Psoriasis and Psoriatic Arthritis Treatment

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Abstract

Over the past several years, an increased understanding of the pathophysiology of psoriasis and psoriatic arthritis (PsA) has led to the development of several new biologic therapies. Appropriate treatment selection and timing may slow, and even halt, the progression of psoriasis and PsA; as a result, it can decrease the economic burden. As treatment options vary based on individual disease characteristics and patient preferences, reviewing the patient's complete clinical picture is imperative. An updated treatment algorithm, based on patients' most severe disease domain, is now available to guide the selection of optimal therapy. Special care should be given to patients with both psoriasis and PsA who experience multiple disease domains, a heavy symptom burden, and an increased risk of comorbidities.

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For author information and disclosures, see end of text.

Overarching Principles of Psoriasis and Psoriatic Arthritis Treatment

Several best practices have emerged to guide the management of patients with psoriasis and psoriatic arthritis (PsA). The current goals for treatment include minimizing disease activity, maintaining functional status, improving quality of life, and preventing or minimizing both disease- and treatment-related complications. The optimal choice of therapy may depend on disease severity, prognostic factors, prior treatment, comorbidities, access to therapy, and patient preferences. Multidisciplinary assessment and management are critical to addressing each aspect of PsA care. In addition, frequent monitoring and treatment adjustments will be necessary to achieve and maintain disease control.[1]

Lifestyle Modifications

Smoking and obesity are examples of risk factors that exacerbate the signs and symptoms of psoriasis and/or PsA and contribute common comorbidities, such as cardiovascular disease.[2] In addition, smoking can potentially reduce the effectiveness of anti-tumor necrosis factor-α (TNF-α) therapy.[3] Nonpharmacologic interventions, such as smoking cessation, dietary advice, weight loss counseling and physical activity, are important components of comprehensive patient care.[2] It is essential to diagnose signs or symptoms of psoriatic joint disease early to minimize, even prevent, joint destruction, as psoriatic joint disease usually takes 5 to 12 years to develop after the onset of skin psoriasis.[4]

Treat to Target

The treat-to-target (T2T) principle of PsA management involves close monitoring and frequent treatment adjustments designed to achieve early and tight control of inflammatory disease activity. In the TICOPA trial, 206 patients with newly diagnosed PsA were randomly

assigned to tight control using a T2T strategy or assigned to usual care. In the T2T arm, patients started treatment with methotrexate (MTX) that was escalated to 25 mg after 6 weeks. If patients did not achieve minimal disease activity by week 12, combination disease-modifying antirheumatic drug (DMARD) therapy was started. After another 12 weeks, patients with residual disease activity started anti-TNF therapy or switched to an alternate DMARD in combination with MTX. By comparison, patients receiving standard care were seen every 3 months by a rheumatologist but otherwise followed no set treatment protocol.[5]

After 48 weeks, 62% of patients in the T2T arm achieved a 20% improvement from baseline in the American College of Rheumatology response criteria (ACR20) compared with 45% of patients in the standard care group (odds ratio [OR], 1.91; $P = .0392$). Patients managed with the T2T strategy were also more likely than those in the standard care group to gain control of the skin manifestations of psoriasis (59% vs 33%), defined as a reduction of 75% or more from baseline in the Psoriasis Area and Severity Index score (PASI 75). Although the frequency of adverse events (AEs) increased in the tight control group relative to standard care, most patients tolerated treatment well. The most common AEs were nausea, liver function abnormalities, and respiratory tract infections. These findings support the T2T strategy to improve outcomes across multiple measures in patients with early PsA, including those with skin involvement.[5]

Comorbidity Management

Comorbidity screening and management are essential components of psoriasis and of PsA care. Several comorbidities occur with increased frequency in these patients including cardiovascular disease, diabetes, obesity, metabolic syndrome, osteoporosis, liver disease, and depression. Furthermore, patients with psoriasis and PsA are at an increased risk of exhibiting extra-articular manifestations of their underlying autoimmune disease, including inflammatory bowel disease and uveitis. Although the same comorbidity screening and management approaches apply to patients with psoriasis and PsA as to the general population, current guidelines stress the importance of identifying any comorbidities to provide optimal care for these patients.[1]

Treatment Options for Psoriasis and PsA

Multiple treatment options, ranging from local therapies (ie, topical medications and phototherapy) to nonbiologic systemic therapies (nonsteroidal anti-inflammatory drugs [NSAIDs] and traditional DMARDs) and biologics, are available for patients with psoriasis and PsA. Most clinical studies regarding psoriasis evaluate monotherapy and exclude even potent topical steroids as adjunctive therapy, whereas the majority of patients enrolled in PsA clinical studies will receive maintenance MTX, NSAIDs, and systemic steroids from the outset. In many cases, combination therapy is recommended to enhance treatment efficacy and minimize AEs.[1,6,7] For instance, combining biologic agents such as etanercept or adalimumab with MTX results in greater control of psoriasis disease activity than either agent alone. For patients experiencing psoriasis flares, the use of short-term cyclosporine in combination with other systemic or biologic agents is an effective strategy for reducing disease activity. Furthermore, the combined use of biologic therapy, especially etanercept and phototherapy, is more effective against psoriatic lesions than either modality used alone.[6] Additional combination regimens are reviewed in the following discussion of psoriasis and PsA therapies.

Local Therapies

Topical Therapies

Topical medications are the first-line treatment option for the majority of patients with psoriasis who have limited disease, which is often defined as up to 5% of the body surface area (BSA). In addition, topical therapies continue to be used in adjunct with systemic therapies in patients with extensive disease (>5% BSA) who require more aggressive intervention. Options for topical treatment include emollients, topical corticosteroids, topical vitamin D analogs (eg, calcipotriene/calcipotriol, calcitriol, and tacalcitol), retinoids (eg, tazarotene), and calcineurin inhibitors (eg, topical tacrolimus 0.1% and pimecrolimus 1%). In addition, a combination of a potent topical steroid and a vitamin D analogue in one preparation has shown to be effective. The amount of topical medication required to treat various BSA percentages can be gauged by the "fingertip unit" method, with 1 fingertip unit corresponding to approximately 2% BSA (**Figure 1**[7,8]); this corresponds to approximately 500 mg.

Multiple factors influence the choice of topical therapy, including body site, thickness and scaling of the psoriasis lesions, patient age, costs, and patient preferences. Poor adherence to topical medications is a major barrier to successful psoriasis treatment, with up to 40% of patients with psoriasis reporting nonadher-

ence due to inconvenience, time constraints, frustration with medication efficacy, unclear instructions, and fear of AEs.[7] Therefore, the successful use of topical medications requires a particular emphasis on patient education and counseling.

Phototherapy

Ultraviolet (UV) irradiation controls psoriatic skin lesions by targeting hyperproliferative epidermal cells and T-cells.[9] Phototherapy is recommended as first-line therapy for moderate to severe psoriasis when skin involvement is too extensive for topical therapy alone. In addition, phototherapy is an appropriate treatment strategy for patients with limited skin involvement, but debilitating symptoms, such as those with severe psoriasis of the palms, soles, and scalp. For patients with PsA, phototherapy is also used to manage the cutaneous manifestations of psoriatic disease.[10] Phototherapy is also appropriate in patients with contraindications to systemic treatment, such as women who are pregnant.[9]

Multiple phototherapy regimens are currently used in the outpatient setting.[9] Pretreatment with topical or oral photosensitizing agents, such as psoralen, enhances the cytotoxic effects of UVA therapy and further inhibits epidermal cell proliferation. Photochemotherapy with oral psoralen and UV-A radiation (PUVA) can lead to dramatic improvements in psoriatic skin lesions.[11] However, PUVA is less tolerated than UV-B-based phototherapy, with an increased risk of nonmelanoma skin cancer after 200 treatments. Phototherapy is cost-effective for controlling psoriatic skin lesions but is less convenient for patients because of travel time and costs associated with absence from work.[9] Thus, several home phototherapy units are available and prescribed under the guidance of dermatologists.

Nonbiologic Systemic Therapies

NSAIDs

NSAIDs play a central role in reducing inflammation and discomfort, particularly in patients with PsA with prominent axial disease, enthesitis, and dactylitis.[1]

Conventional DMARDs

Traditional DMARDs, including MTX, sulfasalazine, leflunomide, and cyclosporine, are frequently used as first-line therapies for patients with PsA.[12] In addition, these agents also form the backbone of many combination regimens for both skin and joints, such as MTX plus phototherapy for skin psoriasis, MTX plus biologic agents for skin and joints, or targeted small-molecule inhibitors. MTX is also the most commonly used systemic therapy worldwide for patients with moderate to severe psoriasis.[13] Although highly effective as short-term monotherapy for skin psoriasis, cyclosporine is not nearly as effective for PsA. Conversely, neither sulfasalazine nor leflunomide, while helpful as adjunctive therapies for PsA, has an appreciable effect on skin psoriasis.[14]

Figure 1. Topical Agent Use and the Fingertip Unit[7,8]

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Prior to initiating MTX, patients should be evaluated for potential drug–drug interactions (eg, MTX and sulfonamide-derived drugs), risk factors, and contraindications. Of note, MTX is absolutely contraindicated during pregnancy and breastfeeding. In the absence of contraindications, MTX is usually started at a dose of 10 to 15 mg/week and titrated to a maximum recommended dose of 25 mg/week. Although most patients begin treatment with oral MTX, parenteral administration is an option for patients who develop gastrointestinal intolerance, for those with an inadequate response to maximally titrated oral therapy, and in cases with high risk of nonadherence and/or dosing errors.[13] In addition, MTX as monotherapy is highly effective in less than half of patients with psoriasis. The addition of oral folic acid (1-5 mg daily) is essential with MTX therapy to minimize adverse effects.

Biologic Therapies

The development of biologic therapies targeting key molecules involved in disease pathogenesis has revolutionized the treatment of moderate to severe psoriasis and PsA.[15] Biologics can be classified as large molecules (eg, monoclonal antibodies), which must be given by injection or infusion, and small molecules, which are given orally.[16] The contraindications, precautions, and common AEs of each treatment option should be considered when selecting biologic therapy for patients with psoriasis and PsA (Table 1[17-26]).

Table 1. Biologic Treatments for Psoriasis and PsA[17-26]

Drug	Target	FDA Approved Indication(s)	Usual Adult Dose
Adalimumab Approved in 2005 for PsA and 2008 for psoriasis	TNF-α	Reducing signs and symptoms, inhibiting structural damage, and improving physical function in adults with active PsA Plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, and when other therapies are medically less appropriate	PsA: SC 40 mg starting dose administered every other week Psoriasis: SC 80 mg initial dose, then 40 mg every other week starting 1 week after the initial dose
Certolizumab pegol Approved in 2013 for PsA	TNF-α	Adults with active PsA	SC 400 mg starting dose at weeks 2 and 4, followed by 200 mg every other week; 400 mg every 4 weeks can be considered for maintenance dosing
Etanercept Approved in 2002 for PsA and 2004 for psoriasis	TNF-α	PsA with or without MTX Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	PsA: SC 50 mg weekly starting dose with or without MTX Psoriasis: SC 50 mg twice weekly starting dose for 3 months, followed by 50 mg once weekly
Golimumab Approved in 2009 for PsA	TNF-α	Adult patients with PsA used alone or in combination with MTX	SC 50 mg once per month; may be given with or without MTX or other nonbiologic DMARDs
Infliximab Approved in 2005 for PsA and 2006 for psoriasis	TNF-α	Reducing signs and symptoms of active PsA, inhibiting the progression of structural damage, and improving physical function Chronic severe plaque psoriasis in adults who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	For PsA and psoriasis: IV 5 mg/kg over ≥2 hours at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter
Ustekinumab Approved in 2009 for psoriasis and 2013 for PsA	IL-12/ IL-23	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy PsA alone or in combination with MTX	PsA: SC 45 mg at week 0 and 4, then 45 mg every 12 weeks PsA and moderate to severe psoriasis: SC 90 mg at week 0 and 4, then 90 mg every 12 weeks in patients weighing >100 kg (>220 lbs) Psoriasis: SC 45 mg at week 0 and 4, then 45 mg every 12 weeks for patients weighing ≤100 kg (≤ 200 lbs); 90 mg at week 0 and 4, then 90 mg every 12 weeks for patients weighing >100 kg (>220 lbs)
Secukinumab Approved in 2015 for psoriasis and in 2016 for PsA	IL-17A	Adults with active PsA Adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	PsA: SC with loading dose: 150 mg at weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter; without loading dose: 150 mg every 4 weeks; consider 300 mg for patients who continue to have active PsA Use psoriasis dosing for patients with PsA and comorbid moderate to severe psoriasis Psoriasis: SC 300 mg at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable
Ixekizumab Approved in 2016 for psoriasis	IL-17A	Adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	SC 160 mg (two 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks
Apremilast Approved in 2014 for psoriasis and PsA	PDE4	Adults with active PsA Patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Oral 10 mg/day starting dose titrated to 30 mg twice daily Reduced dose of 30 mg once daily in severe renal impairment

DMARD indicates disease-modifying antirheumatic drug; HBV, hepatitis B virus; IBD, inflammatory bowel disease; IL, interleukin; IV, intravenous; MTX, methotrexate; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; RPLS, reversible posterior leukoencephalopathy syndrome; SC, subcutaneous; TB, tuberculosis; TNF, tumor necrosis factor.

Table 1. Biologic Treatments for Psoriasis and PsA[17-26] (*continued*)

How Supplied	Contraindications/Precautions	Most Common Adverse Events
Single-use prefilled pens (40 mg/0.8 mL, 40 mg/0.4 mL) and single-use prefilled glass syringes (40 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.4 mL, 10 mg/0.2 mL)	**Contraindications:** none **Precautions:** serious infections, invasive fungal infections, cancers, anaphylaxis or serious allergic reactions, HBV reactivation, demyelinating disease, cytopenias, heart failure, lupus-like syndrome	Infections, injection-site reactions, headache, rash
200 mg lyophilized powder for reconstitution in a single-use vial, with 1 mL sterile water; 200 mg/mL solution in a single-use prefilled syringe	**Contraindications:** none **Precautions:** serious infections, invasive fungal infections, lymphoma and other cancers, heart failure, anaphylaxis or serious allergic reactions, HBV reactivation, demyelinating disease, cytopenias, lupus-like syndrome	Upper respiratory tract infection, rash, urinary tract infections
50 mg single-use prefilled syringe, 40 mg single-use prefilled autoinjector, 25 mg single-use prefilled syringe, 25 mg multiple-use vial	**Contraindications:** sepsis **Precautions:** active infections, invasive fungal infections, demyelinating disease, lymphoma, heart failure, cytopenias, HBV reactivation, anaphylaxis or serious allergic reactions, lupus-like syndrome, autoimmune hepatitis	Infections and injection-site reactions
50 mg/0.5 mL and 100 mg/1 mL single-dose prefilled autoinjector; 50 mg/0.5 mL and 100 mg/1 mL single-dose prefilled syringe	**Contraindications:** none **Precautions:** serious infections, invasive fungal infections, HBV reactivation, lymphoma and other cancers, heart failure, demyelinating disease, lupus-like syndrome, anaphylaxis or serious allergic reactions	Upper respiratory tract infection, nasopharyngitis, injection-site reactions
100 mg lyophilized infliximab in 20 mL vial for IV infusion	**Contraindications:** doses >5 mg/kg in moderate to severe heart failure; previous severe hypersensitivity reactions to infliximab or inactive components **Precautions:** serious infections, invasive fungal infections, lymphoma and other cancers, HBV reactivation, hepatotoxicity, heart failure, cytopenias, hypersensitivity, demyelinating disease, lupus-like syndrome, live vaccines or therapeutic infections agents	Infections, infusion reactions, headache, abdominal pain
45 mg/0.5 mL and 90 mg/mL single-use prefilled syringes; 40 mg/0.5 mL and 90 mg/mL single-use vials	**Contraindications:** clinically significant hypersensitivity to ustekinumab or inactive components **Precautions:** serious infections, other infections, TB, cancers, anaphylaxis or other hypersensitivity, RPLS	Nasopharyngitis, upper respiratory tract infection, headache, fatigue
150 mg/mL in single-use pen and single-use prefilled syringe	**Contraindications:** serious hypersensitivity to secukinumab or inactive components **Precautions:** serious infections, TB, IBD, hypersensitivity; should not be given with live vaccines	Nasopharyngitis, diarrhea, upper respiratory tract infection, oral candidiasis, and Crohn's and ulcerative colitis exacerbation
80 mg/ml solution in a single-dose prefilled autoinjector or prefilled syringe	**Contraindications:** hypersensitivity to ixekizumab or any components **Precautions:** infections, TB, hypersensitivity, IBD; should not be given with live vaccines	Injection-site reactions, upper respiratory tract infections, nausea, tinea infections, oral candidiasis, and Crohn's and ulcerative colitis exacerbation
10-mg, 20-mg, 30-mg tablets	**Contraindications:** hypersensitivity to apremilast or any components **Precautions:** depression, weight decrease, drug interactions with strong cytochrome P450 inducers	**PsA:** diarrhea, nausea, headache **Psoriasis:** diarrhea, nausea, upper respiratory tract infection, headache

DMARD indicates disease-modifying antirheumatic drug; HBV, hepatitis B virus; IBD, inflammatory bowel disease; IL, interleukin; IV, intravenous; MTX, methotrexate; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; RPLS, reversible posterior leukoencephalopathy syndrome; SC, subcutaneous; TB, tuberculosis; TNF, tumor necrosis factor.

TNF Inhibitors

Five TNF inhibitors are currently available for the treatment of PsA: etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Most anti-TNF therapies are available for subcutaneous injection, except infliximab, which is given by intravenous infusion.[15]

Therapies targeting TNF reduce the signs and symptoms of joint disease in the majority of patients with PsA.[15] TNF inhibitors are also effective at addressing extra-articular manifestations of PsA, including skin involvement, axial disease, enthesitis, and dactylitis.[11] Long-term treatment with anti-TNF agents also reduces the need for glucocorticoid therapy for PsA over time. In one study of biologic-naïve patients with PsA (N = 420), 49.6% were taking glucocorticoids at baseline. After starting anti-TNF therapy (adalimumab, etanercept, or infliximab), the rate of glucocorticoid use decreased to 36.5% at 2 years, 29.9% at 3 years, and 22.6% at 4 years. Moreover, among patients taking prednisone, the average daily dose significantly decreased from 5.6 mg at baseline to 4 mg at 4 years.[27]

Adalimumab, etanercept, and infliximab are also approved for the treatment of psoriasis. In an analysis of real-world registry data (N = 6059), 57% of patients with moderate to severe psoriasis achieved clear/almost clear status by Physician's Global Assessment (PGA) after 12 months of treatment with adalimumab; this increased to 65% of patients after 60 months of treatment.[28] In another observational registry study of etanercept in patients with moderate to severe psoriasis (N = 2510), 51% of patients achieved clear/almost clear status by month 6 of treatment and remained stable throughout 5 years of follow-up.[29] Long-term postmarketing surveillance data confirmed the safety of anti-TNF therapy in patients with psoriasis, with no new safety signals emerging after 5 years of treatment.[28,29]

Ustekinumab

New insights into the pathogenesis of psoriasis and PsA led to the identification of novel therapeutic targets across different biologic pathways, including interleukin (IL)-12, IL-23, and IL-17. Ustekinumab, a fully human monoclonal antibody directed against IL-12/23, was the first of these novel targeted therapies to be approved for the treatment of psoriasis and PsA.[15] In 2 phase 3 trials in patients with psoriasis, the majority of patients treated with ustekinumab 45 mg or 90 mg achieved a PASI 75 response after 12 weeks of therapy compared with less than 4% of patients given placebo.[30,31] Ustekinumab is also effective in patients with moderate to severe psoriasis who had an inadequate response to prior TNF inhibition, with approximately 50% of patients achieving a PASI 50 response or better within 28 weeks of switching to ustekinumab.[32]

Ustekinumab demonstrated clinical efficacy in PsA in 2 phase 3 randomized trials. In the first randomized, placebo-controlled, phase 3 trial of patients with active PsA (N = 615), 42% and 50% of patients treated with ustekinumab 45 mg or 90 mg, respectively, achieved an ACR20 response after 24 weeks compared with 23% of patients in the placebo group (P <.001).[33] In another phase 3 trial of patients with active PsA despite prior treatment with conventional DMARD or biologic therapy (N = 312), treatment with ustekinumab 45 mg or 90 mg was shown to significantly improve quality of life and physical functioning in addition to reducing the clinical signs and symptoms of PsA compared with placebo.[34]

IL-17 Inhibitors

The IL-17 signaling pathway plays an important role in the pathogenesis of psoriasis. IL-17 is a proinflammatory cytokine that acts on a wide range of cells, including keratinocytes. It is richly expressed in psoriatic skin lesions and in the synovial fluid of patients with PsA. Targeted therapies that block the activity of IL-17 show potent efficacy in controlling the underlying disease activity associated with psoriasis and PsA.[15]

Secukinumab

Secukinumab, a highly selective, fully human immunoglobulin monoclonal antibody directed against the IL-17A cytokine, is currently approved for the treatment of psoriasis and PsA.[18] A phase 1 proof-of-concept trial confirmed the role of IL-17A as an important therapeutic target in patients with psoriasis. After a single dose of secukinumab 3 mg/kg, patients demonstrated a 58% reduction from baseline in the mean PASI score. By week 12, patients treated with secukinumab maintained a 63% reduction in mean PASI scores compared with a 9% reduction in the placebo group (P = .0005). In addition, an analysis of skin biopsies revealed decreased production of inflammatory chemokines/cytokines and a reduction in T-cell infiltration, supporting the mechanistic rationale of IL-17A inhibition in controlling psoriasis disease activity.[35]

Two subsequent randomized, double-blind, phase 3 trials established the safety and efficacy of secukinumab in plaque psoriasis. Patients with moderate to severe psoriasis (N = 2044) were randomly assigned to treatment with subcutaneous secukinumab (150 or 300 mg

once weekly for 5 weeks, then every 4 weeks), placebo, or etanercept (50 mg twice weekly for 12 weeks, then once weekly) for 52 weeks. After 12 weeks, 67% to 81% of patients in the secukinumab groups experienced either clear or almost clear skin compared with less than 5% of patients in the placebo group and 44% of patients treated with etanercept (*P* <.001 for each comparison with secukinumab). Moreover, 51% to 65% of patients treated with secukinumab achieved a PASI 75 response at week 12 compared with less than 3% of patients in the placebo group and 27% of those treated with etanercept (*P* <.001 for each comparison with secukinumab). In both trials, the rate of infection in the secukinumab group was higher than with placebo and similar to that with etanercept.[36] In early 2015, secukinumab became the first IL-17A inhibitor approved for the treatment of moderate to severe plaque psoriasis.

In 2016, the FDA expanded the secukinumab indication to include PsA treatment based on findings from the phase 3 FUTURE 1 and FUTURE 2 trials.[37-39] In the FUTURE 1 trial (N = 606), 50.0% and 50.5% of patients treated with secukinumab 150 mg or secukinumab 75 mg, respectively, achieved an ACR20 response by week 24 compared with 17.3% of patients in the placebo group (*P* <.001 for both comparisons).[37] In a follow-up analysis of the FUTURE 1 trial, secukinumab was also associated with a significant reduction in radiographic progression of structural joint damage relative to placebo through 52 weeks of treatment. The FUTURE 2 trial compared 3 doses of secukinumab (300, 150, and 75 mg) with placebo in 397 patients with PsA.[38] After 24 weeks, the ACR20 response rates were significantly higher across all secukinumab dosing groups compared with placebo. In particular, patients were 6-fold more likely to achieve an ACR20 response in the 2 highest-dosing groups, secukinumab 300 mg (54%; OR, 6.8; *P* <.0001) or secukinumab 150 mg (51%; OR, 6.5; *P* <.0001) than with placebo (15%).[39] In both trials, secukinumab was associated with an increased risk of infection relative to placebo.[37-39]

Ixekizumab

Ixekizumab is the most recent (2016) anti–IL-17A monoclonal antibody to join the psoriasis treatment armamentarium. Treatment with ixekizumab was initially evaluated in a dose-finding phase 1 trial of 40 patients with psoriasis. Across all dosing groups (5, 15, 50, and 150 mg), ixekizumab demonstrated significant dose-dependent reductions in the clinical presentation of psoriasis, including reductions in keratinocyte proliferation and hyperplasia. Patients treated with the 2 highest doses of ixekizumab (50 mg and 150 mg) achieved near normalization of skin after 6 weeks of treatment, confirmed by biopsy analysis.[40] Subsequent trials with ixekizumab showed greater efficacy than placebo and etanercept, with results seen as early as the first week on ixekizumab treatment. In addition, rapid and significant improvements in itch severity and quality of life were observed.[41]

In 2016, the FDA approved ixekizumab for the treatment of moderate to severe plaque psoriasis based on findings from the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials, which evaluated ixekizumab in patients with moderate to severe plaque psoriasis (N = 3866). Overall, 87% to 90% of patients achieved a PASI 75 response by week 12, which was sustained through 60 months of treatment. The most common AEs were nasopharyngitis, upper respiratory tract infection, injection-site reaction, and headache.[41-43] Ixekizumab was also shown to significantly improve short- and long-term work productivity, which is an important end point for patients that influences the cost burden of psoriasis.[42]

Ixekizumab is currently under evaluation for the treatment of PsA. One recent phase 3 trial compared ixekizumab 80 mg every 2 weeks or every 4 weeks, adalimumab 40 mg every 2 weeks, and placebo in patients with PsA who were naïve to biologic therapy (N = 417). After 24 weeks, 58% to 62% of patients treated with ixekizumab achieved an ACR20 response compared with 30% of those in the placebo group (*P* <.001). In the adalimumab group, 57% of patients achieved an ACR20 response. These findings support the potential role of ixekizumab given every 4 weeks in the treatment of active PsA, which represents improved convenience for patients when compared with standard biweekly treatment.[44]

Brodalumab

Whereas secukinumab and ixekizumab neutralize IL-17A, brodalumab blocks its receptor (IL-17RA). In a phase 1 proof-of-concept study, brodalumab showed a dose-dependent improvement in the clinical signs and symptoms of moderate to severe plaque psoriasis. Brodalumab also demonstrated a rapid reversal of adverse gene expression and histopathologic abnormalities, supporting the rationale for IL-17A–receptor blockade in psoriasis.[45] Brodalumab has been shown to significantly improve the clinical signs and symptoms of psoriasis and PsA.[46-48] However, the clinical development of brodalumab has been complicated by safety concerns, particularly rare reports of suicidal ideation in these

patient populations.[49] The Biologics License Application for brodalumab in moderate to severe psoriasis is currently under review with the FDA; it has an expected action date of November 16, 2016.[50]

Small-Molecule Inhibitors

Small molecular weight inhibitors of inflammatory mediators are another option for targeting the pathogenesis of psoriasis and PsA. With oral bioavailability, this therapeutic class represents improved convenience and the potential for improved adherence among patients with reservations regarding injectable therapy.[12]

Apremilast

Apremilast is an oral inhibitor of phosphodiesterase 4 that indirectly down-regulates the inflammatory response by enhancing the expression of anti-inflammatory cytokines while suppressing the activity of pro-inflammatory cytokines.[51,52] In March 2014, apremilast became the first oral biologic drug approved for the treatment of active PsA. Later that year, in September 2014, the FDA expanded the indication for apremilast to include treatment of moderate to severe plaque psoriasis in patients for whom phototherapy or systemic therapy is appropriate.[51]

The approval of apremilast in PsA and plaque psoriasis was based on the phase 3 PALACE and ESTEEM clinical trial programs.[52] PALACE 1 evaluated apremilast in 504 patients with active PsA despite standard treatment with synthetic DMARDs or biologic therapy. At week 16, approximately 30% and 40% of patients treated with apremilast 20 or 30 mg twice daily, respectively, achieved an ACR20 response compared with approximately 20% of those in the placebo group (P <.001).[53] The ESTEEM 1 trial compared apremilast 30 mg twice daily or placebo in 844 patients with moderate to severe plaque psoriasis. After 16 weeks, 33% of patients in the apremilast group achieved a 75% or greater reduction in the PASI score compared with 5% of patients in the placebo group (P <.0001).[54] Focusing on concomitant PsA and psoriasis, the PALACE 3 trial evaluated apremilast in 505 patients with PsA and current skin involvement. Treatment with apremilast 20 or 30 mg twice daily was associated with clinically meaningful improvements in both PsA and psoriasis measures by week 16, and sustained improvements continued through week 52.[51] Apremilast was well tolerated and exhibited a highly acceptable safety profile. Up to 17% of patients develop gastrointestinal AEs in the first month of therapy.[51-54] However, no laboratory monitoring of patients on apremilast is required.

Tofacitinib

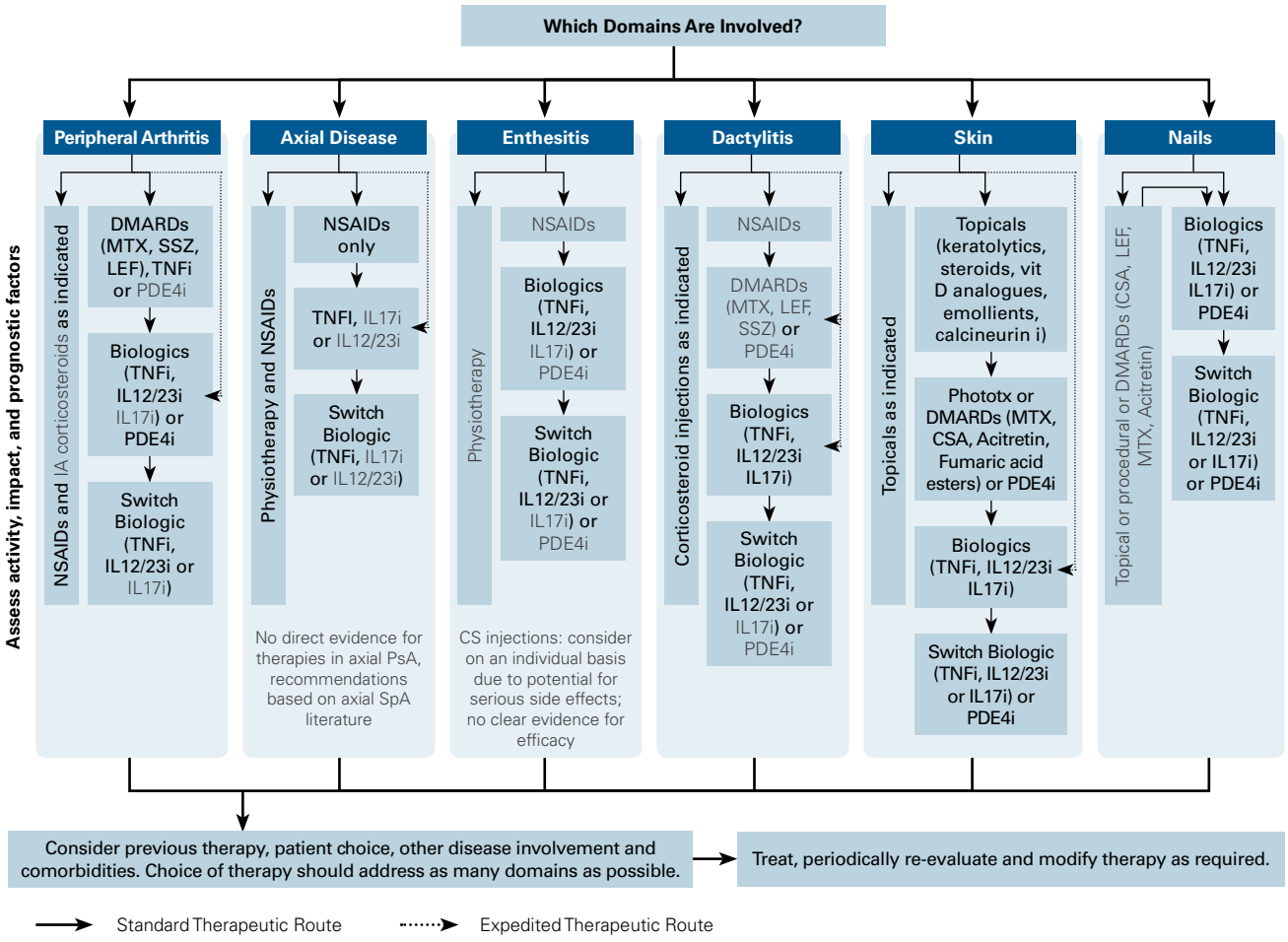
Tofacitinib is a novel oral Janus kinase (JAK) inhibitor currently approved for the treatment of rheumatoid arthritis; it shows promising activity in both psoriasis and PsA.[16,55] In a placebo-controlled phase 2 trial of patients with moderate to severe psoriasis (N = 197), twice-daily treatment with tofacitinib 2, 5, or 15 mg was associated with significant dose-dependent improvements in multiple patient-reported outcomes, including dermatology-related quality of life, itch severity, and Short Form-36 psychological and physical domains.[55]

Two recent identical phase 3 trials confirmed the safety and efficacy of tofacitinib in patients with psoriasis. In total, 1861 patients were randomly assigned 2:1 to treatment with oral tofacitinib (5 or 10 mg) or placebo twice daily. After 28 weeks, 55.6% and 68.8% of patients in the tofacitinib 5-mg and 10-mg groups, respectively, achieved a PASI 75 response; 54.7% and 65.9% of patients, respectively, achieved clear/almost clear status by PGA. Treatment efficacy was sustained in most patients through 24 months. The most common AEs were nasopharyngitis (18.8%) and upper respiratory tract infection (12.6%). Overall, 10.1% of patients developed serious AEs, and 10.7% discontinued treatment due to AEs.[56]

In a phase 3 noninferiority trial, tofacitinib 10 mg twice daily was noninferior to etanercept 50 mg twice weekly and superior to placebo in terms of PASI 75 response and clear/almost clear PGA response in patients with moderate to severe plaque psoriasis. The safety analysis showed similar AE rates at 12 weeks in patients treated with tofacitinib or etanercept, with 2% of patients developing serious AEs and 1% to 3% of patients discontinuing treatment due to AEs.[57]

In patients with PsA, tofacitinib appears to reduce synovial inflammation and other markers of PsA disease activity.[58] In a randomized, double-blind, phase 3 trial of patients with psoriasis and/or PsA (N = 99), treatment with tofacitinib 5 mg or 10 mg twice daily was associated with high response rates, as measured by PASI 75 response (63% and 73%, respectively) and a clear/almost clear PGA response (67% to 68%). In addition, all patients with PsA (N = 12) achieved an ACR20 response by treatment week 12. Four patients (4.3%) developed serious AEs, including 3 cases of herpes zoster infection.[59] Overall, these findings support the potential therapeutic role of JAK inhibition in patients with PsA (similar to rheumatoid arthritis, for which tofacitinib FDA approved). A topical formulation of tofacitinib ointment is currently under development for the treatment of chronic plaque psoriasis.[60]

Figure 2. 2016 GRAPPA Treatment Algorithm for PsA[1]



Light text indicates conditional recommendations for investigational agents or recommendations based on limited clinical data.
CS indicates corticosteroid; CSA, cyclosporin A; DMARDs, disease-modifying antirheumatic drugs; IA, intraarticular; IL-12/23i, interleukin-12/23 inhibitor; LEF, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal antiinflammatory drugs; PDE-4i, phosphodiesterase 4 inhibitor; phototx, phototherapy; SpA, spondyloarthritis; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitor; vit, vitamin.
Printed with permission from 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. doi: 10.1002/art.39573.

Treatment Selection in Practice: 2016 GRAPPA PsA Treatment Algorithm

In 2016, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published updated guidelines on the management of patients with PsA, including those with psoriasis. The new guidance defines the 6 major domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin involvement, and nail disease. While many patients with PsA exhibit multiple manifestations, the selection of therapy should be driven by the most severe component of each patient's clinical presentation (Figure 2[1]).[1]

Peripheral Arthritis

Traditional DMARDs and biologic therapies are strongly recommended for the treatment of PsA. In particular, biologics should be initiated early in patients with poor prognostic factors, such as high inflammatory markers and multiple active joints. For patients with an inadequate response to their first biologic therapy, switching to a second biologic agent is recommended. The GRAPPA guideline supports the conditional use of NSAIDs and corticosteroids to control the signs and symptoms of PsA but also indicates that these agents should be used with caution due to the potential for AEs.

Table 2. Considerations for Systemic Therapy in Psoriasis and PsA[16]

Patient Characteristic	Considerations
Extent or severity of psoriasis	Systemic therapy typically reserved for patients with >10% BSA, or with skin involvement in areas that significantly decrease quality of life
Presence of PsA	Consider systemic therapy, regardless of skin involvement
Woman of childbearing potential	Poor candidate for most oral psoriasis medications
Man attempting to conceive a child	Poor candidate for methotrexate
Chronic or binge alcohol use	Avoid therapies with significant risk of hepatotoxicity
History of hepatitis	Avoid therapies with significant risk of hepatotoxicity
History of hematologic malignancy	Use immunosuppressant therapy with caution
Immunodeficiency	Avoid immunosuppressant therapy
Smoker	Counsel on quitting and refer for smoking cessation

BSA indicates body surface area; PsA, psoriatic arthritis.
Reprinted from *Dermatol Clin*, 33(1), Kelly JB III, Foley P, Strober BE, Current and future oral systemic therapies for psoriasis, 91-109, Copyright (2015), with permission from Elsevier.

If needed, corticosteroids should be given in the lowest doses (eg, <7.5 mg/day) and for short periods of time to provide symptomatic control.[1]

Axial Disease

Given the lack of clinical trial data in PsA-specific axial disease, the GRAPPA recommendations rely on experience in ankylosing spondylitis. Appropriate first-line therapy for axial disease can include NSAIDs, sacroiliac injections, and physiotherapy. However, traditional DMARDs show poor efficacy against axial manifestations. Therefore, patients with PsA with predominant axial disease who require treatment intensification should consider early initiation of anti-TNF therapy.[1]

Enthesitis

Standard first-line treatment for enthesitis involves NSAIDs. As with axial disease, there is a lack of evidence to support the use of DMARDs to treat enthesitis. Therefore, for patients with an inadequate response to NSAIDs alone, biologics are the recommended second-line therapies. In that group, TNF inhibitors and ustekinumab appear to be highly effective in reducing the tendon and ligament inflammation characteristic of enthesitis. Preliminary evidence also supports the use of secukinumab and apremilast to treat enthesitis in patients with PsA.[1]

Dactylitis

Traditional DMARDs are recommended as first-line therapy for patients with dactylitis. If needed, corticosteroid injections are also effective at controlling digit inflammation. Clinical trial data support the use of biologic therapies, particularly TNF inhibitors, ustekinumab, secukinumab, and apremilast. To date, however, there is little evidence to guide further treatment adjustments for patients with an inadequate response to initial biologic therapy.[1]

Skin Involvement

Topical medications are recommended for the first-line treatment of psoriasis, particularly in patients with mild and/or limited disease. Phototherapy and DMARDs provide improved control of psoriatic skin lesions; they should be considered for use in combination with topical medications as initial treatment in patients with more extensive disease. Systemic and biologic therapies are the next step for patients with widespread skin involvement who experience an inadequate response to topical medications, DMARDs, and phototherapy. Until patients find a combination regimen that provides optimal disease control, switching among DMARDs and biologic agents may be necessary.[1]

Nail Disease

Patients with PsA and moderate to severe nail disease respond well to first-line treatment with TNF inhibitors and other biologics, including ustekinumab, anti-IL17 therapy, and apremilast. For patients with milder psoriatic nail disease or contraindications to biologic therapy, treatment options include topical medications, nonbiologic DMARDs, and intralesional corticosteroid injections.[1]

Preventing Complications

Preventing complications in patients with psoriasis and PsA begins with a thorough medical history, with a review of systems covering cutaneous, musculoskeletal, immune, hematologic, cardiac, gastrointestinal, neurologic, reproductive, and family and social history.[16] When selecting systemic therapy, the contraindications, precautions, and side-effect profiles of each agent should be considered (Table 1[17-26]). Clinicians should consider risk-aversion strategies, such as avoiding therapies with a significant risk of liver toxicity in patients with chronic alcohol use or a history of hepatitis (Table 2[16]). The potential for

drug–drug interactions should be assessed and addressed. Patient education and counseling can ensure that patients are willing to attempt the prescribed therapy and have realistic expectations regarding efficacy, tolerability, cost, and convenience.[16]

Table 3. Additional Resources for Pharmacists

Resource Description	Website/Link
Article on patient adherence from *The Pharmaceutical Journal*: "Promoting compliance in psoriasis"	http://www.pharmaceutical-journal.com/careers/career-feature/promoting-compliance-in-psoriasis/11067727.article
Article from the National Psoriasis Foundation: "Traditional systemic medications"	https://www.psoriasis.org/about-psoriasis/treatments/systemics
Patient education booklets from the National Psoriasis Foundation	https://www.psoriasis.org/publications/patient-education/booklets

Addressing Patient Treatment Obstacles

Nearly 40% of patients with psoriasis are untreated in current clinical practice, and over half of those with severe disease are treated with inadequate therapy (Table 3).[61] Even when patients are prescribed guideline-based therapy, adherence is often poor, leading to reduced treatment efficacy.[62] For many patients with psoriasis, correct use of topical medications can be time-consuming and burdensome. In one survey of nearly 18,000 patients with psoriasis, patients spent an average of 26 minutes per day applying topical agents.[63] Poor adherence can lead to reduced treatment efficacy and the need for more aggressive and/or costly therapy. To support adherence, it is important to select a first-line treatment regimen with enough potency to achieve a favorable clinical response.[7]

Addressing comorbidities and incorporating patients' preferences regarding treatment is essential while also improving adherence. One study showed that comorbidities significantly influenced preferences for treatment among patients with psoriasis. Patients with comorbid PsA prioritized treatment efficacy, while those with cardiovascular disease were primarily concerned with the risk of side effects. Among patients with comorbid depression, the duration and cost of treatment were key treatment concerns.[64] Furthermore, it is important to note that patient preferences may change over time, and treatment adjustments may be needed to reflect changing treatment goals.[65]

Conclusion

Multiple treatment options are now available to relieve symptoms, protect physical function, and improve quality of life for patients with psoriasis and PsA. Many patients with moderate to severe disease will require combination regimens that may include traditional DMARDs and biologic therapies to provide appropriate control of inflammatory disease activity. To ensure that optimal therapy is provided, clinicians should take time to discuss the true burden of disease with their patients, including the degree to which their disease interferes with both their physical, as well as mental, health. Effective communication allows patients to have an active role in treatment decisions based on expectations about efficacy, AEs, convenience, and tolerability.

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