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PSORIATIC ARTHRITIS (JU SCHER, SECTION EDITOR)

Psoriatic Arthritis: Newer and Older Therapies

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Abstract

Purpose of Review Psoriatic arthritis (PsA) is an immune-mediated systemic inflammatory disorder with heterogeneous clinical features. Treatment for PsA has progressed rapidly, especially over the past two decades. Herein we review relevant studies and key developments in treatment options for PsA from the past 5 years.

Recent Findings Conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate showed some efficacy for several domains of PsA, albeit less than that achieved with TNF inhibitors (TNFi). TNFi have been shown to be efficacious in treatment across all domains of PsA, particularly preventing radiographic damage, and are highly efficient early in the disease course. Inhibitors of IL-12/23, IL-17A, IL-23, phosphodiesterase 4, T cell costimulation, and janus kinases (JAK) have proven efficacious in the treatment of peripheral arthritis of PsA patients. The introduction of biosimilars to TNFi is expected to impact the treatment algorithm for PsA treatment by increasing access to biologic drugs. Newer treatment modalities including IL-23-specific inhibitors, IL-17A and IL-17F dual inhibitors, and jakinibs (janus kinase inhibitors) with different specificity are currently being developed for treatment of PsA.

Summary The recent development of new therapeutic agents for PsA has led to better control of PsA across all of its disease domains. The future of PsA management will likely usher in treatment with different mechanisms of action, allow for more access to care, and hopefully see the possibility of precision medicine to help select the optimal treatment approach for individual PsA patients.

Keywords Psoriatic arthritis · Treatment · Biologic DMARDs · TNF inhibitors

Introduction

Psoriatic arthritis is a multifaceted, chronic, progressive systemic inflammatory systemic disorder that eventually affects approximately 20 to 30% of patients with skin psoriasis [1]. For most patients, joint involvement follows after years of skin involvement. PsA can present with involvement in a variety of diverse domains including axial and peripheral arthritis, enthesitis, dactylitis, skin and nail psoriasis, and other domains, making early diagnosis and treatment a challenge. A growing body of evidence supports the need for early diagnosis and treatment of PsA, as delays in diagnosis lead to worse outcomes, including radiographic damage and impaired functional status [2, 3]. There are many therapeutic options currently available for the treatment of PsA patients (Table 1). These include adjunctive therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose corticosteroids, injectable forms of corticosteroids, and conventional DMARDs, including methotrexate (MTX), leflunomide, sulfasalazine, and cyclosporine. For patients with an inadequate response to NSAIDs or conventional DMARDs, or even some patients naïve to such treatments, there is now an abundance of biologic DMARDs (bDMARDs) including TNFi, IL-17 inhibitors, IL-12/23 and IL-23 inhibitors, and oral targeted synthetic DMARDs such as phosphodiesterase 4 inhibitors and janus kinase inhibitors (Fig. 1). Pharmacological management of PsA has been an area of rapid and important expansion in the last 5 years. Excitingly, whereas earlier therapeutic developments tended to be follow-ons from earlier studies in rheumatoid arthritis (RA), recent years have witnessed increasing development of

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Table 1 Psoriatic arthritis treatment options

Adjunctive therapy					
NSAIDs COX-2 inhibitors	Oral corticosteroids	Intra-articular corticosteroids	Topical steroids	Physiotherapy	
Conventional DMARDs					
Methotrexate	Leflunomide	Sulfasalazine	Cyclosporine		
Biologic DMARDs					
TNF inhibitor	Infliximab Biosimilars	Etanercept	Adalimumab	Certolizumab	Golimumab
IL-12/23 mAb	Ustekinumab				
IL-17A inhibitor	Secukinumab	Ixekizumab			
T cell costimulation inhibitor	Abatacept				
Targeted synthetic DMARDs					
Janus kinase inhibitor	Tofacitinib				
Phosphodiesterase 4 inhibitor	Apremilast				
Experimental (many others in development)					
Janus kinase inhibitors	Filgotinib (JAK1)	Upadacitinib (JAK1)	Baricitinib (JAK1/2)	BMS-986165 (Tyk2)	
IL-23 mAb	Guselkumab	Risankizumab	Tildrakizumab		
IL-17 inhibitors	Brodalumab (IL-17RA)	Bimekizumab (IL-17A/F)			

agents focusing specifically on the treatment of PsA. In addition, it has been noted that there have also been significant therapeutic response differences across PsA disease domains when utilizing various targeted therapies. Here we review new evidence within the past 5 years regarding efficacy of conventional DMARDs and bDMARDs for PsA treatment and set the stage for new therapies to come.

Methotrexate

Methotrexate (MTX) is the most widely used traditional DMARD for treatment of PsA. The methotrexate in PsA trial (MIPA) was a 6-month, double-blind, randomized, placebo-controlled trial comparing MTX and placebo in PsA. There was no clinical efficacy observed for MTX over placebo in regard to the primary outcome (the PsA response criteria; PsARC), or on secondary outcomes such as ACR20, DAS-28, tender joint count (TJC), swollen joint count (SJC), ESR, CRP, and HAQ. However, aspects of the study design likely contributed to the negative outcome, including relatively lower doses of MTX utilized, and enrollment of patients with low levels of disease activity (entry to the study required one or more active joints). Importantly, analysis of subgroups showed MTX did have clinical efficacy among patients with polyarticular disease and especially those with increased acute phase reactants, suggesting that it could be effective in PsA [4]. Most recently, a randomized, double-blind trial of 851 patients with active psoriatic arthritis naïve to biologic and methotrexate treatment called the Study of Etanercept and Methotrexate in Combination or as Monotherapy (SEAM-PsA) compared MTX with both TNFi monotherapy and combination therapy (TNFi and MTX) [5, 6•]. The study found at the time of the primary outcome assessment 51% of patients in the MTX group reached an ACR20 response, 23% of patients had achieved minimal disease activity (MDA), and 65% of patients had improvement in skin psoriasis > 10% as measured by body surface area (BSA). In comparison, 61% of patients in the etanercept group reached ACR20 and 36% reached MDA. In the MTX and etanercept combination group, 65% reached ACR20 response and 36% reached MDA. Thus, combining MTX with a TNFi did not significantly improve efficacy of the TNFi on the musculoskeletal aspects of PsA, casting doubt on the potential synergy of MTX with TNFi in PsA for those domains; there may have been some synergy as regards skin psoriasis. This differs from the body of data showing clear synergy between TNFi and MTX as regards peripheral arthritis in patients with RA. However, this study also suggested that MTX can achieve clinical efficacy across varied domains of PsA. It must be noted that as the study lacked a comparison against a placebo group, it is not possible to fully estimate the effect size of MTX versus placebo. On the other hand, while the extent of response to MTX was statistically significantly lower than that with etanercept or etanercept plus MTX, the magnitude of the difference in response was less than what might have been predicted a priori.

Tumor Necrosis Factor Inhibitors

The TNF inhibitors infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol have proven efficacy in the treatment of PsA. The most recently published study of

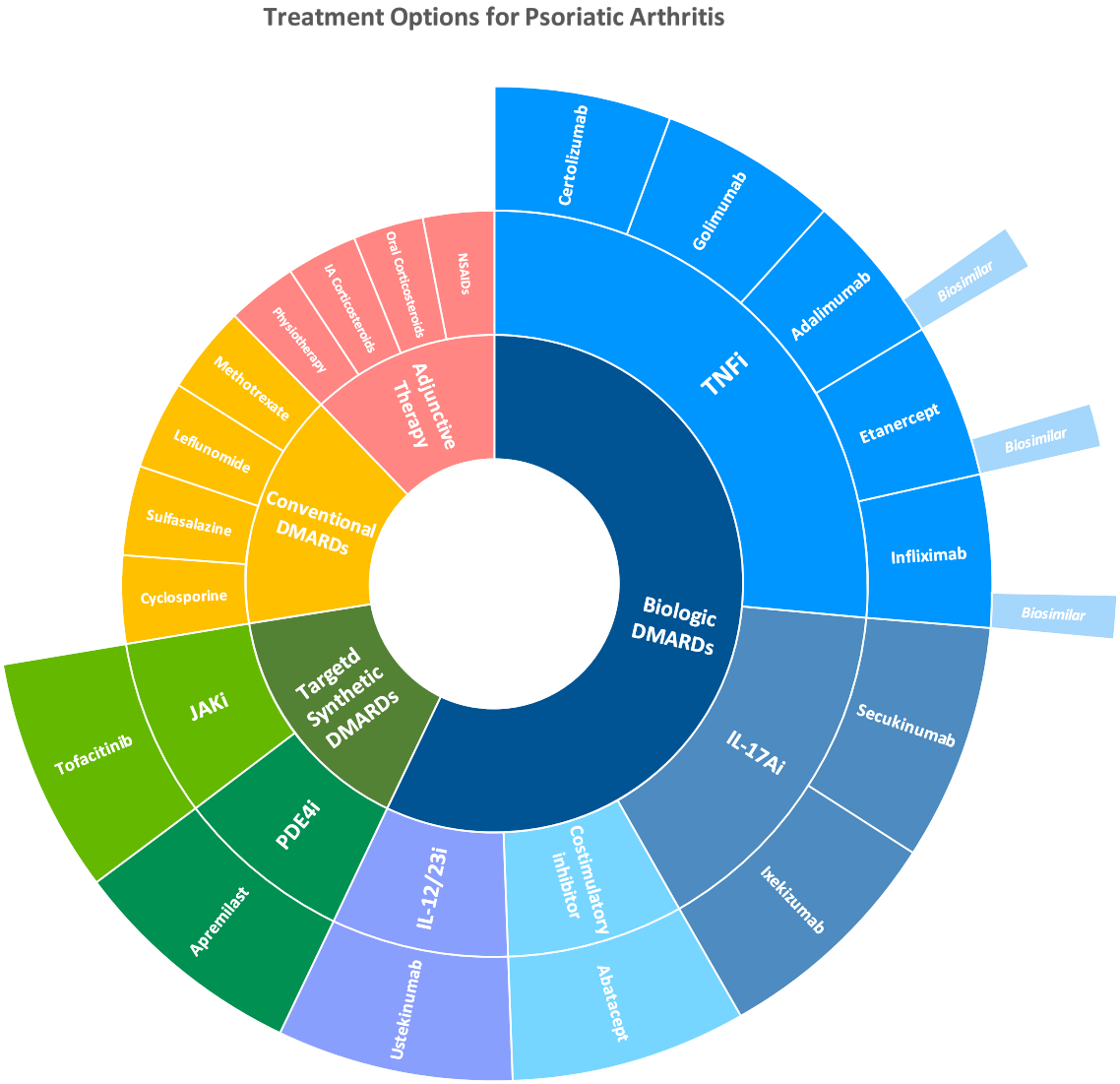

Fig. 1 Treatment options for psoriatic arthritis. Summary of the current available treatment options for psoriatic arthritis. DMARDs, disease-modifying anti-rheumatic drugs; TNFi, tumor necrosis factor inhibitors; IL-17Ai, IL-17A inhibitor; IL-12/23i, IL-12/23 inhibitor; PDE4i, phosphodiesterase 4 inhibitor; JAKi, janus kinase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; IA corticosteroids, intra-articular corticosteroids

TNFi in PsA was the GO-VIBRANT trial, a phase III randomized, double-blind, placebo-controlled trial of 480 PsA patients using IV golimumab compared to placebo. Data from this study showed that 75% of patients in the golimumab group achieved the primary endpoint of an ACR20 response at week 14 compared to 22% in the placebo group; 44% and 25% of patients in the golimumab group reached ACR50 and ACR70 respectively compared to 6% and 2% in the placebo group. Furthermore, 59% of golimumab patients also achieved PASI75 compared to 14% in the placebo group. Additionally, in terms of radiographic progression, there was less progression in the golimumab group compared to placebo (a − 0.4 change in the modified Sharp/van der Heijde score compared to 2.0) [7]. Additional recently published data from longer term follow-up of golimumab administered subcutaneously (GO-REVEAL study) through 5 years of follow-up showed minimal disease activity (MDA) at > 3 consecutive visits was associated with less radiographic progression [8]. A secondary data analysis of the GO-REVEAL trial found that with more structural damage, particularly joint space narrowing, functional outcomes such as HAQ may become irreversible [9]. Golimumab was also more efficacious in preventing radiographic progression in PsA when compared to placebo and more importantly prevention of radiographic progression was independent of clinical response [10].

Several other recent studies of TNFi in PsA have provided additional information that should help refine the use of these agents in PsA. Following on an idea long established in RA,

recent data suggest that early initiation of TNFi in patients with early PsA should also be considered. In a recent double-blind, randomized, placebo-controlled study comparing the combination of golimumab plus MTX versus MTX alone in inducing remission in patients with early, treatment-naïve PsA, the rate of DAS remission at week 22 was almost doubled in the golimumab+MTX group versus MTX alone group [11]. bDMARDs have also been shown to positively impact bone structure and biomechanical properties in patients with PsA. In a cross-sectional study of 165 PsA patients, those treated with biological DMARDs (TNFi, and also IL-12/23 and IL-17 inhibitors) benefited from higher bone mass and better bone strength than those receiving MTX or no DMARDs [12]. In recent years, multiple biosimilars to etanercept, adalimumab, and infliximab have been approved by the FDA and by regulatory agencies in many countries worldwide for the treatment of PsA as well as other rheumatologic conditions [13–15]. Their introduction is expected to improve patient access to biologic drugs and to expand high-quality health care at a lower cost. This will likely also impact the algorithms for sequencing medications with different mechanisms of action. Already, as they were the first class of biologics introduced for the treatment of PsA, TNFi are often the first class of biologics used. If their acquisition costs fall to levels significantly lower than other classes of biologics, this may be expected to reinforce their primary place in treatment algorithms and may even increase the practice of switching among TNFi, for example, before moving to agents with different mechanisms of action.

IL-12/23 Inhibitors

The first approved biologic targeting IL-23 was ustekinumab, a monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23. The PSUMMIT 1 trial was a phase III, multicenter, double-blind, placebo-controlled study of 615 patients assigned to 45 mg ustekinumab, 90 mg ustekinumab, and placebo. More ustekinumab treated (42% in the 45 mg group and 50% in the 90 mg group) achieved ACR20 at 24 weeks compared to 23% in the placebo group [16]. The ustekinumab 90 mg group showed a significant improvement in enthesitis assessed by MASES scores compared to placebo. In addition, there was also significant improvement in dactylitis and PASI75 in the ustekinumab treatment groups. Similar findings were validated in the subsequent PSUMMIT 2 trial including patients previously treated with conventional and/or biological agents [17]. Combined radiographic data from PSUMMIT 1 and PSUMMIT 2 trials showed significantly less radiographic progression in patients on ustekinumab at week 24 compared to placebo [18]. Additional data on ustekinumab has recently been published. The open-label ECLIPSA study assessed the efficacy of ustekinumab for 23 PsA patients compared with TNFi for 24 patients, focusing on a group of patients with active enthesitis. At week 24, 74% of ustekinumab patients achieved a SPARCC of 0 (indicating clearance of enthesitis) compared to 42% of TNFi patients [19]. While it may not be possible, given aspects of the study design, to conclude anything about relative efficacy, it certainly appears that ustekinumab can be effective for enthesitis, an important domain among PsA patients. In contrast, ustekinumab has not been shown to be efficacious in treatment of ankylosing spondylitis after two phase III trials were terminated since ustekinumab did not achieve key endpoints [20, 21]. By analogy, among PsA patients with axial arthritis that has a significant impact on their overall disease, it would not be expected that ustekinumab would be effective for that domain.

Recently, three new IL-23p19 subunit–specific inhibitors, guselkumab, tildrakizumab, and risankizumab, have shown efficacy in treatment of skin psoriasis [22–25]. Other IL-23-specific inhibitors are in development. While studies are underway for PsA, to date, the majority of data has been presented with these agents in skin psoriasis. The VOYAGE trial was a randomized, double-blind, phase III trial comparing 870 patients with skin psoriasis on guselkumab, adalimumab, or placebo. At week 16, 73% of guselkumab-treated patients achieved PASI90 compared to 2.9% of patients on placebo and 49.7% of adalimumab-treated patients [22]. The reSURFACE trial was a randomized, double-blind, phase III trial comparing 1772 patients with skin psoriasis on tildrakizumab or placebo. Both groups of tildrakizumab (100 mg and 200 mg) achieved higher PASI75 (64% and 62%, respectively) compared to placebo (6%) [23]. Phase III trials of risankizumab in treatment of skin psoriasis are ongoing due to promising phase II trials [24]. Most recently, a phase III, randomized, double-blind, active comparator–controlled trial of 605 patients with moderate to severe plaque psoriasis compared those receiving subcutaneous risankizumab with those receiving subcutaneous adalimumab. The study reached its primary endpoint as 72% of the risankizumab group reached PASI90 at week 16 compared with 47% of the adalimumab group. Subsequently after week 16, adalimumab intermediate responders were re-randomized to continue adalimumab or switch to risankizumab. Of those who switched to risankizumab, 66% achieved PASI90 at week 44 compared with 21% of those who continued on adalimumab [25]. Although it certainly remains to be specifically shown, by analogy to data with ustekinumab, it might be expected that specific IL-23 inhibitors may achieve efficacy in the peripheral arthritis of PsA. Also, it would not be unreasonable to hypothesize that these agents may also improve enthesitis. However, a recent phase II study of risankizumab for treatment of AS did not meet the study's primary endpoint and showed no evidence of meaningful improvement, suggesting IL-23 may not be a relevant driver of

disease pathogenesis in AS, and by extension, in the axial arthritis of PsA patients [26].

IL-17 Inhibitors

IL-17 inhibitors have been studied for treatment of PsA. Two IL-17A-specific monoclonal antibodies (mAb), secukinumab and ixekizumab, have been approved for treatment of PsA. Two other agents, bimekizumab (a dual IL-17A and IL-17F inhibitor) and brodalumab (an IL-17 receptor A inhibitor), are still undergoing further research in PsA. Regarding secukinumab, while the pivotal trials (and subsequent regulatory approval) were several years ago, newer data continues to emerge. The FUTURE 5 study showed improvement in symptoms in PsA patients taking both doses of secukinumab (150 mg and 300 mg) with and without loading dose when compared to placebo. Sixty-three percent of patients on secukinumab with loading dose achieved ACR20 response at week 16 compared with 56% of 150 mg secukinumab with loading dose, 60% of 150 mg secukinumab without loading dose, and 27% of patients on placebo. Prominent efficacy was seen in skin psoriasis with 70% of 300 mg secukinumab with loading dose achieving PASI75 at week 16 compared with 60% of 150 mg secukinumab with loading dose, 58% of 150 mg secukinumab without loading dose, and 12% on placebo. Radiographic progression was also significantly inhibited at week 24 in all secukinumab arms compared to placebo [27]. Other phase III trials have also proven secukinumab to be efficacious in treatment of plaque psoriasis [28]. IL-17 inhibition has been studied for control of inflammatory bowel diseases; not only was IL-17 inhibition ineffective, there was also the potential for increases of disease activity with treatment [29]. Ixekizumab has been studied in the SPIRIT-P1 and SPIRIT-P2 trials. SPIRIT-P1 focused on biologic-naïve PsA patients with 58% of the ixekizumab arm achieving ACR20 at week 24 compared with 30% of placebo. Progression of structural damage along with dactylitis and enthesitis symptoms was significantly less in the ixekizumab group compared to placebo [30]. SPIRIT-P2 focused on patients who failed one or two TNFi with 53% of the ixekizumab arm reaching ACR20 at 24 weeks compared to 20% on placebo [31]. Several studies have shown ixekizumab is efficacious in treatment of plaque psoriasis [32]. As a continuation of the SPIRIT-P2 study, at week 16, inadequate responders in the ixekizumab group were continued on the same dose until week 52 and inadequate responders in the placebo group were re-randomized to different ixekizumab doses (80 mg every 4 weeks and 80 mg every 2 weeks). At week 24, ixekizumab-treated patients reported significant improvements in patient-reported outcomes compared to the placebo group in the 36-item short form health survey, European Quality of Life visual analogue scale, Bath Ankylosing Spondylitis Disease Activity Index, and Work Productivity and Activity Impairment Questionnaire-Specific Health Problem. In addition, 52% and 54% of the ixekizumab group (every 4 weeks and every 2 weeks, respectively) compared to 9% of placebo group reported Dermatology Life Quality Index scores of 0 or 1. In terms of the Itch Numeric Rating Scale, 24% of the ixekizumab group achieved a score of 0 compared to 0% of the placebo group. These improvements in patient-reported outcomes in terms of disease activity, skin symptoms, quality of life, and work productivity persisted through week 52 [33]. An analysis of data from the SPIRIT studies proved what many experienced rheumatologists would have likely predicted from treating PsA patients; namely that the largest improvements in quality of life are achieved when patients experience the greatest improvement in multiple domains of disease. Thus, while PsA patients experiencing peripheral joint involvement with ixekizumab but lesser skin improvement still had improvements in quality of life, and PsA patients with improving skin but lesser improvement in peripheral joints also improved their overall quality of life somewhat; patients who had substantial improvements in both skin and joints had the greatest improvement in quality of life [34•].

There is promising data on the dual IL-17A and IL-17F inhibitor bimekizumab with phase II studies showing significant dose-response at week 12 for ACR20, ACR50, and PASI90 in PsA patients on bimekizumab compared to placebo [35]. Phase II studies of the IL-17 receptor A inhibitor brodalumab show improved response rates in PsA patients compared to placebo; however, further development in PsA has not progressed as of yet [36, 37]. It will be interesting to assess whether there may be any important difference in efficacy and safety among the various IL-17 inhibitors with different mechanisms of action of IL-17 inhibition.

Phosphodiesterase 4 Inhibitors

Apremilast is an oral phosphodiesterase 4 inhibitor approved for the treatment of psoriatic arthritis and moderate to severe plaque psoriasis. The PALACE 1 study was a 24-week, placebo-controlled study involving 504 PsA patients randomized to apremilast 20 mg BID, apremilast 30 mg BID, and placebo. ACR20 was reached at week 16 in 38% of the 30 mg BID group, 30% in the 20 mg BID group, and 19% of the placebo group. There was a significant improvement in enthesitis as documented by change in MASES in the apremilast 30 mg BID group compared to placebo. In terms of skin psoriasis, 51% of the apremilast 30 mg BID group and 34% of the apremilast 20 mg BID group achieved PASI50 compared with 19% in the placebo group [38]. In patients who continued taking apremilast, ACR20 response of 30 mg BID at week 52 was 54.6% [39].

Janus Kinase Inhibitors

The janus kinase (JAK) family of tyrosine kinases (JAK1, JAK2, JAK3, and TYK2 in humans) are key signaling proteins vital for downstream intracellular signal transduction from a number of cytokine receptors. Tofacitinib, an oral janus kinase inhibitor that preferentially inhibits signaling through JAK3 and JAK1 more than JAK2, has been approved for treatment of active psoriatic arthritis in patients who have had an inadequate response to MTX or other DMARDs. In a 6-month, randomized, double-blind, placebo-controlled phase III trial of 395 patients with active PsA who previously failed TNFi therapy, patients were randomized to tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo. ACR20 response rates at 3 months were 50% in the tofacitinib 5 mg BID group, 47% in tofacitinib 10 mg BID, and 24% in placebo. There was also significantly higher rate of PASI75 response in each tofacitinib group compared to placebo as well as a greater decrease in Leeds Enthesitis Index score in the 10 mg tofacitinib group [40]. In a randomized, double-blind, placebo and active-controlled trial in PsA patients who had inadequate response to DMARD therapy, ACR20 response rates were 50% in the tofacitinib group compared to 52% with adalimumab and 33% with placebo [41]. Filgotinib is a selective JAK1 inhibitor recently studied in a randomized, placebo-controlled phase II trial (EQUATOR). A total of 131 patients with active PsA who had an insufficient response or intolerance to conventional DMARDs were randomized to filgotinib 200 mg or placebo. Eighty percent of the filgotinib group reached ACR20 at week 16 compared to 33% of the placebo group and no new safety signals were identified [42]. BMS-986165 is a TYK2 inhibitor currently being studied for treatment of moderate to severe psoriasis. A recent phase II, double-blind trial of 267 patients showed significant improvement in terms of skin psoriasis at week 12 with 75% of patients on 12 mg daily achieving PASI75 compared to 7% on placebo [43]. Furthermore, this drug is currently being studied in PsA.

T Cell Costimulation Inhibitors

Abatacept is a fusion protein which interferes with T cell activation by selectively modulating the CD28 costimulatory signal required for T cell activation and blocking the process which then helps triggers the inflammatory cascade. Abatacept has been approved for treatment of active psoriatic arthritis. An earlier 6-month, randomized, double-blind, placebo-controlled trial conducted on 170 patients with active PsA showed 47.5% of those who received IV abatacept achieved ACR20 response compared to 19% of placebo [44]. Recently, a phase III, randomized, double-blind, placebo-controlled study of abatacept in 424 patients with active PsA showed that 39.4% of patients receiving subcutaneous abatacept reached ACR20 response compared to 22.3% of placebo [45].

Discussion

There is clear evidence from the most recent data showing treatment for PsA is continuing to progress at a rapid pace. However, as therapeutic options evolve, there also appears to be clear differences in treatment of disease domains within PsA. Treatment of peripheral arthritis remains a cornerstone of PsA treatment and common primary endpoint for most trials. Due to the lack of evidence from randomized controlled trials, conventional DMARD monotherapy such as with MTX was usually quickly escalated to TNFi or combination therapy with TNFi. However, recent studies such as the SEAM study showed a respectable MTX monotherapy response and, moreover, did not show a synergistic effect of MTX with TNFi. TNFi have clearly shown efficacy in controlling essentially all domains of PsA including peripheral arthritis, as well as reducing radiographic progression, reducing dactylitis, and enthesitis. In addition, TNFi therapy was effective in treatment of skin and nail psoriasis [46–50]. Furthermore, by association from studies in ankylosing spondylitis and inflammatory bowel diseases, TNFi should be also effective for PsA patients with active disease in those domains. Other bDMARDs such as IL-17 inhibitors, IL-12/23 inhibitors, T cell costimulation inhibitors, PDE inhibitors, and JAK inhibitors have all proven efficacy in control of peripheral arthritis. A new dual IL-17A and IL-17F inhibitor has shown early promising results in phase II studies for treatment of peripheral arthritis as well.

In terms of axial disease, studies in ankylosing spondylitis have proven that conventional DMARD monotherapy (e.g., MTX, SSZ) is not effective for this domain. TNFi have proven effective in axial disease and are therefore a sound therapeutic choice for PsA with axial disease. IL-17A inhibitors have also proven efficacy in treatment of axial disease especially in AS patients. However, similar studies on IL-12/23 and IL-23 inhibitors failed to show efficacy in axial arthritis. Classically, NSAIDs are regarded as the first-line agents for treatment of enthesitis in PsA, despite a lack of randomized controlled trials [51]. TNFi and IL-12/23 inhibitors have proven efficacy in treating enthesitis and recently, the SEAM study showed some efficacy of MTX for treatment of enthesitis. The ECLIPSA study established efficacy of IL-12/23 inhibitors in achieving clearance of enthesitis in PsA patients. IL-17A inhibitors, JAK inhibitors, and PDE4 inhibitors have also recently been proven efficacious for treatment of enthesitis. Similarly, for treatment of dactylitis, TNFi, MTX, IL-17A inhibitors, IL-12/23 inhibitors, and PDE4 inhibitors have all recently proven efficacy in PsA patients.

Treatment for PsA remains difficult due to the heterogeneity of disease domains involved. Yet, therapeutic advancement has clearly flourished recently and will likely continue to expand in the future. The future may see further substantial advances that will allow further optimization of the care of patients with PsA (Table 2). One area of development centers

Table 2 Future developments in psoriatic arthritis

Prediction and prevention of disease
• Predict which patients with skin or nail psoriasis will develop psoriatic arthritis
• Prevention of psoriatic arthritis in patients with psoriasis
Early treatment
• Identify and treat early psoriatic arthritis
• Alter disease course by early intervention
• Early intervention leading to better outcomes with ultimate tapering of treatment
New treatment options
• Drugs with new mechanisms of action
• Combination therapy with different DMARDs and bDMARDs
Precision medicine
• Targeted therapy based on cellular and clinical phenotypes

around predicting which psoriasis patients will develop PsA in the future. Previous studies have examined human leukocyte antigen risk alleles and genetic signature to predict which patients with psoriasis may go on to develop PsA [52, 53]. Other studies focused on assessing the degree and change over time of non-specific musculoskeletal symptoms (joint pain, fatigue, and stiffness) to predict the development of PsA [54]. Furthermore, future research should focus on if development of PsA can be prevented among patients with psoriasis, for example by early intensive therapy of patients with skin psoriasis. It is anticipated that clinical trials will continue to focus on treatment of early PsA. As the usage of ultrasonography and MRI rises and becomes more readily available, it may be anticipated this will aid in the earlier diagnosis of patients with PsA. This will hopefully guide the way for trials to validate if early intervention may alter the disease course of PsA; this may also ultimately allow for better outcomes with tapering of treatment. Conventional DMARDs and bDMARDs have been used in combination for treatment of PsA; however, data on combination therapy with two bDMARDs is limited. Thus far, there are only anecdotal reports on combinations such as TNFi and IL-12/23 inhibitors [55]. Ultimately, certain combinations of agents may prove to have greater efficacy while maintaining an acceptable safety profile. Given the rapid development of bDMARDs with different mechanisms of action, combination bDMARD therapy such as IL-17 inhibition and TNFi and T cell co-stimulation inhibition and TNFi may prove to be efficacious, especially in those with resistant disease despite bDMARD monotherapy. It may be anticipated that the arrival of newer drugs with new mechanisms of action holds promise in the treatment of PsA. Finally, given the abundance of bDMARDs available today, precision medicine remains a new frontier in tailoring treatment specific for each patient. In one study investigating the selection of specific bDMARDs based on lymphocyte phenotypes, PsA patients were classified based on Th1 and Th17 phenotypes. Targeted therapy such as secukinumab to the Th17 cell–predominant patients and ustekinumab to the Th1 cell–predominant patients achieved significant improvement in simplified disease activity index, DAS28, and PASI when compared to those of the standard bDMARD group, indicating the value of precision medicine [56]. As more data emerge from clinical trials targeting various immune mediators, a "bedside to bench" approach may help physicians better understand the immunopathogenesis of PsA, which will ultimately lead to advancements in targeted therapy [57]. In the past 5 years, treatment options for PsA have continued to develop and diversify, from biosimilars to precision medicine; we anticipate even more exciting therapies in the next 5 years.

Compliance with Ethical Standards

Conflict of Interest Robert Chao declares that he has no conflict of interest. Arthur Kavanaugh declares he has professional relationships with several companies that have products mentioned in this paper, including Amgen, AbbVie, Eli Lilly, Pfizer, Gilead, Novartis, Celgene, Janssen, and BMS.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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