Long-term Success for Treatment of Psoriatic Disease

After reading this chapter, click the green button at the end of the text to complete the evaluation and post-test questions.

Learning Objectives
After completing this activity, the participant should be better able to:

- Identify the signs and symptoms of psoriasis and psoriatic arthritis to allow for early diagnosis and treatment
- Counsel patients on newer treatment options for moderate to severe psoriatic disease management
- Implement treatment guidelines and evidence-based strategies to provide patient-centered management of moderate to severe psoriatic disease as part of the collaborative care team

Introduction
Psoriatic disease, comprising psoriasis and psoriatic arthritis (PsA), affects 3.2% of adults in the United States, or about 7.4 million persons. The burden of psoriatic disease is substantial. Although psoriatic symptoms can develop at any age, they usually manifest before age 35. Approximately 20% of patients with psoriasis have moderate to severe disease, which may involve the hands, feet, or genitals. Between 6% and 42% of patients with psoriasis will also have PsA; lower estimates may reflect missed diagnoses or misdiagnoses. Up to 20% of patients with PsA present before the development of psoriasis.

Psoriatic disease has a pronounced negative effect on quality of life, productivity, and daily function, so much so that it is considered as debilitating as cancer, heart disease, or chronic lung disease. As clinicians proceed with the care of patients with psoriasis and PsA, they should understand that psoriatic disease affects not only the skin and joints; it is a systemic auto-inflammatory condition that adversely affects the patient’s entire physical and mental well-being.
A majority of patients with moderate to severe psoriatic disease are undertreated (Figure 1). By some estimates, 30% of patients with moderate psoriasis do not receive guideline-recommended treatment (ie, they receive topical agents alone), and 36% go untreated. For patients with severe psoriasis, the corresponding numbers are 22% and 30%. A survey by the National Psoriasis Foundation (NPF) found that topical monotherapy remains the most common treatment for moderate to severe psoriasis. Neither traditional systemic nor biologic therapies are widely used, either alone or in combination with topical therapy. Biologic therapies are used for only 9% of patients with moderate psoriasis and 15% with severe disease. Of course, treatments vary by practice setting and the involvement of specialists such as rheumatologists in the management team. Undertreatment also stems partly from the reluctance of patients with psoriasis to seek medical attention due to depression or embarrassment.

**Plaque Psoriasis: Characteristics and Pathophysiology**

Psoriasis manifests as five different types of inflammatory skin lesions: plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis is the most common, affecting 80% to 90% of patients with psoriatic disease. The lesions of plaque psoriasis appear as inflamed, irregularly shaped, dry, thin plaques up to several centimeters in diameter, with silvery-white scaling. They tend to appear symmetrically, most often on the scalp, trunk, buttocks, or limbs.

Eczema figures prominently in the differential diagnosis of plaque psoriasis, and many patients have both conditions (Figure 2). Other diseases in the differential diagnosis are mycosis fungoides (with higher risk for patients with HIV), plaque stage cutaneous T-cell lymphoma (with higher risk for patients with rheumatoid arthritis [RA]), tinea corporis, and Bowen's disease. Systemic lupus does not typically look like eczema but can mimic plaque psoriasis.

The leading risk factors for plaque psoriasis are smoking, obesity, and genetic predisposition. The Utah Psoriasis Initiative, a cross-sectional study, reported a significantly higher preva-
lence of smoking among persons with psoriasis (37%) than in the general Utah population (13%); and a prospective study of more than 78,000 American women in the Nurses’ Health Study II showed that current and past smoking were associated with psoriasis. The risk of psoriasis does diminish after smoking cessation, such that former smokers have risk comparable to that of never-smokers after 20 years.

Patients with psoriasis also are more likely to be obese. The Nurses’ Health Study II implicated adiposity and weight gain as strong risk factors for psoriasis, with relative risk increasing with increasing body mass index (BMI). The Utah Psoriasis Initiative found a significantly higher prevalence of obesity among patients with psoriasis (34%) than in the general Utah population (18%). Obesity is a particularly challenging comorbidity because patients with obesity may not respond as well to therapies for psoriasis.

Genetic susceptibility has also been implicated. Psoriasis is 19 times more common among first-degree relatives of persons with PsA than it is in the general population. Further, persons with psoriasis are at higher risk of having autoimmune diseases such as inflammatory bowel disease and multiple sclerosis. Multiple genes are believed to be candidates for causing susceptibility to psoriatic disease and for influencing responsiveness to traditional and biologic therapies.

Psoriatic disease is driven by chronic inflammation. Locally, psoriatic skin lesions are characterized by inflammatory cells as well as epidermal hyperproliferation and abnormal differentiation and proliferation of keratinocytes. They are raised, inflamed, scaly, and extremely itchy. Itching and scratching are serious problems because, like smoking, scratching may cause stress on the keratinocytes and exacerbate inflammation.

Beyond local inflammation, systemic inflammation is believed to underlie psoriatic disease and perhaps explains the common coexistence of psoriasis and cardiovascular disease. Specifically, psoriasis is viewed as a disease of disordered immune regulation mediated by inflammatory cytokines. The systemic inflammatory markers of psoriatic disease also drive vascular endothelial dysfunction, which may adversely affect the liver, adipose tissue, and skeletal muscle, and ultimately promote the progression of atherosclerosis. In addition to TNF-α, these markers include interferon (IFN)-γ; IFN-α; and interleukin (IL)-1, -6, and -7. Thus,

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**Figure 2. Characteristics of plaque psoriasis versus eczema.**

In plaque psoriasis, plaques are irregularly shaped, dry, and thin, with silvery-white scaling. They may be up to several centimeters in diameter. They most often appear on the scalp, trunk, buttocks, or limbs.
as inflammation perpetuates psoriatic disease, it may also drive the progression of cardiovascular dysfunction (Figure 3).\textsuperscript{17} Psoriasis is associated with an estimated excess of 11,500 major adverse cardiovascular events each year.\textsuperscript{6}

Assessment of Psoriasis Disease Severity

Investigators in clinical treatment trials calculate the extent of psoriasis based on the affected body surface area (BSA) in order to classify patients as having mild, moderate, or severe disease. In clinical practice, these classifications can serve as a basis for treatment decisions and assist in communications with health insurers about determining treatment coverage.

Affected BSA may be estimated using the palm of the hand as an area representing 1% of the body surface (Figure 4).\textsuperscript{2} According to the National Psoriasis Foundation, mild psoriasis (<3% BSA) often affects the knee and elbow; moderate psoriasis (3%-10% BSA) affects the knees, elbows, chest, and abdomen; and severe psoriasis (>10% BSA) affects the forearms, lower extremities, and abdomen. The scalp may also be affected at any severity. Psoriasis that is present on the palms, soles of the feet, and genitals may also be classified as moderate or severe due to its impact on quality of life.\textsuperscript{8} Of course, quality-of-life impact and the presence of disability are considered in classifying disease severity as well.\textsuperscript{2,8}

All patients with psoriatic disease should undergo assessment of comorbidities. In a recent guideline update, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) emphasized the “overarching principle” of comprehensive assessment of not only cardiovascular disease but obesity, metabolic syndrome, diabetes, liver disease, depression, and anxiety, which are known comorbidities of psoriatic disease.\textsuperscript{18} The GRAPPA guidelines call for multidisciplinary and multispecialty assessment. Rheumatology specialists would, accordingly, screen patients with PsA for comorbidities, or refer patients to their primary care

![Table of inflammatory mediators](image)

**Figure 3.** Psoriatic disease and atherosclerosis: shared inflammatory mediators.\textsuperscript{17} LDL-C = low-density lipoprotein cholesterol; MCP-1 = monocyte chemotactic protein-1.
providers for the necessary evaluation and treatment. This recommendation would also apply
to dermatology practices, which may focus on managing psoriasis itself.

The GRAPPA approach is well justified, particularly regarding cardiovascular comorbidities. Psoriasis is associated with an estimated excess of 11,500 major adverse cardiovascular
events each year. Diabetes, hypertension, ischemic heart disease, and obesity are all significantly more prevalent in patients with psoriasis than in control populations. Hypertension,
for example, is present in approximately 28% of patients with psoriatic disease, compared with
14% of controls. The corresponding rates for ischemic heart disease are 14% versus 7%. A
pressing goal of biologic treatment research is to reduce both psoriatic disease activity and
cardiovascular disease by targeting their common pathobiology. New evidence from this
research is imminent, but until it is available, clinicians caring for patients with psoriatic disease
should make optimal use of traditional methods of cardiovascular risk reduction: lipid and
blood pressure control, weight management, and patient education on diet and exercise.

Even young adults with psoriatic disease are at increased risk for cardiovascular disease. Patients as young as age 30 with only mild psoriasis have a relative risk of a myocardial infarction of 1.29; with severe disease, their relative risk is 3.10. Further, severe psoriasis is associated with chronic kidney disease, even in young persons and independent of traditional risk
factors. At age 20, patients with severe psoriasis have five times the risk of kidney disease than
patients with mild psoriasis. Thus, it is important to engage in early and appropriate man-
gagement of cardiovascular and kidney disease in young patients with psoriasis to prevent major
complications later on.

Psoriatic Arthritis

The diagnosis of PsA, a seronegative spondyloarthritis, is often missed and therefore goes
untreated; 21.5% of patients with moderate to severe PsA are not being treated. As many

Figure 4. Calculating the extent of psoriasis.
as 20% of cases with severe PsA receive only topical therapy, which has no effect on the joints. About half of patients with PsA have progressive, disabling disease.\textsuperscript{3,4,6} Compared with patients with psoriasis only, those with PsA report even worse quality of life.\textsuperscript{4}

PsA typically develops between ages 30 and 50, but it can occur at any time, and occasionally before cutaneous disease is evident.\textsuperscript{3} Enthesitis (inflammation at the insertion sites of tendons on bone) is the predominant characteristic of PsA.\textsuperscript{4} Usually, one to three joints are involved. The fingers and toes (usually in an asymmetric pattern) are very commonly affected and may become “sausage digits” due to dactylitis, an inflammation along the entire periosteum of the bone.\textsuperscript{3,8} In many patients, Achilles tendinitis or lateral epicondylitis (“tennis elbow”) develop. Importantly, the severity of PsA does not correlate with the severity of cutaneous psoriatic disease: patients may have severe psoriasis and no PsA, or severe PsA and mild psoriasis.\textsuperscript{3}

**Diagnostic Criteria**

The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria are widely used in the process of PsA diagnosis. These criteria relate to five domains of PsA: evidence of psoriasis, psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis, and juxta-articular new bone formation. In the CASPAR scoring system, current evidence of psoriasis counts for the most points (2 points), but personal and family history also carry weight (1 point each), as does a history of dactylitis (1 point); thus, it is important to obtain a thorough, focused history. The other domains count as 1 point each. To meet CASPAR criteria for PsA, a patient must have inflammatory articular disease involving the joint, spine, or enthesis, and a CASPAR score of \( \geq 3 \) points (Table 1).\textsuperscript{23}

The differential diagnosis of PsA includes RA, osteoarthritis, gout, and polyarticular pseudogout (Table 2).\textsuperscript{3,4,24,25} All of these conditions involve joint stiffness. Only RA has sym-

<table>
<thead>
<tr>
<th>Table 1. CASPAR Criteria for PsA\textsuperscript{23}</th>
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</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
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<tr>
<td>Evidence of psoriasis</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Psoriatic nail dystrophy</td>
</tr>
<tr>
<td>Negative for rheumatoid factor</td>
</tr>
<tr>
<td>Dactylitis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Juxta-articular new bone formation</td>
</tr>
</tbody>
</table>

To meet CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine, or enthesis) plus \( \geq 3 \) points from the categories listed above.
metric involvement of joints. Only PsA is accompanied by nail lesions, and psoriasis is uncommon with the alternative diagnoses. Still, the differential diagnosis may be challenging: patients with PsA may also have acute gout (including enthesitis); x-ray and examination may both be needed to differentiate osteoarthritis and PsA; patients who are rheumatoid factor–positive may have RA with PsA. The ratio of female to male patients is 3:1 for RA but 1:1 for RA with PsA. In patients with psoriasis, clinicians should look for signs and symptoms of PsA at each visit. If PsA is suspected but unclear, referral to a rheumatologist is indicated.

### Treatment of Psoriatic Disease

Pharmacologic treatments for moderate to severe psoriatic disease broadly include topical therapies, phototherapy, conventional systemic agents, biologics, and, most recently, the oral agent apremilast, a phosphodiesterase type 4 inhibitor. Some of these agents are approved for both psoriasis and PsA and some for psoriasis only or PsA only. Topical therapies and phototherapy may be used in combination with systemic therapies for patients with moderate to severe disease, but they should be used in combination only.

Guidelines from the NPF and the American Academy of Dermatology recommend first- and second-line treatments for psoriasis but do not state preferences within the categories. First-line treatments are adalimumab, cyclosporine, etanercept, infliximab, methotrexate, psoralen-ultraviolet A (PUVA), systemic retinoids (eg, acitretin), and ustekinumab. Second-line treatments are combination regimens, rotational therapy, or sequential therapy. Consensus guidelines further note that conventional systemic drugs such as methotrexate, while effective, carry the risk of end-organ toxicities and require monitoring of liver and kidney function. Because biologic therapies do not carry risks of end-organ toxicities, they may be considered as first-line therapy in some cases. For example, a patient with existing nonalcoholic fatty liver disease or cardiovascular disease may be more safely treated with a biologic agent.

<table>
<thead>
<tr>
<th>Peripheral disease</th>
<th>PsA</th>
<th>RA</th>
<th>Osteoarthritis</th>
<th>Gout</th>
<th>Polyarticular Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric</td>
<td>Symmetric</td>
<td>Asymmetric</td>
<td>__</td>
<td>Asymmetric</td>
<td></td>
</tr>
<tr>
<td>Axial joint/ spondylitis</td>
<td>Yes</td>
<td>__</td>
<td>No</td>
<td>Less often</td>
<td>Less often</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Morning/immobility</td>
<td>Morning/immobility</td>
<td>With activity</td>
<td>Yes</td>
<td>Morning</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nail lesions</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Yes</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Female:male ratio</td>
<td>1:1</td>
<td>3:1</td>
<td>1.7:1</td>
<td>__</td>
<td>1:1</td>
</tr>
</tbody>
</table>
PSORIATIC DISEASE

A successful treatment regimen includes patient education as well as clinician awareness of the patient’s experience with psoriatic disease. How does the patient feel? Is daily living affected by embarrassment, itching, or pain? What is the patient’s experience with treatment, and what expectations does the patient currently have for treatment? How does he or she feel about injectable infusion-based therapy versus oral therapy or topical agents? Asking about these issues, and then offering information about the options, is vital for encouraging adherence to therapy.28

**Phototherapy**

Phototherapy has anti-inflammatory actions, decreases keratinocyte proliferation, and is especially effective for psoriasis on the soles and palms. Use of a narrowband UVB light is preferred over broadband UVB light; however, broadband PUVA may be considered if narrowband UVB is unsuccessful. Phototherapy can be used alone or in combination with topical agents. However, phototherapy is not used as widely as it once was. A drawback is the time commitment and cost: phototherapy is generally administered three times per week for $\geq 3$ months, with each visit typically requiring insurance copayment. Patients are also at risk of burns, especially with narrowband UVB and PUVA.8,29

**Conventional Systemic Therapies**

Methotrexate is the most widely used systemic therapy for psoriatic disease; other conventional systemic agents are cyclosporine and acitretin, an oral retinoid (Table 3).29-31 Cyclosporine is not

| Table 3. Conventional Systemic Therapies for Moderate to Severe Psoriatic Disease29-31 |
|----------------------------------|------------------|------------------|
| **Cyclosporine** | **Acitretin** | **Methotrexate** |
| Suppresses immune system | Often used with UV light; least effective as monotherapy | Most widely prescribed systemic therapy for psoriasis; not approved (though often prescribed) for PsA |
| For severe psoriasis after failure of $\geq 1$ other systemic therapy | Response takes 3-6 mo | PASI 75 achieved in 36%-60% of patients after 16 wks |
| PASI 75 achieved in 50%-70% of patients after 8-16 wks | Efficacy is dose-dependent; can be used with biologics | For moderate or severe psoriasis; can be used in combination with biologics |
| Use limited to 1 yr | PASI 75 highly variable | Folic acid analogue |
| Initial dose is 3 mg/kg/d, usually divided into 2 doses | Oral retinoid; starting dose 10-25 mg/d; increase every 2 wks until xerosis appears | Single weekly dose: 15 mg and titrating up, if needed, to 25 mg Divided oral dose schedule: 2.5 mg every 12 h for 3 doses |
often used; it is usually chosen only after at least 1 other treatment has failed. This immunosuppressant is relatively effective, achieving PASI 75 (75% improvement in psoriasis area and severity index) in 50% to 70% of patients. However, cyclosporine can raise blood pressure and exacerbate gout, and it is contraindicated in patients with abnormal renal function. Acitretin is usually used in conjunction with phototherapy. The PASI 75 rates of acitretin are highly variable, but the drug has been less effective when used as monotherapy. Acitretin is also associated with increased triglyceride levels, which may already be elevated in patients with psoriatic disease.

Methotrexate is a folic acid analogue indicated for moderate or severe psoriasis; it is not approved by the US Food and Drug Administration (FDA) for PsA but is often prescribed for it. Like acitretin, methotrexate can be used in combination with biologic agents for psoriasis. It is associated with PASI 75 rates of 36% to 60% after 16 weeks. Patients take methotrexate in a single weekly dose of 15 mg (six 2.5-mg tablets), with titration to 25 mg (10 tablets) if needed. The regimen must be completed within 24 hours; hence, some practitioners switch from the oral drug to injectable methotrexate if titration reaches the higher ranges. Patients taking methotrexate must significantly limit or eliminate alcohol consumption due to a risk of hepatotoxicity. Those with liver disease are not good candidates for cyclosporine; methotrexate may reduce the incidence of cardiovascular disease in patients with psoriatic disease. Methotrexate, like acitretin, is contraindicated in pregnant women. Cyclosporine is a category C drug (may be beneficial to pregnant women despite risks).

Systemic Biologic Therapy: Moderate to Severe Psoriatic Disease
The largest category of biologics is TNF-α inhibitors. Etanercept, adalimumab, and infliximab are indicated for both psoriasis and PsA. Etanercept and adalimumab are delivered by patient self-injection and infliximab by IV infusion. Adalimumab and infliximab each have achieved PASI 75 rates of about 80%, and etanercept about 50%. Once achieved, these rates are usually maintained. With adalimumab treatment, for example, the PASI 75 response achieved at 16 weeks was still evident at 2 years. Two other TNF-α inhibitors, golimumab and certolizumab, are indicated for PsA only. They have been shown to improve clinical and radiographic findings of disease progression. Golimumab and certolizumab may be self-injected subcutaneously; the lyophilized form of certolizumab may be injected by a clinician but is too viscous to be self-injected. Both agents are associated with upper respiratory infections and, like all TNF-α inhibitors, may increase the risk of infections and malignancies, as noted in black-box warnings on their labeling (Table 4).

Several biologic therapies target the IL cytokines activated in psoriatic disease. Ustekinumab is an IL-12/23 inhibitor approved for both psoriasis and PsA. It achieved PASI 75 in 33% of patients with psoriasis after 12 weeks. Like other IL inhibitors, ustekinumab is not associated with increased risks for infection or malignancy. Further, it is not associated
### Table 4. Biologic Therapies: Moderate to Severe Psoriatic Disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Studies</th>
<th>Common AEs</th>
<th>Black-Box Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-α Inhibitors</strong></td>
<td></td>
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</tr>
<tr>
<td>Etanercept (psoriasis, PsA)</td>
<td>PASI 75 after 12-24 wks ~50%; &gt;3 yrs of clinical data show maintenance of effect</td>
<td>Injection site reaction, +ANA</td>
<td>Infection, malignancies</td>
</tr>
<tr>
<td>Adalimumab (psoriasis, PsA)</td>
<td>After 16 wks, ~80% of patients had PASI 75 response; response maintained over 2 yrs</td>
<td>Injection site reaction, +ANA, elevated alkaline phosphatase and cholesterol</td>
<td>Infection, malignancies</td>
</tr>
<tr>
<td>Infliximab (psoriasis, PsA)</td>
<td>3 major trials assessing efficacy; at wk 10, 80% (242/301) of patients treated with infliximab achieved PASI 75 response; after maintenance phase, patients maintained PASI 75</td>
<td>Infusion reactions, +ANA, elevated liver function tests, neutralizing antibodies</td>
<td>Infection, hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Golimumab (PsA only)</td>
<td>Effective in maintaining clinical improvement through 5 yrs</td>
<td>URIs, nasopharyngitis, injection site reactions</td>
<td>Serious infections, malignancies</td>
</tr>
<tr>
<td>Certolizumab pegol (PsA only)</td>
<td>Phase 3 trial: 200 mg every other wk resulted in greater reduction in radiographic progression vs placebo at wk 24 (ACR 20 60% vs 20% with placebo)</td>
<td>URIs, rash, urinary tract infections</td>
<td>Serious infections, malignancy</td>
</tr>
<tr>
<td><strong>IL-12/-23 Inhibitor</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ustekinumab (psoriasis, PsA)</td>
<td>2 phase 3 clinical trials: 33% of patients achieved PASI 75 after 12 wks</td>
<td>Nasopharyngitis</td>
<td>No</td>
</tr>
<tr>
<td><strong>IL-17A Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secukinumab (psoriasis, PsA)</td>
<td>4 clinical trials; with 300 mg, &gt;80% of patients achieved PASI 75 after 12 wks, and this was maintained at 52 wks in most patients</td>
<td>Nasopharyngitis, diarrhea, URIs; continued vigilance with respect to the potential for <em>Candida</em> infection needed</td>
<td>No</td>
</tr>
<tr>
<td>Ixekizumab (psoriasis only)</td>
<td>3 clinical trials, &gt;3800 patients; at 12 wks, 87%-90% of patients had 75% improvement in PASI score; response maintained in 75%</td>
<td>Injection site reactions, URIs, nausea, tinea infections</td>
<td>No</td>
</tr>
</tbody>
</table>

Serious AEs of tuberculosis, cancer, heart failure, and hepatitis B reactivation occur in <0.1% of patients taking biologics, which are generally considered safe during pregnancy. 

AE = adverse event; ANA = antinuclear antibodies; URI = upper respiratory infection.
with multiple sclerosis, whereas TNF-α therapy should be avoided in patients with demyelinating disease. Accordingly, ustekinumab may be an appropriate first-line agent for patients with psoriatic disease with multiple sclerosis or a history of cancer. Secukinumab, an IL-17A inhibitor, is approved by the FDA for both psoriasis and PsA, as well as for ankylosing spondylitis. This agent achieves a PASI 75 rate of 82% after 12 weeks and 81% after 52 weeks. Another IL-17A inhibitor, ixekizumab, received approval in 2016 for psoriasis only. At 12 weeks, ixekizumab achieved PASI 75 with 87% to 90% of patients and the response maintained in 75% of cases. IL therapies can all be administered by the patient as subcutaneous injections (Table 4).

Apremilast, an Oral Option
Apremilast, a phosphodiesterase type 4 inhibitor, is the newest oral treatment for moderate to severe psoriatic disease. It prevents the conversion of cyclic adenosine monophosphate within immune cells, thereby reducing multiple inflammatory cytokines underlying psoriasis and PsA. Apremilast is taken as a pill twice daily. Dose titration is recommended at the start of therapy; for patients with creatinine clearance <30 mL/min, the maximal dose of apremilast should be ≤30 mg/day. Patients should undergo screening for depression, as apremilast is associated with increased risk of depression. Other side effects (occurring in ≥5% of patients) are diarrhea, headache, nausea, and upper respiratory infection. Some patients lose substantial weight while taking apremilast, so weight should be monitored over time. Apremilast has been used safely with other systemic or biologic agents for psoriatic disease, but these combinations are off label; clinical trials are ongoing. Strong cytochrome P450 inducers, such as rifampin, reduce the efficacy of apremilast.

Treatment of PsA
The goals of treatment in PsA are to alleviate signs and symptoms of arthritis, inhibit structural damage to joints, and maximize quality of life. The GRAPPA guidelines note that therapeutic decisions should be individualized and reflect patient preferences; patient education on all treatment options is essential. Treatment choices are also individualized by the state of disease activity, extent of structural damage, presence of comorbid conditions, and use of previous psoriatic disease therapies.

Safety and Long-term Treatment Considerations
Before beginning treatment with a biologic drug, patients with psoriatic disease should be up to date on all necessary vaccinations; otherwise, they may have to interrupt biologic therapy (4 weeks before and after vaccination) to ensure that it does not weaken any live vaccine. TNF-α inhibitors can be associated (although rarely) with bone marrow toxicity, hence the need for a routine monitoring of complete blood cell counts with platelet count. Liver function testing is appropriate if the patient is receiving combination therapy with methotrexate, leflunomide, or azathioprine. Tuberculosis screening (skin or blood test) is necessary before and during therapy with TNF-α inhibitors and before therapy with IL inhibitors. TNF-α inhibitors may reactivate hepatitis B viral activity; thus, candidates for these biologics require
screening for hepatitis B virus using triple serology (surface antigen, surface antibody, and core antibody). Candidates for secukinumab, ustekinumab, ixekizumab, cyclosporine, and methotrexate should undergo the same screening.\textsuperscript{43}

Over time, the most common adverse effects of biologic therapy are upper respiratory infections, injection site reactions, headache, and fatigue. In a follow-up of adalimumab therapy, overall malignancy rates across 12 years did not differ from rates in the general population. No new safety signals emerged from the data.\textsuperscript{8,44,45} Ustekinumab has shown no evidence of dose-related or cumulative toxicity with exposure of $\leq 5$ years. IL-17A inhibitors also show maintenance of effect and no new safety signals. More than half of patients treated with ixekizumab as maintenance therapy achieved complete resolution of psoriasis at 60 weeks.\textsuperscript{8,45,46}

**Summary**

Psoriatic disease, comprising psoriasis and PsA, is a chronic systemic inflammatory condition. It is closely linked with numerous comorbidities, perhaps the most notable being cardiovascular comorbidities; in fact, it is now clear that there is a pathogenetic link via insulin resistance with cardiovascular diseases. Psoriatic disease is underdiagnosed and undertreated—an irony, considering the availability of effective treatments, including biologics, that can bring about rapid improvement.

**Presentation**

George, 59, presents with a flare of psoriasis. He has a 15-year history of mild to occasionally moderate psoriasis, for which he applies calcipotriene. Now he reports more frequent flares and severe itching, mainly on his hands, and his affected BSA is 10\% (severe psoriasis). George also has elevated blood pressure (141/91 mm Hg), fasting plasma glucose (121 mg/dL), and triglycerides (260 mg/dL). He is verging on obesity (BMI: 29 kg/m$^2$). He takes simvastatin 20 mg and hydrochlorothiazide 25 mg.

**Clinical Decision Point**

*In addition to assessing psoriatic disease activity and quality-of-life impairment, what assessment is most appropriate for George?*

A. Central adiposity  
B. C-reactive protein (CRP)  
C. Cardiovascular disease risk assessment  
D. Erythrocyte sedimentation rate (ESR)
Comment
Cardiovascular disease risk assessment is the most appropriate next step for George. His findings indicate metabolic syndrome, which is strongly associated with psoriatic disease. As psoriatic disease progresses, so do the chances of hypertension, diabetes, and dyslipidemia—components of metabolic syndrome—and the risk of cardiovascular events. Clinicians should alert their patients to these associations and ensure guideline-based cardiovascular risk assessment. George requires medication adjustments and education on weight loss, exercise, and diet. Nonspecific inflammatory markers such as CRP or ESR may be useful in classifying psoriatic disease severity and response to treatment, but they may also reflect adiposity, arthritis, or cardiovascular disease. Correct answer: C.

Case Study (cont’d)
After reviewing treatments with George, he selects methotrexate. After 1 year, his hands are free of psoriasis and his affected BSA is 6%. He has lost and regained 10 lbs; his metabolic parameters are somewhat improved. However, George says he has become depressed since separating from his wife. He is seeing a therapist but has begun drinking two or three martinis nightly.

Clinical Decision Point
What should you do next to manage George’s psoriatic disease?
A. Add a biologic to methotrexate
B. Recommend a biologic agent in place of methotrexate
C. Switch him to apremilast
D. Switch him to cyclosporine

Comment
Greater than moderate alcohol consumption is an important risk factor for liver and blood toxicities in patients taking methotrexate. George must discontinue methotrexate as either monotherapy or in a combination regimen. Cyclosporine is inappropriate for him, given this drug’s propensity to increase blood pressure and triglycerides. With both psoriatic disease and depression associated with increases in TNF-α, the hope has been that TNF-α inhibition would improve both conditions. Limited data from studies of etanercept, ustekinumab, and adalimumab suggest improvement in depression among patients with psoriatic disease. Depressive symptoms were reduced by 55% with etanercept. However, George expresses anxiety and fear about self-injection—concerns reported by about 25% of patients using biologics. Although apremilast has the potential to promote depression, it is also associated with weight loss: in the ESTEEM trials, approximately 19% of patients taking apremilast lost 5% of their body weight over 2 years. George attributes much of his depression to his weight struggles, and he would like to see if he can lose weight in the course of treating his psoriasis. Correct answer: B or C.
Case Conclusion
George begins therapy with apremilast. At 3 months, his psoriasis is diminished (4% BSA) and he has begun to limit his drinking and has lost weight. He continues seeing his therapist and reports a mild improvement in his depression.

References


