Targeted therapies for psoriatic arthritis: an update for the dermatologist

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Abstract

Dermatologists are on the front line to identify psoriatic arthritis (PsA) in their patients with psoriasis. PsA is a prevalent and underdiagnosed disease with potential long-term complications and sequelae for patients. Targeted biologics have transformed the landscape of psoriasis and PsA therapy. These medications vary in clinical manifestations of psoriatic disease: skin psoriasis, peripheral and axial arthritis, enthesitis, and nail disease. With many new medications either on the market or currently being evaluated by the Food and Drug Administration, the purpose of this article is to review PsA for the dermatologist, to identify the current therapies that are available, and to help select which patients may benefit from these medications. Overall, it is important to decide therapy for patients based on the active domains of their disease, their comorbidities, and the safety profiles of these medications, as well as patient preference for route of administration, frequency, and tolerability.

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Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disorder occurring in up to a third of psoriasis patients that frequently requires targeted treatment based on clinical manifestations, symptom severity, comorbidities, and other factors. Individuals with PsA typically experience stiffness, pain, swelling, and tenderness of affected joints and surrounding sites of ligament and tendon insertion, known as entheses. The severity of PsA ranges from mild—resulting in a nondestructive arthritis—to a more severe and potentially erosive and destructive arthropathy. PsA often leads to impairment in function and a reduced quality of life, further compounded by psoriatic skin disease and numerous associated comorbidities.

As the first-line providers for psoriasis patients, it is of particular importance that dermatologists identify and screen for PsA early because early treatment has been shown to reduce damage and improve quality of life. Although diagnostic criteria have not been validated, classification criteria—known as the Classification Criteria for Psoriatic Arthritis (CASPAR), published in 2006 for the purpose of enrolling patients into clinical trials—do exist. These criteria include a personal or family history of psoriasis, psoriatic nail dystrophy, negative test for rheumatoid factor (RF), presence or a history of dactylitis, and radiographic evidence of juxta-articular new bone formation.

Once PsA is identified, it is important to make treatment considerations that address the aspects of both the musculoskeletal as well as the skin components of disease. There are 3 major classes of disease-modifying anti-rheumatic drugs (DMARDs): conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX) and sulfasalazine (SSZ), biological DMARDs (bDMARDs) such as tumor necrosis factor alpha inhibitors (TNFis), and targeted synthetic (tsDMARDs) such as phosphodiesterase (PDE)-4 inhibitors and Janus kinase (JAK) inhibitors. While csDMARDs are frequently considered first line, there is a relative paucity of high-quality controlled clinical trial data supporting their use in PsA. It is of particular importance for the dermatologist to recognize that not every skin therapy adequately or equally treats every domain of psoriatic musculoskeletal disease. For these reasons, targeted therapy has recently emphasized the increasing use of bDMARDs and tsDMARDs in PsA.

In many respects, targeted biologics have transformed the landscape of psoriasis and PsA treatment. These medications have demonstrated an ability to effectively treat all clinical manifestations of PsA and psoriasis, including arthritis, enthesitis, dactylitis, and spondylitis, as well as skin and nail disease.

With many new medications on the market or currently being evaluated by the Food and Drug Administration (FDA), the purpose of this article is to review PsA considerations for the dermatologist, to identify current therapies available, and to identify which patients may benefit from these medications.

Clinical manifestations

In addition to skin and nail manifestations, relevant domains of PsA include peripheral arthritis, enthesitis, dactylitis, and spondyloarthritis. To review, enthesitis is inflammation at the sites of ligament or tendon insertion into bone and is observed in 30% to 50% of patients with PsA, most often involving the Achilles tendon. Dactylitis, which is often referred to as a “sausage digit,” is inflammation of the entire digit. Dactylitis is most common in the third and fourth toes, although involvement of the fingers is commonly reported (Figure). It is believed that dactylitis is more commonly associated with severe PsA. Spondylitis refers to inflammation of the spine and/or sacroiliac joints.

Five clinical PsA phenotypes have been described. The oligoarticular subtype, which has been estimated to occur in 50% of patients, is one in which 4 or fewer joints are affected, typically in an...
Psoriatic Arthritis Screening Questionnaire.26,27 We believe that the goal should be to screen all patients with psoriasis for PsA. Furthermore, we do encourage comanagement of patients with suspected joint disease with the rheumatologist.

PsA is a clinical diagnosis that relies on a thorough history and physical exam. Other data can be helpful, including laboratory testing for RF and anti-cyclic citrullinated peptide. These tests will be negative in as many as 95% of patients with PsA, although 8% to 12% of patients may have low-titer positive markers.25 Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are often sent and may be elevated in 40% of patients. Normal inflammatory markers do not rule out active PsA, and elevated inflammatory markers may be associated with more erosive and progressive disease.25

Radiographs may be helpful to aid in the diagnosis because radiographs of peripheral joints may show evidence of erosion and joint space narrowing. Other sensitive findings include the presence of new bone formation, such as bony ankyloses and enthesophytes. Increasingly, ultrasound is being used to help aid in the diagnosis of enthesitis.28

Outcome measures for PsA

The American College of Rheumatology 20 response (ACR 20) is the most common primary endpoint used in the evaluation of PsA. The ACR 20 is a composite response measure developed for RA; achieving this score requires an improvement of at least 20% in tender and swollen joint counts and a 20% improvement in 3 out of 5 criteria from baseline to the end of the exam period. These 5 criteria are patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, the Health Assessment Questionnaire, and an inflammatory marker (ESR or CRP).22 The ACR 20 has been validated as a discriminative outcome measure in PsA.29,30

It is important to note that the improvements in joint symptoms in PsA are typically less substantial than the improvements seen in skin symptoms. This is demonstrated by a comparison of the standard benchmarks for joint and skin symptoms. ACR 20, which quantifies a 20% improvement in joint symptoms, is the standard benchmark for improvement in joint symptoms, whereas the Psoriasis Area and Severity Index (PASI) 75, which represents a 75% improvement in skin symptoms, is the standard benchmark for cutaneous disease.31

We would like to note that ACR 20 does fail to capture many of the domains of PsA, including enthesitis and spondylitis. There are several other composite scores that do account for more disease domains. The Composite Psoriatic Disease Activity Index

FIGURE. Dactylitis, inflammation of the entire digit.
accounts for disease involvement in peripheral joints, skin, entheses, and the spine, as well as accounts for dactylitis, health-related quality of life, and function. Furthermore, the shift in PsA to a treat to target approach with the goal of achieving minimal disease activity (MDA) has resulted in an additional PsA grading tool (Table). The GRAPPA guidelines in particular consider an approach based on domains of psoriasis and/or PsA involvement.

In this section, we review the current FDA-approved therapies for the treatment of PsA. Because this article is intended for dermatologists, we have selected only those therapies that have benefits and indications for both psoriasis and PsA. Furthermore, we note that comments about axial disease in PsA are typically extrapolated from ankylosing spondylitis trials.

csDMARDs
This group of medications includes MTX, SSZ, and leflunomide (LEF), historical mainstays of therapy for PsA. However, only MTX has been shown to be efficacious in treating skin disease as well as joint disease as discussed below, so we will not discuss SSZ and LEF here.

MTX: background
MTX was approved by the FDA to treat psoriasis in 1971. MTX is a competitive inhibitor of dihydrofolate reductase with once-weekly administration. MTX was introduced before the randomized controlled trial became the gold standard—therefore, no large, high-quality studies have been performed to demonstrate the efficacy or safety of the medication in PsA.

MTX is administered weekly as a dose typically ranging between 7.5 and 25 mg, either orally or subcutaneously. Folic acid is concurrently given, ranging between 1 and 5 mg daily to reduce side effects. The efficacy of MTX has been evaluated in 3 recent trials. In one study, out of 206 enrolled patients with active PsA, 188 patients received MTX at a dose greater than 15 mg weekly for the first 12 weeks. At 12 weeks, ACR 20 was achieved in 40.8% of patients, although in this open-label study, there was no placebo group for comparison. In a second study, RESPOND, MTX alone was compared to the combination of MTX and infliximab. In the MTX arm, ACR 20 was achieved in 66.7% of patients at 16 weeks; however, there was again no placebo comparator. In the third study, MTX administered at a target dose of 15 mg per week (although could increase to 20 or 25 mg per week at discretion of clinician) was compared to placebo; at 6 months, there was no statistically significant indication that MTX was more likely than placebo to improve PsA using several rheumatology-related global response indices. However, we would like to point out that the limitations of this study include a small sample size, missing data requiring imputation, and a significant dropout rate.

Common side effects of MTX include nausea and stomatitis. Rare severe toxicities include hepatotoxicity, myelosuppression, and pulmonary fibrosis. A controversial aspect of MTX monitoring is the role of liver biopsy; dermatologists are moving away from liver biopsy and opting more for laboratory monitoring as well as newer noninvasive technologies such as transient elastography.

MTX: recommendations
According to GRAPPA guidelines, MTX should be considered as a first-line therapy for patients with peripheral arthritis as their main PsA phenotype. MTX can also be considered as an early therapy for dactylitis, as well as an early systemic to be considered for skin disease not controlled with topicals alone. For the practicing dermatologist, it is very important to note that MTX is not considered effective in the setting of axial PsA and may be of less benefit in enthesitis as well. Of note, the impending ACR guidelines for PsA treatment appear to move away from MTX as the first line in the treatment of PsA in favor of other biologic and targeted therapies.

In terms of prescribing, patient tolerability of MTX should be considered with regard to gastrointestinal upset and fatigue, which can be limiting in some patients.

DMARDs
There are currently 5 FDA-approved TNF inhibitors for the treatment of PsA, including certolizumab pegol (Cimzia; UCB, Brussels, Belgium), etanercept (Enbrel; Amgen, Thousand Oaks, California), adalimumab (Humira; AbbVie, North Chicago, Illinois), infliximab (Remicade; Janssen Biotech, Horsham, Pennsylvania), and golimumab (Simponi; Janssen Biotech, Horsham, Pennsylvania). Also worth noting are a variety of approved and “coming soon” biosimilars to the earlier-mentioned drugs. However, only 3 are approved for the treatment of psoriasis—adalimumab, etanercept, and infliximab—which we will discuss here.

### TABLE. Minimum disease activity and very low disease activity for PsA

| MDA is defined as meeting 5 of the following 7 criteria; VLDA is defined as meeting all 7: |
| Tender joint count ≤1 |
| Swollen joint count ≤1 |
| Psoriasis Activity and Severity Index ≤1 or body surface area ≤3% |
| Patient pain VAS ≤15 |
| Patient global disease activity VAS ≤20 |
| Health Assessment Questionnaire ≤0.5 |
| Tender enthesal points ≤1 |

**Abbreviations:** MDA, minimum disease activity; PsA, psoriatic arthritis; VAS, visual analogue scale; VLDA, very low disease activity.
Adalimumab
Adalimumab is a fully human monoclonal antibody against TNFα. For PsA, it is administered subcutaneously at a dose of 40 mg every other week (QOW), which is different than in psoriasis, for which it is administered as an initial single dose of 80 mg followed by maintenance dosing of 40 mg QOW 1 week after initial dose. The efficacy of adalimumab in PsA was established in the AD-EPT trial, in which 313 patients were randomized. At 12 weeks, 58% of patients achieved ACR 20 compared with 14% in the placebo-treated group. Furthermore, adalimumab demonstrated inhibition of radiographic progression of disease. The efficacy of adalimumab in skin psoriasis was established in the REVEAL and CHAMPION studies. In REVEAL, 71% of patients achieved PASI 75 at 16 weeks versus 7% in placebo, and in CHAMPION, 79.6% of patients achieved PASI 75 at 16 weeks versus 18.9% in placebo. The efficacy of adalimumab may decrease over time as a result of antidrug antibodies but has been shown to be maintained with the concurrent use of MTX.

Etanercept
Etanercept is a soluble receptor fusion protein that inhibits TNFα. For PsA, the approved dosing is 50 mg once weekly, whereas for psoriasis, this medication is dosed 50 mg twice weekly (BIW) for 3 months followed by maintenance dosing of 50 mg once weekly.

The efficacy of etanercept in PsA was demonstrated in a phase 3 trial including 205 patients. At 12 weeks, 59% of patients achieved ACR 20, 38% of patients achieved ACR 50, and 11% of patients achieved ACR 70, whereas only 15% of the patients in the placebo group achieved ACR 20. Etanercept was also shown to improve enthesitis and dactylitis in patients with PsA, as well as inhibit progressive joint disease as measured by serial radiographs of the hands and feet.

Etanercept has also demonstrated efficacy in skin psoriasis. In one study, 46% of patients achieved PASI 75 at week 12, and 50% achieved PASI 75 at week 24 compared with 3% of patients at week 12 receiving placebo.

Infliximab
Infliximab is an intravenously administered TNFi that has also been approved for PsA. The dosing of infliximab is 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 8 weeks (Q8W) thereafter. Infliximab has shown success in PsA. In one study at 14 weeks, 58% of patients achieved ACR 20, 36% of patients achieved ACR 50, and 15% achieved ACR 70. In the placebo group at 14 weeks, 11% of patients achieved ACR 20. Infliximab significantly reduced rates of dactylitis and enthesitis, as well as inhibited progression of radiographic damage in patients with active PsA.

Infliximab has also demonstrated success in treating skin psoriasis. Two phase 3 trials, EXPRESS I and EXPRESS II, were performed. In these trials, 80% and 75% of patients receiving infliximab achieved PASI 75 at week 10 compared with only 3% in the placebo group. At week 50, 61% of patients achieved PASI 75.

A concern with the use of infliximab is the production of neutralizing antibodies, which is believed to drop the efficacy of the medication over time. However, some have demonstrated that concurrent use of MTX, often at a low dose of 7.5 to 10 mg per week, may help achieve a sustained response using infliximab.

TNFis: recommendations
Patients should be screened for latent tuberculosis (TB) and viral hepatitis prior to initiation of TNFi therapies.

Treatment recommendation guidelines do not differentiate among TNFis. TNFi medications can be used as first or second line for peripheral arthritis, first line for nail disease, second line for axial disease and enthesitis after nonsteroidal anti-inflammatory drugs (NSAIDs), and third line for dactylitis after NSAIDs and csDMARDs, and they can be tried after a trial of topicals, phototherapy, or csDMARDs for skin disease.

In the authors’ experiences, TNFi medications are a safe option because these medications have been around the longest with the most data to support their use. When choosing among TNFi medications, the percentage of patients achieving PASI 75 is less with etanercept than other options in the same class. Furthermore, infliximab appears to work the most rapidly, with upwards of 56% of patients reaching PASI 75 at week 6. The ability to dose adjust infliximab also offers a unique advantage in weight-based dosing and altered frequency of dosing as needed to control underlying disease activity. The off-label dose escalation of other anti-TNFs represents another alternative method for controlling skin and/or joint disease that is incompletely responding to a given therapy.

Decisions often need to be made regarding systemic therapy in patients with concomitant comorbidities. TNFis in general are effective in a large group of psoriatic-related comorbidities and comorbid conditions such as spondyloarthritis, uveitis, inflammatory bowel disease, hidradenitis suppurativa, and more. In general, TNFis should be avoided in patients with comorbid conditions such as New York Heart Association (NYHA) class III or IV heart failure as well as in patients with demyelinating disease. TNFis should be used with caution in patients with NYHA class I or II heart failure as well as in patients with malignancy. When thinking about patients’ comorbidities, certain medications are approved for additional indications. For example, adalimumab, infliximab, and golimumab are approved in patients with ulcerative colitis, and adalimumab, infliximab, and certolizumab are approved in patients with Crohn disease. Most recently, certolizumab received special mention for use in pregnancy and lactation because it does not cross the placenta or enter breast milk meaningfully. Recent large analysis of pregnancy outcomes does not indicate a teratogenic effect of certolizumab.

IL-12/23 inhibitors
Ustekinumab
Ustekinumab (Stelara; Janssen Biotech, Horsham, Pennsylvania) is a fully human monoclonal antibody that binds to the common p40 subunit of interleukin 12 (IL-12) and IL-23. Ustekinumab is approved by the FDA at a dose of 45 mg for patients who weigh less than 100 kg and 90 mg for those who weigh greater than 100 kg. Furthermore, ustekinumab is also approved for PsA in the absence of moderate to severe psoriasis at a dose of 45 mg. Ustekinumab is administered subcutaneously at baseline, 4 weeks, and then Q12W.
Ustekinumab was assessed in 2 phase 3 trials of PsA, PSUMMIT 1 and 2. In PSUMMIT 1, 615 patients (independent of weight) were randomized to 45 mg, 90 mg, or placebo. In this study, 42.3% of patients on the 45-mg dose and 49.5% of patients on the 90-mg dose achieved the ACR 20 endpoint at week 24 compared with only 22.8% of those who received placebo. Key measures of enthesis, dactylitis, skin and nail disease, function, and quality of life were also improved.61

In comparison, PSUMMIT 2 used a similar trial design but incorporated a patient population in which approximately 60% of patients had previously been treated with a TNFi. In the TNFi-naive group, ACR 20 was achieved at 24 weeks in 53.5% of patients receiving 45 mg, 55.3% of patients receiving 90 mg, and 28.6% receiving placebo, while in the TNFi group, ACR 20 was met in 36.7% of the patients receiving 45 mg, 34.5% receiving 90 mg, and 14.5% receiving placebo.69

Ustekinumab has shown good responses in psoriasis. In PHOENIX 1, 766 patients were treated with either 45 mg of ustekinumab, 90 mg of ustekinumab, or placebo; of these groups, 67.1%, 66.4%, and 3.1%, respectively, achieved PASI 75 at 12 weeks.60 In PHOENIX 2, 1,230 patients were treated with either ustekinumab 45 mg, 90 mg, or placebo. PASI 75 was achieved by 66.7%, 75.6%, and 3.7%, respectively.61

**Ustekinumab: recommendations**

Ustekinumab should be avoided in patients with active infections, including TB, hepatitis B or C, and HIV. Caution should be used in those with malignancy.

Per GRAPPA treatment schema, ustekinumab can be used similarly to TNFis. Per GRAPPA recommendations, ustekinumab can be considered as a first-line therapy for nail disease, a second-line therapy for both axial disease and peripheral arthritis after the use of NSAIDs, and a third-line therapy for dactylitis (following NSAIDs and csDMARDs) and skin (following topicals and csDMARDs).36

Among the authors, we believe that the benefits of ustekinumab include a good safety profile and a less frequent injection schedule. An overall impressive safety profile has been underscored by the Psoriasis Longitudinal Assessment and Registry data, which demonstrate, among other things, a particularly bland infection and malignancy signal relative to other mechanisms in this space.62

Hesitations include its weight-based dosing, which may pose a problem in real-world clinical practice as we find that patients in the <100-kg weight category may have a lesser response with the FDA-approved 45-mg dosing.

We have found it to be a particularly useful agent in patients with comorbid inflammatory bowel disease (Crohn disease) who have intolerance to or failure of anti-TNF therapy such as those with anti-TNF-induced psoriasis. Needle-phobic patients appreciate the quarterly, often in-office, injection schedule.

**IL-17 inhibitors**

Two IL-17 inhibitors, secukinumab (Cosentyx; Novartis, Basel, Switzerland) and ixekizumab (Taltz; Eli Lilly and Company, Indianapolis, Indiana), are approved for the treatment of psoriasis and PsA.

**Secukinumab**

Secukinumab is a human monoclonal immunoglobulin G1k (Ig-G1k) antibody that targets IL-17A. It can be administered with a loading dose of 150 mg at weeks 0, 1, 2, 3, and 4 followed by administration of 150 mg Q4W. It can also be given without a loading dose as 150 mg Q4W. In patients with coexistent moderate to severe plaque psoriasis, the same dosage schedule can be applied but at a dose of 300 mg.

The efficacy of secukinumab has been evaluated in 2 phase 3 trials for PsA, FUTURE 1 and 2. FUTURE 1 enrolled 606 patients with active PsA who were then randomized to placebo or an intravenous loading dose of secukinumab at 10 mg/kg administered at baseline, week 2, week 4, and then either 75 mg or 150 mg Q4W starting at week 8. In this study, 30% of patients had previously received TNFi therapy. At 24 weeks, 50.0%, 34.7%, and 18.8% of those in the 150-mg arm achieved ACR 20, ACR 50, and ACR 70, respectively; 50.0%, 30.7%, and 16.8 of those in the 75-mg arm achieved ACR 20, ACR 50, and ACR 70, respectively; and 17.3%, 7.4%, and 2.0% of those in the placebo arm achieved ACR 20, ACR 50, and ACR 70 of 17.3%, respectively. Secondary endpoints of improvement in enthesitis, dactylitis, skin disease, and radiographic evidence of inhibition of disease progression did better in each treatment arm than in placebo.63

FUTURE 2 enrolled 397 patients with active PsA who were then randomized to receive either 300 mg, 150 mg, 75 mg, or placebo at weeks 1 through 4 and Q4W thereafter. In this study, 35% of patients had previously been treated with a TNFi. ACR scores were like those achieved in FUTURE 1. Notably, the group of patients who previously failed TNFi therapy had better outcomes in the 300-mg dosing group than either the 150-mg or 75-mg groups.53,64

A more recent study, FUTURE 5, enrolled patients to be randomized to secukinumab at a dose of 300 mg Q4W following a 300-mg loading dose weekly for 4 weeks, 150 mg Q4W following a 150-mg loading dose weekly for 4 weeks, and 150 mg Q4W without a loading dose. Patients in these arms experienced significantly reduced radiographic progression at week 24 than those receiving placebo, although these data were recently published and have not yet made it to its label.66

Secukinumab has also demonstrated efficacy in psoriasis in 2 phase 3 trials, ERASURE and FIXTURE. In both studies, 77% to 82% of patients randomized to 300 mg of secukinumab achieved PASI 75, whereas 67% to 72% of patients randomized to 150 mg of secukinumab achieved this endpoint. Only 3% to 5% of patients randomized to placebo reached these values.67

**Ixekizumab**

Ixekizumab is a humanized IgG4 monoclonal antibody against IL-17A. It was recently approved by the FDA for PsA. The dosing schedule is a loading dose of 160 mg followed by 80 mg Q4W. The regimen for plaque psoriasis is 160 mg once followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12 and then 80 mg Q4W. In those with coexisting disease, we recommend the dosing regimen for plaque psoriasis.

Ixekizumab’s efficacy has been evaluated in 2 phase 3 trials for PsA, SPIRIT P1 and P2. SPIRIT P1 enrolled patients who were naive to previous biologic therapy, whereas SPIRIT P2 enrolled...
patients who were inadequate responders to previous biologic therapy. In SPIRIT P1, patients with active PsA were dosed with ixekizumab either Q2W or Q4W and were compared against adalimumab and placebo. ACR 20 was achieved in 57.9% of patients receiving ixekizumab Q4W, 62.1% of patients receiving ixekizumab Q2W, and 30.2% of patients receiving placebo. In SPIRIT P2, patients were dosed with ixekizumab Q2W or Q4W, and after 24 weeks, ACR 20 was achieved in 53% of patients receiving ixekizumab Q4W, 48% of patients receiving ixekizumab Q2W, and 28.5% of patients receiving placebo. Furthermore, disease activity and functional disability were significantly improved with both regimens of ixekizumab, and there was also significantly less radiographic progression of structural damage in both treatment arms. However, it is important to note that despite a trend toward improvement, in both trials, endpoints of resolution of enthesitis were not statistically significantly different between ixekizumab Q2W or Q4W regimen versus placebo.68,69

Ixekizumab has also been proven efficacious in the treatment of psoriasis. At week 12, PASI 75 was achieved in 89.1% of the Q2W dosing group compared with 82.6% in the Q4W dosing group. Only 3.9% of patients in the placebo group achieved this endpoint.70

**IL-17 inhibitors: recommendations**

Per GRAPPA treatment schema for active PsA, IL-17 inhibitors are considered second line (with the other bDMARDs) for peripheral arthritis after csDMARDs, are considered second line (along with the other bDMARDs) for axial disease and enthesitis after NSAIDs, and are considered after TNF/IL-12/23 biologics for dactylitis. bDMARDs, including IL-17 inhibitors, are considered first line for nail disease.

These medications have a very good safety profile, with no reported opportunistic infections in any of the above-mentioned trials. The authors believe that anti-IL-17 therapy could easily be considered a first-line biologic therapy for patients with both psoriasis and/or PsA given the high efficacy in all domains of psoriatic disease and targeted mechanism with good safety and tolerability profiles. Furthermore, the particularly rapid onset of action makes the IL-17 class of medications a potential contender for use in erythrodermic psoriasis or severe skin disease over other classes when PsA exists. Importantly, both medications did have increased risk of mucocutaneous candida infections. Like the other bDMARDs, IL-17 inhibitors should be avoided in patients with active infections (HIV, hepatitis B, hepatitis C). Furthermore, caution should be employed when deciding to choose these medications for patients with active malignancy or personal history of inflammatory bowel disease.71

**PDE-4 inhibitors: apremilast**

Apremilast (Otezla; Celgene Corporation, Summit, New Jersey) is an oral PDE-4 inhibitor that inhibits the conversion of cyclic adenosine monophosphate to adenosine monophosphate; this downregulates the inflammatory response.70 Apremilast is dosed at 30 mg twice daily (BID) and is titrated to this dose in a 6-day regimen to minimize the risk of gastrointestinal side effects.

Three phase 3 randomized clinical trials—PALACE 1, 2, and 3—were performed. In these studies, patients with active PsA, despite prior conventional therapy, were randomized to 20 mg BID, 30 mg BID, or placebo. In PALACE 1, 504 patients were randomized to the above regimes. At 16 weeks, patients in the placebo group who did not meet ACR 20 were rerandomized to either treatment group. At 24 weeks, all placebo patients were rerandomized to either treatment group. All patients were followed through 52 weeks. In PALACE 1, 2, and 3, ACR 20 was met at week 16 by between 32.1% and 40.7% of patients receiving 30 mg BID compared with 18.3% to 19.0% observed in patients receiving placebo. Overall, ACR 20 rates at 52 weeks ranged between 52.6% and 63.0% in patients dosed with 30 mg BID.

Other endpoints included the effect of apremilast on enthesitis and dactylitis. Enthesitis was measured by the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). Compared with placebo, apremilast 30 mg BID was associated with a significantly greater mean change in MASES from baseline to week 24 across all 3 PALACE trials. Furthermore, the mean change from baseline of dactylitis count between week 0 and 24 was significantly greater with apremilast than placebo.72-74

Apremilast has shown to be effective in the treatment of plaque psoriasis. The ESTEEM I study demonstrated PASI 75 achieved by 33.1% at 16 weeks versus 5.3% in placebo.75

**Apremilast: recommendations**

Overall, apremilast demonstrated an acceptable long-term safety and tolerability profile in the PALACE trials, although the most common adverse events included diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis. Although weight loss was only appreciated in <2% of patients in PALACE 1, weight loss >5% was experienced in approximately 15% of patients in PALACE 2 and 3.76-78 Furthermore, there was also a higher risk of depression in apremilast-treated patients compared with placebo, and while the overall incidence was low, it is recommended that the risks and benefits of apremilast be weighed carefully in those with a history of depression. Close monitoring for worsening of depression or suicidal thoughts during therapy is advised.76

Benefits of apremilast include its convenience as an oral pill that does not require prescreening or ongoing laboratory monitoring. There does not appear to be an increased risk of TB. However, it is unclear whether apremilast inhibits the radiographic progression of PsA because this was not studied in either trial. Additionally, the medication is not approved for axial disease.79 Lastly, in patients with active psoriasis, PASI scores are lower than those achieved with bDMARDs; overall skin improvements are modest.

Per GRAPPA treatment scheme, apremilast can be chosen as first line for peripheral arthritis, after NSAIDs for enthesitis or dactylitis, or first line for nails.80 Overall, the authors find its benefits in skin and joint disease to be modest compared with some other mechanisms reviewed herein and find mixed tolerability but excellent safety and convenience among patients using this agent.

**JAK inhibition**

**Tofacitinib**

Tofacitinib (XELJANZ; Pfizer, New York, New York) is a JAK 1 and 3 inhibitor that interferes with nuclear signaling and resultant
DNA transcription. Although tofacitinib does not directly control the response to TNF or IL-17, it indirectly decreases their production by inhibiting more upstream cytokines such as IL-6 and IL-23.

Tofacitinib was recently approved by the FDA for the treatment of PsA. In the immediate-release form, it is dosed at 5 mg BID. In the extended-release form, it is dosed at 11 mg daily.

Tofacitinib has been evaluated for the treatment of PsA in 2 phase 3 trials: OPAL-Broaden studied patients with active PsA who had an inadequate response to at least one csDMARD but no previous administration of a TNFi, and OPAL-Beyond studied patients with active PsA who had been previously treated with at least one TNFi. At 12 weeks, 50.5% of patients with active PsA not previously treated with a TNFi achieved ACR 20 at a dose of 5 mg BID, 60.6% at a dose of 10 g BID, and 33.3% on placebo.78 A total of 49.9% of patients with active PsA previously treated with a TNFi achieved ACR 20 at a dose of 5 mg BID, 40.7% at a dose of 10 mg BID, and 23.7% on placebo.79 In each of these studies, patients also saw improvement in dactylitis and enthesis in both active treatment regimens.

Tofacitinib has also been shown to treat psoriasis; however, it is not currently FDA approved for this indication. In a phase 3 randomized controlled trial, 1,101 patients with psoriasis received either tofacitinib 5 mg BID, 10 mg BID, or etanercept 50 mg BIW. A total of 63.6% of patients who received tofacitinib 10 mg BID enjoyed PASI 75 at 12 weeks versus etanercept, for which 58.8% of patients enjoyed PASI 75. Only 5.6% of the patients assigned to placebo achieved this endpoint. The 5 mg BID dosing did not perform as well. Notably, 90% of patients in each arm had previously received systemic treatment, 11% in each arm with a previous biologic agent.80

**Tofacitinib: recommendations**

Because this medication was recently approved by the FDA, it is not included in the GRAPPA or EULAR treatment schema. The full ACR recommendation will include tofacitinib in its treatment algorithm. We find that tofacitinib is a consideration for patients with active PsA despite treatment with a TNFi as well as for patients with enthesitis who prefer an oral medication.

It is important to mention that there were significantly more reported cases of herpes zoster in patients on tofacitinib than placebo in these trials. However, now that a nonlive recombinant zoster vaccine (Shingrix; GlaxoSmithKline, Middlesex, United Kingdom) is available for immunosuppressed patients, the increased risk of herpes zoster may be mitigated, although this has not yet been studied. Furthermore, it will be important for more studies to determine the long-term efficacy and safety.

Tofacitinib provides an oral option for the treatment of PsA, with ACR 20 numbers similar to bDMARDs in both patients who were previously exposed or unexposed to TNFis. This may make tofacitinib a good option for patients choosing a therapy after failing TNFis. At approved doses, tofacitinib is of only modest efficacy in skin psoriasis but seems to have increased efficacy in this compartment over time, beyond 6 months of use.

**Summary**

Dermatologists are on the front line to identify PsA in their patients with psoriasis. PsA is a prevalent and underdiagnosed disease with potential long-term complications and sequelae for patients. Furthermore, there is heterogeneity in PsA phenotypes, and not every psoriasis skin-directed therapy works to treat all domains of the disease. Overall, it is important to decide therapy for patients based on the active domains of their disease, their comorbidities, and the safety profiles of medications, as well as patient preference for route of administration, frequency, and tolerability.

This is an exciting time in psoriasis and PsA, with many new emerging therapies that can significantly reduce disease symptoms and progression, many of which are already approved and outlined here. However, the landscape of therapy is continually changing, and many new medications are coming down the pipeline. For example, specific IL-23 inhibitors such as guselkumab (Tremfya; Janssen, Biotech, Horsham, Pennsylvania), risankizumab (Boehringer Ingelheim, Rhein, Germany; AbbVie, North Chicago, Illinois), and tildrakizumab (Ilumya; Sun Pharmaceuticals, Mumbai, India), as well as an IL-17 inhibitor brodalumab (Siliq; Valeant Pharmaceuticals, Bridgewater Township, New Jersey), have demonstrated promising early phase data.81-84 New JAK inhibitors, such as baricitinib (Incyte, Palo Alto, California; Eli Lilly and Company, Indianapolis, Indiana) and upadacitinib (AbbVie, North Chicago, Illinois) are actively being investigated.

MDA, as defined previously, is a goal for both psoriasis and PsA. However, while many of these newer medications are leading to dramatic results in the clearance of skin psoriasis, we are still only seeing modest improvements in PsA. While the lack of improvement in PsA may be secondary to limitations in our measurements of PsA, there is certainly a need for a better understanding of PsA pathophysiology as well as targeted therapies for this disease. Ongoing, active collaboration, as demonstrated by groups such as Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network as well as the National Psoriasis Foundation, is important to further the causes of patient identification, education, and treatment.

**References**


