doi:10.36849/JDD.2020.4690

 ORIGINAL ARTICLE

Efficacy and Safety of Systemic Treatments for Skin and Joint Manifestations in Patients With Psoriasis

William Abramovits MD,[a] Joel Schlessinger MD[b]
[a]Dermatology Treatment and Research Center, Dallas, TX
[b]Advanced Skin Research Center, Omaha, NE

ABSTRACT

Psoriasis is a chronic, systemic disease with features suggestive of autoimmune dysregulation. Patients with psoriasis vulgaris frequently experience systemic comorbidities, including cardiovascular and metabolic diseases, and approximately 30% develop psoriatic arthritis (PsA), which requires treatment. It is important that physicians and patients are aware of the breadth of treatment options available to treat the complete spectrum of psoriasis manifestations. This narrative review summarizes clinical information from approved systemic psoriasis therapies relevant to the treatment of PsA and related systemic pathologies. We include pivotal clinical trials of biologic therapies that are approved by the US Food and Drug Administration for psoriasis and PsA and additional studies identified from PubMed and congress abstract searches through August 21, 2019. We comment on the real-world effectiveness of traditional nonbiologic treatment options, including methotrexate, cyclosporine, acitretin, systemic corticosteroids, and nonsteroidal anti-inflammatory drugs and consider targeted synthetic and biologic disease-modifying antirheumatic drugs and their efficacy and safety in treating skin and joint manifestations. Finally, we discuss key considerations when managing patients with PsA as a comorbidity of psoriasis. The individual treatment needs of patients should be met while psoriasis and its systemic complications are managed. When addressing these needs, it is important to consider modern biologics and other systemic therapies.

J Drugs Dermatol. 2020;19(3):306-313. doi:10.36849/JDD.2020.4690

INTRODUCTION

Overview of Psoriasis and Psoriatic Arthritis

In addition to itch and pain associated with plaques, patients with psoriasis often have comorbidities, including cardiovascular disease, diabetes, obesity, metabolic syndrome, risk of malignancies, fatty liver disease, and/or depression.[1,2] An increased risk of death from all causes was recently demonstrated.[3] Approximately 30% of patients with psoriasis develop psoriatic arthritis (PsA),[4-6] a chronic, systemic inflammatory disease characterized by peripheral arthritis, enthesitis, dactylitis, axial disease, and skin and nail involvement.[7-9] PsA arises through a series of complex immune signaling pathways.[4] Activated T cells and macrophages play an important role in inflammatory processes through mediators such as tumor necrosis factor α (TNF-α) and various interleukin (IL) cytokines.[4,7] The combination of musculoskeletal components with cutaneous disease highlights that a multidisciplinary approach may be needed for the management of individual patients.[9] This narrative review discusses the efficacy and safety of systemic treatments for skin and joint manifestations in patients with psoriasis to provide dermatologists and rheumatologists with an updated summary of the benefits and risks of currently available treatments on several disease domains. We review data from pivotal clinical trials of biologic therapies that are approved by the US Food and Drug Administration for psoriasis and PsA, as well as additional clinical studies of biologics identified from PubMed and congress abstract searches through August 21, 2019.

Management of Psoriasis and PsA

Recommended therapies for psoriasis and PsA include traditional nonbiologic medications (eg, topical treatment, phototherapy, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and/or conventional disease-modifying antirheumatic drugs [DMARDs]), biologic agents, and targeted synthetic (ts) DMARDs. Because PsA is treated as a complication of psoriasis, there is an unmet need for comprehensive treatment guidelines. Recommendations for the management of PsA were recently published by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which considered dermatologic and musculoskeletal manifestations,[9] and the European League Against Rheumatism (EULAR), which focused solely on musculoskeletal manifestations.[8] Because PsA is a heterogeneous disease involving multiple domains either alone or in combination, GRAPPA recommended that the goals of therapy for all patients with PsA are to achieve the lowest possible level of disease activity in all domains (peripheral arthritis, spondylitis/axial disease, enthesitis, dactylitis, skin disease, and nail disease); optimize functional status, improve quality of life and well-being, and prevent structural damage to the greatest extent possible; and avoid or minimize complications, both from untreated active disease and from therapy.[9] The GRAPPA recommendations are designed to aid in the decision-making process for patients; therefore, the choice of therapy for an individual patient should address as many involved domains

as possible and likely be driven by the most severe element.[9] Optimal therapy for patients with PsA as a complication of psoriasis should demonstrate efficacy in skin, peripheral joints (eg, arthritis, enthesitis, dactylitis), and the axial skeleton (including sacroiliitis) when those features are present.[10,11]

Efficacy of Traditional Systemic Medications

Historically, methotrexate (MTX), cyclosporine, and acitretin have been commonly used to treat extensive psoriasis that is unresponsive to topical therapy and/or phototherapy.[12] MTX has been prescribed for over 50 years and is still used by itself and alongside biologic agents, particularly TNF inhibitors (TNFis),[8,12] although the appropriateness of its use becomes a question given the availability of potentially less toxic drugs. In patients who have PsA as a complication of psoriasis, traditional non-biologic treatment options include NSAIDs, glucocorticoids, and conventional DMARDs such as MTX, sulfasalazine, leflunomide, and cyclosporine.[10] Some of these agents may be effective for both skin and joint manifestations (Table 1).

NSAIDs and glucocorticoids are often used initially to alleviate PsA symptoms. Conventional DMARDs are recommended for

TABLE 1.

Traditional Systemic Treatments: Efficacy in Psoriasis and Psoriatic Arthritis and Safety Considerations

	Efficacy	Safety
Methotrexate	• Efficacy demonstrated in 3 well-designed studies in patients with psoriasis[12] • Recommended as the DMARD of choice by EULAR for treatment of joint manifestations in PsA based on observational studies • A large randomized trial in PsA showed no improvement in measures of peripheral arthritis (PsARC, ACR20, and DAS28) vs placebo[74] • Improvements were observed in global assessments of disease and PASI scores[74]	• Associated with hepatic, pulmonary, and marrow toxicity as well as teratogenicity[7] • Careful monitoring required[12] • Long-term use limited in patients with risk factors for liver disease (eg, fatty liver and alcoholism)[7] • Hepatotoxicity monitoring guidelines more stringent than in rheumatology • Obesity more likely in patients with severe psoriasis, so susceptibility to underlying non-alcoholic steatohepatitis is increased[12] • Obesity a greater risk factor than alcohol or viral-induced hepatitis and cumulative MTX treatment • Monitoring liver transaminase levels in obese patients is advised[75] • Associated with cognitive impairment at high doses in patients with cancer[76]
Cyclosporine	• Effective treatment for cutaneous disease; can relapse following treatment discontinuation[12] • Efficacious in numerous clinical trials of patients with psoriasis[12] • Modest efficacy in skin and joints has been observed in a few small studies of PsA[7,77]	• Associated with nephrotoxicity and hypertension and recommended only for short-term use[7]
Leflunomide	• Quality of evidence in placebo-controlled trials supporting use in psoriasis is not very convincing[12] • 1 large randomized trial in PsA showed improvement in PASI scores and PsARC vs placebo[12]	• Associated with gastrointestinal toxicity, elevated liver enzyme levels, increased risk of infections, and leucopenia[7] • Relatively well tolerated in PsA[10] • Adverse effects similar to those observed in RA[10]
Sulfasalazine	• Quality of evidence in placebo-controlled trials supporting use in psoriasis is not very convincing[12] • Modest efficacy in joints has been observed in some pilot trials and controlled studies of PsA[10]	• Associated with gastrointestinal intolerance, neurological disturbances, increased liver enzyme levels, impaired renal function, hypertension, arthralgia, reversible oligospermia, leukopenia, and agranulocytosis[7,77]
Glucocorticoids	• Not recommended for patients with psoriasis due to lack of clinical data and association with flares in skin lesions during or after dose tapering[7] • Local and systemic administration may be useful for patients with few affected joints, tendon sheaths, or entheses or those with polyarticular disease with a few persistently active joints[10,73]	• Recommended only for short-term use to minimize adverse effects[8,9] • Systemic glucocorticoids should be used with caution due to potential psoriasis flares upon withdrawal[7,10]
NSAIDs	• Not effective for treatment of psoriasis • May worsen skin lesions in patients with PsA who receive NSAID treatment for peripheral arthritis or axial disease[7] • Effective for treating signs and symptoms of peripheral arthritis in PsA[8,10,78] • Additional therapy should be considered if benefit is not observed within a few weeks[8]	• Use with caution due to potential adverse effects, including gastrointestinal effects and exacerbation of psoriasis[9,7,78]

ACR20, American College of Rheumatology 20% improvement in response; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; RA, rheumatoid arthritis.

treating PsA on the basis of observational studies as well as their relatively low cost and universal access.[9] Most of the evidence for conventional DMARDs relates to treatment of the signs and symptoms of peripheral arthritis as well as skin manifestations; data on enthesitis, dactylitis, and axial disease are lacking, and inhibition of structural progression in peripheral joints has not been demonstrated.[7] The term "DMARD" is based on historical nomenclature used in rheumatoid arthritis rather than on solid evidence demonstrating inhibition of joint damage in PsA.[9] The real-world comparative effectiveness of traditional systemic medications has proven difficult to rigorously assess due to lack of standardization in outcome definitions used across studies.[13]

Efficacy of Biologics and tsDMARDs

Several biologics and tsDMARDs are effective in treating psoriasis, including monoclonal antibodies targeting TNF-α, IL-12/23, IL-17A, and IL-23, and an oral phosphodiesterase 4 inhibitor. An early comparison of biologics in a phase III trial of patients with psoriasis found that the IL-12/23 inhibitor ustekinumab was more effective than the TNFi etanercept at clearing skin symptoms.[14] Over time, TNFis and ustekinumab became biologic comparators for newer classes of biologics; the IL-17A inhibitors secukinumab, ixekizumab, and brodalumab are more likely to improve skin manifestations as assessed by achievement of Psoriasis Area and Severity Index (PASI) responses than ustekinumab and etanercept.[15-19] The IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab are more effective than adalimumab, etanercept, and ustekinumab in patients with psoriasis as assessed by achievement of PASI75 and PASI90 responses, or the Investigator's Global Assessment modified 2011 scale.[20-23] More recent head-to-head studies directly compared IL-17A inhibitors with IL-23 inhibitors. One such study (ECLIPSE; NCT03090100) found superior efficacy for guselkumab vs secukinumab in achievement of PASI90 response after 48 weeks of treatment.[24] A study comparing ixekizumab vs guselkumab (IXORA-R; NCT03573323) is ongoing, and topline results demonstrate superiority of ixekizumab in achievement of PASI100 at Week 12 (data not yet published).

Most of these agents approved for use in psoriasis have demonstrated efficacy in PsA in placebo-controlled trials (Table 2).[25-42] Although the IL-17A receptor inhibitor brodalumab and the IL-23 inhibitors guselkumab, risankizumab, and tildrakizumab have some efficacy in PsA in phase II trials to date, and guselkumab has also shown efficacy in topline results from the phase III DISCOVER 1 and 2 trials (NCT03162796 and NCT03158285; data not yet published), they are not currently approved for PsA.[40,41,43,44] Patients enrolled in the placebo-controlled PsA clinical trials were inadequate responders or intolerant of ≥ 1 nonbiologic systemic therapy for PsA; some had also experienced an inadequate response to a biologic agent.[25-43] Concomitant medication as background therapy, including ≥1 nonbiologic systemic therapy for PsA such as a conventional DMARD, glucocorticoid, or NSAID, but not apremilast, was allowed to be continued in all treatment arms.[25-43] These trials confirmed that biologic agents and tsDMARDs were efficacious in patients with PsA who had not responded to nonbiologic systemic therapies and were more effective than traditional treatments. Biologic agents and tsDMARDs target a range of molecules involved in the pathogenesis of PsA; it is therefore likely that a differential response of the various domains of PsA to treatment may be observed. Although data from individual trials cannot be directly compared due to variations in patient selection and study design, evidence can be used to determine which agents might be best suited to treat specific PsA manifestations.

The primary endpoint for most randomized controlled trials in PsA is the achievement of American College of Rheumatology 20% improvement in response criteria (ACR20) vs placebo (Table 2). Prevention of joint damage is an important goal in the long-term management of arthritic manifestations of PsA; all biologic agents approved to date for use in both psoriasis and PsA reduce radiographic progression of structural damage.[25,26,35,36,38,45-48] Importantly, all biologic agents and tsDMARDs approved for use in both conditions also improved skin lesions vs placebo in the same PsA trials (Table 2).[26-39,42] Following the pivotal trial of etanercept in PsA,[25] a subsequent study showed that a higher dose of etanercept already approved for use in patients with psoriasis alone (50 mg twice weekly) may be suitable as an alternative strategy for treating patients with PsA.[49]

Aside from joint inflammation and damage, enthesitis and dactylitis are characteristic features of PsA,[7] and effective treatment options are essential for long-term disease management. Most biologic agents and tsDMARDs that are approved for psoriasis and have efficacy in PsA effectively treat enthesitis and dactylitis in patients with PsA.[27-29,33-37,41,49-51] Improvements in enthesitis and dactylitis have not been observed thus far with brodalumab.[40] The efficacy of apremilast was also variable in PsA trials: an improvement in enthesitis was observed in PALACE 1 but not in PALACE 3, and an improvement in dactylitis was observed in PALACE 3 but not in PALACE 1.[31,32]

To date, only 1 study has evaluated the effect of an approved agent for psoriasis with efficacy in PsA on axial involvement in patients with PsA.[52] In the MAXIMISE trial (NCT02721966), patients receiving secukinumab were more likely than those receiving placebo to achieve a 20% improvement in Assessment of Spondyloarthritis International Society response criteria.[52] However, biologic agents and tsDMARDs have been approved (adalimumab, certolizumab pegol, etanercept, infliximab, and secukinumab)[53,54] and evaluated (ustekinumab and ixekizumab)[55-57] in patients with axial spondyloarthritis. EULAR has identified the need for efficacy data in the treatment of axial disease in patients with PsA.[8]

TABLE 2.

Biologic Agents and tsDMARDs Approved for Use in Psoriasis: Assessment of Efficacy in the Joints and Skin of Patients With Psoriatic Arthritis

					Response with active treatment vs placebo, %	
Target	**Agent**	**Trial**	**Biologic naive?**	**Time, weeks**	**ACR20**	**PASI 75**
tsDMARDs						
Phosphodiesterase 4	Apremilast	PALACE 1[32]	No[a]	16	40[b] vs 19	21[b] vs 5
		PALACE 2[30]	No[a]	16	32[b] vs 19	22[b] vs 3
		PALACE 3[31]	No[a]	16	41[b] vs 18	21[b] vs 8
		PALACE 3[31]				
Biologic agents						
TNF-α	Etanercept	Phase III[25]	Yes	12/24[c]	59[b] vs 15	23[b] vs 3
	Adalimumab	ADEPT[26]	Yes	24	57[b] vs 15	59[b] vs 1
	Infliximab	IMPACT[27]	Yes	16	65[b] vs 10	68[d] vs 0
		IMPACT 2[28]	Yes	14	58[b] vs 11	64[b] vs 2
	Certolizumab pegol	RAPID-PsA[29]	No[e]	12	58[b] vs 24	47[b] vs 14
IL-12/23	Ustekinumab	PSUMMIT 1[34]	Yes	24	42[b] vs 23	57[b] vs 11
		PSUMMIT 2[33]	No[f]	24	44[b] vs 20	51[b] vs 5
IL-23	Guselkumab[g]	Phase II[41]	No	24	58[b] vs 18	79[b] vs 13
	Tildrakizumab[h]	Phase II[44]	No	16	--	74[b] vs 4
	Risankizumab[i]	Phase II[43]	No	24	48[b] vs 31	68[b] vs 14
IL-17A	Secukinumab	FUTURE 1[36,j]	No	24	50[b] vs 17	61[b] vs 8
		FUTURE 2[42,k]	No	24	51[b] and 54[b] vs 15	48[b] and 63[b] vs 16
		FUTURE 3[37,k]	No	24	42[b] and 48[b] vs 16	50[b] and 47[b] vs 10
		FUTURE 5[35,k]	No	16	56[b] and 63[b] vs 27	60[b] and 70[b] vs 12
	Ixekizumab	SPIRIT-P1[38]	Yes	24	58[b] vs 30	71[b] vs 10
		SPIRIT-P2[39]	No	24	53[b] vs 19	56[b] vs 15
IL-17 receptor A	Brodalumab[l]	Phase II[40]	No	12	37[b] and 39[b] vs 18	--

ACR20, American College of Rheumatology 20% improvement in response; IL, interleukin; PASI 75, Psoriasis Area and Severity Index 75% reduction in score; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.
All trials were placebo controlled, and SPIRIT-P1 in ixekizumab[38] also included adalimumab as an active reference arm.
[a]Patients who experienced therapeutic failure with TNF inhibitors comprised ≤10% of the study population; [b] $P < .05$ vs placebo; [c]ACR20 response was assessed at week 12 and PASI 75 response was assessed at week 24; [d] P value not provided; [e]Up to 40% of patients could have received prior treatment with a TNF inhibitor; [f]The protocol specified that 50% to 60% of randomized patients must have been previously treated with a TNF inhibitor; [g] Guselkumab is not approved for use in PsA; phase III trials are ongoing. Up to 20% of patients could have received prior treatment with 1 TNF inhibitor in the phase II trial; [h]Tildrakizumab is not approved for use in PsA; phase II/III trials are ongoing; treatment data are for subcutaneous tildrakizumab 200 mg at weeks 0 and 4; [i]Risankizumab is not approved for use in PsA; treatment data are the average of all 4 treatment arms; [j]Treatment data are for secukinumab 10 mg/kg intravenous loading dose followed by subcutaneous secukinumab 150 mg every 4 weeks, respectively. Note that a subcutaneous loading regimen of secukinumab is approved for use in PsA; [k]Treatment data are for secukinumab 150 or 300 mg subcutaneous once weekly loading dose for 4 weeks followed by subcutaneous secukinumab 150 or 300 mg maintenance every 4 weeks, respectively. [l] Brodalumab is not approved for use in PsA; phase III data are pending. Phase II treatment data are for brodalumab 140 or 280 mg.

Several studies have indirectly compared the efficacy of biologic agents and tsDMARDs in PsA, with most showing no differences between treatments.[58-63] However, 2 matching-adjusted indirect comparisons (MAICs) demonstrated some differences between biologics in the treatment of PsA.[64,65] One MAIC revealed that adalimumab was more effective than etanercept (in skin as assessed by PASI50/75/90 and joints as assessed by ACR20/50/70) and infliximab (in joints as assessed by ACR20/50/70).[64] Another MAIC revealed that ACR response rates were higher during the first year of treatment with secukinumab than with adalimumab, with significance reached at multiple time points.[65] Some patient-reported outcomes, including Health Assessment Questionnaire Disability Index, pain (visual analogue scale), patient global assessment, and Functional Assessment of Chronic Illness Therapy–Fatigue scores, were also better with secukinumab than with adalimumab at week 24 or 48.[65]

To date, few large head-to-head trials of an approved biologic agent or a tsDMARD in PsA have been initiated. Topline results from a recently completed study (SPIRIT-H2H; NCT03151551) suggest that patients receiving ixekizumab are more likely than those receiving adalimumab to achieve ACR50, resolution of enthesitis, and PASI100 after 24 weeks of treatment.[66] A study comparing secukinumab vs adalimumab (EXCEED 1;

NCT02745080) is ongoing. The awaited complete results of these trials will provide evidence for the comparative efficacy of these IL-17A inhibitors vs TNFis and may influence treatment guidelines and recommendations.

Safety Considerations

Specific adverse effects have been observed with biologic agents and tsDMARDs. Because biologic agents and tsDMARDs are immune modulating in nature, most have warnings regarding the risks of infection and malignancy.[53,54] Apremilast carries no such warning, but its use is associated with an increased risk of gastrointestinal events, unexplained weight loss, and depression; the dose requires adjustment in patients with severe renal disease.[54] TNFis have been used to treat psoriasis and PsA for several years, and long-term safety in patients with PsA is well established.[67,68] The risk-benefit profiles of TNFis need to be considered before treatment is initiated because all 4 available TNFis (adalimumab, certolizumab pegol, etanercept, and infliximab) were approved with warnings regarding the serious or life-threatening risks of infection and malignancy.[53] These include bacterial and viral infections such as tuberculosis, listeria, legionellosis, and reactivation of latent hepatitis B and tuberculosis and invasive fungal infections such as histoplasmosis and candidiasis.[54] The British Association of Dermatologists suggests that decisions regarding the use of TNFis during pregnancy be made on a case-by-case basis[69]; however, the use of certolizumab pegol in pregnant women results in minimal transplacental transport.[70] Newer agents (ustekinumab, secukinumab, ixekizumab, and apremilast) have been approved for use in PsA, and the IL-23 inhibitor guselkumab has been approved for use in psoriasis, with no warning of potential serious or life-threatening risks.[53] The safety of secukinumab has been proven through 5 years of follow-up in patients with PsA.[71] For other newer agents, long-term safety has yet to be established but is being investigated. Data evaluating the use of newer biologics during pregnancy are not yet available.

Some safety signals are associated with agents according to their particular mechanism of action. TNFis have been associated with an increased risk of congestive heart failure, and monitoring of patients with mild heart failure is required to ensure that the heart failure does not worsen.[53,54] Caution should be exercised when prescribing IL-17A inhibitors (secukinumab, ixekizumab, and brodalumab) to patients with inflammatory bowel disease (IBD), and these patients should be closely monitored.[53,54] Some cases of fungal *Candida* infection have been reported with IL-17A inhibitors.[35-39,53,54] Brodalumab has a black box warning for suicidal ideation and behavior.[53,54] Comparative safety data between biologic agents and tsDMARDs are lacking; ongoing head-to-head trials in PsA (EXCEED 1 and SPIRIT-H2H) are likely to allow comparisons at least in the short term. A reference arm of adalimumab was included in a recent trial of ixekizumab that also assessed safety; although the trial was not statistically powered to compare ixekizumab with adalimumab, the number of adverse events and serious adverse events appeared to be similar at week 24.[38]

These safety concerns must be compared with those seen with existing alternatives, particularly corticosteroids and methotrexate, the traditional mainstays of many rheumatologists. It remains to be seen whether the cost savings with these conventional therapeutics outweigh the risks with prolonged use.

Considerations for the Management or Treatment of Psoriasis With PsA

Several issues must be considered when choosing an appropriate treatment strategy to manage patients with psoriasis who have PsA as a complication. Because patients with psoriasis can have several disease domains affected, it is important to consider which manifestations are present and more pronounced in each individual. The choice of treatment should address as many facets as possible.[9] The GRAPPA treatment schema for PsA summarizes recommendations according to 6 domains to aid in appropriate individualization of treatment.[9] Conventional DMARDs are often used to treat PsA following an inadequate response to NSAIDs or local glucocorticoid injections.[8] Most of the evidence regarding conventional DMARDs relates to psoriasis and peripheral arthritis, so these drugs may not be useful in cases with axial symptoms, enthesitis, or dactylitis. Some biologics and tsDMARDs are effective in the simultaneous treatment of multiple manifestations of psoriasis and PsA.[9] Brodalumab has not demonstrated efficacy in enthesitis or dactylitis,[40] whereas secukinumab and ixekizumab appeared to improve both enthesitis and dactylitis in phase III studies.[51,72] Treatment choice should be discussed and agreed upon with the individual patient because certain aspects of psoriasis or PsA may have an overriding negative impact on an individual. For example, it may be more important for the patient to resolve skin manifestations in a prominent location of the body than focus on symptoms of peripheral arthritis or enthesitis. Still, the risk of PsA progression must be discussed. Optimal management may require a multidisciplinary approach.[9] EULAR guidelines recommend that a dermatologist be consulted in cases with major skin involvement.[8] Similarly, input from rheumatologists is likely to be beneficial in cases when PsA domains are evident. Comorbidities associated with psoriasis and PsA, such as IBD and metabolic syndrome, may further complicate the picture, and expert advice from additional specialists may be needed.[8,9]

Severity of disease is also important when considering the most appropriate treatment for psoriasis and PsA. GRAPPA guidelines for PsA state that the most severe element of disease will likely guide the choice of treatment.9 EULAR guidelines for PsA recommend bypassing traditional treatments and beginning therapy with a biologic agent when active disease is present with ≥ 1 adverse prognostic factor (including involvement of

> 5 active joints, evidence of radiographic damage, elevated acute-phase reactant levels, and the presence of extra-articular manifestations), particularly in patients with predominant axial disease or those with severe enthesitis.8

The presence and identification of comorbidities may help guide the choice of treatment.[8,9] For example, under some circumstances, it may be appropriate for patients at risk of heart failure to avoid the use of TNFis.[73] The presence of IBD may limit the use of IL-17A inhibitors due to their potential to exacerbate that disease; TNFis may be a good choice for patients with IBD because adalimumab and infliximab are approved for use in patients with Crohn disease and ulcerative colitis.[73] Caution should be taken when considering the use of TNFis in patients with a history of certain chronic or currently active viral infections, such as hepatitis B, hepatitis C, HIV, and tuberculosis,[73] although effective treatments may exist for these infections.

CONCLUSION

Psoriasis is a systemic disease resulting in a spectrum of possible extracutaneous symptoms, complications, and comorbidities, including PsA. A primary goal of PsA treatment is to improve patient quality of life and well-being by controlling symptoms, reverting or preventing further structural damage in joints, normalizing function, and improving social interaction.[8,9] The spectrum of modern biologic agents, each with unique efficacy and safety profiles, provides clinicians and patients with multiple options for treatment of the varied systemic manifestations of psoriatic disease. Consideration of the aspects of disease that have the greatest impact on the patient's everyday life, together with thoughtful choice of an appropriate treatment balancing efficacy in skin and joints, is likely to offer the most significant improvement in individual patients.

DISCLOSURES

W.A. has served on advisory boards, as a speaker, as a consultant, and as an investigator for AbbVie, Akros, Allergan, Amgen, AnaptysBio, Asana, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Encore, EPI Health, Galderma, Glenmark, GSK, Innovaderm, Janssen Biotech, Kyowa Hakko Kirin, LEO Pharma, MediMetricks, Novartis, Parexel, PharmaDerm, Pfizer, Premier, Promius, Regeneron, Sanofi, Sun Pharma, UCB, Vanda, Valeant, and Xenoport. J.S. has served on advisory boards and as an investigator for AbbVie, Boehringer Ingelheim, Celgene, Dermira, Merck, Novartis, Pfizer, and Valeant.

ACKNOWLEDGMENTS

The authors thank Victoria Kinsley, PhD, of SciMentum, Inc, and Richard Karpowicz, PhD, of Health Interactions, Inc, both of Nucleus Global, for providing medical writing support/editorial support, which was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

REFERENCES

1. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.
2. Carvalho AV, Romiti R, Souza CD, Paschoal RS, Milman LM, Meneghello LP. Psoriasis comorbidities: complications and benefits of immunobiological treatment. *An Bras Dermatol.* 2016;91(6):781-789.
3. Dhana A, Yen H, Yen H, Cho E. All-cause and cause-specific mortality in psoriasis: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2019;80(5):1332-1343.
4. Coates LC, FitzGerald O, Helliwell PS, Paul C. Psoriasis, psoriatic arthritis, and rheumatoid arthritis: is all inflammation the same? *Semin Arthritis Rheum.* 2016;46(3):291-304.
5. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64(suppl 2):ii14-ii17.
6. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol.* 2012019;80(1):251-265.e19.
7. Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs.* 2014;74(4):423-441.
8. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis.* 2016;75(3):499-510.
9. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol.* 2016;68(5):1060-1071.
10. Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. *Ann Rheum Dis.* 2005;64(suppl 2):ii74-ii77.
11. Haroon M, Winchester R, Giles JT, Heffernan E, FitzGerald O. Clinical and genetic associations of radiographic sacroiliitis and its different patterns in psoriatic arthritis. *Clin Exp Rheumatol.* 2017;35(2):270-276.
12. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol.* 2009;61(3):451-485.
13. Mason KJ, Williams S, Yiu ZZN, et al. Persistence and effectiveness of non-biologic systemic therapies for moderate-severe psoriasis in adults: a systematic review. *Br J Dermatol.* 2019 Jan 10. [Epub ahead of print].
14. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128.
15. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol.* 2015;73(3):400-409.
16. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med.* 2015;373(14):1318-1328.
17. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol.* 2017;177(4):1014-1023.
18. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541-551.
19. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.
20. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417.
21. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276-288.
22. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661.
23. Kimball A, Foley P, Thaci D, et al. Long-term efficacy and safety of guselkumab in psoriasis patients with and without psoriatic arthritis: A pooled analysis from VOYAGE 1 and VOYAGE 2. *24th World Congress of Dermatology.* 2019;Abstract.

24. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019 [Epub ahead of print].
25. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum*. 2004;50(7):2264-2272.
26. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52(10):3279-3289.
27. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum*. 2005;52(4):1227-1236.
28. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis*. 2005;64(8):1150-1157.
29. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014;73(1):48-55.
30. Cutolo M, Myerson GE, Fleischmann RM, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol*. 2016;43(9):1724-1734.
31. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016;75(6):1065-1073.
32. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. 2014;73(6):1020-1026.
33. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis*. 2014;73(6):990-999.
34. McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet*. 2013;382(9894):780-789.
35. Mease P, van der Heijde D, Landewé R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Ann Rheum Dis*. 2018;77(6):890-897.
36. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med*. 2015;373(14):1329-1339.
37. Nash P, Mease PJ, McInnes IB, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). *Arthritis Res Ther*. 2018;20(1):47.
38. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017;76(1):79-87.
39. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet*. 2017;389(10086):2317-2327.
40. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med*. 2014;370(24):2295-2306.
41. Deodhar A, Gottlieb AB, Boehncke WH, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2018;391(10136):2213-2224.
42. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;386(9999):1137-1146.
43. Mease PJ, Kellner H, Morita A, et al. OP0307 Efficacy and safety of risankizumab, a selective il-23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. *Ann Rheum Dis*. 2018;77(suppl 2):200-201.
44. Langley RG, Thaçi D, Reich K, et al. FRI0445 Tildrakizumab treatment improved measures of psoriatic arthritis in adults with chronic plaque psoriasis. *Ann Rheum Dis*. 2016;75(Suppl 2):596-597.
45. van der Heijde D, Kavanaugh A, Gladman DD, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis Rheum*. 2007;56(8):2698-2707.
46. van der Heijde D, Fleischmann R, Wollenhaupt J, et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann Rheum Dis*. 2014;73(1):233-237.
47. Kavanaugh A, Ritchlin C, Rahman P, et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis*. 2014;73(6):1000-1006.
48. Kavanaugh A, Puig L, Gottlieb AB, et al. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, placebo-controlled phase III trial. *Arthritis Care Res*. 2015;67(12):1739-1749.
49. Sterry W, Ortonne JP, Kirkham B, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *BMJ*. 2010;340:c147.
50. Gladman DD, ACCLAIM Study Investigators, Sampalis JS, Illouz O, Guerette B. Responses to adalimumab in patients with active psoriatic arthritis who have not adequately responded to prior therapy: effectiveness and safety results from an open-label study. *J Rheumatol*. 2010;37(9):1898-1906.
51. Gladman DD, Orbai AM, Klitz U, et al. Ixekizumab and complete resolution of enthesitis and dactylitis: integrated analysis of two phase 3 randomized trials in psoriatic arthritis. *Arthritis Res Ther*. 2019;21(1):38-019-1831-0.
52. Baraliakos X, Coates LC, Gossec L, et al. Secukinumab improves axial manifestations in patients with psoriatic arthritis and inadequate response to NSAIDs: primary analysis of the MAXIMISE trial. *Ann Rheum Dis*. 2019;78:195-195-196.
53. U.S. food and drug administration. U.S. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Updated 2018. Accessed August/15, 2018.
54. European medicines agency. European Medicines Agency Web site. https://www.ema.europa.eu/en/medicines. Updated 2018. Accessed August/15, 2018.
55. Deodhar A, Poddubnyy D, Pacheco-Tena C, et al. Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: 16 week results of a phase 3 randomized, double-blind, placebo controlled trial in patients with prior inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol*. 2019;71(4):599-611.
56. Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(2):258-270.
57. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet*. 2018;392(10162):2441-2451.
58. Kawalec P, Holko P, Mocko P, Pilc A. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. *Rheumatol Int*. 2018;38(2):189-201.
59. Ungprasert P, Thongprayoon C, Davis JM3. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis. *Semin Arthritis Rheum*. 2016;45(4):428-438.
60. Strand V, Betts KA, Mittal M, Song J, Skup M, Joshi A. Comparative effectiveness of adalimumab versus secukinumab for the treatment of psoriatic arthritis: a matching-adjusted indirect comparison. *Rheumatol Ther*. 2017;4(2):349-362.
61. Song GG, Lee YH. Relative efficacy and safety of apremilast, secukinumab, and ustekinumab for the treatment of psoriatic arthritis. *Z Rheumatol*. 2018;77(7):613-620.
62. Thorlund K, Druyts E, Avina-Zubieta JA, Mills EJ. Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. *Biologics*. 2012;6:417-427.
63. Migliore A, Bizzi E, Broccoli S, Lagana B. Indirect comparison of etanercept,

infliximab, and adalumimab for psoriatic arthritis: mixed treatment comparison using placebo as common comparator. *Clin Rheumatol.* 2012;31(1):193-194.
64. Kirson NY, Rao S, Birnbaum HG, Kantor E, Wei RS, Cifaldi M. Matching-adjusted indirect comparison of adalimumab vs etanercept and infliximab for the treatment of psoriatic arthritis. *J Med Econ.* 2013;16(4):479-489.
65. Nash P, McInnes IB, Mease PJ, et al. Secukinumab versus adalimumab for psoriatic arthritis: comparative effectiveness up to 48 weeks using a matching-adjusted indirect comparison. *Rheumatol Ther.* 2018;5(1):99-122.
66. Mease PJ, S. Smolen J, Behrens F, et al. Lb0005 multicentre, randomised, open-label, assessor-blinded, parallel-group head-to-head comparison of the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naive to biologic disease-modifying anti-rheumatic drugs: 24-week results. *Ann Rheum Dis.* 2019;78(Suppl 2):261-262. doi: 10.1136/annrheumdis-2019-eular.8709.
67. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and crohn's disease. *Ann Rheum Dis.* 2013;72(4):517-524.
68. Kivelevitch D, Mansouri B, Menter A. Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. *Biologics.* 2014;8:169-182.
69. Johansen CB, Jimenez-Solem E, Haerskjold A, Sand FL, Thomsen SF. The use and safety of TNF inhibitors during pregnancy in women with psoriasis: a review. *Int J Mol Sci.* 2018 May 3. [Epub ahead of print].
70. Mariette X, Forger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis.* 2018;77(2):228-233.
71. Tahir H, Mease PJ, Kavanaugh A, et al. 258 Secukinumab provides sustained improvements in the signs and symptoms in psoriatic arthritis: final 5-year efficacy and safety results from the FUTURE 1 phase 3 trial. *Rheumatology.* 2019;58(Supplement_3).
72. Gottlieb A, McInnes I, Mease P, Mpofu S. Secukinumab is effective in reducing dactylitis and enthesitis using multiple measures in patients with psoriatic arthritis. Results from two phase 3 randomized, multicenter, double-blind, placebo-controlled studies (FUTURE 1 and 2). *J Am Acad Dermatol.* 2016;74(5, S1):AB271.
73. Gossec L, Coates LC, de Wit M, et al. Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations. *Nat Rev Rheumatol.* 2016;12(12):743-750.
74. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology.* 2012;51(8):1368-1377.
75. Jensen P, Skov L. Psoriasis and obesity. Dermatology. 2016;232(6):633-639.
76. Gibson E, Nagaraja S, Ocampo A, et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. *Cell.* 2019;176:1-13.
77. Salvarani C, Macchioni P, Olivieri I, et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol.* 2001;28(10):2274-2282.
78. Sarzi-Puttini P, Santandrea S, Boccassini L, Panni B, Caruso I. The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. *Clin Exp Rheumatol.* 2001;19(1 suppl 22):S17-S20.

AUTHOR CORRESPONDENCE

William Abramovits MD
E-mail:..... dra@dermcenter.us