When researchers discovered in 1979 that the immunosuppressant cyclosporine successfully cleared psoriatic plaques, the scientific community began to consider psoriasis not “just a skin disease.”\(^1\) The cause of this chronic, multisystemic disease is dysregulation of the immune system.\(^1\) Approximately 3.2% of the American population has some form of psoriasis. Psoriasis vulgaris, the most common form of plaque psoriasis, affects 80% of people with psoriasis.\(^1\)

The hallmarks of plaque psoriasis are red-pink plaques with silvery scales ranging in size from small to medium to large. They are symmetrically distributed on the scalp, elbows, knees, and lower torso.\(^1\) Plaques can also appear on the nails and intertriginous areas, such as the abdominal folds, axillae, inframammary folds, as well as the genitalia.\(^1\) Pruritus is among the most prominent and bothersome of psoriasis symptoms.\(^1\)

### Pathogenesis of Psoriasis

The inflammation and excess skin growth in psoriasis is the result of the interactions between the innate and adaptive immune systems; however, the adaptive immune system plays a key role.\(^4\) The inflammatory process involves dendritic cells that secrete the cytokines interleukin (IL)-12 and IL-23, which then stimulate naïve T cells to differentiate into either type 1 or type 17 helper T cell (TH1, TH17) pathways (Figure 1).\(^2,4\)

Over time it was determined that the TH17 pathways play a larger role in psoriasis than do the TH1 pathways. The TH1 pathways lead to the release of cytokines such as tumor necrosis factor (TNF)-α and interferon gamma. Activated TH17 cells produce inflammatory cytokines including IL-17A, IL-17F, IL-22, and TNF-α.\(^2\) The cytokines in turn cause skin thickening and erythema due to vasodilation and angiogenesis.\(^1\)

![Figure 1: Maintenance Phase of Psoriasis With Putative Targets of Current and Emerging Drugs](https://example.com/figure1.png)

**Keywords**

Biologics; phototherapy; psoriasis pathophysiology; systemic oral therapy; topical therapy

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IL-17 and IL-23 and their receptors play a crucial role in psoriasis because they respond to dendritic and T-cell cytokines. The three approved IL-17 inhibitors exert a slightly different effect on the IL-17 signaling pathway. The first two agents approved, secukinumab and ixekizumab, neutralize IL-17A, whereas brodalumab blocks the IL-17A receptor.

IL-23 is one of the key cytokines that affect the production of IL-17. Ustekinumab, an IL-23 inhibitor, targets the shared p40 subunit of the IL-12 and IL-23 cytokines. Guselkumab and tildrakizumab, and the investigational agent, risankizumab, bind to the p19 subunit of the IL-23 cytokine.

Our understanding of the inflammatory cascade that results in psoriasis continues to evolve. For example, the enzyme phosphodiesterase-4 (PDE-4) has been found in many inflammatory cells, and its role is being elucidated in psoriasis. In preclinical studies, the small molecule apremilast, a PDE-4 inhibitor, blocked proinflammatory cytokines responsible for chronic inflammatory diseases such as psoriasis and psoriatic arthritis (PsA) in humans. By blunting the expression of the cytokines TNF-alpha, IL-12, and IL-23, apremilast reduced keratinocytes and skin thickness.

Landscape of Psoriasis Treatment
Prior American Academy of Dermatology (AAD) guidelines, which are currently being updated, recommend that clinicians first ascertain whether a patient with psoriasis also has PsA. Patients who have PsA require systemic medications that treat both psoriasis and PsA.

If a patient does not have concurrent PsA, the AAD treatment algorithm recommends using topical therapies for mild disease. For patients with moderate to severe psoriasis, the use of biologics, oral systemic medications, and phototherapy is required.

Topical Therapies
Topical therapies for psoriasis include topical corticosteroids, topical vitamin D analogues, and keratolytic agents. The most commonly used topical agents in psoriasis are corticosteroids, which reduce swelling and redness through their anti-inflammatory effects. Examples of topical steroids include betamethasone dipropionate, clobetasol propionate, desoximetasone, fluocinonide, fluticasone propionate cream, and hydrocortisone. Topical steroids, which are applied once or twice daily, come in a variety of strengths and vehicles: ointments, creams, foams, lotions, shampoos, sprays, tape, and gels.

In the last decade, innovations in topical treatment for psoriasis have focused on combinations such as topical steroids with vitamin D analogues, which reduce skin cell growth and scaling. Examples of this combination are betamethasone, dipropionate, and calcipotriene (vitamin D3)—which are available in multiple vehicles, with the current foam vehicle shown to be optimal with only once daily application. These topical medications represent advances in vehicle technology, whereby different active ingredients can be combined in an efficacious and safe manner to confer therapeutic effect.

Phototherapy
Phototherapy has evolved from using broadband UVB to narrow-band UVB. Psoralen plus UVA (PUVA), although frequently more effective, poses a higher risk of skin cancer. A typical regimen starts with narrow-band UVB 3 times a week for 3 months. If patients improve, they can decrease the frequency to weekly UVB therapy.

Office-based UVB phototherapy is the predominant type of administration; an office treatment may take less than 5 minutes. Home UVB is an option, but because units intended for home use are calibrated at a lower strength, home treatment can take up to an hour, which poses a risk that patients may not adhere to an effective regimen.

The advantage of phototherapy is that it does not create adverse immunosuppressive effects that potentially result from use of topical and systemic therapies. In short-term data, UVB therapy has not been definitively linked to skin cancer; however, the potential risk of skin cancer with cumulative long-term UVB therapy is an ongoing concern.

Targeted light therapy treatments using an excimer laser can deliver higher-dose UVB therapy to focused, sensitive areas such as the scalp. This therapy is not available in most offices.

Oral Systemic Therapy
Patients with moderate to severe psoriasis benefit most from systemic therapies. Traditional oral therapies used for psoriasis include methotrexate, cyclosporine, and acitretin. A newer oral therapy for psoriasis is apremilast.

Methotrexate. The oral and injectable antimetabolite methotrexate increases extra-cellular adenosine with its anti-inflammatory properties. Methotrexate is the mainstay of systemic treatment for psoriasis in the US and Europe, despite its significant adverse effects on major organs—liver function enzyme elevation, bone marrow suppression, and pulmonary fibrosis—which limit its long-term use. Methotrexate is contraindicated in women who are actively conceiving, pregnant, or lactating. Warren and colleagues found that at week 16, 41% of patients who received subcutaneous MTX achieved PASI 75 vs 10% of those in the placebo group.

Cyclosporine. Although the calcineurin inhibitor cyclosporine is effective, it is reserved for short-term interventional use in patients with psoriasis who are experiencing flares. Because long-term use of cyclosporine is associated with hypertension and irreversible renal damage, it is typically used for no more than 3 to 6 months and then discontinued.

Acitretin. The oral retinoid acitretin has been used with variable success for pustular psoriasis and palmoplantar psoriasis. It has a synergistic effect when combined with UV therapy. Patients using a combination of acitretin and UV therapy can reduce the UV dose. Acitretin has modest efficacy in patients with moderate to severe psoriasis. Significant potential adverse effects include dyslipidemia and less frequently liver function test abnormalities.

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<th>Psoriasis ± Psoriatic Arthritis</th>
<th>Anti-TNF ± MTX</th>
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<td>Limited Disease</td>
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<td>Topicals/Targeted Phototherapy</td>
<td>UVB/PUVA Systemic Biologic</td>
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<td>Lack of Effect</td>
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<th>FIGURE 2 American Academy of Dermatology Psoriasis Treatment Algorithm</th>
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<td>MTX=methotrexate; PUVA=psoralen-ultraviolet A; TNF=tumor necrosis factor; UVB=ultraviolet B.</td>
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<td>Source: American Academy of Dermatology</td>
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Apremilast, an oral PDE-4 inhibitor approved in 2014, is modestly effective in patients with psoriasis and PsA. Its short-term, ie, initial first month of therapy, effect on the immune system is not well understood. Common adverse effects include diarrhea, nausea, and rare cases of upper respiratory tract infection, and headache. Warnings for apremilast include rare cases (1%) of depression.

Biologic Therapy

For patients whose psoriasis is moderate to severe, biologics play a significant role in therapy because they target the specific cytokines that cause inflammation and skin lesions. Before starting a biologic regimen, it is essential that clinicians ascertain the patient’s PsA status. Biologics can be prescribed with oral systemic and topical agents concurrently.

TNF-alpha inhibitors are monoclonal antibodies that block TNF, a cytokine that can induce inflammation. When introduced more than a decade ago, these biologics changed the landscape of psoriasis treatment for patients with moderate to severe disease who had not achieved adequate control of their symptoms. TNF-alpha inhibitors also significantly benefit people who have PsA.

Etanercept, approved by the US Food and Drug Administration (FDA) in 2004, was among the first of the biologics to appear on the market for psoriasis. Etanercept is now approved for use in both adults and children with moderate to severe psoriasis. In pivotal trials, injectable etanercept demonstrated efficacy at 12 weeks, as defined by a Psoriasis Area and Severity Index (PASI) score of 75, in 49% of patients receiving etanercept 50 mg in the twice-weekly (BIW) group, 34% of patients in the 25-mg BIW group, and 3% in the placebo group (P<0.0001 for each etanercept group vs placebo). At week 24, 54% of patients whose dose was reduced from 50 mg BIW to 25 mg BIW achieved PASI 75, as did 45% of patients receiving continuous 25 mg BIW and 28% of the group that received placebo followed by etanercept 25 mg BIW.

Common adverse effects of etanercept include infections and injection site reactions. Etanercept use in the psoriasis population has not been associated with significantly increased risk of serious infections compared to placebo. Long-term registry data with etanercept also demonstrated a tolerable safety profile. Patients with a history or signs and symptoms of tuberculosis need to be evaluated and appropriately treated, if necessary, before etanercept is considered.

Adalimumab, approved in 2006, neutralizes the tumor necrosis factor responsible for inflammation in psoriasis. In the phase 3 trial, 71% of patients who received adalimumab achieved PASI 75 vs 7% of patients given placebo at week 16.

Like etanercept, adalimumab was well tolerated in clinical trials. However, because serious infections can occur, patients must be screened carefully before initiating therapy with adalimumab. Children and adolescents are also at a slight increased risk for malignancies such as lymphoma.

Infliximab, administered intravenously, was approved in 2006 for the treatment of plaque psoriasis. At week 10, 75.5% of patients receiving infliximab 5 mg/kg vs 5% of patients receiving placebo achieved PASI 75. Despite the efficacy and safety of infliximab, dermatologists tend to use other TNF-alpha agents because few practices are equipped to administer drugs intravenously. Although adverse events in the pivotal trials were mild, postmarketing surveillance found that patients can develop serious infections and malignancies. Infliximab is contraindicated at higher doses in patients with heart failure.

Ustekinumab, approved in 2009 for moderate to severe plaque psoriasis and in late 2017 for adolescent psoriasis, blocks the IL-12 and IL-23 cytokines. In the PHOENIX 1 pivotal trial, 67.1% of patients who received ustekinumab 45 mg and 66.4% of patients who received ustekinumab 90 mg achieved PASI 75 scores vs 1% of those who received placebo at week 12 (P<0.0001). The study found that dosing ustekinumab every 12 weeks maintained efficacy for 1 year or more in most patients.

The PHOENIX 2 trial found that more partial responders (patients who had achieved ≥50% but <75% PASI improvement from baseline) who received the higher dose of ustekinumab (90 mg) every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose of 90 mg every 12 weeks (68.8% vs 33.3%; 95% confidence interval [CI], 12.7-58.1; P=0.004). Common adverse events include upper respiratory infection, headache, and fatigue. As is the case with other biologics, patients treated with ustekinumab are at risk for infection and should not initiate treatment if they have an active infection.

Secukinumab, approved in 2015, was the first IL-17A ligand inhibitor indicated for moderate to severe plaque psoriasis. In a pooled analysis of four phase 3 trials involving nearly 1,400 patients worldwide, secukinumab demonstrated peak efficacy at week 16, with 75.6% of patients achieving PASI 90 and 47.2% achieving PASI 100. The 150-mg and 300-mg doses of secukinumab were tested in these trials (ERASURE, FIXTURE, FEATURE, and JUNCTURE). Patients received weekly injections for the first 5 weeks, followed by maintenance doses every 4 weeks for up to 52 weeks. As measured by PASI 90/100 in a multiple imputation (to replace missing data), secukinumab 300 mg at week 52 achieved a 62.9%/37.9% response in North American (NA) patients, respectively, and 70.2%/42.0% in non-NA patients, respectively. Secukinumab 150 mg achieved a PASI 90/100 response in 30.9%/17.5% of NA patients, respectively, and in 53.9%/26.9% of non-NA patients, respectively. Both populations had similar adverse events. The most common adverse effect was nasopharyngitis, followed by upper respiratory tract infection. There were rare cases of Crohn disease and ulcerative colitis in the trials.

Ixekizumab, also an IL-17A ligand inhibitor injectable, was approved in 2016 for patients with moderate to severe plaque psoriasis. In a pooled analysis (N=3,866 patients) of the phase 3 pivotal trials (UNCOVER 1-3), at week 12 ixekizumab demonstrated superior vs both placebo and etanercept, as measured by the static Physician Global Assessment (sPGA) and PASI 75 (both P<0.001). At week 12, patients who received ixekizumab achieved PASI 75/90/100 of 90%/70%/40%, respectively. Adverse event rates were similar between the ixekizumab and etanercept groups; injection site reaction was the most common adverse event. In the ixekizumab-treated group, patients reported more injection site pain and nausea than did patients treated with etanercept. Candida infections occurred in 0.5% of patients treated with placebo, in 0.7% in the etanercept group, and 2.9% treated with ixekizumab every 4 weeks, and 1.4% treated with ixekizumab every 2 weeks. Rare cases of Crohn disease and ulcerative colitis occurred during clinical trials.

Brodalumab, an IL-17 receptor A inhibitor, was approved in 2017 for patients with moderate to severe plaque psoriasis. In a pooled analysis of the three phase 3 trials (AMAGINE 1, 2, and 3), 4,373 patients with psoriasis were assessed based on the PASI 75 and an sPGA score of 0 (clear) or 1 (almost clear) by week 12 on treatment. The PASI 75 response rates for brodalumab 210 mg in AMAGINE 1, 2, and 3 were 83%, 86%, and 85%, respectively. Brodalumab 210 mg was statistically superior to ustekinumab at 12 weeks as measured by PASI 90, PASI 100, and sPGA 0 or 1 (P<0.01). The pooled adverse event rate at 12 weeks in the three studies was 57.6% among patients taking brodalumab 210 mg every 2 weeks and 51.0% among patients on placebo. The most commonly reported adverse events were nasopharyngitis, headache, upper respiratory tract infection, and arthralgia. Brodalumab is available only through a Risk Evaluation and Mitigation Strategy (REMS) program because it has a black box warning for suicidal ideation and behavior. Longer-term studies are warranted to assess the safety of patients with depression and other mental health disorders.
Guselkumab, an IL-23 monoclonal antibody that binds to the p19 subunit of IL-23, was approved in 2017 for patients with moderate to severe psoriasis. Initially, the injectable is administered in one 100-mg/mL injection, followed by another injection 4 weeks later, and thereafter every 8 weeks. In a pooled analysis of 1,829 patients with moderate to severe psoriasis, guselkumab was superior to adalimumab in the VOYAGE 1 and 2 pivotal trials, as measured by the Investigator Global Assessment (IGA 0/1 = cleared or minimal psoriasis; IGA 0 = cleared). At week 24, patients treated with guselkumab achieved a response rate of 83.8% for IGA 0/1 and 52.1% for IGA 0 vs those treated with adalimumab, who achieved rates of 63.1% for IGA 0/1 and 30.2% for IGA 0. The most frequently reported adverse events included upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea, and rare cases of herpes simplex infections.

Tildrakizumab, another IL-23 inhibitor, has completed phase 3 trials (reSURFACE 1 and 2), and in March 2018 was approved by the FDA. Both injectable dosages of tildrakizumab (100 mg and 200 mg) were superior to etanercept and placebo. At 12 weeks, 66% of patients receiving 200 mg tildrakizumab and 61% receiving 100 mg tildrakizumab achieved PASI 75, vs 6% for the placebo group and 48% in the etanercept group (P<0.0001 for comparisons of both tildrakizumab groups vs placebo; P<0.0001 for 200 mg vs etanercept and P=0.001 for 100 mg vs etanercept). There was one death in the reSURFACE 2 trial in a patient who received 100 mg of tildrakizumab; however, the cause of death could not be determined.

Risankizumab, an immunoglobulin G1 (IgG1) monoclonal antibody that also inhibits IL-23, completed phase 3 trials in 2017. In a phase 2 trial of 166 patients with moderate to severe psoriasis, risankizumab was superior to ustekinumab at week 12 (PASI 90, 77% vs 40%, respectively). Because of the small trial size, safety for the biologic could not be determined.

Factors That Drive Treatment Choice
With so many new agents for psoriasis on or coming to the market, selecting the right initial therapy can be daunting. However, making the correct choice is crucial to alleviating the often overwhelming burden of psoriasis. Because both short- and long-term efficacy are essential to treatment choice, many clinicians opt for biologics, which can benefit patients who have comorbidities such as PsA.

In addition, because multiple efficacious treatment options are available, it is important to understand established treatment targets and help patients achieve them. In the United States, the treatment target is long-term control of psoriasis such that patients will have 1% or less body surface area involvement when they have achieved the optimal dose. Treatment targets can be achieved with FDA-approved dosing, dose escalation of the same medication, or a combination of medications. Evaluation of benefits and risks on an individual basis is critical when working with patients toward these treatment goals.

Within the biologic class, for patients with both psoriasis and PsA, TNF-alpha inhibitors have longer-term data showing efficacy in PsA. Other considerations include patient weight, disease severity, and patient preference regarding injection frequency. For example, biologics that allow for weight-based dosing tend to be more effective in obese patients than are fixed-dose therapies.

The safety profile of any therapy is a major consideration in treatment initiation because certain drug classes have shown a propensity for opportunistic infections. Progression of tuberculosis or reactivation of hepatitis B are potential risks associated with TNF inhibitors, and therefore patients need to be screened and monitored for these potential risks.

Patient preference and convenience should be factored into the treatment decision. The route of administration, dosing frequency, and concomitant medications all play a role in determining whether patients will remain adherent to their regimens. Although office-based phototherapy may be effective for mild to moderate psoriasis, patients are often unable to attend the frequent phototherapy visits to the doctor’s office. Similarly, patients may be less adherent to an oral regimen that requires taking the medication more than once a day.

For biologics, the trend has been toward medications that have robust efficacy while requiring fewer injections. For patients already being treated with a systemic agent, adding another immunomodulatory drug may alter their immune profile; therefore, one must perform a careful assessment of the safety profile of combined systemic agents.

Conclusion
When the clinician selects the appropriate agent or combination therapy, patients with psoriasis can certainly expect to achieve significant relief from their symptoms. Clinicians need to first determine whether a patient has PsA and other comorbidities, because these factors will guide their medication choice. In general, therapeutic selection is based on the severity of the psoriasis, taking individual patient needs and preferences into account. Mild disease can usually be treated with topical agents, while for patients with moderate to severe psoriasis, clinicians need to consider biologics, oral systemic agents, and/or phototherapy as monotherapy or in combination.

References


