease, above all in TNFi-naïve patients.[153]

Thus, controlled trials will be needed for more definitive understanding of the RTX role in the treatment of PsA, especially in patients who may have a relative contraindication to TNFi. In this small study, no serious adverse event was observed but more data concerning side-effects derive from extensive clinical experience of RTX in the treatment of lymphoma. The majority of patients receiving their first infusion of RTX experience flu-like symptoms; other common symptoms include nausea, headache, fatigue, and rash. About 10% of patients develop more severe symptoms such as bronchospasm, hypoxia, and hypotension. The profile of AEs in patients with RA receiving RTX was similar to that observed in the oncology setting, but the overall incidence was notably lower, and AEs were also less severe. This may be explained by the absence of the cytokine release syndrome associated with tumor cell lysis seen in patients with B cell malignancies, as well as by often associated use of steroids and other immunosuppressive drugs.[154] Decreases in Ig levels were observed in some patients following RTX treatment, although the clinical consequences of this fact are unclear. Analysis of registry data has shown that a low IgG level (<6 g/L) before RTX treatment was associated with an increased risk of serious infection events; on the contrary, patients with low IgM had no increased risk of infections. The myocardial infarction rate reported for RTX-treated patients is consistent with epidemiological data from a general RA population receiving TNFi and there was no evidence to suggest an increased risk of MI or other CVD associated with rituximab treatment.[155]

Tocilizumab (TCZ) showed efficacy in RA, and some studies suggested a potential pathogenic role for IL-6 in PsA, describing increased IL-6 serum levels in PsA patients and a correlation between its levels and disease severity.[156] Several case reports have been published showing conflicting results concerning the efficacy in PsA treatment.[157] Ogata et al[158,159] reported two cases of peripheral PsA refractory to several DMARDs treated with TCZ every 4 weeks (for 7 and 9 month durations, respectively), without achieving disease remission. Madureira et al[160] presented three case reports of PsA patients with a personal history of psoriasis and exclusive peripheral joint involvement treated with TCZ: all patients experienced an improvement of the articular disease activity, inflammatory markers, and HAQ, without deterioration of the cutaneous disease (PASI). Based on these conflicting data, TCZ cannot be recommended as an alternative treatment for PsA with predominant peripheral

involvement. Only a few cases showed a significant improvement with TCZ therapy and the reduction of DAS28 score may be due to the reduction of inflammation markers, used in DAS28 calculation.[161] Nevertheless, further studies are necessary to validate these observations. Studies on the pathogenesis of immune-mediated diseases have been leading to the hypothesis that the concurrent blockade of more inflammatory cytokines may be a winning strategy of treatment, resulting in a more efficient suppression of critical pathogenic pathways and in a reduced risk of developing alternative circuits driving disease inflammation.[162] Specifically, TNF and IL-17A may represent two targets to be simultaneously neutralized as they are considered the most relevant mediators in PsA pathogenesis.[163,164] In a double-blind study by Mease et al,[165] ABT-122 was superior to placebo in all clinical outcomes and superior to adalimumab on ACR50/70 and PASI75 responses. Frequencies of adverse events, were similar across all treatment groups, causing no discontinuations. No serious infections or systemic hypersensitivity reactions were reported with ABT-122. Efficacy assessed by ACR response was maintained over the 24 weeks, with no differences in safety and tolerability assessments.[165] Another bispecific agent is COVA322, a TNF-α/IL-17A inhibitor that is currently being tested in psoriasis patients.[166] In preclinical models, COVA322 has been shown to improve acute inflammation, with a good safety profile and pharmacokinetics similar to ADA.[167] To evaluate the role that bispecific agents could have in the treatment of PsA, large-scale population, and head-to-head studies are necessary. A promising therapeutic target for the treatment of inflammatory diseases is represented by the A3 adenosine receptor (A3 AR). A3AR is a Gi protein-associated receptor, which is over-expressed in inflammatory cells and is involved in the regulation of mitogen-activated protein kinase (MAPK) pathways, managing functions of almost all immune cells.[168] CF101 is an A2AR agonist and inhibits the activation of inflammatory pathways, preventing the release of cytokines and metalloproteinases.[169] It was found to be safe and well tolerated in all preclinical and human clinical studies and showed promising results, particularly in PsO and RA.[170,171] Randomized clinical trials available for emerging therapies in PsA are summarized in Table 4.

Discussion

The thorough knowledge of the pathogenic mechanisms together with the systemic features of the disease suggest tailored treatments for a better management for PsA patients.[1,2,172] The therapeutic paradigm is further expanded by new emerging targets: new drugs capable of inhibiting several inflammatory pathways are appearing in the pharmacological scenario.[9] Challenges in PsA treatment arose from different clinical manifestations, the presence of comorbidities and patient characteristics such as the elderly, BMI, and gender.[3] PsA patients may present several comorbidities due to the systemic nature of the disease and consequently their presence influences treatment choice. The presence of CVD considerably reduced in both PsA and PsO patients, treated with TNFi.[39,173] Pharmacological characteristics among TNFi may influence their use in different clinical pictures.[39] TNFi use, in particular of monoclonal antibodies, is also suggested when patients present uveitis or gastrointestinal involvement due to their efficacy and mechanism of action in these pathologies.[174] Concerning uveitis, a 2-year follow-up analysis reported a better efficacy and safety profile of ADA than IFX for the treatment of refractory juvenile idiopathic arthritis-associated uveitis.[175] As well as, in fertile and pregnant women or in child-bearing women, TNFi, in particular ETN and CZP, may be preferred due to their physical characteristics and their safety profile. ETN and CZP may be considered for use throughout pregnancy due to the low rate of transplacental passage. In particular, among bDMARDs, continuation of TNFi during the first part of pregnancy should be considered. SpA tend to be stable or to get worse during pregnancy, even though the available literature is scarce.[176] According to the EULAR overarching principles, family planning must be part of our routine practice in each patient of reproductive age and adjustment of therapy must be considered before a planned pregnancy.[177,178] On the contrary, female gender influence bDMARDs efficacy: female sex is a negative predictive factor for TNF-i response in PsA.[179] This was not demonstrated in real life data on PsA patients concerning SEC and UST treatment. We recently evaluated gender influence in PsA patients treated with UST and in PsA patients treated with SEC: gender did not influenced the efficacy of SEC nor the efficacy of UST.[14,79] The presence of moderate-to-severe skin or nails PsO in "difficult areas" benefits treatment with inhibitors of Il-17 and IL-23 drug axes.[3] However, the same superiority in treating articular and axial manifestations in PsA or in radiographic progression is still missing. In patients with comorbidities such as IBD treatment with UST suggests the patient is

Table 4 Therapeutical Indications and Main Clinical Trials for Emerging Therapies for PsA Treatment

Drug	FDA/EMA-Approved Therapeutic Indications	Dosage; Administration Route	Studies and Trials in PsA	Study Size	Follow-Up Period
Abatacept	Adult RA Adult PsA	- 500 mg (for body weight of <60 Kg), 750 mg (for body weight from 60–100 Kg) or 1000 mg (for body weight of >100 kg) at 0, 2, and 4 weeks, then every 4 weeks; IV - 125 mg weekly; SC	Phase III (ASTRAEA[146])*** Phase IV (ABEPSA_BB[214])** Observational (ALTEA[215])**	489 participants 20 participants 200 participants	52 weeks 6 months 12 months
	JIA (in patients >2 years of age and older)	- From 2– 6 years of age: 50 mg (for body weight from 10 to less than 25 Kg), 87.5 mg (for body weight from 25 to less than 50 Kg) or 125 mg (for body weight ≥50 kg) weekly; SC - from 6 years of age and older: 10 mg/Kg (for body weight of <75 Kg) or adult RA dosage (for body weight ≥75 Kg) at 0, 2, and 4 weeks, then every 4 weeks; IV			
Rituximab	RA Pemphigus vulgaris	- two 1000 mg separated by 2 weeks every 24 weeks; IV	Exploratory Phase I (Jimenez-Boj et al[153])	23 participants	6 months
	GPA MPA FL DLBCL CLL	- 375mg/m^2 or 500 mg/m^2; IV			
Tocilizumab	RA GCA (only SC injection)	- 4mg/Kg or 8 mg/Kg monthly; IV - 162 mg biweekly (for body weight <100 Kg) or weekly (for body weight ≥100 Kg); SC	Case reports (Costa et al.[157]; Ogata et al.[159]; Madureira et al.[160]; Hughes et al[161])		
	Polyarticular JIA	- 10 mg/Kg (for body weight <30 Kg) or 8 mg/Kg (for body weight ≥30 Kg) monthly; IV - 162 mg every 3 weeks (for body weight <30 Kg) or biweekly (for body weight ≥30 Kg); SC			
	Systemic JIA CRS (only IV infusion)	- 12 mg/Kg (for body weight <30 Kg) or 8 mg/Kg (for body weight ≥30 Kg) biweekly; IV			
ABT-122 COVA322	Not yet approved	/	Phase II (Mease et al)[165] Preclinical study (Silacci et al)[167]	240 participants 24 participants	12 weeks 12 weeks

Notes: **Recruitment status. ***Active, not recruiting.
Abbreviations: A3AR, adenosine A3 receptor; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; CTLA-4, cytotoxic-T-lymphocyte-associated antigen 4; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food And Drug Administration; FL, follicular lymphoma; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; Ig, immunoglobulin; IL, interleukin; IM, intramuscular; IV, intravenous; JIA, juvenile idiopathic arthritis; MPA, microscopic polyangiitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor; SC, subcutaneous.

affected by PsA or Crohn's Disease.[180] In addition, tofacitinib may be indicated in PsA patients presenting ulcerative colitis.[181] Up to 50% of SpA patients present documented microscopic subclinical gut inflammation, although it is still unclear if the proportion of PsA patients presenting this bowel mucosa changes; even though Scarpa et al [32] found microscopic changes in all PsA patients among a small population and none of them

presented macroscopic mucosal changes or IBD symptoms. The screening of gastrointestinal involvement has been suggested in PsA patients, in particular in patients undergoing IL-17 inhibitors or ETN, in order to avoid onset or recrudescence of IBD. The safety profile and infections clearly have an impact on the treatment choice. In this context, latent TB is not a contraindication to the use of other bDMARDs over TNFi, as well as patients with malignancies who underwent APR treatment. According to all this, the well-known screening procedures, for TB and B and C hepatitis, should be applied for all of the bDMARDs but not for APR.[12] As suggested by treatment recommendations, Heart failure class III or IV and demyelinating disorders, drugs such as UST, SEC, and APR did not reported contraindications their use. In particular, SEC may have a good effect in neurological disease, such as multiple sclerosis.[182] TNFi efficacy is influenced by BMI.[12] Gremese et al[183] demonstrated that patients affected by SpA presenting overweight or obesity showed a reduced response to TNF-i. Clinical phenotype, such as BMI, should address the treatment choice. We support the hypothesis, from real life data on SEC and UST treatment, that for both treatments, their efficacy is not influenced by high BMI nor by the presence of comorbidities.[184] Not uncommonly, the disease can also start in individuals aged >60 years, defined as late-onset PsA. The increase in life expectancy and the improvement of diagnostic imaging tools will likely lead to an increase in the number of elderly subjects with PsA.[185]

However, treatment opportunities in these patients differ from the general population. Studies have shown that NSAIDs are associated with mild or poor responses in elderly SpAs patients and corticosteroids are not strongly recommended because of the risk of serious long-term adverse effects, such as hypertension, diabetes, osteoporosis, skin atrophy, and cataracts.[186] Moreover, csDMARDs effectiveness and safety derived from randomized placebo-controlled trials (RCTs) and longitudinal observational cohorts are scarce and mainly focused on methotrexate and sulfasalazine.[187] Esposito et al[188] retrospectively evaluated the effectiveness and safety of subcutaneous etanercept and adalimumab in 89 elderly patients with PsO and PsA, aged between 65 and 82 years (mean age 69.7 years). The results showed that TNF-i are appropriate in the long-term management of elderly patients. Additionally, in this study, a good safety profile was reported.[187] When appropriate, APR can be useful and relatively safe. On the contrary, data on tofacitinib in elderly patients are very

few, and, among those, age older than 65 years has been reported as an independent predictor of increased risk of serious infections.[189]

Here, we summarized different studies supporting the efficacy and safety of TNFi in PsA, but discontinuation or switching is quite common.[190] PsA patients can experience TNFi, lack of efficacy, or adverse events: a mean of 40% of PsA reported switching to a second TNFi.[190] However, several studies exist on the effectiveness of switching among different TNFi. Recently, the concept of "swapping" emerged in PsA management: switching to another mode of action, such as to APR, SEC, UST, and IXE. In clinical trials considering these drugs, response to the drug was considered, both in patients naïve to TNFi and in patients failure to TNFi. All trials confirm their efficacy, both in TNF-naïve patients and those previously treated with TNFi. Data from real-life settings also support these results: UST, SEC, and IXE treatment were effective in a population of PsA patients who previously experienced failure to TNF-i.[14,88] The use of biosimilars was introduced in our daily clinical practice, with the advantage of economic benefit and savings for the national health system. TNFi biosimilar drugs have been investigated in PsA switching from the originator drug to a biosimilar molecule, demonstrating that switching from the originator molecule to a biosimilar is not inferior to continued treatment with the originator drug.[190,193]

PsA is a multifaceted disease with a complex pathogenesis involving both innate and acquired immune response. In the near future, the advent of newest therapeutic antibodies neutralizing more than one cytokine (TNF and IL-17) may have the advantage of contemporarily blocking multiple key steps of the pathogenic cascade conversely to one-cytokine-blocking antibody.[1,9] Of note, oral small molecules may already block different pathways, however their efficacy should be validated by relevant clinical data in the real-life practice. Treatment options, such as rituximab and abatacept, effective in treating RA, demonstrated their efficacy in only a few cases of PsA patients, bounding their use only in limited cases.[153] Guidance for clinicians is directed by patients clinical characteristics, such as age, gender, BMI, and the presence of comorbidities. bDMARDs and tsDMARDs variety, at present and in the near future, give us the possibility for the best choice in the best moment in PsA patients management. The drugs used for PsA patients management should be tailored based on the characteristics of any single patient and to the presence of complex age- and disease-related aspects.

Abbreviations

ACR, American College of Rheumatology; ADA, Adalimumab; AEs, adverse events; APR, Apremilast; AS, Ankylosing Spondylitis; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARDs, biological DMARDs; BMI, Body Mass Index; BMK, Bimekizumab; BRD, Brodalumab; BSA, body surface area; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; CRP, C-reactive Protein; csDMARDs, conventional DMARDs; CTLA-4, cytotoxic-T-lymphocyte-associated antigen 4; CV, cardiovascular; CVD, cardiovascular disease; CZT, Certolizumab pegol; DAPSA, Disease Activity in PSoriatic Arthritis; DAS, Disease Activity Score; DIP, distal interphalangeal; DM, diabetes mellitus; ETA, Etanercept; EULAR, European League Against Rheumatism; FDA, US Food and Drug Administration; GOL, Golimumab; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; GSK, Guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL-c, high-density lipoprotein cholesterol; HZ, varicella zoster; IBD, inflammatory bowel disease; IFX, Infliximab; IL, interleukin; IXE, Ixekizumab; JAK, Janus kinases; JAKi, Janus kinases inhibitors; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MDA, minimal disease activity; MAPK, mitogen-activated protein kinase; MetS, metabolic syndrome; MTX, methotrexate; PASI, Psoriasis Area Severity Index; PDE4, phosphodiesterase 4; PROs, Patient-Reported Outcomes; PsA, Psoriatic Arthritis; PSARC, PsA Response Criteria; PsO, psoriasis; RA, Rheumatoid Arthritis; RCTs, randomized controlled trials; RR, risk ratios; RSK, Risankizumab; RTX, Rituximab; SEC, Secukinumab; SpA, spondyloarthritis; SUCRA, surface under the cumulative ranking curve; SysPsD, Systemic Psoriatic Disease; TB, tuberculosis; TCZ, Tocilizumab; TLK, Tildrakizumab; TNF, Tumor Necrosis Factor; TNFi, Tumor Necrosis Factor inhibitors; tsDMARDs, targeted-synthetic DMARDs; TYK, tyrosine kinase; URTI, upper respiratory tract infection; UST, Ustekinumab.

Disclosure

The authors report no conflicts of interest in this work.

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