Switching biologics in the treatment of psoriatic arthritis

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\textbf{A B S T R A C T}

\textbf{Objective:} Psoriatic arthritis (PsA) is a heterogeneous inflammatory disorder that requires targeted treatment based on clinical manifestations, symptom severity, comorbidities, and other factors. Moderate or severe peripheral arthritis symptoms are typically treated with disease-modifying antirheumatic drugs (DMARDs) or biologic DMARDs (bDMARDs), and early and aggressive treatment is recommended in order to prevent permanent damage. Although rheumatologists are now able to choose between several bDMARDs for PsA that have different chemical structures, pharmacokinetic properties, dosing regimens, immunogenicity, safety profiles, and mechanisms of action, there is a lack of typical patient profiles or detailed treatment algorithms that can be followed when patients require alterations in their therapeutic regimens.

\textbf{Methods:} PsA treatment recommendations were evaluated to identify consensus guidelines on switching between bDMARD therapies. PubMed literature searches were then conducted using the terms psoriatic arthritis, switch/switching, biologic, and TNF/tumor necrosis factor. Articles were deemed relevant if they presented data on switching between different bDMARDs in patients with PsA.

\textbf{Results:} Data from the clinical literature on switching bDMARD therapies in PsA are limited. Evidence suggests that response to adalimumab, etanercept, and ustekinumab is lower after previous tumor necrosis factor inhibitor (TNFi) therapy and the efficacy of infliximab is independent of previous bDMARD treatment. Trials of ustekinumab and secukinumab showed efficacy responses were greater compared with placebo in patients who failed to respond to ≥ 1 TNFi.

\textbf{Conclusion:} Switching bDMARD therapies is a recommended strategy for patients who experience treatment failure. Many factors must be considered for determining which agent to switch to including PsA disease characteristics, comorbidities, cardiometabolic risk factors, treatment history, and patient preference. Switching between TNFis can be effective for many patients, but bDMARDs with different mechanisms of action may be superior alternatives.

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Introduction

Psoriatic arthritis (PsA) is a complex, heterogeneous, and chronic inflammatory condition that affects roughly 25% of patients with psoriasis [1]. Individuals with PsA typically experience stiffness, pain, swelling, and tenderness of the joints as well as the surrounding ligaments and tendons [1,2]. Disease presentation can range from mild, nondestructive arthritis to severe and debilitating arthropathy [1].

Initial treatment considerations should be based on discrete clinical manifestations and symptom severity [3]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines provide recommendations for treatment based on the involvement of the following 6 domains: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail [4]. The choice of initial treatment should also take into account comorbidities commonly associated with PsA, and the GRAPPA guidelines provide considerations for treatment based on the presence of concomitant comorbidities [4]. When making treatment decisions, it is important to consider that early and aggressive treatment of some patients can result in significant improvements in joint and skin symptoms, thus preventing permanent damage [5,6].

Biologic disease-modifying antirheumatic drugs (bDMARDs) have transformed the PsA treatment landscape and their use has steadily increased over the last decade [7]. These agents are recommended for patients requiring rapid control of skin and joint symptoms, and those who have failed to respond to nonbiologic DMARDs after 3–6 months of treatment [8,9]. Numerous bDMARDs have demonstrated efficacy in PsA, including the tumor necrosis factor inhibitors (TNFis) adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, the interleukin (IL)-12/23 inhibitor ustekinumab, and the IL-17A inhibitor secukinumab [10–12]. The small-molecule phosphodiesterase-4 inhibitor apremilast also has demonstrated efficacy and safety in patients with PsA [13,14]. However, other bDMARDs that are approved for the treatment of rheumatoid arthritis (such as abatacept, anakinra, and rituximab) have either demonstrated limited evidence of efficacy or failed to demonstrate consistent improvements in PsA [15]. In addition, updated GRAPPA guidelines for the management of axial disease in PsA noted that abatacept, rituximab, and the IL-6 inhibitors sarilumab and tocilizumab have failed to show efficacy in ankylosing spondylitis [16], making it unlikely that these agents would benefit patients with axial PsA. The key clinical trials assessing apremilast did not analyze axial disease outcomes [17], thus the updated GRAPPA guidelines were unable to make a recommendation for this therapy in axial PsA [16].

Rheumatologists are now able to choose between bDMARDs for PsA that have different chemical structures, pharmacokinetic properties, dosing regimens, immunogenicity, safety profiles, and mechanisms of action [18]. When a patient fails to respond or no longer responds to one bDMARD due to lack of efficacy or poor tolerability, evidence suggests that switching to another bDMARD can be a safe and effective treatment strategy [10]. However, data to guide clinicians on switching between different bDMARDs are limited [10]. This review discusses factors to consider when switching between bDMARD therapies for patients with PsA in the context of efficacy, safety, and evidence-based treatment guidelines, with a particular focus on extra-articular manifestations and comorbid conditions.

Methods

PsA treatment recommendations from organizations including the European League Against Rheumatism (EULAR) [9], Outcome Measures in Rheumatology (OMERACT) panels [19], GRAPPA [3,4,16,20,21], and other national rheumatology societies [22,23] were evaluated to identify consensus guidelines on switching between bDMARD therapies. PubMed literature searches were then conducted to identify more detailed information on the efficacy and safety of switching bDMARDs in randomized controlled trials or real-world settings. Searches were conducted using combinations of search terms including psoriatic arthritis, switch/switching, biologic, and TNF/tumor necrosis factor. Search results were supplemented based on the reference citations in articles identified in initial searches and based on the authors’ familiarity with the published literature. Articles were deemed relevant if they presented data on switching between different bDMARDs in patients with PsA.

Considerations for switching

PsA is a heterogeneous disease, and there is a paucity of data from controlled clinical trials to guide decisions related to therapy changes in this disease area [9]. First, it should be understood that there are no “typical” patient profiles or detailed algorithms that can be followed when patients require alterations in their treatment regimens. Treatment of PsA is complicated by the need to manage both skin and joint disease, along with the increased incidence of comorbid disorders such as inflammatory bowel disease (IBD) [4], all of which may collectively drive therapeutic decisions. Further, skin, joint, and some other systemic manifestations of PsA may have common or differing pathophysiology, such that various treatments may differentially affect articular and extra-articular symptoms [9].

To better guide therapeutic decisions, the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group has defined core PsA domains that should be measured to assess the effects of treatment [19]. These include peripheral joint activity, skin activity, pain, patient global assessment, physical function, and health-related quality of life [19]. With these domains in mind, criteria were developed to define minimal disease activity (MDA), which can serve as a target for treatment in clinical practice [24]. Subsequently, the tight control of inflammation in early psoriatic arthritis (TICOPA) study showed that patients assessed every 4 weeks to determine whether they had achieved MDA targets had better joint and skin outcomes than patients who were followed according to the current standard of care [5,6,25]. According to this tight control protocol, if a patient did not achieve MDA criteria at any visit, their treatment regimen was modified, either by increasing therapeutic doses or by adding or switching therapies [25]. Findings from the TICOPA study suggest that an aggressive treatment strategy that assesses and potentially modifies treatment every 4 weeks is a better approach to PsA management than making changes every 3–6 months, as needed, according to current guidelines [6,9]. Although TICOPA favors a tight control approach, extensive use of sulfasalazine is typically avoided in clinical practice. We recommend not changing biologic medications within 3 months of initiation unless there are serious safety concerns or virtually no response. The current MDA criteria for PsA are compromised by the fact that it is not a composite measure, and does not recognize that patients with significant skin activity may still meet MDA criteria. Therefore, an MDA strategy that addresses these limitations and accounts for skin, joint, and related disease activity in patients on systemic therapy is being developed.

When tracking patients’ improvements, even when utilizing tight control strategies such as those in TICOPA, it is important for dermatologists to understand that expected improvements in joint symptoms are typically far less substantial than...
improvements in skin symptoms. For example, the American College of Rheumatology (ACR) 20 response is the standard benchmark for improvement in joint symptoms [25], whereas Psoriasis Area and Severity Index (PASI) 75 is the minimum benchmark for improvement in skin symptoms [26]. Despite improvements in measuring MDA, clear guidance is not yet available on how to best use imaging [magnetic resonance imaging (MRI) and ultrasonography] to measure radiographic progression in PsA. It is also important to note that EULAR has identified addressing this gap as part of their recommended future research agenda [9].

**Guidance for switching therapies**

*Published literature and consensus guidelines*

Data from the clinical literature on switching bDMARD therapies in PsA are limited [27]. Most studies have been retrospective or observational and involved switching patients from one TNFi to another TNFi. Key findings from studies published to date are summarized in the Table. In general, treatment responses and the length of drug survival decreased in patients receiving a 2nd or 3rd TNFi. In a study of the Danish DANBIO registry, Glintborg et al. [28] reported that for ACR20 responses the number needed to treat to have one positive outcome was 2.2, 4.5, and 5.3 patients for the 1st, 2nd, and 3rd TNFi treatment course, respectively. Predictors of switching included female sex, shorter disease duration, high health assessment questionnaire (HAQ) scores, high 28-joint count Disease Activity Score (DAS28), high fatigue/pain scores, and more swollen and tender joints [28]. It is not clear which patient characteristics influence efficacy after switching, but high baseline C-reactive protein levels (>10 mg/L) are associated with treatment response in TNFi-naïve patients [29]. Glintborg et al. [28] also reported that patients who switched due to adverse events had a lower chance of achieving ACR20 and ACR50 responses than those who switched due to lack of effect. In contrast, Conti et al. [30] observed similar efficacy between patients who switched for lack of efficacy or poor tolerability, but this study was limited by a small number of patients.

In addition to these studies, large-scale randomized controlled trials of ustekinumab and secukinumab showed that ACR20 and PASI 75 responses were significantly improved compared with placebo in patients who failed to respond to one or more TNFi, and that these agents inhibit radiographic disease progression [12,42–44]. However, the onset of action for ustekinumab is slower than that of TNFis in patients with PsA [42]. Further, an increase in the number of TNFi exposures or failures predicted a poorer response to subsequent ustekinumab therapy [42], underscoring the idea that bDMARD therapy failure may suggest a different patient phenotype or change in immune response with subsequent bDMARD exposure.

Guidelines that specifically address switching therapy were developed when all available bDMARDs were TNFis and therefore did not include any agents with different mechanisms of action [9,22,23]. Thus, these guidelines recommended that patients who failed to respond to one TNFi should be switched to a second TNFi [9,22,23]. However, in the recent GRAPPA treatment recommendations for PsA, a conditional recommendation based on observational studies was given for switching to an alternative biologic either within a drug class or to a drug with a different mode of action for patients who failed biologic therapy [4].

Choice of bDMARD therapy should be determined by the treating physician [8,45]. The expert consensus (74%) from a recent Delphi survey of 23 Spanish dermatologists was that patients with primary treatment failure with one bDMARD should switch to a bDMARD with a different mechanism of action [46]. Patients with a loss of efficacy due to formation of neutralizing antibodies may particularly benefit from switching to another agent with the same therapeutic target but with lower immunogenicity [13,46–48]. However, it is the authors’ expert opinion that some patients may benefit from dose escalation (including a change in dose and/or interval of dosing) within class, or the addition of methotrexate, before changing to an agent with a different mechanism of action.

**Efficacy considerations**

Limited evidence suggests that the response to adalimumab, etanercept, and ustekinumab is lower in patients previously treated with another TNFi, while the efficacy of infliximab has been shown to be independent of previous bDMARD treatment [45]. Further, data from randomized controlled trials suggest that the efficacy of ustekinumab and apremilast may be lower than that of TNFis for the treatment of PsA, although in the absence of studies with any direct comparisons these observations are based on relative improvements in ACR20 over placebo within individual studies [13]. Further indirect treatment comparisons of randomized evidence or head-to-head trials are needed to support the comparative effectiveness of these various bDMARDs in PsA. No differences have been reported for the available bDMARDs based on efficacy in controlling dactylitis and enthesitis [13].

The potential benefits of combining a bDMARD with methotrexate or adding methotrexate to a bDMARD to extend drug survival are controversial [22,45]. Methotrexate at doses ranging from 5–50 mg/week has been shown to increase the risk of developing liver fibrosis in patients with psoriasis, and should be used with caution in obese patients, patients who consume alcohol, and patients with other risk factors for hepatotoxicity such as diabetes and hepatitis [49]. However, recent evidence-based guidance from the Medical Board of the National Psoriasis Foundation states there is strong evidence supporting combination of etanercept and methotrexate in selected patients when efficacy of monotherapy with either agent is not sufficient [50]. In addition, methotrexate in combination with TNFis or other bDMARDs has been shown to decrease the side effects of either agent as lower doses can be used; however, the majority of evidence suggests that this combination does not improve clinical symptoms of PsA beyond those attained by bDMARDs alone [51]. Physician surveys of dermatologists have found that etanercept is the preferred first-line bDMARD for treatment of patients whose skin symptoms are controlled with methotrexate and who continue to experience persistent dactylitis or enthesitis [46]. However, there remains a lack of evidence showing a direct benefit for etanercept and methotrexate in both clinical studies and CRAPPA recommendations for dactylitis and enthesitis [3]. Further, evidence supporting the combination of a bDMARD with phototherapy, acitretin, cyclosporine, or another bDMARD for the treatment of psoriasis is not strong [50].

Clinical trials have not assessed the efficacy of bDMARDs for managing axial disease [13]. Current guidance recommends TNFis for the management of axial PsA, which is based on the treatment guidelines for ankylosing spondylitis and nonradiographic spondyloarthritis [8,13,23]. In contrast, nonbiologic DMARDs such as methotrexate are not recommended for axial PsA [3]. In addition to TNFis, recent data suggest that IL-23 and IL-17 are also promising targets for the treatment of axial PsA [13].

Different dosing regimens, routes of administration, and mechanisms of action for the different TNFis and other bDMARDs can impact their effectiveness due to different half-lives, peak and trough serum levels, and actions on receptors versus direct cytokine binding [52]. Immunogenic and pharmacokinetic properties that may affect treatment response should be considered
<table>
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<td>NOR-DMARD [31]</td>
<td>Longitudinal, 3-year, observational study; Norway</td>
<td>Included patients taking ETN, IFX, ADA, GOL, and CTZ ($n = 95/439$ switched TNFi)</td>
<td>Switchers had significantly poorer responses to their 2nd TNFi than nonswitchers had to their 1st TNFi</td>
<td>Study highlights the need for PsA treatments with novel MOAs</td>
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<td>DABIO Registry [28]</td>
<td>Observational cohort study, up to 10 years; Denmark</td>
<td>Included patients taking ADA, ETN, IFX, GOL, CTZ, RTX, TOC, and ABA</td>
<td>ACR20 response rates for the 1st, 2nd, and 3rd treatments were 47%, 22%, and 18%, respectively</td>
<td>Switching was more common in women who had short disease duration, high HAQ, DAS28, and fatigue/pain scores, with more swollen and tender joints than nonswitchers. Patients who switched due to an AE had a lower chance of ACR20 and ACR50 responses than those who switched due to lack of effect</td>
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<td>BIBADASER Registry [32]</td>
<td>Observational study over 4 years; Spain</td>
<td>Included patients taking ADA, ETN, and IFX</td>
<td>Over the first year of treatment, 55/289 patients failed on 1st TNFi; 8/15 failed on 2nd TNFi</td>
<td>Older age was a predictor of treatment failure. Treatment discontinuation rates were higher with IFX than with ETN or ADA; 48% of discontinuations were due to AEs</td>
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<td>Conti et al. [30]</td>
<td>Longitudinal, 5-year, prospective, observational study; Italy</td>
<td>15 patients with PsA switched treatment: $n = 8$ IFX $\rightarrow$ ETN, $n = 5$ ETN $\rightarrow$ ADA, $n = 2$ IFX $\rightarrow$ ETN $\rightarrow$ ADA</td>
<td>PsARC improved from 10% to 70% in patients who switched from IFX to ETN. PsARC improved from 14% to 57% in patients who switched from ETN to ADA</td>
<td>Outcomes were similar whether switch was due to lack of efficacy or poor tolerability</td>
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<td>Coates et al. [33]</td>
<td>Retrospective analysis of data from a 3-year study with prospectively collected clinical data from patients in the Leeds Spondyloarthritis and Resistant Arthritis databases; UK</td>
<td>Included 60 patients who took IFX ($n = 47$), ETN ($n = 26$), and ADA ($n = 7$) over the course of the study</td>
<td>For the 1st TNFi, 14/60 patients did not respond (2 lack of efficacy, 10 loss of efficacy, 2 AEs). For the 2nd TNFi, 7/12 patients did not respond (5 lack of efficacy, 1 loss of efficacy, 1 AEs). For the 3rd TNFi, 3/7 patients did not respond (2 lack of efficacy, 1 loss of efficacy).</td>
<td>Serious side effects that led to switching or treatment cessation included 2 patients with elevated LFTs on IFX and 1 patient with symptoms of possible myelitis</td>
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<td>STERO [34]</td>
<td>Open-label 12-week study with an optional extension phase</td>
<td>66 patients with PsA and prior treatment failure were switched to ADA IFX $\rightarrow$ ADA ($n = 18$) ETN $\rightarrow$ ADA ($n = 34$) IFX and ETN $\rightarrow$ ADA ($n = 14$)</td>
<td>At week 12, ACR50 was achieved by 42% and mPsARC was achieved by 71% of patients who switched to ADA</td>
<td>Likelihood of clinical response did not differ significantly for patients with and without prior TNFi treatment</td>
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<td>Saad et al. [35]</td>
<td>Prospective study of treatment persistence in patients with PsA registered with the BSR Biologics Register</td>
<td>Included patients taking ADA ($n = 88$), ETN ($n = 316$), and IFX ($n = 162$) as their initial TNFi</td>
<td>After 12 months, 9.5% of patients discontinued initial therapy due to inefficacy, 10% due to AEs, and 5% due to other reasons. 74% of patients who switched were still taking their 2nd therapy at 12 months</td>
<td>Higher initial TNFi discontinuation rates were observed for females, those with comorbidities, and those taking IFX</td>
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<td>Haberhauer et al. [36]</td>
<td>Observational study of patients at an Austrian rheumatology outpatient clinic from 2004 to 2008</td>
<td>63 patients with PsA taking IFX, ETN, or ADA</td>
<td>33% (21/63) of patients were treated with &gt; 1 TNFi. Loss of efficacy was the most common reason for switching</td>
<td>Response to the 2nd TNFi was better in PsA than in patients with RA or AS</td>
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<tr>
<td>Jani et al. [37]</td>
<td>Regional survey of PsA patients in northwest England</td>
<td>548 patients enrolled; 1st therapy was ADA ($n = 350$), ETN ($n = 186$), IFX ($n = 11$), or GOL ($n = 1$) 2nd/3rd/4th-line therapies included ADA ($n = 51$), ETN ($n = 38$), IFX ($n = 13$), GOL ($n = 5$), RTX ($n = 3$), CTZ ($n = 1$), TOC ($n = 1$), and UST ($n = 1$)</td>
<td>52/94 patients who switched therapy achieved adequate response with their 2nd biologic 8/94 achieved response to the 3rd or 4th biologic 19/94 had AEs and 19/94 had inadequate response to 2nd biologic</td>
<td>Switching practices were generally aligned with BSR and EULAR guidelines</td>
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when choosing therapies [53,54]. Additionally, bDMARDs with weight-based dosing may provide better efficacy for overweight and obese patients [45,46]. It should be noted, however, that higher doses based on body weight may be associated with additional costs [45].

Off-label dose escalation of bDMARDs has been explored in numerous clinical studies, as reviewed by Brezinski and Armstrong [18]. Evidence currently suggests that nontraditional dosing regimens can be safe and effective [18], but further studies are needed to determine whether changes in product labeling are warranted. Additionally, it should be noted that safety data are currently limited to small patient populations, thus further studies are required to establish the safety profile of these bDMARDs at nontraditional doses.

Safety considerations

Physicians should be mindful of contraindications and other safety considerations when prescribing bDMARDs, including the risk of serious infections and how these agents may affect cardiovascular comorbidities [45,55]. In addition, numerous cases have been reported in which TNFis or ustekinumab have induced or worsened symptoms of psoriasis or PsA [56–58]; in such cases, switching to another agent with a similar mechanism of action is inadvisable.

TNFis are generally not recommended as first-line bDMARD therapy in patients with advanced congestive heart failure, systemic lupus erythematosus (SLE), demyelinating diseases such as multiple sclerosis, and other autoimmune disorders [45]. However, there is some evidence from smaller studies that suggests treatment with TNFis in patients with SLE does not result in short-term harm, and may even have a possible benefit in patients with lupus nephritis [59,60]. Further, a recent retrospective study showed that the TNFis ustekinumab and abatacept may be valid treatment options for patients with concomitant SLE and psoriasis, as patients reported a relatively low incidence of 0.92% lupus flares per patient-year of TNFi use [61]. Drug-provoked psoriasiform dermatitis has been observed in patients receiving TNFis [62] and a switch to a different agent is appropriate in this situation.

Careful consideration of disease severity and risk of adverse outcomes is warranted in women of childbearing age [45]. bDMARDs are reported to have different transplacental transmission throughout pregnancy, with virtually no transplacental transmission in the first trimester [63]. The pregnancy in IBD and neonatal outcomes (PIANO) registry of 1000 pregnant women with IBD demonstrated no association between TNFi use and any pregnancy or neonatal complications, although the combination of TNFis and thiopurines did lead to an increase in infant infections at 12 months of age [64]. Data from the ongoing prospective cohort of the organization of teratology information specialists (OTIS) registry showed no evidence of an association between adalimumab exposure and major birth defects, or a specific pattern of malformation, among women treated for rheumatoid arthritis or Crohn’s disease during their first trimester and subsequently followed for 1 year postpartum [65]. One case of infant mortality was reported in Europe when a child received disseminated Bacillus Calmette–Guérin vaccine at 3 months of age after the mother, who suffered from Crohn’s disease, had received the TNFi infliximab throughout her pregnancy [66]. Treatment with certolizumab pegol, which is not thought to be actively transported across the placenta due to its structure, may offer a potentially safer outcome for use in pregnancy [67]. In particular, an analysis of safety surveillance records showed no indication of adverse pregnancy outcomes associated with first trimester certolizumab pegol use [68]. It is our recommendation that during pregnancy women can continue bDMARD therapy through the first trimester and feasibly into the second trimester depending on their level of disease severity, but patients should be advised of the potential risks. Data in breastfeeding patients are quite limited; however, no notable adverse events have been reported in infants exposed to TNFis during breastfeeding [69].

As cardiovascular disease is a major comorbidity for patients with psoriasis and PsA [70], comprehensive disease management...
should involve cardiologists, as well as rheumatologists, dermatologists, and primary care physicians [71]. Elevated cytokine levels associated with PsA can result in systemic inflammation that heightens a patient's risk for developing insulin resistance; such inflammation also increases endothelial cell dysfunction and oxidative stress, which raises a patient's risk of developing atherosclerosis [71]. TNF inhibition has favorable effects on certain subclinical markers of inflammation and atherosclerosis, including C-reactive protein, carotid intima media thickness, and aortic stiffness [72]. However, results from a small (N = 32), 2-year, prospective, observational study in patients with PsA found that TNFi therapy did not prevent progression of atherosclerosis [73]. A major goal of any first-line therapy is the treatment of known and modifiable risk factors, and an improved understanding of the cardiovascular and cardiometabolic effects of therapies for PsA has the potential to revolutionize treatment strategies, allowing for the incorporation of therapies with cardioprotective effects. The ongoing psoriasis, atherosclerosis, and cardiometabolic disease initiative, a large prospective observational trial, will provide new information on the role of systemic inflammation derived from a chronic autoimmune disease on the development of vascular inflammation [74].

It has been postulated that therapies targeting IL-17A may improve cardiovascular outcomes in patients with PsA based on the shared pathogenic roles of Th17 cytokines in both cardiovascular and psoriatic disease, as demonstrated by the elevated levels of IL-17 observed in atherosclerotic lesions [75]. The Th17 pathway has also been implicated in immune dysfunction associated with IBD, obesity, and insulin resistance, suggesting that targeting this pathway could result in improvements in these common comorbidities that are associated with PsA [54].

Future therapies/state of care

With the recent approvals of certolizumab pegol, ustekinumab, and apremilast, patients and physicians have more options for managing PsA than ever before, including treatments with mechanisms of action different from TNF inhibition [13]. Several other bDMARD agents are in development, suggesting that the PsA treatment landscape may expand further in the near future. Additionally, there is currently a poor ability to predict response to a therapy but through further study of biomarkers predictability may improve.

IL-17 inhibitors

The IL-17A inhibitor secukinumab is approved for the treatment of moderate-to-severe plaque psoriasis, ankylosing spondylitis, and PsA. Results of large-scale phase 3 studies indicate that secukinumab significantly improves signs and symptoms of PsA in both TNFi-naive and TNFi-experienced patients [12,43]. Ixekizumab, another IL-17A inhibitor, had positive results in TNFi-naive patients with PsA [79]. A placebo-controlled phase 3 trial of ixekizumab in patients with PsA, SPIRIT-P2, is ongoing and includes patients with previous biologic exposure [80]. Additionally, results are awaited from 2 phase 3 studies comparing the IL-17 receptor A inhibitor brodalumab to placebo in patients with PsA [81,82]; following positive phase 2 results [83]. Bimekizumab, which inhibits IL-17A and IL-17F, is also being investigated in PsA [84].

IL-23 inhibitors

IL-23 is a key cytokine in the pathogenesis of psoriasis and PsA [85]. To date, 2 inhibitors of the IL-23 p19 subunit, guselkumab and tildrakizumab, are being studied in clinical trials. Phase 3 studies of guselkumab are ongoing in patients with psoriasis [86], and phase 2 studies are underway in patients with PsA [87]. Risankizumab, an IL-23p19 subunit inhibitor, is currently being investigated in a phase 2 trial of patients with PsA [88]. Phase 3 studies of tildrakizumab (MK-3222) are ongoing in patients with psoriasis [89], and PsA may be evaluated as a potential indication in the future.

Oral Janus kinase (JAK) inhibitors

The JAK inhibitor tofacitinib is approved for the treatment of rheumatoid arthritis, and in recent conference proceedings, it demonstrated superior efficacy to placebo in patients with PsA with inadequate response to ≥ 1 TNFi [90].

Abatacept

The fusion protein abatacept blocks T-cell activation and is approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis [91]. In a 6-month phase 2 study in patients with PsA, ACR20 response rates were significantly higher with abatacept compared with placebo [91]. For the treatment of psoriasis symptoms, however, the benefits of abatacept were minimal when compared with standard psoriasis therapies [91]. A phase 3 study of abatacept in PsA is ongoing [92].

IL-6 inhibitors

The IL-6 inhibitor tocilizumab is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. Case studies have reported the efficacy of tocilizumab in patients with refractory PsA [93,94]; however, no studies of tocilizumab in PsA are currently registered with ClinicalTrials.gov. Data suggest that the pathogenic roles of IL-
6 are different in rheumatoid arthritis and PsA, such that IL-6 is not an appropriate therapeutic target in PsA [95]. However, studies to further distinguish the pathophysiological role of IL-6 are ongoing.

Conclusions

Overall, switching bDMARD therapies in PsA is a recommended strategy when patients experience treatment failure. When determining which agent to switch to, physicians should consider the patient's unique PsA disease characteristics, comorbidities, cardiometabolic risk factors, treatment history, and personal preferences. Switching from one TNFi to another TNFi can be effective for a substantial proportion of patients, but as bDMARDs with different mechanisms of action become available, they may establish themselves as viable, and in some cases superior, alternatives.

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References

A study to evaluate the efficacy and safety/tolerability of subcutaneous Tildrakizumab (SCH 900222/MK-3222) in participants with moderate-to-severe chronic plaque psoriasis followed by a long-term extension study (MK-3222-011), ClinicalTrials.gov; https://clinicaltrials.gov/ct2/show/NCT01729754; 2016 [accessed 16.05.16].


Efficacy and safety of subcutaneous Abatacept in adults with active psoriatic arthritis (ASTRAEA), ClinicalTrials.gov; https://clinicaltrials.gov/ct2/show/NCT01860976; 2016 [accessed 20.04.16].

