REVIEW ARTICLE

Recent advances in the management of psoriatic arthritis: practical considerations

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KEY WORDS

biologic/targeted synthetic disease--modifying antirheumatic drugs, guidelines, management, psoriatic arthritis, treatment

ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory arthritis characterized by inflammation of peripheral and/or axial joints, with or without other tissue manifestations, including skin psoriasis, dactylitis, enthesitis, uveitis, and inflammatory bowel disease. There has been an exponential increase in PsA treatment options over the last 2 decades, and while guidelines have attempted to keep up with the deluge of emerging data, there are several areas in which guidance remains sparse. This is, in part, due to a lack of robust strategy trials, head-to-head studies, and real-world observational data. In addition, trials seldom address key questions, such as the complex need to balance the treatment of joint disease with the other competing tissue manifestations of PsA, as well as other relevant medical comorbidities and patient lifestyle and personal preferences, all of which may change several times over the course of an individual's lifetime. This article provides a concise summary of the current state of guidelines for the management of PsA, and an in-depth discussion of some of the areas where guidelines and evidence are still lacking. These areas of unmet clinical need in the treatment of PsA should be a priority for further PsA research in the coming years. Only by working with patients and addressing these gaps in our knowledge can we strive for a future where all PsA patients are able to receive treatment that is the best for them, and tailored to their specific needs at any particular time point in their disease trajectory.

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Received: October 25, 2023.
Revision accepted: December 8, 2023.
Published online: January 2, 2024.
Pol Arch Intern Med. 2024; 134 (1): 16639
doi:10.20452/pamw.16639

Introduction Psoriatic arthritis (PsA) is characterized by entheseal and synovial joint inflammation (axial and/or peripheral pattern) associated with a current, personal, or family history of skin or nail psoriasis and/or extramusculoskeletal manifestations (EMMs), including dactylitis, inflammatory bowel disease (IBD), and uveitis.[1] It is part of the wider family of spondyloarthropathies (SpA), alongside axial spondyloarthritis (axSpA), enteropathic arthritis, and reactive arthritis, all of which share overlapping clinical, biochemical, and genetic features.[2] Several new biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have been licensed for PsA in recent years[3]; nevertheless, they are not universally efficacious, and can be associated with disabling adverse effects. On top of this, global population aging and increasing multimorbidity have the potential to impact on PsA in a particularly profound way, since PsA itself is a risk factor for cardiometabolic and psychosocial diseases, all of which, in turn, impact on both the patient quality of life and the efficacy/safety of PsA treatments.[4] PsA is a dynamic spectrum of disease that changes over time.[1] However, in the absence of biomarkers for personalized medicine, there is currently no way to predict the right treatment, for the right patient, at any one point in time.[5] This review aims to provide the reader with an overview of the similarities and differences between the major PsA treatment guidelines, including a detailed discussion of areas where guidelines and evidence are lacking, and that should be addressed urgently to further advance PsA care in the next decade and beyond.

Conventional treatments for psoriatic arthritis Pharmacologic therapies should always be used in conjunction with lifestyle and nonpharmacologic interventions, such as smoking cessation, weight management, physiotherapy, hydrotherapy, podiatry, occupational therapy, and/or clinical psychology. Guidance on these interventions is covered elsewhere.[6] Similarly, while there is a wide

TABLE 1 Summary of all approved treatments for psoriatic arthritis and their licensed indications across all extramusculoskeletal manifestations

b/tsDMARD		Peripheral arthritis	Axial arthritis	Psoriasis	Dactylitis	Enthesitis	IBD	Uveitis	Nail psoriasis
Class	Name								
TNFi	Adalimumab	x	x	x	x	x	x	x	x
	Certolizumab	x	x	x	x	x	x	–	x
	Etanercept	x	x	x	x	x	–	–	x
	Golimumab	x	x	x	x	x	x	–	x
	Infliximab	x	x	x	x	x	x	x	x
IL-17Ai	Ixekizumab	x	x	x	x	x	–	–	x
	Secukinumab	x	x	x	x	x	–	–	x
IL-12/23i	Guselkumab	x	–	x	x	x	x	–	x
	Risenkizumab	x	–	x	x	x	x	–	x
	Tildrakizumab	x	–	x	x	x	x	–	x
IL-23i	Ustekinumab	x	–	x	x	x	x	–	x
JAKi	Tofacitinib	x	x	x	x	x	x	–	–
	Upadacitinib	x	x	x	x	x	x	–	–
PDE-4i	Apremilast	x	–	x	x	x	–	–	x
CTLA-4i	Abatacept	x	–	x	x	x	–	–	x
IL-17A/Fi	Bimekizumab	x	x	x	–	–	–	–	–

Abbreviations: b/tsDMARD, biologic/targeted synthetic disease-modifying antirheumatic drug; CTLA-4i, cytotoxic T-lymphocyte–associated antigen 4 inhibitor; IBD, inflammatory bowel disease; IL-12/23i, interleukin 12/23 inhibitor; IL-17A/Fi, interleukin 17 inhibitor; IL-23i, interleukin 23 inhibitor; JAKi, Janus kinase inhibitor; PDE-4i, phosphodiesterase 4 inhibitor; TNFi, tumor necrosis factor inhibitor

range of potential pharmacologic therapies used in PsA, the most recent and clinically relevant developments concern b/tsDMARDs, which are the focus of this review.

Biologic and targeted synthetic treatments for psoriatic arthritis: what's new? In the last 2 decades, there has been an unprecedented increase in the number of available agents, which, as of October 2023, include tumor necrosis factor inhibitors (TNFis; adalimumab, certolizumab, etanercept, golimumab, and infliximab), interleukin (IL)-17A inhibitors (IL-17Ais; ixekizumab and secukinumab), IL-12/23 inhibitors (IL-12/23is; ustekinumab), IL-23 inhibitors (IL-23is; guselkumab, risankizumab, and tildrakizumab), Janus kinase inhibitors (JAKis; tofacitinib and upadacitinib), cytotoxic T-lymphocyte–associated protein 4 blockade (abatacept), phosphodiesterase 4 inhibitors (apremilast) and, most recently, a IL-17A/IL-17F inhibitor, bimekizumab. Licensed indications for these agents (in PsA and related EMMs) are shown in TABLE 1.[7-10]

IL-17 is a heterodimeric cytokine with dimeric forms (IL-17A and IL-17F) capable of forming both homodimers or heterodimers that bind and activate the IL-17 receptor, thereby activating downstream proinflammatory signaling pathways.[11] In vitro and in vivo studies have consistently demonstrated a role of these cytokine pathways in axSpA, PsA, and psoriasis, supported by the success of phase III clinical trials of IL-17Ais, secukinumab, ixekizumab, and bimekizumab.[12-17] Historically, bDMARDs have only targeted the IL-17A dimer, as this was believed to be the most important in the disease pathogenesis. However, emerging data suggest that dual inhibition of IL-17A and IL-17F could provide superior therapeutic benefit, particularly in patients with psoriasis and/or subsets of patients resistant to IL-17Ais,[18] although the original study reporting these results remains subject to further peer review before publication. Bimekizumab is capable of binding and neutralizing both IL-17A and IL-17F.[19-23] Phase III randomized controlled trials of bimekizumab in bDMARD-naive and bDMARD-exposed PsA patients (BE OPTIMAL and BE COMPLETE), in axSpA (BE MOBILE 1 and BE MOBILE 2), and in psoriasis (BE READY and BE VIVID) were published in January 2023.[16,17,21,22,24] The drug reached the primary end point for both the skin and joint domains. Moreover, 2-year phase IV trial data for bimekizumab in psoriasis have not revealed unexpected safety signals, and demonstrate ongoing treatment efficacy.[25] There are no head-to-head trials comparing different IL-17is, so it is impossible to directly compare the efficacy of these agents. However, a visual comparison of the primary end points for all phase III trials of each IL-17i (TABLE 2) shows at least a comparable performance of bimekizumab vs other IL-17is.[12-15,24,26] Moving forward, further postmarketing surveillance, including efficacy in patient subgroups and long-term safety data, will be important to establish longer-term efficacy and tolerability, and potentially to determine the optimal positioning for bimekizumab in the treatment algorithms for PsA and other diseases.

TABLE 2 Summary of American College of Rheumatology, Psoriasis Area and Severity Index, and minimal disease activity outcomes across all phase III trials of interleukin-17 inhibitors licensed in the United Kingdom

Trial name	Treatment arms	Primary end point	ACR, PASI, and MDA response						
			ACR20	ACR50	ACR70	PASI75	PASI90	PASI100	MDA
BE OPTIMAL[17]	Bimekizumab 160 mg Q4W	Wk16	62.2	43.9[a]	24.4	77.4	61.3	47.5	45
	Placebo	Wk16	24	10[a]	4.3	12.9	2.9	2.1	13.2
	Adalimumab 40 mg sc Q2W[b]	Wk16	68.5	45.7[a]	27.9	66.2	41.2	20.6	45
BE COMPLETE[24]	Bimekizumab 160 mg Q4W	Wk16	67	43.3[a]	26.6	82.4	68.8	58.5	44.2
	Placebo	Wk16	15.8	6.8[a]	0.8	10.2	6.8	4.5	6
SPIRIT P1[12]	Ixekizumab Q4W	Wk24	57.9[a]	40.2	23.4	71.2	56.2	42.5	NA
	Ixekizumab Q2W	Wk24	62.1[a]	46.6	34	79.7	67.8	52.5	NA
	Placebo	Wk24	30.2[a]	15.1	5.7	10.4	6	3	NA
	Adalimumab Q2W[b]	Wk24	57.4[a]	57.4	25.7	54.4	36.8	23.5	NA
SPIRIT P2[13]	Ixekizumab Q4W	Wk24	53[a]	35	22	56	44	35	28
	Ixekizumab Q2W	Wk24	48[a]	33	12	60	50	28	24
	Placebo	Wk24	23[a]	5	0	15	12	4	3
FUTURE 1[15]	Secukinumab 150 mg Q4W	Wk24	50[a]	34.7	NA	61.1	45.4	NA	NA
	Secukinumab 75 mg Q4W	Wk24	50.5[a]	30.7	NA	64.8	49.1	NA	NA
	Placebo	Wk24	17.3[a]	7.4	NA	8.3	3.7	NA	NA
FUTURE 2[14]	Secukinumab 300 mg Q4W	Wk24	54[a]	35	NA	63	49	NA	NA
	Secukinumab 150 mg Q4W	Wk24	51[a]	35	NA	48	33	NA	NA
	Secukinumab 75 mg Q4W	Wk24	29[a]	18	NA	28	12	NA	NA
	Placebo	Wk24	15[a]	7	NA	16	9	NA	NA

The table includes the outcomes for ACR, PASI, and MDA. Readers are advised to consult the primary literature for other secondary outcomes.

a Primary study outcomes

b Studies not powered to detect significant differences between bimekizumab, ixekizumab, or placebo with regard to the reference drug (adalimumab)

Abbreviations: ACR, American College of Rheumatology; MDA, minimal disease activity; NA, not applicable; PASI, Psoriasis Area and Severity Index; sc, subcutaneously; Q2W, 2-weekly dosing; Q4W, 4-weekly dosing; Wk, week

Current treatment guidelines for psoriatic arthritis

The rapid expansion of therapeutic options for PsA has made having a set of comprehensive, up-to-date treatment guidelines more important than ever. However, experts disagree about the strength and quality of evidence, which results in subtle differences in their recommendations. A brief summary of the key principles of all the major guidelines published in the last 5 years is presented in FIGURE 1.

In general, all guidelines place emphasis on continuous assessment and rapid, early escalation of treatment to a b/tsDMARD in the case of conventional synthetic (cs)DMARD failure (FIGURE 1), particularly in severe disease.[7-10] The exact timing of drug escalation and aim of treatment are to be agreed upon by the patient and physician, setting an individualized target of low / minimal disease activity that strikes a balance between disease control and the potential complications of polypharmacy and side effects of bDMARDs that can arise in some patients. Broadly speaking, all guidelines also suggest that patients with predominant peripheral joint involvement should be trialed on at least 1 csDMARD before escalating to a bDMARD. Conversely, for patients with predominant axial symptoms, enthesitis, dactylitis, nail psoriasis, or IBD / uveitis, first-line bDMARD use is advisable. Furthermore, the treatment chosen should take into account other disease manifestations. Given their overall complexity and nuance, implementation of these guidelines, and their overarching principles, can be challenging in a real-world setting, even more so in lower-income countries, where access to the more costly b/tsDMARD treatments is limited. Even in developed countries, national policy or health insurance policy restrictions may limit patient access to the treatment with the best evidence base. An example of this is the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guideline, which still recommends that patients fail 2 csDMARDs before they are offered a bDMARD, irrespective of other disease manifestations.[2]

Thus, overall, while guidelines for the treatment of PsA are useful and provide evidence for efficacy, there remain many unanswered questions. There is a significant unmet need for more robust research in a number of areas, as outlined below, before solid guidance can be produced to inform the shared decision-making process between the rheumatologist and patient with PsA.

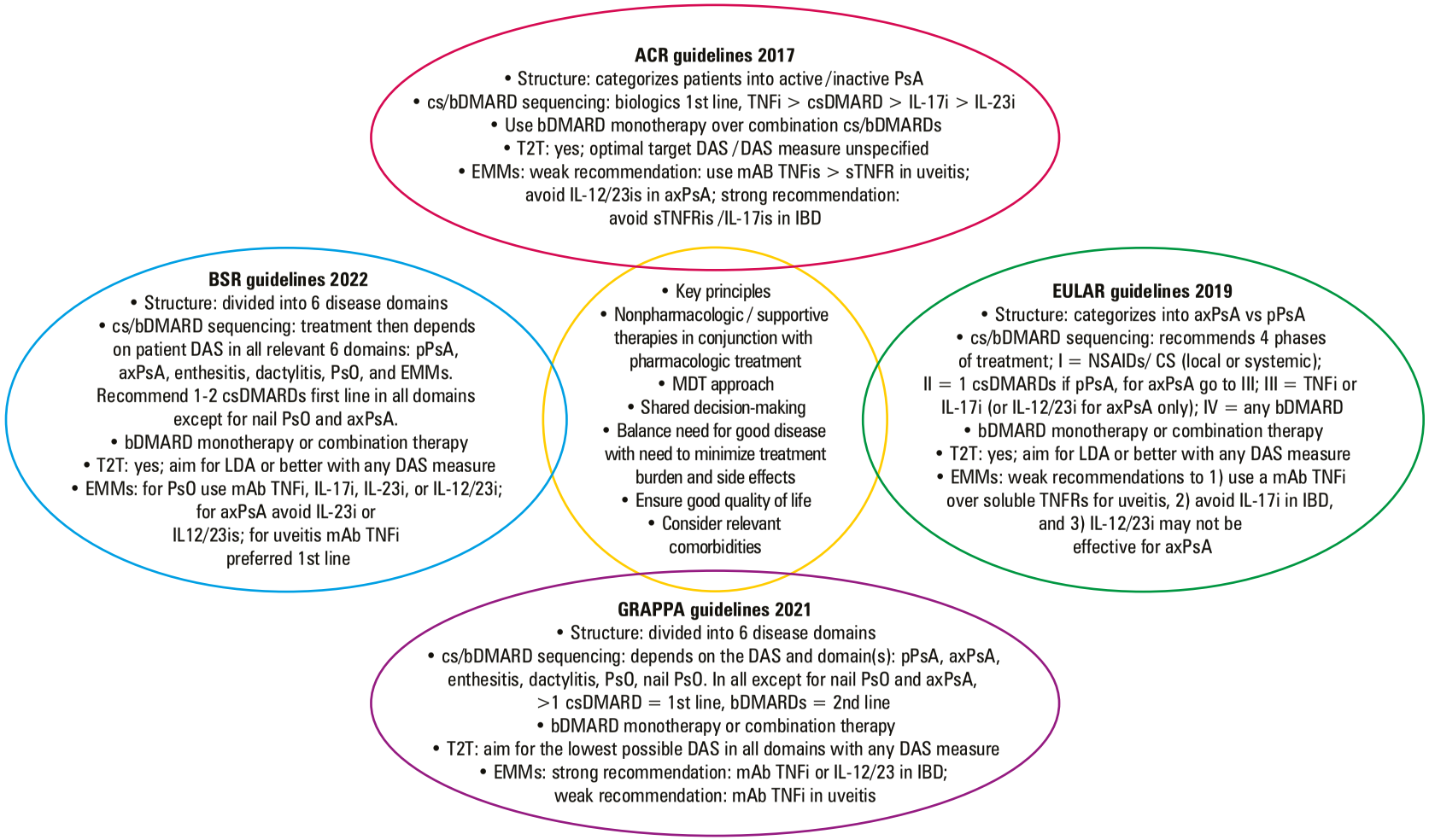

FIGURE 1 Infographic summarizing the key similarities and differences between the major treatment guidelines for psoriatic arthritis

Abbreviations: axPsA, axial psoriatic arthritis; BSR, British Society for Rheumatology; CS, corticosteroid; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, disease activity score; EMMs, extramusculoskeletal manifestations; EULAR, European Alliance of Associations for Rheumatology; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; LDA, low disease activity; mAb, monoclonal antibody; MDT, multidisciplinary team; pPsA, peripheral psoriatic arthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; PsO, psoriasis; sTNFRi, soluble tumor necrosis factor receptor inhibitor; T2T, treat-to-target; others, see TABLES 1 and 2

What are the significant areas of unmet need for therapeutics in psoriatic arthritis? **Classification and management of axial vs peripheral psoriatic arthritis** Hitherto guidance and studies have focused on PsA as a single entity. However, there is evidence that patients with axial PsA (axPsA)may respond better to earlier use of bDMARDs over csDMARDs.[27] International guidelines now reflect this observation, but this does not always translate to local/national guidance, as per the abovementioned example of NICE in the UK. Some patients may be reclassified as axSpA to access bDMARDs sooner; however, this decision is at the discretion of the treating rheumatologist, and can therefore result in variations in treatment.

There is thus a need for evidence to make a stronger case for NICE to change their guidance. One of the barriers for NICE is a lack of diagnostic or even classification criteria for what constitutes axial involvement in PsA. While we are unable to clearly classify patients, it is difficult to decide how they would meet the "criteria" for axPsA, and therefore qualify for bDMARDs. Work on this area is ongoing as part of the AXIS (Axial Involvement in Psoriatic Arthritis) study,[28] spearheaded by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Preliminary results are expected in December 2023. Results from studies such as AXIS are vital to develop consensus diagnostic criteria for axPsA, both for the purpose of the development of consensus treatment strategies and for ongoing research, which requires consistent and robust use of standardized diagnostic criteria to facilitate consistency and reproducibility of research output. This applies to current trials, such as the STAR trial (Efficacy and Safety of Guselkumab in Biologic-Naive Patients with Active Axial Psoriatic Arthritis),[29] which aims to establish the efficacy of guselkumab specifically in the axPsA subpopulation.

Divergent tissue responses PsA is a multisystem disease. Point prevalence of EMMs in PsA is approximately 85% for active skin disease, 50% to 80% for nail psoriasis,[30] around 4% for IBD,[31] around 8% for uveitis,[32] 50% for enthesitis, and 40% for dactylitis.[30] These differing tissue manifestations can pose unique challenges if they respond differently to the same biologic treatment. In most cases, this is idiosyncratic, and in the absence of biomarkers for treatment stratification determining divergent tissue responses in each individual patient is a matter of trial and error.

Somewhat more predictable are the established contraindications for some b/tsDMARDs once a patient develops EMMs. These in themselves also give invaluable insight into the biology of PsA and indeed SpA in general. In 2006–2007, an analysis of registry data from the United States, UK, and France revealed unexpectedly high rates of anterior uveitis in both rheumatology and ophthalmology patients taking etanercept.[33,34] This effect appeared to be drug-specific, with 126 out of 152 registry cases of anterior uveitis attributable to etanercept alone. This apparent paradox is thought to be due to the molecular structure of different TNFis. Etanercept is a recombinant fusion protein, whereas all other TNFis are monoclonal antibodies that bind and neutralize circulating TNF.[35] Some authors suggested that etanercept may bind TNF, and therefore potentially release it back into the circulation,[33,36] which could paradoxically increase the duration and concentration of TNF, triggering anterior uveitis in susceptible individuals. Etanercept also only binds TNF in the circulation, whereas monoclonal antibodies, such as infliximab and adalimumab, also bind TNF on target cells, such as T lymphocytes, inducing lysis.[37] Increased cytotoxic T cells have been reported in the vitreous humor of patients with anterior uveitis.[38] Furthermore, in Crohn disease, etanercept, unlike adalimumab or infliximab, fails to induce apoptosis of disease-causing cytotoxic T cells and is thus differentially ineffective.[39]

Another notable paradoxical treatment effect is the observation that IL-17i can cause or worsen IBD.[40-42] The IL-23/IL-17 pathway is heavily implicated in SpA and also in IBD,[43] and plays a role in regulation of gut permeability to host microbiome.[40] While initially it was thought that targeting this pathway would help treat IBD, it appears that IL-17Ai induces a breakdown of the gut epithelial barrier, predisposing to infection and inflammation, which can trigger or exacerbate IBD. As such, IBD is an absolute contraindication for IL-17i therapy in PsA. However, there is potentially a high prevalence of subclinical IBD, both in PsA and, to a lesser extent, in psoriasis. For example, in a study involving 50 patients with active psoriasis, 58% had elevated fecal calprotectin (>43.2 μg/g) and 15 of these had signs of inflammation on sigmoid mucosal biopsy.[44] There is real concern that in these higher-risk patients, treatment with IL-17i could trigger onset of clinical IBD. However, it can be very hard to identify such patients, since symptoms of IBD can be similar to those of irritable bowel syndrome, and diagnostic tests are often inconclusive.[45]

Notwithstanding all this, it remains unclear why some patients develop side effects with medication, and some do not, and why some develop problems at the onset of treatment, and some after many years of good drug response. The answer undoubtedly lies, at least in part, in an individual's genes. PsA is not a single disease, but a spectrum of different clinical phenotypes which have both shared and distinct genetic architecture.[46] Large genome-wide association studies to date have reported 412 and 74 gene polymorphisms associated with axSpA and PsA, respectively, of which at least 11 are shared.[47] However, there have been no detailed comparative genomics analyses of the clinical subtypes of axSpA and PsA, including axial vs peripheral disease, human leukocyte antigen B27–positive vs negative disease, etc. Such granular detail is needed to fully

elucidate the genetic differences and similarities of these diseases, and to better identify which patients may be at the highest risk of treatment complications.

Early psoriatic arthritis Around 20% of patients with psoriasis will develop PsA.[48] However, to date there are no diagnostic biomarkers, which can make identification of at-risk patients and early diagnosis challenging. In 2021, the Delphi Consensus Study[49] proposed a definition of 3 stages of early PsA; psoriatic individuals at risk of PsA, subclinical PsA, and symptomatic early PsA. However, the conundrum of how to identify patients progressing through these stages, and then from early to established PsA, remains unsolved.[50] Unsurprisingly, this has resulted in heterogeneity in the published literature, making interpretation of data and direct comparisons between studies difficult. Bedside ultrasonography can help with detection of asymptomatic and subclinical synovitis in symptomatic tender joints[51,52]; however, it is not necessarily widely available. Moreover, subclinical synovitis can be present in asymptomatic joints and in healthy individuals, and ultrasonography cannot help with detection of axial symptoms.[53] For the latter, magnetic resonance imaging (MRI) is required; however, MRI features of axPsA can also be nonspecific and may be falsely reassuring if the patient is scanned during a quiescent phase of the disease.[54] In fact, the rate of positive MRI findings is low, even in patients with convincing clinical symptoms of inflammatory back pain.[54] MRI is also potentially expensive and time-consuming, and a significant number of patients fail to tolerate the scan due to claustrophobia or inability to lie flat for the duration of the scan (approximately 45 minutes).

Even if there was an agreed definition of early PsA, there is still no consensus on how this group of patients should be treated. There is a wealth of evidence that early and aggressive intervention improves short- and long-term outcomes in rheumatoid arthritis (RA)[55]; conversely, in PsA the evidence is less clear. TICOPA (Effect of Tight Control of Inflammation in Early Psoriatic Arthritis)[56] was the first study to investigate the effects of tight disease control in early PsA. Two-hundred and six patients with PsA of less than 2-year duration were randomized to either tight control (target minimal disease activity [MDA]) vs standard care. The primary outcome (proportion of patients in each group meeting the American College of Rheumatology definition of improvement by 20% in the core set measures [ACR20] at 48 weeks) was achieved in 44% of patients in the tight control group vs 32.4% of those receiving standard care (P = 0.019), with no increase in adverse treatment effects. Subsequently, all TICOPA patients then went into routine National Health Service care, and the 5-year follow-up of medical records (n = 110/206) found a similar level of disease activity in both treatment arms. Biologic use was higher in the tight control group, methotrexate (MTX) use diminished in both arms, and more than 50% of patients with PsA were taking biologics in the long term.[57]

While TICOPA explored the potential benefits of early, aggressive intervention in PsA, it did not establish which intervention(s) produce the best short-to-long term outcomes. Two published trials have attempted to answer this question, and 2 further trials are expected to be published in the near future.

The first study[58] compared MTX and golimumab combination therapy for 22 weeks followed by MTX monotherapy for up to 1 year vs placebo plus MTX therapy for 22 weeks followed by methotrexate MTX for 1 year. The authors found that the combination therapy was more effective. However, only 8 placebo and 18 treatment patients completed the 1-year follow-up, and while the authors classified the patients as early PsA, in fact, 25% of cases had a disease duration of more than 2 years. Data on the average disease duration (median or mean and range) would be preferable to facilitate interpretation of the results.

The second trial, CONTROL (Comparison between Adalimumab Introduction and Methotrexate Dose Escalation in Patients with Inadequately Controlled Psoriatic Arthritis),[59] compared rapid-dose escalation of MTX (15 mg to 25 mg) (R-MTX) vs 15 mg MTX plus adalimumab (MTX+ADA) in bDMARD-naive PsA patients not responding to 15 mg MTX. The primary outcome was the percentage of patients achieving MDA at week 16. A total of 245 patients were enrolled. The primary outcome was achieved by 41% of patients in the MTX+ADA group and 13% of those in the R-MTX group (P <0.0001), and the response was maintained at 32 weeks in 80% and 67% patients, respectively. Nonresponders at week 16 were then escalated as follows: in the ADA+MTX group, adalimumab was increased to once weekly and in the R-MTX group, adalimumab was added. Overall, 30% and 55% of the nonresponders achieved MDA at week 32, respectively. Unfortunately, disease duration was not reported, making it unclear if the patients were truly early PsA.

In a third study (the COMPLETE-PsA [Comparing Methotrexate Monotherapy with Methotrexate Plus Leflunomide Combination Therapy in Psoriatic Arthritis] trial[60]), the strategy of using combination csDMARDs in contrast to a single csDMARD was assessed in a double-blind, randomized, controlled, single-center analysis of treatment-naive patients with early PsA. The combination of MTX and leflunomide was superior to MTX alone, though there were more adverse events in the combination group. Importantly, csDMARD therapy response rates in both groups were similar to those achieved with bDMARDs (MDA at 16 weeks, 59% and 32% in the combination and MTX groups, respectively). Thus, both the CONTROL and COMPLETE-PsA trials suggest that, at least in some patients, a strategy

of escalating csDMARDs can be as effective as bDMARD treatment. Further trials of combination or escalation csDMARD use in early PsA should therefore be a priority for future research.

Two further studies focusing on the treatment of early PsA are registered in the clinical trials database, but as yet are unreported: the FOREMOST trial[61] (apremilast vs placebo in patients <5 years since the PsA symptom onset) and the GOLMEPsA trial[62] (MTX vs golimumab monotherapy in PsA <24 months since the diagnosis). Thus, there remains an unmet need for large, robust clinical trials in this area.

Finally, other important questions to answer are whether PsA can be prevented by intervening in at-risk patients with psoriasis, and whether there is a preclinical phase of PsA that could be identified and treated to prevent PsA.[63] The GRAPPA has recently reported that only 3 out of 5 trials in these areas to date found early bDMARD use to reduce progression to PsA.[64] On the other hand, all these trials were retrospective, and there is a need for dedicated prospective, robustly designed trials in this area. In a recent systematic literature review and meta-analysis, the authors attempt to tentatively define risk factors for PsA in patients with psoriasis,[65] with the main ones being positive imaging findings for synovitis, enthesitis, tenosynovitis, erosions, and new bone formation at the entheses, arthralgia, high Psoriasis Area and Severity Index (PASI) and high body surface area, nail psoriasis, family history of PsA, and raised body mass index. In the future, the PsA research community should be working toward developing more sophisticated risk prediction models, using a combination of clinical, laboratory, imaging, and genetic indices through large omics / artificial intelligence approaches.[66]

Difficult-to-treat psoriatic arthritis Another area of unmet clinical need is management of the so-called difficult-to-treat PsA (D2TPsA) population. Broadly speaking, this refers to individuals who have failed multiple cs/bDMARDs, and is estimated to be up to 30% patients.[67] The European Alliance of Associations for Rheumatology (EULAR) recently convened an expert task force to develop a consensus definition for difficult-to-treat RA along with specific treatment recommendations to allow for research in this area.[68] The first step was defining the clinical problem, and as yet there is no consensus definition of what constitutes D2TPsA; however, EULAR and GRAPPA have committed to developing consensus definitions and ultimately bespoke treatment guidelines for D2TPsA. The barriers are likely to be a lack of available evidence for different treatment approaches in this relatively small subset of PsA patients, who will not have been studied as a discrete clinical entity in any phase III/IV trials.

Another consideration for the conceptualization of D2TPsA is whether drug failure should be defined as failure to respond by just 1 tissue compartment alone, such as the skin, or by using composite scores. Given that patients need drug(s) to treat all their disease manifestations, it seems inevitable that defining D2TPsA and its treatment is certain to be quite complex. In addition, PsA patients have higher rates of comorbid cardiometabolic diseases due to various factors both dependent and independent of their PsA.[69] For example, severity of psoriasis / PsA and raised C-reactive protein (CRP) levels are independent predictors of nonalcoholic fatty liver disease and other cardiometabolic disease in PsA, irrespective of metabolic syndrome.[70] D2TPsA patients may also have chronic pain and pain centralization, which can be a cause for treatment nonresponse.[71] These factors, in turn, impact on drug response and side effects, and should therefore be taken into account in the definition and future guidelines for D2TPsA.[71] Finally, any D2TPsA guideline should be developed in partnership with other key stakeholder specialties, including dermatology, gastroenterology, ophthalmology, and primary care, so as to meet the needs of the aging, multimorbid PsA population.[72]

Einstein said that insanity is "doing the same thing over and over and expecting different results"[73]; and indeed, when the treatment is not working, one must question the validity of the diagnosis. This can be challenging for several reasons. Often the diagnosis will have been made many years ago, in most cases by a different doctor, often at a different hospital, using clinical information not privy to the current team. Also, many patients struggle to understand and accept an alternative diagnosis after years of identifying themselves as having PsA. Even if the diagnosis is correct, it may not be the cause of current symptoms. Osteoarthritis and pain central sensitization syndromes, including fibromyalgia, are more common in PsA.[74,75] Disentangling these pain manifestations and other organic morbidities from true drug nonresponse will be at the core of understanding the mechanisms for these so-called difficult to manage or treat disease subsets.

Treat-to-target approaches Currently, treatment guidance in PsA lacks detail regarding treat-to-target approaches, and when is the right time to consider switching / combining drugs. As discussed previously, this is due to a lack of robust data in this area. TICOPA,[57] the largest study of tight disease control in early PsA, did not show reduced 5-year disease activity with the use of biologics, as compared with standard care. However, although data were incomplete, the authors were able to demonstrate that with adherence to the current standard of care, there was little radiographic progression and good drug survival, as compared with historic treatment approaches. Additionally, with time, the standard care arm has improved to such an extent that many standard care patients in TICOPA went on to receive comparable care to the tight control arm, and this may explain some of the reasons for the lack

of differences in the TICOPA follow-up results. An alternative hypothesis is that in certain subgroups of patients tighter control may be more important, or more successful, in achieving superior outcomes in the longer term. Clearly, dissecting the nuances of the treat-to-target approach in PsA, of if / when to use it, and what targets to aim for, is an area where further research would be invaluable to guide therapeutic strategies.[76]

Tapering and withdrawal of treatment in remission At the other end of the spectrum there are patients who do exceptionally well on treatment, and who wish to consider tapering or even withdrawing treatment. Evidence suggests that complete withdrawal of medications usually results in relapse.[77,78] However, with the aid of biomarkers it may be possible to identify patients in whom tapering may be implemented.

Head-to-head drug trials Although baseline characteristics across the phase III trials for PsA for all drug groups (TNFis, IL-23is, IL-17Ais, JAKis, and IL-17A/Fis) are similar, and as the trials all achieved their primary end points, one may surmise that each class of bDMARDs would perform similarly well in real-world clinical practice. However, this assumption is prone to bias, and more head-to-head (H2H) drug trials are needed.[79] Some H2H results have been reported; for example, in 2019, Deodhar et al[80] published the results of a phase III trial (COAST-V) that compared ixekizumab in bDMARD-naive radiographic axSpA patients with placebo and adalimumab. Although the study was not adequately powered to detect significant differences, ixekizumab achieved numerically superior Assessment of Spondyloarthritis International Society (ASAS)40 response at the primary end point (week 16). Subsequently, the SPIRIT H2H trial[81] in PsA was published in 2020. This time, the authors made a direct statistical comparison between ixekizumab and adalimumab in bDMARD-naive PsA. When used without concomitant MTX, ixekizumab was superior to adalimumab for all end points (ACR50, PASI100, minimal disease, and very low disease activity). On the other hand, the EXCEED H2H trial,[82] which compared adalimumab and secukinumab in active bDMARD-naive PsA, failed to demonstrate superiority of secukinumab for the primary end point (ACR20 at 52 weeks). The SELECT PsA trial[83] compared adalimumab with upadacitinib, reporting that the 30-mg dose, but not the 15-mg dose of upadacitinib was superior to adalimumab (response was defined as the proportion of patients achieving ACR20 by week 12); however, the 30-mg dose is not currently licensed for PsA or psoriasis, thus limiting the clinical relevance of these findings. Finally, active drug comparator arms (adalimumab and secukinumab) were also included in trials of bimekiumab in psoriasis, which demonstrated noninferiority and superiority of bimekizumab against both comparator drugs.[84,85]

In contrast, phase III trials of bimekizumab in PsA and axSpA did not include active drug comparator groups[16,17,24]; instead, adalimumab was included as a reference drug in these trials, which were not powered to detect significant difference between placebo or bimekizumab vs adalimumab. The introduction of active drug comparator arms in at least some recent clinical trials may in the future guide decisions about bDMARD sequencing for PsA. Robust, longitudinal data are now needed to corroborate these findings. These should include the results of both phase IV and real-world evidence that considers the comparative long-term effects of each bDMARD on disease activity, comorbidities, and EMMs.

Combination therapies Combination cs/bDMARD therapies are commonly used in real-world practice; however, there are scarce trial data on the effectiveness of these therapies for PsA.[86] One of the most commonly used combinations is MTX plus a bDMARD. Indeed, a recent meta-analysis of controlled trials did find that MTX improved the efficacy of biologics for skin psoriasis, with no significant increase in side effects; however, there was no additive effect on PsA symptoms, and the overall quality of evidence was low.[87] Combining bDMARDs is only considered in extreme cases that have been described in case reports.[88] Although trials of these combinations would never be feasible due to low patient numbers, in some of the most challenging cases, combination ts/bDMARD therapies may have a role.

Personalized medicine: the magic bullet? Central to nearly all of the unmet treatment needs in PsA is the lack of biomarkers for patient stratification and prediction of complications / treatment response.[89] If we had biomarkers for psoriatic patients or their relatives to determine who was at risk of PsA, such individuals could be offered regular screening, monitoring, and early intervention to detect and treat PsA sooner if it does occur. Disease activity scores, such as the Disease Activity Score for Psoriatic Arthritis, show high inter-rate and intra-rate variability,[90] and similarly to blood markers, including CRP, are neither sensitive nor specific for PsA.[91] While ultrasonography provides a more objective measure of subclinical inflammatory changes, it is not widely available at the bedside. Furthermore, ultrasonography can be time-consuming to examine all joints. Joint tenderness does not always correlate with subclinical synovitis or overtly swollen joints, and studies are needed to establish standardized screening ultrasonography protocols for PsA to make US a useful screening test.[92] Ultrasonography is also not useful for the assessment of axial joints. Here, MRI is needed; however, MRI findings of PsA can also be nonspecific.[93] Finally, plain film X-rays are inadequate biomarkers, since they only detect changes once irreversible damage has occurred.

Genetics are determined at birth, fixed throughout an individual's lifetime, and are unique to a person (except for identical twins), making them potentially attractive as biomarkers. However, PsA is a polygenetic disease, with thousands of genes each having a very small incremental effect on each trait of PsA, and so genetic studies requires large numbers of patients.[94] Different risk alleles may be more or less important in different populations (population stratification), which makes it difficult to develop single biomarkers for transethnic use.[95] Li et al[96] recently published a novel polygenic risk score that outperformed clinical tests for axSpA. Thus, it seems plausible that a similar tool could be developed for PsA, which one day in the future could inform decision making in real-world clinical practice. Overall, it is unlikely that a single biomarker will fit all; instead, a combination approach using information from clinical assessments, laboratory / imaging / genetic tests, and artificial intelligence approaches may one day allow for personalization of medicine in axSpA. GRAPPA is now exploring this through the HIPPOCRATES program; an ambitious collaboration between several European countries and the United States to combine cohorts of PsA patients with detailed clinical data and biosamples for research, including research into diagnostic and treatment response biomarkers.[97]

Patient and public involvement Another important part of the future of PsA care is empowering patients to manage their own condition. Increasing utilization of virtual / remote consultations means that using traditional tools to measure and monitor changes in disease activity will be difficult, though self-completed tools have been developed.[98] Biomarkers can help shape the conversations with patients around their individual risk and inform treatment decisions with more objective evidence. Despite this, much remains to be understood about how we can ensure, via remote consultation, that the patient's treatment is closely monitored and escalated when necessary, in a timely manner.[99,100] Perhaps more importantly, the feasibility and acceptability of this approach by patients are still unclear. The COVID-19 pandemic has spearheaded increased use of remote working practices, and there is indeed a growing preference for remote consultations which can fit in with patients' busy lifestyles. However, certain subsets of the population still prefer face-to-face reviews, and may not respond well to virtual clinics. Similarly, to date, most trainee doctors receive very little formal training in appropriate and effective use of these different types of remote working that were rapidly adopted during the pandemic.

Conclusions There have been several important advances in the treatment of PsA in recent years, including a growing number of available therapeutic agents. These have expanded options for patients, but at the same time brought new challenges in understanding how to make the most efficient and effective use of these agents to treat the complex needs of PsA, a multisystem disease with increasing prevalence of multimorbidity. The focus of PsA research now needs to be on the unmet areas of need, many highlighted in this review, to provide the best possible care for all patients with PsA, which considers their disease phenotype, comorbidities, preferences, and lifestyle choices.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The views expressed are those of the authors and not necessarily those of the United Kingdom (UK) National Health Service (NHS), the National Institute for Health and Care Research, or the UK Department of Health.

FUNDING SRH is supported by a Wellcome Trust 4Ward North Clinical PhD Fellowship Grant. HMO and PSH are supported by the Leeds NIHR Biomedical Research Centre.

CONFLICT OF INTEREST SRH has received speaker fees from Novartis and Janssen, and sponsorship from Janssen and UCB to attend medical conferences. ADBNR has no conflicts of interest to declare. HM-O has received grant support from Janssen, Novartis, and UCB, and honoraria and/or speaker fees from AbbVie, Biogen, Eli-Lilly, Janssen, Moonlake, Novartis, Pfizer, Takeda, and UCB. PSH has received lecturing fees from Novartis.

HOW TO CITE Harrison SR, Aung Din BNR, Marzo-Ortega H, Helliwell PS. Recent advances in the management of psoriatic arthritis: practical considerations. Pol Arch Intern Med. 2024; 134: 16639. doi:10.20452/pamw.16639

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