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Seronegative Arthritis (N Haroon, Section Editor)

Disease Modification in Psoriatic Arthritis

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Abstract

Purpose of review To provide clinicians evidence-based strategies to diagnose and treat psoriatic arthritis (PsA) patients based on involvement of the key domains peripheral arthritis, psoriasis and nails, axial involvement, dactylitis, and enthesitis, with the goal of improving outcomes for PsA patients by lessening joint pain and swelling and the degree of inflammation in the other key domains. It is also imperative to limit or eliminate progressive X-ray damage. *Recent findings* Evidence from phase III randomized trials demonstrate that agents that inhibit tumor necrosis factor (TNF), interleukin (IL)-17, and IL12/23 relieve joint inflammation and decrease or completely inhibit radiographic progression. Agents that block TNF and IL-17 are also effective for axial disease. Additional agents effective for psoriatic arthritis but without documentation of effect on progressive damage include apremilast, abatacept, and tofacitinib. Most agents have demonstrated efficacy for treatment of enthesitis and dactylitis. *Summary* A number of therapies that effectively treat the key domains of psoriatic arthritis are now available. Comprehensive assessment of patients to determine the extent and degree of domain involvement is essential to properly individualize treatment, improve outcomes, and limit progressive joint damage.

Introduction

Psoriatic arthritis, a prevalent disorder characterized by psoriasis and widespread musculoskeletal inflammation, frequently leads to joint damage and chronic pain that can alter function and quality of life and in some cases result in long-term disability [1, 2]. This disorder is diverse in presentation and course and is associated with an array of comorbidities that may complicate diagnosis and therapy [3]. The prevalence of this disease varies

from 10 to 30% of patients with psoriasis and up to 6 million individuals in the USA may have psoriatic arthritis [4]. Diagnosis of this disorder is often delayed resulting in significantly worse outcomes [5]. Fortunately, over the last 15 years, a dramatic expansion of treatment options have improved outcomes for patients with psoriatic arthritis (PsA) [2, 6•]. A wide variety of therapeutic agents are now available to treat psoriatic arthritis and they are directed towards specific disease pathways.

The vast expansion of treatment options presents patients and clinicians with great opportunities and challenges [7]. PsA patients often present with involvement of multiple domains including skin and nails, peripheral arthritis, axial disease, dactylitis and enthesitis [8]. Given that medications used to treat PsA target multiple specific pathways, it is important to consider that some medications may be more effective for certain patients. In addition, safety considerations should be factored into treatment decisions. The central importance of drug cost combined with the anticipated impact of biosimilar drugs must also be considered and will drive treatment decisions for many patients. Lastly, the role of combination therapies for treatment of psoriatic arthritis is largely unexplored but undoubtedly will be examined given that therapies directed to a wide variety of disease mechanisms either as monotherapy or in combination with methotrexate have not significantly increased the magnitude of treatment response. This inability to improve treatment outcomes in PsA with newer agents stands in stark contrast to psoriasis where biologic therapies directed against interleukin (IL)-12/23, IL-23, and IL-17 have resulted in remarkably impressive treatment outcomes and, in many cases, complete resolution of all plaques. Despite these impressive advances, under-treatment of this disorder is common [9, 10].

The expansion of treatment options has been accompanied by increased awareness of psoriatic arthritis. In particular, dermatologists are often the first to interact with psoriatic patients with musculoskeletal features. The co-occurrence of psoriasis and psoriatic arthritis creates collaborative opportunities for dermatologist and rheumatologist to optimize patient care [11]. A major gap in this interaction, however, is a lack of understanding regarding the proper selection of specific medications for the diverse array of psoriatic arthritis phenotypes In part, this inability to differentiate therapies is related to the absence of head-to-head trials that compare agents in PsA, the lack of uniform outcome measures included in clinical trials (e.g., dactylitis, enthesitis), and the limited understanding of PsA pathogenesis [12, 13]. Nonetheless, recent publications combined with clinical experience provide some guidance about preferred therapies in certain clinical scenarios. In this review, we will focus attention on agents with proven ability to relieve symptoms and slow or stop joint and soft tissue damage and X-ray progression in PsA. We will also consider disease modification from a broader perspective focusing on the ability of agents to maintain or increase function, improve quality of life, and enhance participation both at home and at work. The first section will center on therapy for specific PsA domains followed by how the various therapeutic agents have been shown to modify function, quality of life, and productivity and conclude with personal observations regarding tips for optimizing diagnosis and treatment in PsA.

Disease modification in PsA: a domain approach

A patient who presents with symptoms suggestive of PsA challenges the clinician from both the diagnostic and therapeutic perspective. Musculoskeletal symptoms commonly follow a long period of psoriatic skin disease and may be insidious in onset or appear abruptly, without warning [14]. Tissue involvement is often widespread and the absence of a specific biomarker may result in delayed diagnosis and sub-optimal treatment outcomes [5]. In the diagnostic evaluation, assessment of the multiple potential domains of involvement including skin and nails, peripheral arthritis, axial involvement, enthesitis, and dactylitis is essential so that a personalized treatment plan can be developed and initiated. It is not uncommon for a single patient to present with involvement of multiple domains and the impact of inflammation at specific sites on the level of pain, quality of life,

and function varies widely from patient to patient [15]. For example, for some patients, any involvement of skin and nails may overshadow joint involvement whereas another patient may find that peripheral arthritis, axial symptoms, or enthesitis is debilitating and will tolerate a relatively high burden of psoriasis. The central importance of the five domains is reflected in PsA clinical trials where peripheral arthritis is the primary outcome measure but the four other domains are assessed as critical secondary outcomes. Moreover, recent outcome measures such as the minimal disease activity (MDA) include assessment of all these domains to fully assess treatment response in PsA [16]. When faced with patients who have involvement of multiple domains, clinicians face therapeutic challenges—how does one treat these different sites with regimens that are effective, safe, and feasible? Fortunately, over the past 20 years, agents with widespread anti-inflammatory actions are now available to relieve symptoms and modify disease activity. The ability of individual agents to significantly alter disease activity in the specific domains will be discussed below and results from published clinical trials are outlined in Table 1. The oral synthetic medications (OSM) methotrexate, sulfasalazine, and leflunomide are not included in this table due to lack of published data regarding efficacy in the different domains.

Table 1. Efficacy of therapies in psoriatic arthritis

Drug	Signs and symptoms		Structural modification	Axial	Enthesitis	Dactylitis
	Joints	Skin	Joints*			
osDMARDs						
Apremilast	++	+	NA	NA	++	+
Tofacitanib	+++	+	NA	±	++	+
Anti-TNF agents						
Adalimumab	+++	++	++	++	++	++
Certolizumab	+++	++	++	++	++	++
Etanercept	+++	+	++	++	++	++
Golimumab (sc, iv)	+++	++	++	++	++	++
Infliximab	+++	++++	++	++	++	++
CTLA4-IG abatacept	+		NA	NA	Nil	Nil
Anti-IL17 agents*						
Ixekizumab	+++	++++	+	++	+	++
Secukinumab	+++	++++	+	++	++	++
Anti-IL12/23*						
Ustekinumab	+++	+++	+	–	++	++
Anti-IL-23*						
Guselkumab	+++	++++	+	NA	++	++

NA not assessed, *Nil* assessed but not significant
*Radiographic progression not as advanced in trials with these agents compared to earlier trials resulting in lower effect on structural modification
+ mild response, ++ moderate response, +++ very good response, ++++ excellent response

Peripheral arthritis

Two PsA treatment recommendations manuscripts were published over the last 2 years and methotrexate is listed as an agent to be strongly considered in patients unresponsive to non-steroidal anti-inflammatory medications [7, 17]. Unfortunately, we lack high-quality phase III data for the OSMs hydroxychloroquine, methotrexate, and sulfasalazine. Indeed, the one double-blind randomized trial of methotrexate in PsA failed to show benefit over placebo although the study may have been underpowered, the methotrexate was not aggressively dosed, and the burden of arthritis was low [18]. We also have no high-quality data regarding the efficacy of methotrexate for the treatment of axial disease, enthesitis, or dactylitis although data on efficacy in psoriasis is available (discussed below). The SEAM Trial (NCT02376790), currently in progress, compares methotrexate monotherapy with etanercept and combination etanercept and methotrexate in PsA patients. This large study will provide critical information regarding the efficacy of methotrexate as monotherapy or in combination with an anti-tumor necrosis factor (TNFi) treatment of PsA. In the case of sulfasalazine, a well-designed trial was carried out over 30 years ago which did not demonstrate a significant improvement of sulfasalazine over placebo in PsA although current outcome measures were not applied [19]. Data for leflunomide are available in a phase IIb study which showed a significant impact on arthritis but not psoriasis [20]. The efficacy of a step-up therapy with defined treatment targets versus usual care was examined in the Tight Control of Psoriatic Arthritis (TICOPA) study [21•]. Patients who were in the treat to target arm were more likely than the usual care arm to reach minimal disease activity (MDA) and to be on biologics but side effects were higher in this group and radiographic progression was not improved with the more aggressive treat to target approach. Additional treat to target studies that employ different treatment regimens are required to better understand how which strategies will improve outcomes, lower side effects, and lessen costs.

Apremilast and tofacitinib are effective for the treatment of peripheral arthritis in PsA. In the PALACE I-III studies, the gap between the placebo and ACR 20 (ΔACR 20) response for the 30-mg BID dose was significant and ranged from 14 to 22 points in DMARD-exposed and 15 points in DMARD-naïve patients [22]. Two studies examined the efficacy of tofacitinib in patients at 12 weeks unresponsive to DMARDs or anti-TNF agents and the ΔACR 20 response was 25.9 and 17.5 points, respectively, in the two studies. In the first trial, radiographic progression was examined using the van der Heijde modified Sharp score at baseline and at 12 months. The percentage of non-progressors at 12 months between the different treatment groups was 91 and 98%, respectively.

The TNFi agents etanercept, infliximab, adalimumab, golimumab, and certolizumab are all approved for treatment of PsA in North America and Europe based on results from large-phase III randomized trials in which approximately half the subjects were continued on methotrexate at baseline. The ΔACR 20 were as follows: etanercept was 44 at week 24, adalimumab 44 at week 24, subcutaneous golimumab 39 at week 14, infliximab 47 at week 14, and certolizumab 27.6 at week 12 [23–27]. Recent data on intravenous golimumab showed a ΔACR 20 of 53.3 at week 14 [28]. Serious adverse events were similar in nature and frequency across the different agents although serious infection rates may be slightly higher with infliximab. The patients in the methotrexate groups in these studies did not show a higher response than patients on TNFi monotherapy but these patients were inadequate responders to methotrexate when

they entered the trials. All anti-TNF agents inhibited radiographic progression [29]. No head-to-head trials of anti-TNF agents in PsA have been published.

The anti-IL-12/23 agent ustekinumab was effective for the treatment of PsA patients who were inadequate responders to methotrexate or patients who did not respond to anti-TNF agents [30, 31]. In PSUMMIT 1, half the patients were inadequate responders to methotrexate and the ΔACR20 was 19.6 for the 45-mg and 26.7 for the 90-mg dose. In PSUMMIT 2, 34% of the patients were inadequate responders to anti-TNF agents and the ACR response was less impressive in those patients with prior TNFi exposure (ACR 20 23.6 compared to those with prior exposure, DACR20 21.1). This medication was well tolerated with few reported adverse events. Inhibition of radiographic progression was demonstrated in a combined analysis of the PSUMMIT1 and two datasets [30].

The CTLA4-Ig molecule abatacept was recently approved for treatment of PsA based on results from a phase III trial [32•]. In the phase III study, the ΔACR 20 was 12.1 at 12 weeks and the effect of treatment on radiographic progression has not been published. Abatacept was well tolerated with few adverse events.

Secukimumab and ixekizumab, antibodies to IL-17A, showed efficacy for treatment of peripheral arthritis. The ΔACR20 for secukimumab was 47.2 for the 300-mg dose and 44.4 for the 150-mg dose at 24 weeks in TNFi-naïve patients [33]. The responses dropped to 38.2 and 23.2 for those previously exposed to TNFi for the 300- and 150-mg doses, respectively. Ixekizumab, 80 mg every 4 weeks, demonstrated a ΔACR20 of 27.7 in TNFi-naïve patients at 24 weeks and in a second study, patients exposed to TNFi had a ΔACR20 of 19.2 [34••, 35••). The agents were well tolerated with rare candida infections. Secukinumab and ixekizumab inhibited X-ray progression. The efficacy and safety of the anti-IL-23 agent guselkumab was analyzed in a phase II clinical trial [36]. The gap between placebo and ACR 20 was 40.4 at week 24 and serious adverse events were uncommon and did not differ significantly from placebo. This agent is currently approved for psoriasis and phase III trials in PsA are underway.

Psoriasis and nail disease

Psoriasis and associated nail disease can be associated with significant disturbance of body image and an increased prevalence of anxiety and depression [37]. Fortunately, new treatment options are now available that are dramatically effective for psoriatic plaques. While it is true that the burden of psoriasis may be low or moderate in many PsA patients, moderate and severe phenotypes are observed and when combined with arthritis and other comorbidities can wield devastating effects on quality of life and function. Traditionally, methotrexate is the first systemic agent prescribed for psoriasis. In the CHAMPION study which compared the Psoriasis Area and Severity Index (PASI) 75 response at 16 weeks between methotrexate and adalimumab, the ΔPASI 75 for methotrexate was 16.6 and for adalimumab 60.7; both agents were statistically superior to placebo [38]. The methotrexate was rapidly escalated to a maximum dose of 25 mg but the time point of 16 weeks may have been too early to see a full methotrexate response. In the apremilast ESTEEM 1 clinical trial, the Δ PASI75 was 28.8 and was significantly different than placebo [39]. In the Oral treatment Psoriasis (OPT) 1 Pivotal Trial that examined the efficacy of tofacitinib, the ΔPASI75 was 32.9 in the 5-mg and 50.2 in the 10-mg dose; a similar magnitude of response was observed in the OPT 2 pivotal trial [40].

Currently, seven distinct biologic therapies are licensed for use in Europe and the USA: adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab, all of which perform significantly better than placebo [41]. Guselkumab, an inhibitor of the IL-23 pathway, showed impressive results in psoriasis [42]. In a network meta-analysis that applied hierarchical cluster analysis to account for efficacy and tolerability based on phase III clinical trial data, adalimumab, secukinumab, and ustekinumab were characterized with high efficacy and tolerability and ixekizumab and infliximab with high efficacy and poorer tolerability [43]. In a second meta-analysis, infliximab and secukinumab were the most effective biologics but were most likely to produce adverse or infectious events whereas ustekinumab was the third most effective biologic and did not show increased adverse events compared to placebo [44]. It must be stressed that these two meta-analyses are based on examination of short-term phase III clinical trial data and more complete long-term data will arise from disease registries. Also, skin results tend to be less impressive in PsA studies because the extent of skin involvement is lower than in psoriasis studies and the change in PASI score is more challenging to evaluate when the baseline skin scores are lower. A major challenge in the treatment of PsA patients with psoriasis is that high body mass indices (BMIs) are often observed in these patients. Two agents, infliximab and IV golimumab, which are both dosed according to weight, are often more effective in this patient subgroup particularly when other anti-TNF agents do not provide prolonged response. Abatacept and golimumab have not been formally evaluated in psoriasis trials although in the intravenous golimumab PsA trial, the ΔPASI75 was 45.6. Abatacept was not effective for treatment of psoriasis in the phase III PsA trial [32•].

Nail disease is a prevalent feature in both psoriasis and PsA and it can negatively impact quality of life [45]. Most studies use the Nail Psoriasis Severity Index (NAPSI) or variations of this measure. Therapies range from topical to intra-lesional and systemic therapies. Response of nail disease to therapies is typically included as a secondary outcome in psoriasis clinical trials. All the biologic agents (reviewed in [46]) including agents targeting TNF, IL-17, IL-23, and IL-12/23 are effective for nail disease. Apremilast and tofacitinib are also effective. Unfortunately, the differences in outcome measures, study design, and follow-up do not provide accurate comparative analyses and head-to-head trials are not available. Nonetheless, the entire range of biologic agents along with apremilast and tofacitinib demonstrate excellent results on nail psoriasis providing a wide range of options.

Axial disease

Involvement of the axial skeleton is prevalent in PsA and the negative impact on pain, quality of life, and function is similar to that observed in ankylosing spondylitis [47]. Unfortunately, axial measures have not been included as secondary outcomes in most PsA trials so data on response has been obtained from trials in axial spondyloarthritis. Phase III trials demonstrated that agents targeting TNF and IL-17 are effective for axial spondyloarthritis [48]. Phase III data on the efficacy and safety of secukimumab in ankylosing spondylitis are published but data on ixekizumab are not yet available [49]. Interestingly in a recent interventional trial, ustekinumab, which targets IL-12/23, was not effective and the trial was stopped early (personal communication). The effect of IL-

23 antagonists on axial disease is not known at this time. In a phase II trial, tofacitinib 5 mg BID, was more effective than placebo in achieving the ASAS20 outcome in ankylosing spondylitis but significant improvement was not observed for the 10-mg dose [50]. It is also important to note that TNFi agents were demonstrated to inhibit radiographic progression in ankylosing spondylitis if given early in disease course and continuously [51, 52]. Recently, very little disease progression was noted in a recent phase III trial of secukinumab in ankylosing spondylitis [53]. Results from these studies suggest that blockade of TNF or IL-17 will inhibit axial progression in axial PsA but no data are available to confirm this view.

Enthesitis

Enthesitis is a classic and prevalent manifestation of PsA identified in approximately 30–50% of patients in published registries and trials [54]. The presence of enthesitis corresponds with disease severity as well as functional limitation and pain scores [55, 56]. The plantar fascia, Achilles, and lateral epicondyle insertion points are the most commonly affected sites but enthesitis also occurs periarticular to finger joints and in the shoulders, hips, knees, and axial structures. In recent years, significant discoveries underscore the importance of enthesitis in PsA [57, 58]. The "enthesis organ" is a complex structure that effectively dissipates biomechanical stress. As such, enthesitis in PsA is theorized to represent a form of the Koebner phenomenon generating an inflammatory cascade in response to biomechanical stress [59]. Additionally, enthesitis occurring in a passive transfer model of collagen antibody-induced arthritis (CAIA) appears to be IL-23-dependent and mediated by resident T helper type-17 cells although this model remains to be confirmed [60].

Enthesitis presents challenges in both clinical practice and trial assessments. Entheseal inflammation is frequently mistaken for non-inflammatory enthesopathy or centralized pain leading to diagnostic and specialist referral delays. Once identified, it can be challenging to treat, often requiring both rest and immunomodulatory therapy. In clinical trials of PsA, enthesitis is commonly assessed as a core secondary outcome. However, understanding the magnitude of response across studies has been complicated by the use of different indices and a lack of an established minimally clinically important difference (MCID). Common indices used include the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), the Mander Enthesitis Index (MEI), the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index, and the Leeds Enthesitis Index (LEI), although some clinicians may simply assess for tenderness at targeted sites such as the Achilles and plantar enthesial insertions [54, 61].

Despite the difference in outcome measures employed, phase III studies of all currently available biologic therapies targeting TNFα, IL-17, IL-12/23, and IL-23, as well as the oral synthetic medication apremilast and tofacitinib, demonstrate treatment efficacy for enthesitis. Statistically significant improvements of enthesitis are reported in trials of certolizumab pegol [27] and subcutaneous and intravenous golimumab [28, 62].

Adalimumab showed non-significant differences from placebo in a phase III trial [25, 50]. Enthesitis is responsive to tofacitinib and apremilast [63••, 64–66]. Only modest improvements in enthesitis scores were noted for ixekizumab in patients who had previously failed TNFi therapy [3]. IL-12/23 inhibition with

ustekinumab was shown to be significantly effective for enthesitis [30, 31]. In a recent randomized observational head-to-head trial of ustekinumab versus TNFi in 51 PsA patients, complete resolution of enthesitis was observed in 73.9% of patients treated with ustekinumab versus 41.7% of patients on TNFi, a significant difference [67]. The study population was somewhat unusual in the mean ages of the two groups were 62 and 58 for ustekinumab and TNFi subjects, respectively. Nonetheless, these findings are intriguing and await confirmation in a larger trial. In a phase II trial, guselkumab demonstrated complete resolution of enthesitis in 56.6% of patients compared to 29% of patients on placebo at week 24 [36]. Unique in this category, however, is abatacept. Resolution of enthesitis at 24 weeks was not statistically different between abatacept- and placebo-treated groups although a high percentage of participants were not biologic-naïve [32•].

Dactylitis

Dactylitis is a distinguishing and common clinical manifestation of psoriatic arthritis identified in approximately 15–50% of patients in published registries and trials [68]. The presence of dactylitis is associated with greater disease severity and pain [55], as well as increased risk of bony damage [69]. Dactylitis is characterized by diffuse digital swelling and tenderness and exam findings can include features of synovitis, tenosynovitis, and central slip enthesitis leading to variation in identification and reporting.

Similar to enthesitis, comparing the magnitude of dactylitis treatment response is complicated by the use of different outcome measures and the lack of a defined MCID [54, 61, 70]. In general, phase III trial results for available targeted biologic therapies show efficacy for dactylitis with few exceptions. Significant improvements in dactylitis scores were found with intravenous, but not with subcutaneous golimumab [26, 28, 62]. Statistically significant improvements were reported for dactylitis at week 24 in patients treated with certolizumab pegol compared with placebo [27]. Although not placebo-controlled, the PRESTA, a phase IV study of two different etanercept doses, reported a 75% reduction in dactylitis scores at week 24 with 50-mg weekly dosing [71]. The SPRIT-P1 trial found both ixekizumab and adalimumab effective for dactylitis as compared with placebo [34••]. Ustekinumab [30, 31], secukinumab [72•, 73], and ixekizumab [34••, 35••] demonstrated good efficacy for dactylitis; the latter showed significant results in patients who previously failed TNFi therapy [35••]. Clinical trials with tofacitinib [63••, 32•] and apremilast [66, 65] have documented mild dactylitis responses, though they have not yet shown statistical significance. In the phase II guselkumab, 55.2% of patients on drug compared to 17.4% of patients on placebo achieved complete resolution of dactylitis at week 24. Abatacept was not found to be effective for dactylitis [32•].

Quality of life and functional status

Quality of life and functional status for many patients with PsA are improved with TNFi therapy. Recent large randomized, phase III placebo-controlled trials with subcutaneous golimumab, certolizumab, and adalimumab demonstrated clinically meaningful and statistically

significant improvements in physical function and health-related quality of life by week 24 of treatment [34••,74, 75]. These results are summarized in Table 2. The beneficial effects of golimumab observed at 24 weeks relative to placebo were sustained at 5 years, further supporting the disease-modifying role of TNFi therapy for PsA [74]. TNF-inhibition has also been shown to reduce the impact of PsA on work productivity. In the golimumab trial, treatment arms reported benefits in productivity (VAS scale) at 16 weeks [74]. A multicenter observational study of PsA treatment and work disability in the UK found that TNFi treatment (etanercept, adalimumab, or infliximab) was associated with a 30% improvement in presenteeism ($P < 0.001$) and 40% improvement in work productivity ($P < 0.001$) at 6 months [14].

Recent trials of IL-17A inhibition in PsA found significant improvements in health-related quality of life, physical function, and productivity measures. At 24 weeks of treatment, secukinumab was associated with improved Health Assessment Questionnaire Disability Index (HAQ-DI) and Short Form (SF)-36 physical and mental component scores as well as patient global assessment [75]. These results are summarized in Table 2. Improvements were sustained or even improved at 52 and 104 weeks in follow-up analysis [78•]. Regarding productivity, the phase III trial with secukinumab reported a 15% reduction in PsA-related work impairment at 24 weeks. Ixekizumab demonstrated clinically meaningful and statistically significant improvements in HAQ-DI. SF-36 physical components scores were also improved at 24 weeks relative to placebo [34••]. This effect is supported by similar findings in the trial of Ixekizumab in patients who were inadequate responders to TNFi [35••].

Clinical pearls

In order to modify disease outcomes, it is essential to perform a through initial evaluation on all patients suspected to have PsA. The marked heterogeneity of disease, the complex mix of domain involvement in a single patient, and the lack of defining diagnostic biomarkers present significant challenges to clinicians in both establishing a diagnosis and developing a comprehensive treatment plan. A diagnostic approach to help guide therapeutic decision-making is shown in Fig. 1, first carefully evaluating the patient for the presence of skin and nail disease (including scalp, inguinal, axillary, and perianal involvement). Close attention should be placed on thorough assessment of peripheral arthritis and axial involvement as well as examination of the entheses and digits for dactylitis. The extent of involvement in each domain should not only consider the findings from the physical exam but also the degree of pain according to the patient and the negative impact on function and quality of life. For example, the co-occurrence of centralized pain and psoriatic arthritis can negatively affect treatment outcomes so it should be noted and therapeutic approaches to address this entity included in the treatment plan.

Table 2. Summary of patient-reported outcomes: mean change in HAQ-DI, SF-36 physical and mental component scores, and patient global VAS at 24 weeks, except for the PALACE 2 trial with endpoints reported at 16 weeks. When multiple doses were studied in a trial, the dose arm corresponding to the currently approved starting dose in the USA, or as with ustekinumab, the reported combination of dose arms, was included in the table

Drug class	Medication (trial name), dose	*N*	HAQ-DI Mean change % MCID (≥ 0.3) All $P < 0.05$	SF-36 PCS mean change % MCID (≥ 5) All $P < 0.05$	SF-36 MCS mean change % MCID (≥ 5)	Patient GA (0–100)	Reference
TNFi	Golimumab (GO-REVEAL), 50 mg Q 4 weeks	146	− 0.33 45%	+ 7.42 60%	+ 3.4 40%		(Kavanaugh, McInnes et al. 2013) [74]
	Certolizumab (RAPID-PSA), 400 mg Q 4 weeks	135	− 0.5			− 29	(Mease, Fleischmann et al. 2014) [27]
	Adalimumab (SPIRIT 1), 40 mg Q 2 weeks	101	− 0.37 49%	+ 6.8		− 32	(Mease, van der Heijde et al. 2017) [34••]
	Etanercept 50 mg Q 1 weeks, adalimumab 40 mg Q 2 weeks, or infliximab	121	− 0.3			− 20	(Tillett, Shaddick et al. 2017) [76]
IL-17A i	Secukinumab (FUTURE 1), 150 mg SQ Q 4 weeks	202	− 0.4	+ 5.9	+ 5.7	− 20	Strand V, Mease P et al. 2017 [75]
	Secukinumab (FUTURE 2), 150 mg SQ Q 4 weeks	100	− 0.5	+ 5	+ 6.1	− 26	(McInnes, Mease et al. 2015) [72•]
	Ixekizumab (SPIRIT-P1), 80 mg every 4 weeks	107	− 0.44 49%	+ 7.5		− 34	(Mease, Heijde et al. 2017) [34••]
	Ixekizumab (SPIRIT-P2), 80 mg every 4 weeks	122	− 0.6	+ 8.9	+ 3.6		(Nash, Kirkham et al. 2017) [35••]
Il-12/23i	Ustekinumab (PSUMMIT 1), 45 + 90 mg Q 12 weeks	409	− 0.25 48%	+ 4.7	+ 3.5		(McInnes, Kavanaugh et al. 2013) [77]
	Ustekinumab (PSUMMIT 1), 45 + 90 mg Q 12 weeks	208	− 0.25 36%	+ 3.3	+ 1.2		(Ritchlin, Rahman et al. 2014) [31]
PDE4i	Apremilast (PALACE 1), 30 mg BID	161	− 0.26	+ 5.1		− 12.1	(Kavanaugh, Mease et al. 2014) [65]
	Apremilast (PALACE 2), 30 mg BID	162	− 0.23	+ 3.5		− 9.8	(Cutolo, Myerson et al. 2016) [17]

All studies applied intent-to-treat imputation

N number of patients included in the treatment arm of interest, *HAQ-DI* Health Assessment Questionnaire Disability Index, *SF-36 PCS* Short Form (36 item) physical component summary, *SF-36 MCS* Short Form (36 item) mental component summary, *MCID* minimal clinically important difference

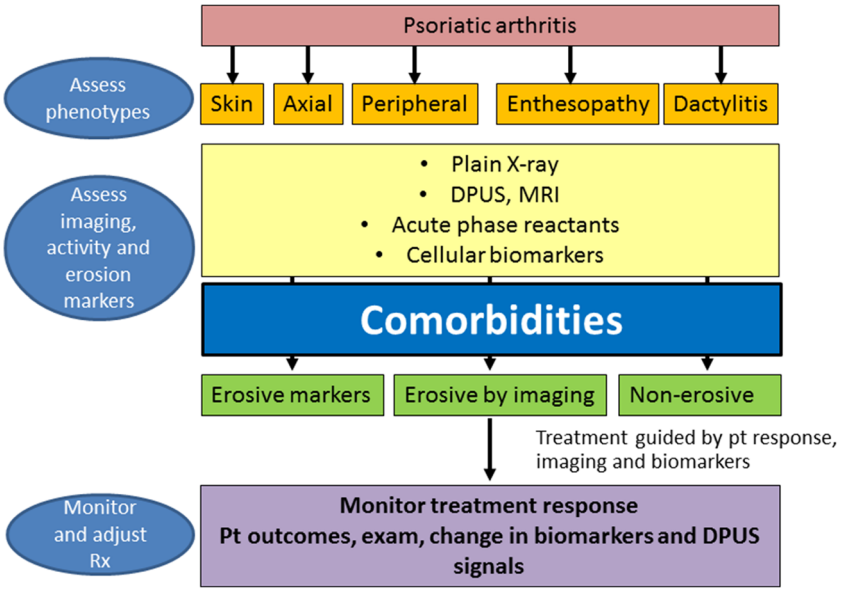

Fig. 1. Diagnostic evaluation and therapeutic approach in psoriatic arthritis. DPUS Doppler power ultrasound, MRI magnetic resonance imaging, pt patient, Rx treatment.

Following assessment of domain involvement and exclusion of other rheumatic disorders (rheumatoid arthritis, axial spondyloarthritis, crystalline disease, systemic lupus erythematosus, and other systemic autoimmune disorders), appropriate imaging can assist in tailoring a specific treatment plan. Plain radiographs of symptomatic peripheral joints provide critical information regarding presence of erosions, joint space narrowing, and proliferative bony changes. These radiographic findings of baseline damage are indicators of future progression and treatment selection should focus on agents with proven ability to retard X-ray damage including antibodies to TNF, IL-12/23, and IL-17. Radiographs of the SI joints and cervical, thoracic, and lumbar spine, even in patients without axial symptoms, can reveal bone damage in the form of erosions, syndesmophytes, and bony fusion in up to 40% of patients and should be strongly considered. Axial involvement can be addressed therapeutically with antibodies to TNF and IL-17. Elevated acute-phase reactants, particularly CRP, are associated with more X-ray progression and should also be assessed. Power Doppler ultrasound is very effective in the identification of early erosions, synovitis, tendonitis, and enthesitis. MRI imaging can aid in the assessment of axial pain in the absence of X-ray findings and to better understand the extent and degree of inflammation (bone marrow edema) and damage in peripheral joints, particularly in centers without the availability of power Doppler ultrasound. PsA patients are at increased risk to develop osteoporosis, particularly patients with active axial inflammation [79, 80]. Baseline DEXA scans should be performed in perimenopausal females and in younger patients with persistently active arthritis and treatment initiated for patients with T scores in the osteoporotic range. Lastly, periodic monitoring longitudinally using clinical, serologic, and imaging modalities is often required to maintain treatment response and to document disease flare.

A comprehensive initial assessment of the patient with psoriatic arthritis must include a full evaluation of associated comorbidities to maximize treatment response and minimize adverse outcomes [3, 81]. Obesity, metabolic syndrome, type II diabetes, and peripheral vascular disease along with anxiety and depression are prevalent comorbidities that may impede treatment response and contribute to untoward side effects [82–84, 85•]. For example, patients with a high BMI may lose efficacy to TNFi with subcutaneous dosing so treatment with a TNFi that is dosed according to weight or a non-TNFi agent may provide a more sustained response [86–89]. Obese patients and those with diabetes often have fatty liver disease [85•, 90], a relative contraindication to methotrexate therapy based on serial biopsy studies in patients with psoriasis [91]. These patients may have baseline elevated liver function tests that can also rise following treatment with biologic agents. Obesity is also strongly associated with obstructive sleep apnea, a major risk factor for centralized pain and this should be formally assessed and treated when present. Consultation with a nutritionist, dietician, and, when indicated, endocrinologist to help with a supervised weight loss regimen is a critical intervention required for many patients to achieve a significant and durable treatment response. Most importantly, the presence of diabetes may increase the risk of infection in patients on systemic therapies for PsA, particularly in patients with poorly controlled disease and persistently elevated HbA1c levels. It is also well recognized that PsA patients are at risk for cardiovascular disease, particularly younger patients with a high burden of psoriasis, so close collaboration with the primary care physician, dermatologist, and cardiologist, if relevant, is critical to harmonize therapies and avoid adverse events. Inflammatory bowel disease may also complicate treatment in PsA. Agents that target TNF, with the exception of etanercept and IL-12/23 antibodies, can be very effective for Crohn's disease while the impact of IL-17 inhibition on exacerbating colonic inflammation remains controversial. At this time, it is reasonable not to prescribe agents that block IL-17 in patients with known inflammatory bowel disease. Lastly, anxiety and depression may strongly impede treatment response and when noted should be formally assessed and treated by a psychologist or psychiatrist [92].

The efficacy of treat to target approaches in psoriatic arthritis has been advocated although more formal studies demonstrating superior outcomes using these strategies compared to standard therapy are not yet available [78•]. The emergence of biologic therapies and more recently oral targeted agents such as apremilast and tofacitinib greatly expands treatment choices for patients suffering from PsA. Regrettably, the marked increased in efficacy observed with the newer biologic agents for psoriasis has not been observed in PsA. The lower response in PsA may stem from the complex interactions of domain involvement described above and the presence of multiple comorbidities or to the existence of disease pathways targeting musculoskeletal structures yet to be revealed. It is likely that a combination of these variables may limit treatment response in many patients. Biomarker development which integrates genomics, epigenomics, proteomics, and metabolomics combined with more advanced imaging modalities currently in development will likely lead to a more personalized treatment approach and greatly improve outcomes for PsA patients.

Compliance with ethical standards

Conflict of interest

Dr. Ritchlin reports grants and personal fees from Abbvie, grants and personal fees from Amgen, grants and personal fees from UCB, personal fees from Novartis, personal fees from Pfizer, personal fees from Lilly, and personal fees from Janssen, during the conduct of the study. Dr. Lieberman declares no conflict of interest.

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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- •• Of major importance

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