

# Pathophysiology, Clinical Presentation, and Treatment of Psoriasis

## A Review


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**IMPORTANCE** Approximately 125 million people worldwide have psoriasis. Patients with psoriasis experience substantial morbidity and increased rates of inflammatory arthritis, cardiometabolic diseases, and mental health disorders.

**OBSERVATIONS** Plaque psoriasis is the most common variant of psoriasis. The most rapid advancements addressing plaque psoriasis have been in its pathogenesis, genetics, comorbidities, and biologic treatments. Plaque psoriasis is associated with a number of comorbidities including psoriatic arthritis, cardiometabolic diseases, and depression. For patients with mild psoriasis, topical agents remain the mainstay of treatment, and they include topical corticosteroids, vitamin D analogues, calcineurin inhibitors, and keratolytics. The American Academy of Dermatology-National Psoriasis Foundation guidelines recommend biologics as an option for first-line treatment of moderate to severe plaque psoriasis because of their efficacy in treating it and acceptable safety profiles. Specifically, inhibitors to tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) include etanercept, adalimumab, certolizumab, and infliximab. Other biologics inhibit cytokines such as the p40 subunit of the cytokines IL-12 and IL-13 (ustekinumab), IL-17 (secukinumab, ixekizumab, bimekizumab, and brodalumab), and the p19 subunit of IL-23 (guselkumab, tildrakizumab, risankizumab, and mirikizumab). Biologics that inhibit TNF- $\alpha$ , p40IL-12/23, and IL-17 are also approved for the treatment of psoriatic arthritis. Oral treatments include traditional agents such as methotrexate, acitretin, cyclosporine, and the advanced small molecule apremilast, which is a phosphodiesterase 4 inhibitor. The most commonly prescribed light therapy used to treat plaque psoriasis is narrowband UV-B phototherapy.

**CONCLUSIONS AND RELEVANCE** Psoriasis is an inflammatory skin disease that is associated with multiple comorbidities and substantially diminishes patients' quality of life. Topical therapies remain the cornerstone for treating mild psoriasis. Therapeutic advancements for moderate to severe plaque psoriasis include biologics that inhibit TNF- $\alpha$ , p40IL-12/23, IL-17, and p19IL-23, as well as an oral phosphodiesterase 4 inhibitor.

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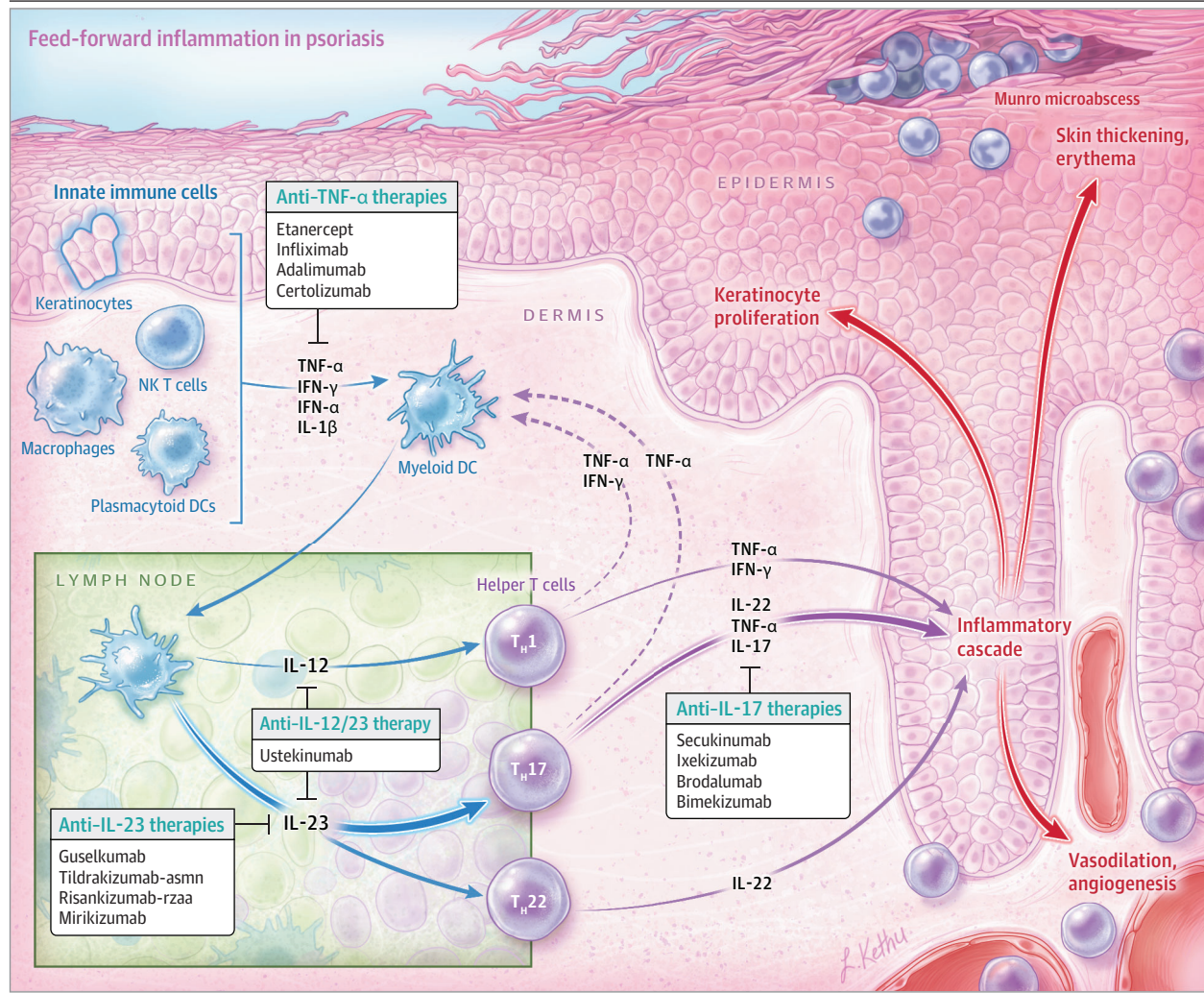
**P**soriasis is a chronic, immune-mediated skin disease that affects approximately 3% of the US population and an estimated 125 million people worldwide.<sup>1-3</sup> Plaque psoriasis is the most common variant, accounting for more than 80% of the psoriasis cases. Plaque psoriasis is characterized by erythematous scaly patches or plaques that occur commonly on extensor surfaces, but it can also affect the intertriginous areas, palms, soles, and nails. Psoriasis affects men and women equally, and it affects adults more than children.<sup>1,3,4</sup> The most rapid advancements in plaque psoriasis have been in its pathogenesis, genetics, comorbidities, and biologic treatments. The pathogenesis of plaque psoriasis involves a feed-forward mechanism of inflammation including primarily the T-helper cell type 17 (T<sub>H</sub>17) pathway. Genetic factors play a critical role in the development of psoriasis, and environmental factors can exacerbate psoriasis. Other morphologic variants of psoriasis include guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. This review discusses pathogenesis, clinical

presentation, diagnosis, and treatments for psoriasis, with a focus on plaque psoriasis.

## Methods

A literature search was conducted through February 13, 2020, using PubMed and the Cochrane databases for the terms *psoriasis* and *epidemiology*, *psoriasis* and *pathophysiology*, *psoriasis* and *diagnosis*, *psoriasis* and *comorbidities*, and *psoriasis* and *treatment*. The authors selected articles that described pivotal and novel insights in psoriasis. Additional studies were found using the bibliographies of selected articles as well as studies that were cited in treatment guidelines published by the American Academy of Dermatology.<sup>5-9</sup> Specific searches were made for citations dated after the year 2000 to ensure more recent literature on the topic had not been missed.

Figure 1. Pathophysiology of Psoriasis



The pathophysiology of psoriasis involves excessive feed-forward activation of the adaptive immune system. Activated myeloid dendritic cells secrete excess IL-12 and IL-23. IL-12 induces differentiation of naive T cells to T-helper cells type 1 ( $T_H1$ ). IL-23 is central to the survival and proliferation of  $T_H17$  and  $T_H22$  cells.  $T_H17$  cells (and a multitude of other inflammatory cells) secrete IL-17;  $T_H1$  cells

secrete tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ); and  $T_H22$  cells secrete IL-22. These secreted cytokines activate intracellular signal transduction in keratinocytes to bring about gene transcription of cytokines and chemokines. This results in an inflammatory cascade that leads to psoriatic disease manifestations. DC indicates dendritic cell; IFN, interferon; NK, natural killer.

## The Pathogenesis of Psoriasis

The pathogenesis of psoriasis is complex and not fully elucidated. Excessive activation of parts of the adaptive immune system is thought to be central to the pathogenesis of psoriasis.<sup>10</sup> In the initial steps of psoriasis pathogenesis, a variety of cell types, including plasmacytoid dendritic cells, keratinocytes, natural killer T cells, and macrophages, secrete cytokines that activate myeloid dendritic cells (Figure 1). For example, DNA-LL37 complexes stimulate plasmacytoid dendritic cells to secrete interferon alfa (IFN- $\alpha$ ) which, in turn, activates myeloid dendritic cells. Once activated, myeloid dendritic cells secrete IL-12 and IL-23. IL-12 induces differentiation of naive T cells to  $T_H1$  cells. IL-23 is central to the survival and proliferation of  $T_H17$  and  $T_H22$  cells.  $T_H1$  cells secrete interferon gamma (IFN- $\gamma$ ) and TNF- $\alpha$ ;  $T_H22$  cells secrete IL-22; and  $T_H17$  cells secrete IL-17, IL-22,

and TNF- $\alpha$ .<sup>11</sup> Among these pathways, IL-23-mediated activation of the  $T_H17$  pathway is thought to be predominant.<sup>11</sup> IL-23 signaling is mediated intracellularly via Tyk2-Jak2 and STAT3, which leads to transcription of key inflammatory mediators. These cytokines lead to downstream keratinocyte proliferation, increased expression of angiogenic mediators and endothelial adhesion molecules, and infiltration of immune cells into lesional skin (Figure 1).<sup>10</sup>

## Epidemiology

In the United States, psoriasis affects approximately 3.2% of adults, 0.13% of children,<sup>1,3,4</sup> and the incidence is approximately 80 new cases per 100 000 person-years.<sup>12</sup> Worldwide, approximately 125 million people have psoriasis, and psoriasis prevalence is highly variable across regions, ranging from 0.5% in parts of Asia to as high

as 8% in Norway.<sup>2,12,13</sup> In most regions, women and men are affected equally.<sup>12</sup>

While psoriasis can manifest at any age, a bimodal age distribution exists for psoriasis presentation at ages 18 to 39 years and also at ages 50 to 69 years.<sup>12</sup> Genetic and environmental factors may influence the age at onset of psoriasis. For example, the presence of the human leukocyte antigen (HLA)-C\*06 allele is associated with earlier-onset age of psoriasis.<sup>14</sup>

## Clinical Presentation

Clinical features of psoriasis differ depending on the psoriasis variant. Psoriasis variants include plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. While one variant typically predominates in an individual person, different variants may coexist in a person at any single point in time. Most variants of psoriasis share 3 key clinical features of erythema, thickening, and scale. Because plaque psoriasis is the most common, this review emphasizes the clinical presentation of plaque psoriasis (Box 1).

### Plaque Psoriasis

Plaque psoriasis represents approximately 80% to 90% of all manifestations of psoriasis. Plaque psoriasis presents as sharply demarcated, erythematous, scaly patches or plaques (Figure 2). While plaque psoriasis can occur anywhere on the body, commonly affected areas include the scalp, trunk, gluteal fold, and extensor surfaces such as the elbows and knees. Lesions in plaque psoriasis can range from small erythematous and scaly papules to large thick plaques. Affected areas are characteristically well-demarcated and often symmetric. In the koebner phenomenon, new psoriasis lesions can develop at the site of trauma, such as from scratching, cuts, or pressure. When the scale is lifted from the plaque, pinpoint bleeding may occur and create an Auspitz sign. Patients can experience substantial pruritus with moderate to severe psoriasis or during exacerbation.

Plaque psoriasis has a disproportionate effect on quality of life when it involves certain regions such as the face, palms and soles, nails, or intertriginous areas (also called inverse psoriasis; refers to psoriasis involving the skin folds, eg the axillary, inframammary, and genital regions). Due to the moist skin environment in which intertriginous psoriasis occurs, it lacks the typical scales seen with psoriasis in nonintertriginous areas, and it can be commonly misdiagnosed as a fungal infection. Genital psoriasis occurs in approximately one-third of psoriasis patients and is associated with substantially decreased quality of life. When plaque psoriasis affects the palms and soles, patients develop thick, scaly, and painful plaques that limit their function of the hands and feet. Psoriasis affecting the nail apparatus can lead to pitting, onycholysis (separation of the nail plate from the nail bed), and dystrophy of fingernails and toenails. In most patients, the external triggers for psoriasis are unknown.

### Other Variants of Psoriasis

There are 3 other less-frequently observed variants of psoriasis: guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. Guttate psoriasis comprises 2% of psoriasis cases and is characterized by multiple 3- to 5-mm confetti-like, pink scaly patches. Approximately 66% of new-onset guttate psoriasis is preceded by an up-

### Box 1. Commonly Asked Questions About Psoriasis

How does psoriasis present and how is the diagnosis made?

Psoriasis appears as red, scaly, raised patches or plaques. Psoriasis is often diagnosed clinically, but a biopsy can be used to confirm the diagnosis.

How is a diagnosis of psoriatic arthritis made?

Diagnostic workup of psoriatic arthritis involves evaluation for peripheral inflammatory arthritis, dactylitis (inflammation of a finger or toe), enthesitis (inflammation that occurs when tendons or ligaments insert into bone), and axial involvement. The classification of psoriatic arthritis (CASPAR) criteria and screening questionnaires can be used to aid diagnosis. In all patients suspected of having psoriatic arthritis, a referral to a rheumatologist should be considered.

When psoriasis is present, are there other disease entities that should be investigated?

It is recommended that patients with psoriasis be screened for psoriatic arthritis, psychological illnesses such as depression, cardiometabolic diseases, and inflammatory bowel disease (see Table 1).

What first-line treatments for psoriasis should be implemented in primary care before referring patients to specialists?

In patients with mild psoriasis (body surface area <5%), topical treatments such as topical corticosteroids, topical calcineurin inhibitors, and topical vitamin D analogues should be tried. In patients with moderate to severe psoriasis (body surface area >5%), involvement of special areas, or recalcitrant psoriasis, a referral to a dermatologist should be made for consideration of systemic treatments.

What should I tell patients about medications advertised in the popular media for the treatment of psoriasis?

Most medications advertised in the popular media for the treatment of psoriasis are for patients with moderate to severe disease. Responses to these medications may vary depending on the individual. In addition, the adverse events that are reported in commercials typically occur in only a small proportion of patients. The most important step is to consult with a dermatologist, if the psoriasis is not adequately managed, to help identify an optimal individualized treatment option.

What is the long-term prognosis for psoriasis?

Psoriasis is a chronic skin disease with no known cure at this time. However, the severity of psoriasis can oscillate over time, and its symptoms can be effectively controlled with treatments.

per respiratory tract infection such as streptococcal infection, and most of these cases resolve spontaneously in weeks to months but can become chronic. Erythrodermic psoriasis is an uncommon severe variant in which patients develop coalescent erythema, scales, or exfoliation involving at least 75% of the body. Although erythrodermic psoriasis occurs in only 2% to 3% of psoriasis cases, it is treated as a dermatological emergency because it can be associated with electrolyte disturbances and desquamation that can be life-threatening. Another uncommon variant is pustular psoriasis, which is characterized by sterile pustules and erythema. Pustular psoriasis can be generalized, such as in generalized pustular psoriasis; it is associated with an interleukin 36 receptor antagonist (IL36RN) sequence variation (formerly mutation) and can be triggered by factors such as expeditious steroid tapering, hypocalcemia, pregnancy, or infection. Pustular psoriasis can also be localized, as in pustulosis of palms and soles or acrodermatitis continua of hallopeau.

Figure 2. Clinical Presentation of Psoriasis



Skin thickening and erythema, characteristic of psoriasis, are shown. Panels A, B, and C (patient A) exhibit multiple manifestations of psoriasis on the trunk, extremities, intergluteal fold, and toenails. Panel D (patient B) shows manifestations of psoriatic arthritis including fingernail involvement.

## Risk Factors

Risk factors for the development of psoriasis include genetic, environmental, and behavioral factors, with genetic factors being the largest contributor.<sup>15</sup> Significant progress has been made in the understanding of psoriasis genetics. Psoriasis is a polygenetic disease in which multiple identified alleles (HLA-Cw6, HLADQ\* 02:01, CCHCR1, and CYP1A1) and loci (PSORS1-9, PSORSAS1) confer genetic risks for psoriasis development.<sup>15,16</sup> One European study showed that the risk of psoriasis is approximately 40% if both parents are affected, 14% if one parent is affected, and 6% if a sibling is affected.<sup>17</sup> In genetically susceptible individuals, psoriasis can be exacerbated by several environmental and behavioral factors including skin trauma, infections (eg, streptococcal infection), smoking, certain medications such as lithium and interferon, and possibly stress.<sup>18</sup>

## Comorbidities Associated With Psoriasis

Substantial progress has been made during the last 2 decades in elucidating comorbidities associated with psoriasis (Box 2).<sup>19</sup> Approximately one-third of psoriasis patients develop psoriatic arthritis during their lifetime.<sup>20</sup> In approximately 85% of patients with psoriatic arthritis, psoriasis either precedes or occurs concurrently with psoriatic arthritis. Psoriatic arthritis is characterized by stiffness, pain, and swelling of joints and can progress to debilitating joint destruction. Psoriatic nail pitting and onycholysis are seen in 80% to 90%

of patients with psoriatic arthritis. Screening for psoriatic arthritis can be performed using different screening questionnaires<sup>21,22</sup> such as the Psoriasis Epidemiology Screening Tool (sensitivity, 77%; specificity, 37%; area under the receiver-operating curve, 0.61).<sup>23</sup> Psoriatic arthritis can be classified using CASPAR (classification of psoriatic arthritis) criteria (sensitivity, 99.7% and specificity, 99.1%).<sup>24</sup> CASPAR classifies someone with inflammatory arthritis as having psoriatic arthritis based on the presence of psoriasis and/or nail lesions, dactylitis, negative rheumatoid factor, and/or radiographic evidence of juxta-articular bone growth that is distinctive to osteophytes. It is important to distinguish psoriatic arthritis from other joint diseases in patients with psoriasis because only 56% of patients with psoriasis and joint symptoms have psoriatic arthritis.<sup>25</sup>

Patients with severe psoriasis or those who develop psoriasis at a young age are at higher risk for cardiometabolic comorbidities than the general population.<sup>26-32</sup> Psoriasis is associated with vascular inflammation and high-risk coronary atherosclerotic plaques.<sup>26,27,29</sup> Specifically, the proportion of psoriasis patients with moderate to severe coronary artery calcification is similar to those with type 2 diabetes (18.6% vs 20.9% having coronary artery calcification  $\geq 101$ ;  $P = .45$ ).<sup>26</sup> Furthermore, psoriasis is associated with a prevalence of high-risk coronary atherosclerotic plaques (34%) similar to the prevalence in hyperlipidemic patients (38%;  $P = .58$ ).<sup>27</sup> Regarding major adverse cardiovascular outcomes, severe psoriasis is associated with an increased risk of myocardial infarction (risk ratio [RR], 1.70 [95% CI, 1.32-2.18]), stroke (RR, 1.56 [95% CI, 1.32-1.84]), and cardiovascular mortality (RR, 1.39 [95% CI, 1.11-1.74]).<sup>33-40</sup> After accounting for traditional cardiovascular risk factors, severe

psoriasis appears to remain as an independent risk factor for these adverse cardiovascular outcomes.<sup>31,41</sup>

Patients with psoriasis are also at increased risk of other comorbidities such as depression, anxiety, and suicidal ideation.<sup>42-44</sup> Compared with the general population, patients with psoriasis are at a higher risk of depression (odds ratio [OR], 1.57 [95% CI, 1.40-1.76]), anxiety (OR, 2.91 [95% CI, 2.01-4.21]), and suicidal ideation (OR, 2.05 [95% CI, 1.54-2.74]).<sup>42-44</sup> In addition, psoriasis is associated with a 4-times greater prevalence of inflammatory bowel diseases compared with the general population (1.6% [95% CI, 1.0%-2.2%] vs 0.4%).<sup>45</sup> Psoriasis and Crohn disease share the same susceptibility loci on chromosome 16q, which may account for this association.<sup>46</sup>

## Differential Diagnoses and Workup

The differential diagnoses for psoriasis include inflammatory, infectious, and neoplastic conditions such as atopic dermatitis, seborrheic dermatitis, pityriasis rosea, syphilis, and cutaneous T cell lymphoma. For example, atopic dermatitis can present similarly to plaque psoriasis as pruritic erythematous patches and plaques that can have scale. However, atopic dermatitis lesions itch more consistently and lack the characteristic clear demarcation at the lesion edge seen in plaque psoriasis. The diagnostic workup for psoriasis includes a family history of psoriatic diseases and a comprehensive skin and nail examination, which includes evaluation of morphology and distribution of psoriasis lesions. In most patients, psoriasis can be diagnosed clinically. However, a skin biopsy may be required for cases in which the presentation is not typical.

## Treatments for Mild Psoriasis

The definition of mild psoriasis varies, but it typically involves less than 3% to 5% of affected body surface area. The overall treatment approach for psoriasis begins with evaluation for psoriatic arthritis (Figure 3) because regardless of the extent of psoriasis, the presence of active psoriatic arthritis may alter treatment choices in favor of options that are effective for both psoriasis and psoriatic arthritis.<sup>47</sup> For patients with mild psoriasis, treatment options include topical corticosteroids, vitamin D analogues, calcineurin inhibitors, keratolytics, and targeted phototherapy (Figure 3, Table 1).<sup>5,48-54,56-60</sup>

### Topical Corticosteroids

Topical corticosteroids are the mainstay therapy for most patients with mild or localized psoriasis (Table 1). Topical corticosteroids exert anti-inflammatory, antiproliferative, and locally vasoconstrictive effects via down-regulation of genes coding proinflammatory cytokines. In general, mild or localized psoriasis is responsive to topical corticosteroids if the appropriate strength is used and if the patient is adherent to using as prescribed. The efficacy of topical corticosteroids differ based on the class (determined using vasoconstrictive assays), with class I having the strongest potency (*superpotent*) and class VII having the weakest (*least potent*). The choice of strength and vehicle of topical corticosteroids should be based on body location to minimize adverse effects and maximize adherence (Table 1). For the trunk and extremities, high- to

## Box 2. Psoriasis Comorbidities, Screening Recommendations, and Levels of Evidence<sup>a</sup>

### Psoriatic arthritis

Inform patients of the association between psoriasis and psoriatic arthritis (B)

Consider psoriatic arthritis in all patients with psoriasis (B)

Evaluate for peripheral inflammatory arthritis, dactylitis, enthesitis, and axial involvement (screening questionnaires can be considered such as the Psoriasis Epidemiology Screening Tool) (A)

Start treatment for all patients diagnosed with psoriatic arthritis; refer to a rheumatologist if a diagnosis cannot be confidently made (A)

### Cardiometabolic diseases (eg, myocardial infarction, stroke, and peripheral vascular disease)

Inform patients of the increased risk for metabolic syndrome (B)

Evaluate for cardiometabolic risk factors (including hypertension, diabetes, body mass index<sup>b</sup>  $\geq 25$ , hypercholesterolemia, and hyperlipidemia) using national guidelines (B)

Consider early and more frequent screening of cardiovascular risk factors in patients with more severe disease (B)

Refer to primary care physician for further evaluation if there is evidence of hypertension (A), hyperlipidemia or hypercholesterolemia (B), and/or prediabetes or new-onset diabetes<sup>c</sup> (C)

Encourage patients with obesity to maintain a healthy lifestyle and to schedule regular follow-ups with their physician; consider bariatric surgery if body mass index<sup>b</sup> is  $>40$  and other weight loss measures are unsuccessful (B)

### Psychological illnesses (depression, anxiety)

Inform patients of the association between psoriasis and anxiety and depression (B)

Evaluate for anxiety and depression (screening questionnaires can be considered such as the Patient Health Questionnaire-2 and the Goldberg Anxiety and Depression Scale) (B)

Refer to appropriate specialist for further evaluation if there is evidence of anxiety, depression, or suicidal ideation (A)

Use psoriasis treatments as a means to improve associated anxiety and depression (B)

### Inflammatory bowel diseases: Crohn disease, ulcerative colitis

Inform patients of the association between psoriasis and inflammatory bowel diseases (B)

Refer patients with concern about inflammatory bowel diseases to a primary care physician or gastroenterologist for further evaluation (A)

Start psoriasis treatments for patients with inflammatory bowel diseases who develop psoriasis from lesions while prescribed an anti-TNF- $\alpha$  medication. Consider discontinuation of anti-TNF- $\alpha$  if psoriasiform lesions persist (B)

Avoid IL-17 inhibitors in patients with inflammatory bowel diseases (C)

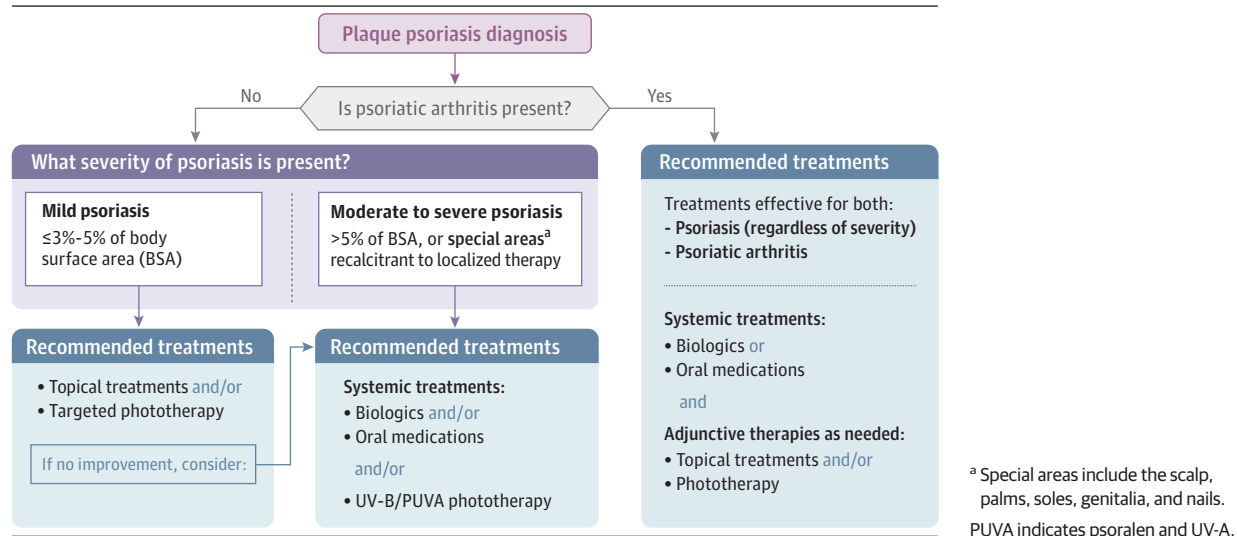
Abbreviation: TNF, tumor necrosis factor.

<sup>a</sup> Recommendations are from the American Academy of Dermatology and the National Psoriasis Foundation (Elmets et al,<sup>8</sup> 2019). Parenthetical A, B, and C indicators reflect levels of evidence.

<sup>b</sup> Body mass index is calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup> Referral to a cardiologist or endocrinologist may be necessary in some cases.

Figure 3. Overall Treatment Approach for Plaque Psoriasis



midpotency topical corticosteroids (classes I-III) can be used. If the lesions are thick, superpotent topical corticosteroids are recommended. For facial, axillary, inframammary, and groin areas, low-potency topical corticosteroids are generally preferred (classes VI and VII).

Multiple regimens exist for the use of topical corticosteroids for mild or localized psoriasis. During the acute phase of active psoriasis, patients can apply the topical corticosteroid twice daily until the lesions are clear or almost clear. Once the lesions are quiescent, patients can switch to applying a topical agent (eg, topical corticosteroid, vitamin D analogue, or calcineurin inhibitor) twice per week (eg, Monday and Thursday [Table 1]). This regimen, in which topical therapies are applied when lesions are quiescent, is known as proactive management during the maintenance phase, and it reduces risk of recurrence.<sup>61</sup>

Topical corticosteroids can be used in conjunction with topical vitamin D analogues or keratolytic agents, either as 2 separate medications applied at separate times or as a single medication in a combined formulation (Table 1). Combined formulations include (1) topical corticosteroids with a topical vitamin D analogue such as betamethasone dipropionate and calcipotriene, or (2) topical corticosteroids with a keratolytic agent such as the halobetasol propionate and tazarotene combination. Combined formulations typically have higher efficacy, fewer adverse effects, and longer remission than either agents used as monotherapy.<sup>56,58</sup>

Adverse effects of topical corticosteroid use are summarized in Table 1. In children, long-term daily use of high-potency corticosteroids (ie, those in the class I or class II categories) over large body surface areas should be avoided, due to the potential risk of suppression of the hypothalamus pituitary and adrenal gland axis and other systemic effects (Table 1).

### Topical Vitamin D Analogues

Topical vitamin D analogues bind to vitamin D receptors on T cells and to vitamin D receptors on keratinocytes to block keratinocyte proliferation and boost keratinocyte differentiation. Three types of topical vitamin D analogues are used in the United States: calcitriol in combination with calcipotriol or calcipotriene (Table 1). The effi-

cacy of topical vitamin D agents is modest when used alone.<sup>48</sup> Topical vitamin D analogues can be used liberally as long as the patient does not have renal impairment. The maximum recommended quantities of topical vitamin D use in children with psoriasis is 50 g per week, and in adults with psoriasis, it is 100 g per week (Table 1).<sup>5</sup> The primary adverse effect is burning and irritation, which can occur in up to 35% of patients and typically lessen over time.<sup>50</sup>

### Topical Calcineurin Inhibitors

Topical calcineurin inhibitors block T cell activation by inhibiting the synthesis of IL-2 and IFN- $\gamma$ . Topical calcineurin inhibitors include tacrolimus and pimecrolimus, and they are frequently used to treat psoriasis in facial and intertriginous areas without the adverse effect of skin atrophy associated with long-term use (Table 1). As many as 71% of patients may experience clear or almost clear psoriasis after 8 weeks.<sup>52</sup> Common adverse effects include skin irritation, especially in highly inflamed lesions, but this can be reduced by treating first with topical corticosteroids before transitioning to topical calcineurin inhibitors (Table 1).

### Topical Keratolytics

Topical keratolytic agents include topical tazarotene and salicylic acid (Table 1). Topical tazarotene is a retinoid that inhibits proliferation of keratinocytes and helps to break down the thick scales on the plaque. As many as 63% of patients may experience at least a 50% improvement of psoriasis after 12 weeks.<sup>54</sup> Common adverse effects include burning and irritation and can be lessened via use of a lower concentration, cream formulation, alternate-day dosing, or use combined with topical corticosteroids (Table 1).<sup>58,59</sup> Topical salicylic acid is another keratolytic that may reduce scaling but can also be associated with irritation and should be avoided in children.

### Targeted Phototherapy

Phototherapy (also called light therapy) consists of exposure to specific wavelengths of light. Phototherapy has been used for decades to treat patients with plaque psoriasis. Unlike sunlight, phototherapy delivers specific wavelengths that are therapeutic for psoriasis, and it minimizes emission of wavelengths responsible for

Table 1. Topical Therapies Used in Psoriasis

Topical therapy	Use and efficacy	Limitations
<b>Topical corticosteroids</b>		
<p>Class I (betamethasone dipropionate, clobetasol propionate 0.05% cream, diflucortolone valerate [not available in the United States], fluocinonide, flurandrenolide 0.1%, halobetasol propionate 0.05%)<sup>a</sup></p> <p>Class II (amcinonide ointment 0.1%, mometasone furoate 0.1% ointment, clobetasol propionate 0.025%, desoximetasone, diflorasone diacetate, fluocinonide 0.05%, halcinonide, halobetasol propionate 0.01%)<sup>a</sup></p> <p>Class III (amcinonide cream or lotion 0.1%, betamethasone dipropionate, betamethasone valerate, desoximetasone, diflorasone diacetate, diflucortolone valerate [not available in the United States], fluocinonide 0.05% cream, fluticasone propionate, mometasone furoate, triamcinolone acetonide)<sup>a</sup></p> <p>Class IV (betamethasone dipropionate, clocortolone pivalate, fluocinolone acetonide, flurandrenolide, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide 0.1% cream)<sup>a</sup></p> <p>Class V (betamethasone dipropionate, betamethasone valerate, desonide, fluocinolone acetonide 0.01% cream, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone valerate, prednicarbate, triamcinolone acetonide)<sup>a</sup></p> <p>Class VI (alclometasone dipropionate, betamethasone valerate, desonide 0.05% gel, fluocinolone acetonide, triamcinolone acetonide)<sup>a</sup></p> <p>Class VII: (hydrocortisone 2.5% cream, hydrocortisone acetate)<sup>a</sup></p>	<p>Efficacy: depends on class</p> <p>Amount and duration:</p> <p>For acute management, use twice daily until lesions are clear or almost clear</p> <p>For proactive maintenance, apply topical corticosteroids, vitamin D analogue, or topical calcineurin inhibitors twice per week to clinically quiescent lesions (eg, Monday and Thursday)</p> <p>Maximum dose for class I use in adults, 50 g per week<sup>5</sup></p> <p>Anatomical site:</p> <p>For sensitive body sites (face, axillae, inframammary, and groin areas), use low-potency topical corticosteroids (class VI or VII)</p> <p>For trunk and extremities, use class I-III topical corticosteroids</p> <p>Vehicle:</p> <p>For scalp, use solution or foam (class I topical corticosteroids)</p> <p>Ointments are typically more effective than creams if same active ingredient is used, but ointments are generally not preferred due to greasiness</p>	<p>With frequent and prolonged use of high-potency topical corticosteroids in normal-appearing skin or intertriginous areas, the following adverse effects may occur: skin atrophy, telangiectasia, and striae</p> <p>Regular examinations are recommended with long-term use</p> <p>Systemic adverse effects such as suppression of the hypothalamus pituitary and adrenal gland axis is rare and can be minimized by limiting long-term use of high-potency topical corticosteroids on large body surface areas—especially limiting such use in children</p>
<p>Vitamin D analogues</p> <p>Calcitriol; combination calcipotriene/calcipotriol</p>	<p>Efficacy:</p> <p>Modest when used alone and relatively slow onset of action<sup>48</sup></p> <p>In the same vehicle, calcipotriene and calcitriol are generally equally efficacious<sup>49</sup></p> <p>Amount and duration: use twice daily</p> <p>Maximum dose in adults: &lt;100 g per week</p> <p>In children: &lt;50 g per week<sup>50,51</sup></p>	<p>The most common adverse effects include skin irritation, burning, pruritus, and edema; systemic absorption generally does not result in adverse outcomes unless patient has severe renal insufficiency</p> <p>Calcipotriene may be inactivated by phototherapy; therefore apply after phototherapy</p>
<p>Topical calcineurin inhibitors</p> <p>Tacrolimus 0.03% or 0.1%; pimecrolimus 1%</p>	<p>Efficacy:</p> <p>Depending on the topical calcineurin inhibitor, they can be similar to class IV to class VII topical corticosteroids of calcipotriol<sup>52,53</sup></p> <p>Tacrolimus 0.03% ointment and pimecrolimus 1% cream are used for face, axillary, and groin regions</p> <p>Amount and duration: use twice daily</p>	<p>Burning and pruritus may occur but typically lessens over time; prior treatment with topical corticosteroids can reduce skin irritation</p> <p>Topical calcineurin inhibitors have acceptable safety profiles; although boxed warning exists for risk of malignancy, no causal link has been identified with topical use in patients with psoriasis</p> <p>Slower onset of action compared with topical corticosteroids</p>
<b>Keratolytics</b>		
Tazarotene	<p>Efficacy: modest when used alone<sup>54</sup></p> <p>Amount and duration: use once daily at night</p>	<p>Irritation and burning may occur</p> <p>UV-B and tazarotene increase efficacy and reduce the dose needed for UV-B<sup>55</sup></p> <p>Avoid in pregnancy</p>
Salicylic acid	<p>Efficacy: unknown</p> <p>Amount and duration: use 1-4 times daily</p> <p>Specific use: with topical corticosteroids to increase penetration (do not exceed class III, IV, and V topical corticosteroids); or with topical calcineurin inhibitors to increase penetration</p>	<p>If applied to &gt;20% of the body surface area or used in combination with oral salicylates, systemic adverse events can rarely occur</p> <p>Do not apply before phototherapy</p> <p>Exercise caution in children</p>

(continued)

Table 1. Topical Therapies Used in Psoriasis (continued)

Topical therapy	Use and efficacy	Limitations
<b>Combination topical therapies</b>		
Combined formulation: topical corticosteroid and vitamin D analogue (eg, calcipotriene/betamethasone dipropionate ointment or suspension/foam)	Efficacy: high efficacy and longer remission than monotherapy with either topical corticosteroid or a vitamin D analogue <sup>56,57</sup> ; also appropriate for proactive management for maintenance  Amount and duration: use once daily; when clear or almost clear, use twice per week	Skin irritation occurs infrequently
Combined formulation: topical corticosteroid and tazarotene (eg, halobetasol propionate and tazarotene)	Efficacy: high efficacy and longer remission than monotherapy with either topical corticosteroid or a topical keratolytic agent <sup>58,59</sup>  Amount and duration: use once daily	Skin irritation occurs infrequently
<sup>a</sup> Definition of class designations: Class I, superpotent; Class II, potent; Class III, upper midstrength; Class IV, midstrength; Class V, lower midstrength; Class VI, mild; Class VII, least potent. Some drugs, available in more than 1		strength and/or form (eg, gel, lotion, ointment, cream), are listed in more than 1 class category.

carcinogenesis. While full-body-surround phototherapy is used to treat more extensive psoriasis, targeted phototherapy is used to treat localized plaque psoriasis. An example of targeted phototherapy is excimer light therapy, which emits high-intensity UV-B (308 nm) (Figure 3). Patients typically undergo phototherapy twice per week and begin to see significant improvement after approximately 2 months. Excimer light therapy has very low carcinogenic potential. The main adverse effects are a burning sensation and blistering.

## Treatments for Moderate to Severe Psoriasis

To date, there is no consensus on the definition of moderate to severe psoriasis. Some clinicians define psoriasis as moderate when it covers 3% to 10% of the body surface area, whereas others define moderate psoriasis as coverage of 5% to 10% of the body surface area. Severe psoriasis is typically considered with a body surface area coverage of 10% or greater. Systemic treatments are the mainstay of treatment for patients with moderate to severe psoriasis (Figure 3, Table 2). Systemic medications can also be used for localized disease involving special areas such as the scalp, palms and soles, and genitals, or recalcitrant local psoriasis unresponsive to topical therapies. The American Academy of Dermatology-National Psoriasis Foundation guidelines recommend consideration of prescribing biologics, oral agents, and phototherapy concurrently for patients with moderate to severe psoriasis (Table 2). Overall, biologics have higher efficacy compared with oral medications or phototherapy (Figure 4).<sup>89</sup> Topical therapies can be used as adjunct treatments but not as monotherapy in treating moderate to severe psoriasis.

### Phototherapy

The use of phototherapy for moderate to severe psoriasis has decreased since the advent of biologics. The main types of phototherapy used to treat psoriasis include narrowband UV-B, broadband UV-B, or psoralen and UV-A (PUVA). In general, treatment using narrowband UV-B is preferred over the broadband form, because it is more efficacious. Use of narrowband UV-B is also preferred over PUVA because it has a more favorable safety profile. Targeted phototherapy, such as excimer light, is used for localized psoriasis (see Targeted Phototherapy under Treatments for Mild Psoriasis). One challenge with phototherapy is that patients need to travel to undergo office-based

phototherapy. Home phototherapy affords a convenient option, but its use is limited by insurance and space considerations.

### UV-B

Use of UV-B decreases DNA synthesis, leading to keratinocyte apoptosis and decreased production of proinflammatory cytokines by T cells. UV-B phototherapy consists of broadband (290-320 nm) and narrowband (311 nm) bandwidths, and both can be used to treat plaque psoriasis. Frequency of initial treatment is typically 3 times per week and is administered in the office or at home. Usually after 2 to 3 months, treatment frequency can be decreased to twice per week to maintain efficacy and may be further reduced later, depending on the patient's response. Adverse effects include erythema, pruritus, blistering, photoaging, and photocarcinogenesis. Compared with broadband UV-B, narrowband UV-B are more commonly used due to greater efficacy, longer duration of remission, lower photocarcinogenic potential, and lessened erythema at the same physical dose. Combination with systemic retinoids may increase the efficacy and reduce the carcinogenic potential of narrowband UV-B radiation.

### PUVA

Treatment with PUVA involves the use of a psoralen, such as methoxalen, administered either orally or topically prior to UV-A (320-400 nm) irradiation. Psoralens are used to intercalate into DNA to suppress DNA synthesis. In the initial treatment phase, patients typically receive oral PUVA 2 to 3 times per week, until psoriasis is clear or almost clear; the frequency of treatment then decreases over time. Although treatment with oral PUVA has superior efficacy to UV-B, it is no longer preferred due to the development of skin cancer with long-term use.<sup>90</sup> Other adverse effects include gastrointestinal upset, burning, pruritus, hypertrichosis, and photoaging. PUVA should not be used in conjunction with tanning beds because of the risk of severe burns. Topical PUVA therapy is typically used for patients with palmoplantar psoriasis and involves soaking hands and feet in water with psoralen and then being irradiated by UV-A.

### Biologics for the Treatment of Moderate to Severe Plaque Psoriasis

Biologics used to treat moderate to severe plaque psoriasis represent one of the most significant therapeutic advancements in the field of dermatology. The 4 classes of biologics used to treat



**Table 2. US Food and Drug Administration–Approved Biologic and Oral Systemic Treatments for Psoriasis**

Systemic treatment	Structure of biologic or target of oral systemic	Dosing for plaque psoriasis <sup>a</sup>	Efficacy at primary end point <sup>b</sup>	Safety considerations
<b>Biologics</b>				
<b>Anti-TNF-α</b>				
Etanercept	Fusion protein between a TNF-α receptor protein and the crystallizable fragment portion of IgG1	Loading/induction dose: 50 mg twice weekly for 12 weeks Maintenance dose: 50 mg once weekly Recommended escalated maintenance dose: 50 mg twice weekly Pediatric dose: 0.8 mg/kg once weekly; maximum dose, 50 mg weekly	Adults: 49% achieve PASI 75 at week 12 (placebo, 3%) <sup>62</sup> Children (aged 4–17 years): 57% achieve PASI 75 at week 12 (placebo, 11%) <sup>63</sup>	Avoid use in patients with demyelinating diseases or hepatitis B Use is not preferred in patients with a history of latent tuberculosis or advanced congestive heart failure Discontinue during serious infection until the infection resolves
Adalimumab	Human monoclonal IgG1 antibody	Loading/induction dose: 80 mg at week 0; 40 mg at week 1 Maintenance dose: 40 mg every 2 weeks	Adults: 71% achieve PASI 75 at week 16 (placebo, 7%) <sup>64</sup> Superior to methotrexate at 16 weeks <sup>65</sup>	Avoid use in patients with demyelinating diseases or hepatitis B Use is not preferred in patients with a history of latent tuberculosis or advanced congestive heart failure Antiadalimumab antibodies in 6%–50% Discontinue during serious infection until the infection resolves
Certolizumab pegol	Pegylated humanized antibody fragment	Loading/induction dose for patients ≤90 kg: 400 mg at weeks 0, 2, and 4 Maintenance dose: ≤90 kg: 200 mg every 2 weeks >90 kg: 400 mg every 2 weeks	Adults: 83% achieve PASI 75 at week 16 (placebo, 12%) <sup>66</sup>	Preferred in pregnant or breastfeeding women due to minimal placental and breast milk transfer Avoid use in patients with demyelinating diseases or hepatitis B Use is not preferred in patients with a history of latent tuberculosis or advanced congestive heart failure Discontinue during serious infection until the infection resolves
Infliximab	Human chimeric monoclonal IgG1 antibody	Loading/induction dose: 5 mg/kg at weeks 0, 2, and 6 (the only intravenously administered biologic) Maintenance dose: 5 mg/kg every 8 weeks Recommended escalated maintenance dose: 5 mg/kg every 4–8 weeks and/or up to 10 mg/kg	Adults: 80% achieve PASI 75 at week 10 (placebo, 3%) <sup>67</sup> ; 55% achieve PASI 75 at week 50 (placebo/infliximab, 77%) <sup>67</sup> Superior to methotrexate at 16 weeks <sup>68</sup>	Avoid use in patients with demyelinating diseases or hepatitis B Use is not preferred in patients with a history of latent tuberculosis or advanced congestive heart failure Discontinue during serious infection until the infection resolves
<b>Anti-IL-17</b>				
Secukinumab	Human monoclonal IL-17A antibody	Loading/induction dose: 300 mg at weeks 0, 1, 2, 3, and 4 Maintenance dose: 300 mg every 4 weeks Recommended escalated maintenance dose: 300 mg every 2 weeks	Adults: 82% achieve PASI 75 at week 12 (placebo, 4%); 65% achieve IGA 0/1 at week 12 (placebo, 2%) <sup>69</sup> Superior to etanercept and ustekinumab at 1 year <sup>69,70</sup> High efficacy for scalp, nail, and palmoplantar psoriasis <sup>71–73</sup>	Avoid use in patients with a history of inflammatory bowel disease Low rates of mild mucocutaneous candidiasis Discontinue during serious infection until the infection resolves
Ixekizumab	Humanized monoclonal IL-17A antibody	Loading/induction dose: 160 mg at week 0; 80 mg at weeks 2, 4, 6, 8, 10, and 12 Maintenance dose: 80 mg every 4 weeks Recommended escalated maintenance dose: 80 mg every 2 weeks	Adults: 90% achieve PASI 75 at week 12 (placebo, 2%); 83% achieve IGA 0/1 at week 12 (placebo, 2%) <sup>60</sup> Superior to etanercept at 12 weeks; ustekinumab at 1 year, and adalimumab at 24 weeks <sup>60,74,75</sup>	Avoid use in patients with a history of inflammatory bowel disease Low rates of mild mucocutaneous candidiasis Discontinue during serious infection until the infection resolves
Brodalumab	Human monoclonal IL-17A receptor antibody	Loading/induction dose: 210 mg at weeks 0, 1, and 2 Maintenance dose: 210 mg every 2 weeks Recommended escalated maintenance dose: 40 mg once weekly	Adults: 86% achieve PASI 75 at week 12 (placebo, 8%); 80% achieve IGA 0/1 at week 12 (placebo, 4%) <sup>76</sup> Superior to ustekinumab at 12 weeks <sup>76</sup>	Avoid use in patients with a history of inflammatory bowel disease Low rates of mild mucocutaneous candidiasis Discontinue during serious infection until the infection resolves Weigh benefit and risks in patients with a history of suicidal ideation or behavior

(continued)

**Table 2. US Food and Drug Administration–Approved Biologic and Oral Systemic Treatments for Psoriasis (continued)**

Systemic treatment	Structure of biologic or target of oral systemic	Dosing for plaque psoriasis <sup>a</sup>	Efficacy at primary end point <sup>b</sup>	Safety considerations
Anti-IL-12/23				
Ustekinumab	Human monoclonal antibody against the p40 subunit, shared by IL-12/23	<p>Loading/induction dose for patients ≤100 kg: 45 mg at weeks 0 and 4; for patients &gt;100 kg: 90 mg at weeks 0 and 4</p> <p>Maintenance dose for patients ≤100 kg: 45 mg every 12 weeks; for patients &gt;100 kg: 90 mg every 12 weeks</p> <p>Recommended escalated maintenance dose for patients ≤100 kg: 90 mg every 8-12 weeks; for patients &gt;100 kg: 90 mg every 8-12 weeks</p> <p>Pediatric loading/induction dose for patients &lt;60 kg: 0.75 mg/kg at weeks 0 and 4; for patients ≥60-100 kg: 45 mg at weeks 0 and 4; for patients &gt;100 kg: 90 mg at weeks 0 and 4</p> <p>Pediatric maintenance dose for patients &lt;60 kg: 0.75 mg/kg every 12 weeks; for patients ≥60-100 kg: 45 mg every 12 weeks; for patients &gt;100 kg: 90 mg every 12 weeks</p>	<p>Adults: 67% (45 mg) and 76% (90 mg) achieve PASI 75 at week 12 (placebo, 4%)<sup>77</sup></p> <p>Children (aged 12-17 years): 78% (45 mg) and 81% (90 mg) achieve PASI 75 at week 12 (placebo, 11%)<sup>78</sup></p> <p>Superior to etanercept at 12 weeks<sup>79</sup></p>	<p>Lower risk of basal cell carcinoma compared with methotrexate</p> <p>Discontinue during serious infection until the infection resolves</p>
Anti-IL-23				
Guselkumab	Human monoclonal IL-23 antibody	<p>Loading/induction dose: 100 mg at weeks 0 and 4</p> <p>Maintenance dose: 100 mg every 8 weeks</p>	<p>Adults: 73% achieve PASI 90 at week 16 (placebo, 3%); 85% achieve IGA 0/1 at week 16 (placebo: 8%)<sup>80</sup></p> <p>Superior to adalimumab and secukinumab at 1 year<sup>81</sup></p>	<p>Efficacy in axial psoriatic arthritis is under investigation</p> <p>Discontinue during serious infection until the infection resolves</p>
Tildrakizumab	Human monoclonal IL-23 antibody	<p>Loading/induction dose: 100 mg at weeks 0 and 4</p> <p>Maintenance dose: 100 mg every 12 weeks</p>	<p>Adults: 64% achieve PASI 75 at week 12 (placebo, 6%); 58% achieve IGA 0/1 at week 12 (placebo, 7%)<sup>82</sup></p> <p>Superior to etanercept at 12 weeks<sup>82</sup></p>	<p>Efficacy in axial psoriatic arthritis is under investigation</p> <p>Discontinue during serious infection until the infection resolves</p>
Risankizumab	Human monoclonal IL-23 antibody	<p>Loading/induction dose: 150 mg at weeks 0 and 4</p> <p>Maintenance dose: 150 mg every 12 weeks</p>	<p>Adults: 75% achieve PASI 90 at week 16 (placebo, 4%); 86% achieve IGA 0/1 at week 16 (placebo, 7%)<sup>83</sup></p> <p>Superior to ustekinumab at 1 year and adalimumab at 16 weeks<sup>83,84</sup></p> <p>High efficacy for scalp, nail, and palmoplantar psoriasis<sup>83,84</sup></p>	<p>Efficacy in axial psoriatic arthritis is under investigation</p> <p>Discontinue during serious infection until the infection resolves</p>
Oral systemics				
Methotrexate	Dihydrofolate reductase inhibitor	Dose: 15-20 mg once weekly with folic acid supplementation	<p>Adults: 36% achieve PASI 75 at week 16 (placebo, 19%)<sup>85</sup></p> <p>Subcutaneous methotrexate may confer greater efficacy and bioavailability<sup>85</sup></p>	<p>Increased risk of hepatic, pulmonary, hematologic, and renal toxicity</p> <p>Check complete blood counts, liver and kidney function, and hepatitis serology</p>
Apremiast	Phosphodiesterase-4 inhibitor	<p>Day 1: 10 mg in the morning</p> <p>Day 2: 10 mg twice per day</p> <p>Day 3: 10 mg in the morning; 20 mg in the evening</p> <p>Day 4: 20 mg twice per day</p> <p>Day 5: 20 mg in the morning; 30 mg in the evening</p> <p>Day 6 onward (maintenance dose): 30 mg twice per day</p>	<p>Adults: 33% achieve PASI 75 at week 16 (placebo, 5%)<sup>86</sup></p>	<p>Renal adjustment for creatinine clearance &lt;30 mL/min/1.73m<sup>2</sup></p>

(continued)

**Table 2. US Food and Drug Administration–Approved Biologic and Oral Systemic Treatments for Psoriasis (continued)**

Systemic treatment	Structure of biologic or target of oral systemic	Dosing for plaque psoriasis <sup>a</sup>	Efficacy at primary end point <sup>b</sup>	Safety considerations
Acitretin	Retinoid (vitamin-A derivative)	Dose: 25 mg–50 mg daily	Adults: 47% achieve PASI 75 at week 12 <sup>87</sup>	Hair loss and xerosis (worse at higher doses), hypertriglyceridemia, hepatotoxicity, and teratogenicity Check liver function and lipids
Cyclosporine	Calcineurin inhibitor	Dose: 5 mg/kg as a twice-daily divided dose; taper when psoriasis is controlled	Adults: 65% achieve IGA 0/1 at week 8 (placebo, 0%) <sup>88</sup> Two formulations are available: lipid or microemulsified (the latter is better absorbed)	Nephrotoxicity with long-term use Hypertension and hyperlipidemia nonmelanoma skin cancer risk in patients with prior PUVA Check renal function levels, electrolytes (magnesium and potassium), and blood pressure

Abbreviations: IGA, Investigator's Global Assessment scale; PASI, Psoriasis Area Severity Index; PUVA, psoralen and UV-A; TNF, tumor necrosis factor.

<sup>a</sup> All doses are for adults unless otherwise specified.

<sup>b</sup> The IGA score range is 0 through 5 (0, clear; 1, almost clear; 2, mild; 3, moderate; and 4, severe). PASI is a validated instrument that enables clinicians to assess psoriasis disease severity. It combines the assessment of session severity (erythema, induration, and scale) and the affected areas into a single score between 0 (no disease) and 72 (maximal disease). PASI scores of 75, 90, and 100 indicate a 75%, 90%, and 100% reduction in PASI score compared with baseline.

psoriasis are TNF inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors (Table 2). Biologics that inhibit TNF- $\alpha$ , p40IL-12/23, and IL-17 are approved by the US Food and Drug Administration to treat psoriatic arthritis. All biologics used to treat psoriasis are administered subcutaneously except infliximab. Overall, there are no increased rates of serious infections or internal malignancies in patients with psoriasis who are treated using biologics. Adverse effects that occur at slightly higher rates than placebo and are common to all biologics include injection site reaction, nasopharyngitis, and upper respiratory tract infections (Table 2).

**TNF- $\alpha$  Inhibitors**

TNF- $\alpha$  inhibitors are the oldest class of currently approved biologics for the treatment of psoriasis and psoriatic arthritis. By inhibiting TNF- $\alpha$ , these biologics decrease the downstream inflammatory cascade central to psoriasis pathogenesis (Table 2).

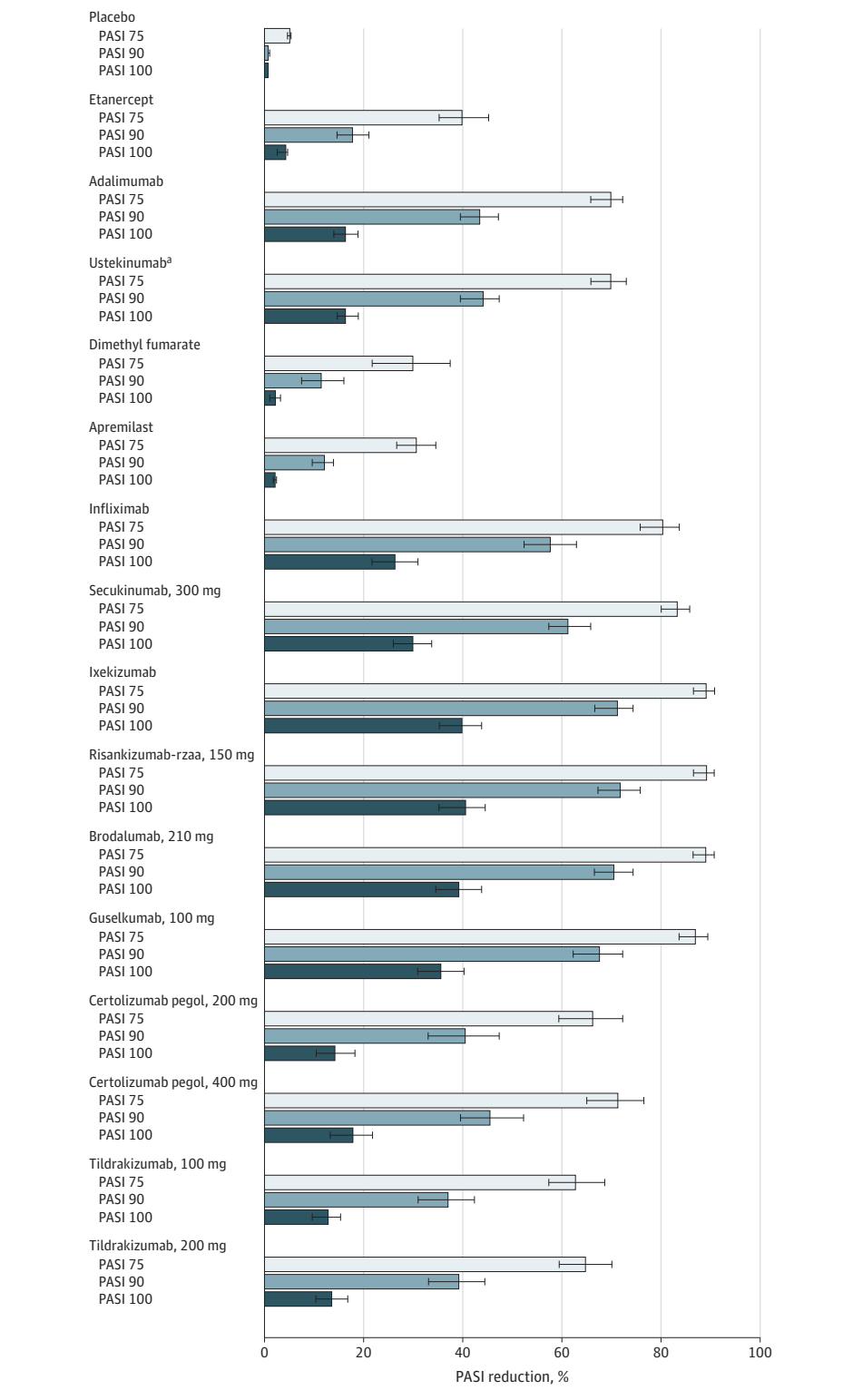
The efficacies of different TNF- $\alpha$  inhibitors in plaque psoriasis vary (Table 2). In the absence of head-to-head trials, network meta-analyses show that among TNF- $\alpha$  inhibitors for psoriasis, infliximab has the highest efficacy, followed by similar efficacies for certolizumab and adalimumab, and then by etanercept.<sup>89</sup> As a class, the dosing of subcutaneously administered TNF- $\alpha$  inhibitors is more frequent when compared with most of the IL-17 inhibitors and IL-23 inhibitors. If the approved dose is not effective and a patient chooses to continue treatment using the TNF- $\alpha$  inhibitor, the general approach to treatment escalation is to increase the dosing frequency of that TNF- $\alpha$  inhibitor.

The long-term safety profile of TNF- $\alpha$  inhibitors is well-described (Table 2). Overall, based on postmarketing registry studies,<sup>91,92</sup> there are no known increased rates of serious infections associated with TNF- $\alpha$  inhibitors when used to treat psoriasis. However, in a registry study that enrolled patients undergoing treatment using different biologics, though direct head-to-head comparisons cannot be made, the rates of serious infections were numerically higher for TNF- $\alpha$  inhibitors compared with ustekinumab.<sup>93</sup> Rates of internal malignancies among psoriasis patients treated with TNF- $\alpha$  inhibitors were not elevated compared with the general population.<sup>93</sup> While phase IV observational studies have not shown potential increased rates of skin cancer, other population-based studies suggest increased rates of nonmelanoma skin cancers, which may be attributed to a history of PUVA treatment among many psoriasis patients in the trials on TNF- $\alpha$  inhibitors.<sup>91,92,94</sup> The most common adverse events are nasopharyngitis, upper respiratory tract infections, and injection site reactions. TNF- $\alpha$  inhibitors are contraindicated in several populations: those with active tuberculosis, advanced congestive heart failure, hepatitis B infection, or demyelinating diseases including multiple sclerosis. Patients with latent tuberculosis can be treated concurrently with a TNF- $\alpha$  inhibitor as long as they are also being treated for latent tuberculosis. It is imperative that patients with latent tuberculosis and undergoing treatment with a TNF- $\alpha$  inhibitor maintain tuberculosis treatment because the risk of conversion to active tuberculosis may be higher in patients using TNF- $\alpha$  inhibitors compared with those receiving other classes of biologics for psoriasis (Box 3).

**IL-12/23 Inhibitor**

The only biologic that inhibits both IL-12 and IL-23 through inhibition of their shared p40 subunit is ustekinumab, which is approved

Figure 4. Comparison of PASI 75/90/100 Short-term Response Rates in US FDA-Approved Oral Systemics and Biologics for Psoriasis



The Psoriasis Area Severity Index (PASI) is a validated instrument that enables clinicians to assess psoriasis disease severity. It combines the assessment of session severity (erythema, induration, and scale) and the affected areas into a single score between 0 (no disease) and 72 (maximal disease). PASI scores of 75, 90, and 100 indicate a 75%, 90%, and 100% reduction in PASI score compared with baseline. Compared with US Food and Drug Administration (FDA)-approved oral systemic and biologics therapies, risankizumab, brodalumab, ixekizumab, and guselkumab have the highest PASI 75/90/100 response rates at weeks 10 to 16 among assessed treatments. Furthermore, risankizumab has significantly higher PASI 75/90/100 response rates compared with etanercept, adalimumab, ustekinumab, secukinumab, infliximab, dimethyl fumarate, apremilast, certolizumab pegol, and tildrakizumab. Error bars indicate 95% credible intervals.

by the US Food and Drug Administration to treat both psoriasis and psoriatic arthritis (Table 2). The therapeutic effect of ustekinumab is primarily mediated through its inhibition of IL-23. Ustekinumab

has weight-based dosing and is administered once every 3 months; the efficacy of ustekinumab is excellent (Table 2). If treatment escalation of ustekinumab is desired, shortening the time between

injections is recommended. The safety profile of ustekinumab is acceptable (Table 2). There are no increased rates of serious infections or malignancies compared with placebo. The most common adverse events in the clinical trials that occurred at rates slightly above that of the placebo were upper respiratory tract infections and headache.

### IL-17 Inhibitors

IL-17 inhibitors are a class of biologics that target either the IL-17 ligand or its receptor. Secukinumab and ixekizumab inhibit the IL-17A ligand; bimekizumab inhibits both the IL-17A and IL-17F ligands. Brodalumab inhibits IL-17 receptor  $\alpha$  (Table 2). As a class, IL-17 inhibitors have fast onset of action, robust response, and good sustainability in treating plaque psoriasis among responders (Table 2). IL-17 inhibitors are also approved for the treatment of psoriatic arthritis in the United States and internationally. IL-17 inhibitors have an acceptable safety profile with no increased rates of serious infections or malignancy (Table 2). Mucocutaneous candidiasis and exacerbation of inflammatory bowel disease have been reported in patients treated with IL-17 inhibitors. As with all other biologics, upper respiratory tract infections and injection site reactions are the most common and manageable adverse reactions.

### IL-23 Inhibitors

IL-23 inhibitors are a class of biologics that specifically inhibit the p19 subunit of IL-23, thereby reducing the activities of  $T_H17$  pathway (Table 2). The IL-23 inhibitors that are approved by the US Food and Drug Administration to treat plaque psoriasis in adults are guselkumab, tildrakizumab, and risankizumab. Mirikizumab is in late-phase development. As a class, IL-23 inhibitors have robust efficacy, acceptable safety profiles, and convenient infrequent dosing regimen (Table 2). Risankizumab is also approved for the treatment of psoriatic arthritis internationally. Individual short-term and long-term efficacies vary among these IL-23 inhibitors (Table 2). The safety profiles are similarly acceptable among these IL-23 inhibitors, with no increased rates of serious infections or malignancies to date (Table 2). Upper respiratory tract infections and injection site reactions are the most frequently reported but manageable adverse reactions.

### Oral Systemic Treatments

Oral agents have been used to treat moderate to severe plaque psoriasis for many years before the advent of biologics (Figure 3). Oral treatment options for plaque psoriasis include methotrexate, apremilast, acitretin, and cyclosporine (Table 2). With the exception of cyclosporine, the efficacy of oral treatments is generally lower than that of biologics in psoriasis. However, oral treatments can be considered for patients who may have limited access to biologics or those who prefer noninjectable medications. The adverse effect profiles differ substantially among the oral options and are discussed in

### Box 3. Biologics and Tuberculosis in Psoriasis<sup>a</sup>

#### Pretreatment screening

Screen for latent tuberculosis using IFN- $\gamma$  releasing assay (eg, Quantiferon Gold<sup>b</sup>) or purified protein derivative skin test  
Refer for chest x-ray if tuberculosis test is positive

#### If diagnosed with tuberculosis

For latent tuberculosis, initiate a prophylactic antituberculosis treatment regimen (eg, 9 months isoniazid); consider starting biologic treatment after 1 month of antituberculosis treatment. While undergoing antituberculosis treatment, monitor for patient adherence and signs of active tuberculosis

For active tuberculosis, consult with infectious disease specialist (relative contraindication in patients receiving anti-TNF- $\alpha$  and anti-IL-12/IL-23 biologics)

#### Ongoing monitoring

Perform annual screening for latent tuberculosis in patients at high risk for tuberculosis (eg, direct contact with tuberculosis-positive person, regular travel to endemic regions); this is especially important for patients receiving anti-TNF- $\alpha$  biologics

Abbreviations: IFN, interferon; TNF, tumor necrosis factor.

<sup>a</sup> Adapted from Menter et al.<sup>7</sup>

<sup>b</sup> Quantiferon Gold results can remain positive even after treatment of latent tuberculosis.

Table 2. Thus, careful consideration is necessary when selecting an oral agent due to the multiple contraindications and precautions associated with some of these oral agents.

## Limitations

This review focused on plaque psoriasis, the most common psoriasis subtype and the form for which there have been the largest advancements in understanding of pathogenesis and development of new therapies. We have not discussed advancements in the genetics and comorbidities associated with plaque psoriasis or covered less-common variants (such as guttate, erythrodermic, and pustular psoriasis, or subtypes involving special locations such as palmo-plantar or nail psoriasis).

## Conclusions

Psoriasis is an inflammatory skin disease that is associated with multiple comorbidities and substantially diminishes patients' quality of life. Topical therapies remain the cornerstone for treating mild psoriasis. Therapeutic advancements for moderate to severe plaque psoriasis include biologics that inhibit TNF- $\alpha$ , p40IL-12/23, IL-17, and p19IL-23, as well as an oral phosphodiesterase 4 inhibitor.

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