CME

Treating patients with moderate-to-severe psoriasis vulgaris

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ABSTRACT

Psoriasis vulgaris is a common inflammatory disease of adults and children. Affected patients often are incorrectly diagnosed, undertreated, or not treated at all. The relapsing course of psoriasis negatively affects a patient's quality of life. The condition is associated with social isolation, anxiety, and depression, and can harm personal relationships and employment status. Psoriasis may have a significant psychologic and socioeconomic effect throughout a patient's life. Skin involvement is the most prominent symptom of this disease; however, understanding that psoriasis is a chronic, multisystem inflammatory disease is essential to proper treatment. Patients with mild-to-moderate psoriasis can control their disease primarily with topical medications or phototherapy. However, when used as monotherapy or combined with phototherapy, topical medication can be inadequate to treat moderate-to-severe psoriasis. Biologic agents offer treatment options with many benefits for controlling psoriasis vulgaris, whether given as monotherapy or combined with topical or systemic medications.

Keywords: psoriasis vulgaris, skin disease, biologic therapy, interleukin-19, interleukin-23, inflammatory

Learning objectives

- Describe the clinical presentation and diagnosis of psoriasis vulgaris.
- Describe the treatment of moderate-to-severe psoriasis vulgaris.
- Outline the screening and maintenance process for biologic therapy and the associated adverse reactions.

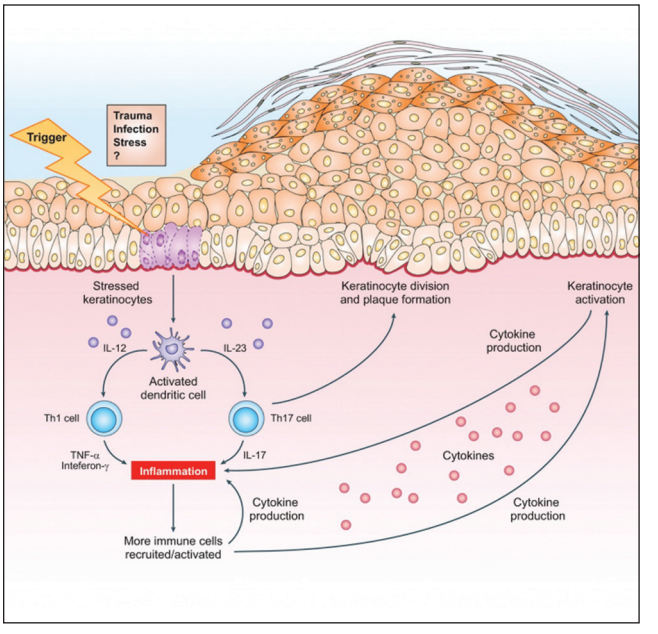

FIGURE 1. Pathogenesis of psoriasis. Stress or damage to the skin can trigger the inflammatory response. Stressed keratinocytes activate dendritic cells that pass on fragments of the microbe to T cells, which in turn release cytokines that play a part in keratinocyte activation and ongoing inflammation.

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Psoriasis vulgaris is a common, immune-mediated inflammatory disease characterized by inflammation of the skin, epidermal hyperplasia, risk of painful and destructive arthritis, cardiovascular morbidity, and psychologic challenges.[1] Psoriasis affects about 3.2% of the US population, but its cause remains unknown.[2] The mode of inheritance for psoriasis vulgaris is described as multifactorial, consisting of polygenetic components and environmental factors. Psoriasis may begin at any age, although it is unusual before age 10 years. It most commonly appears between ages 15 and 30 years.

PATHOGENESIS

A combination of genetic and environmental factors initiates the pathogenesis of psoriasis through a complex process, prompting tumor necrosis factor-alpha (TNF-alpha) production by keratinocytes that activate dendric cells.[3] The triggered dendritic cells provide interleukin-23 (IL-23), which gives rise to helper T cell (TH17) differentiation.[4] TH17 cells produce interleukin-17A (IL-17A), promoting psoriatic skin changes (**Figure 1**).[5]

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DOI:10.1097/01.JAA.0000819580.10133.b1

Key points

- Psoriasis vulgaris is a common immune-mediated inflammatory disease.
- Psoriasis vulgaris manifests as well-demarcated, raised, erythematous plaques with silver scale.
- Treatment can be monotherapy or a multifaceted approach including topical corticosteroids, phototherapy, and systemic medications.

CLINICAL FEATURES

Classically, psoriasis vulgaris is manifested by well-demarcated, elevated, erythematous plaques with a silver scaley surface. Lesions can vary in size from pinpoint papules to large plaques. They are symmetrically distributed and characteristically localized to the extremities' extensor aspects, especially the knees and elbows, along the scalp and lower lumbosacral, buttocks, and genital areas (**Figures 2** through **4**). Psoriasis also can present as generalized erythema and varying degrees of scale known as *psoriatic erythroderma*. Pustular psoriasis and guttate psoriasis are less common types of psoriasis and vary depending on widespread skin involvement and the development of pustules. Nail changes, such as pitting onychodystrophy and oil spots, are seen in 40% of patients with psoriasis (**Figure 5**). The percentage of patients with nail changes increases with age of onset, duration and extent of psoriasis, and whether the patient also has psoriatic arthritis.[6] Psoriatic arthritis is seen in 25% to 30% of patients with psoriasis.[7] A common feature of psoriasis is the Auspitz sign: blood droplets that appear on the erythematous surface when scales are physically removed from a psoriatic plaque.[1] The Koebner phenomenon can be noted as a traumatic induction of psoriatic lesions developing in areas where psoriasis was previously recorded (**Figure 6**).[1]

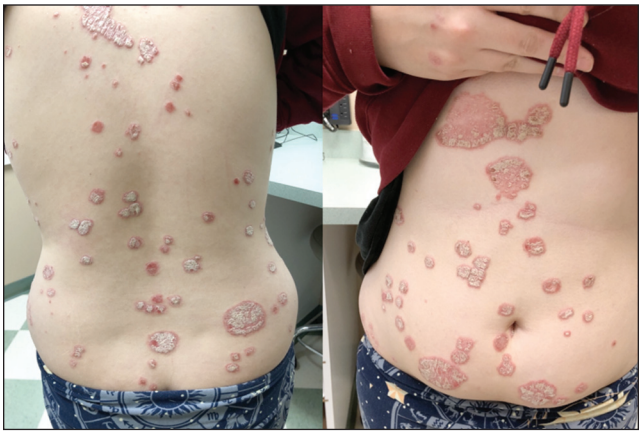

FIGURE 2. Moderate to severe psoriasis vulgaris on the trunk

COMPLICATIONS

Patients with psoriasis vulgaris, especially those with severe disease of prolonged duration, have increased morbidity and mortality from cardiovascular events.[8] Patients with psoriasis also are at higher risk for rheumatoid arthritis, Hodgkin lymphoma, Crohn disease, ulcerative colitis, and cutaneous T-cell lymphoma.[9] Psychosocial ramifications add to the complications of psoriasis: Emotional difficulties from physical appearance of the lesions results in low self-esteem, isolation, and impairment of professional ability.[1] Patients may not adhere to their treatment regimen, worsening disease and resulting in further anxiety and depression.

DIAGNOSIS

Psoriatic lesions usually are characteristic in nature and clinical evaluation is sufficient to establish a diagnosis, yet challenges occur when psoriasis is evolving or entangled with other diseases. The differential diagnosis of psoriasis includes seborrheic dermatitis, eczematous dermatitis, syphilis, pityriasis rubra pilaris and pityriasis lichenoides et varioliformis, candidiasis, tinea, mycosis fungoides or cutaneous T-cell lymphoma, Bowen disease, and Paget disease. If clinical history and examination are not diagnostic, obtain a biopsy to confirm the diagnosis.

FIGURE 3. Moderate to severe psoriasis on the lower extremity

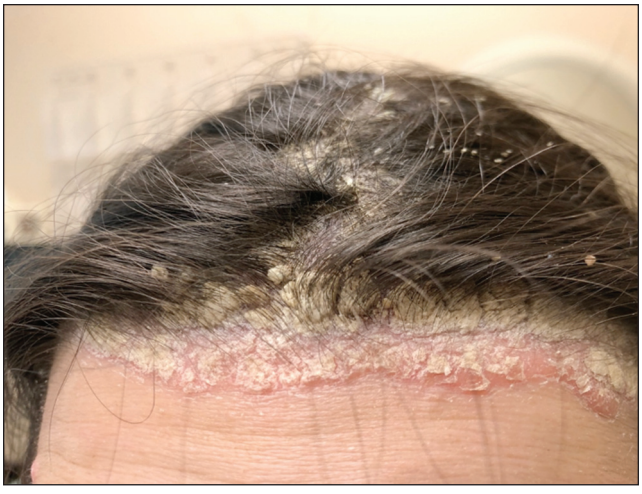

FIGURE 4. Moderate to severe psoriasis on the scalp

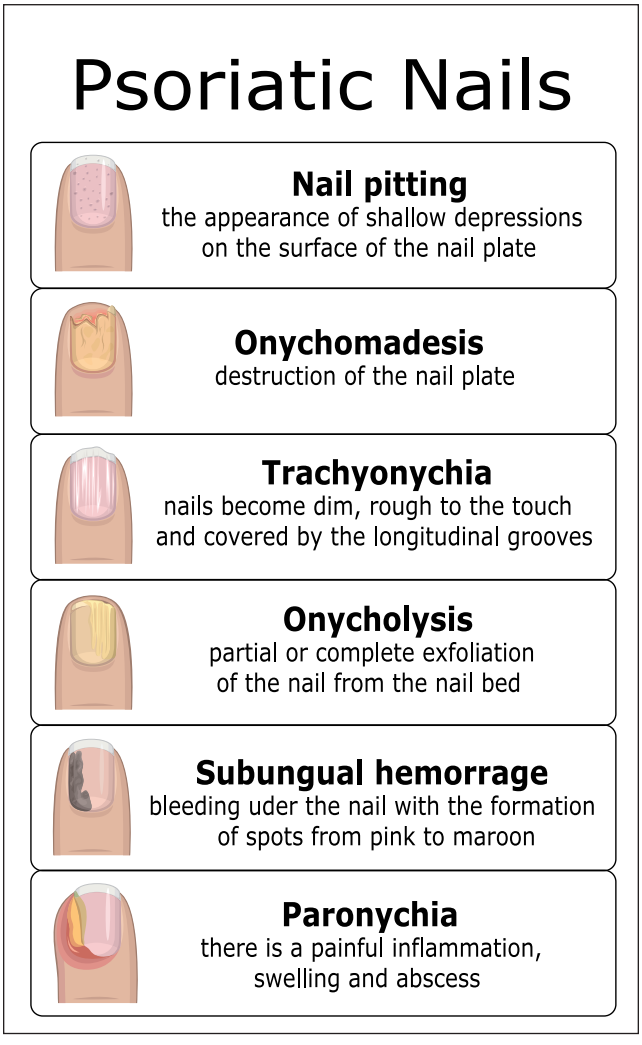

FIGURE 5. Psoriatic nail changes

TREATMENT

The acuteness of psoriasis vulgaris is determined by the total body surface area (BSA) involved. The American Academy of Dermatology defines mild psoriasis as less than 3% BSA, moderate psoriasis as 3% to 10% BSA, and severe psoriasis as more than 10% BSA.[9] The Psoriasis Area Severity Index (PASI) quantifies the extent and severity of disease by taking into account the BSA and the severity of erythema, scale production, and thickness of plaques, resulting in a score from 0 to 72.[9] The PASI score is used for monitoring clinical trials and as a tool in research. It is not used in clinical practice to guide management. **Figure 7** is an algorithm for psoriasis treatment.

Topical treatment The most commonly used agents for managing mild-to-moderate psoriasis are topical medications. The first-line therapy is to use bland emollients to avoid dryness. *Topical corticosteroids* have anti-inflammatory properties, antiproliferative functions, immunosuppressive qualities, and vasoconstrictive effects that make them safe and highly effective for treating localized psoriasis.[9] Topical corticosteroids are organized into seven classes based on their cutaneous vasoconstrictive activity, from ultra-high potency (Class 1) to low potency (Classes 6 and 7).[9] When choosing a corticosteroid, consider the severity of the disease, its extent and location, patient age, and patient preference.[9] Lower-potency corticosteroids commonly are applied to the face and intertriginous areas. In contrast, areas with substantial recurring plaques often necessitate aggressive management with Class 1 corticosteroids.

Initial therapy for adults generally starts with moderate to high potency drugs (Classes 2 through 5).[9] Long-term corticosteroid use requires monitoring because it can result in skin atrophy, telangiectasia, striae, and adrenal suppression.[1] Vitamin D3 analogs are used as an adjunct therapy and reduce reliance on topical corticosteroids, lessening the risk of adverse reactions. Second-line topical treatments include salicylic acid, dithranol, tazarotene, and tar.

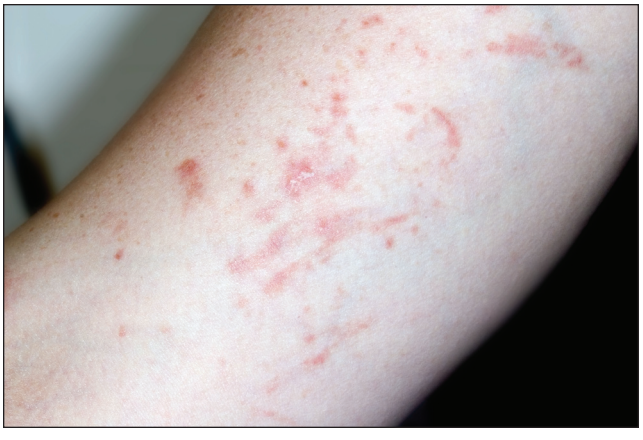

FIGURE 6. Koebner phenomenon

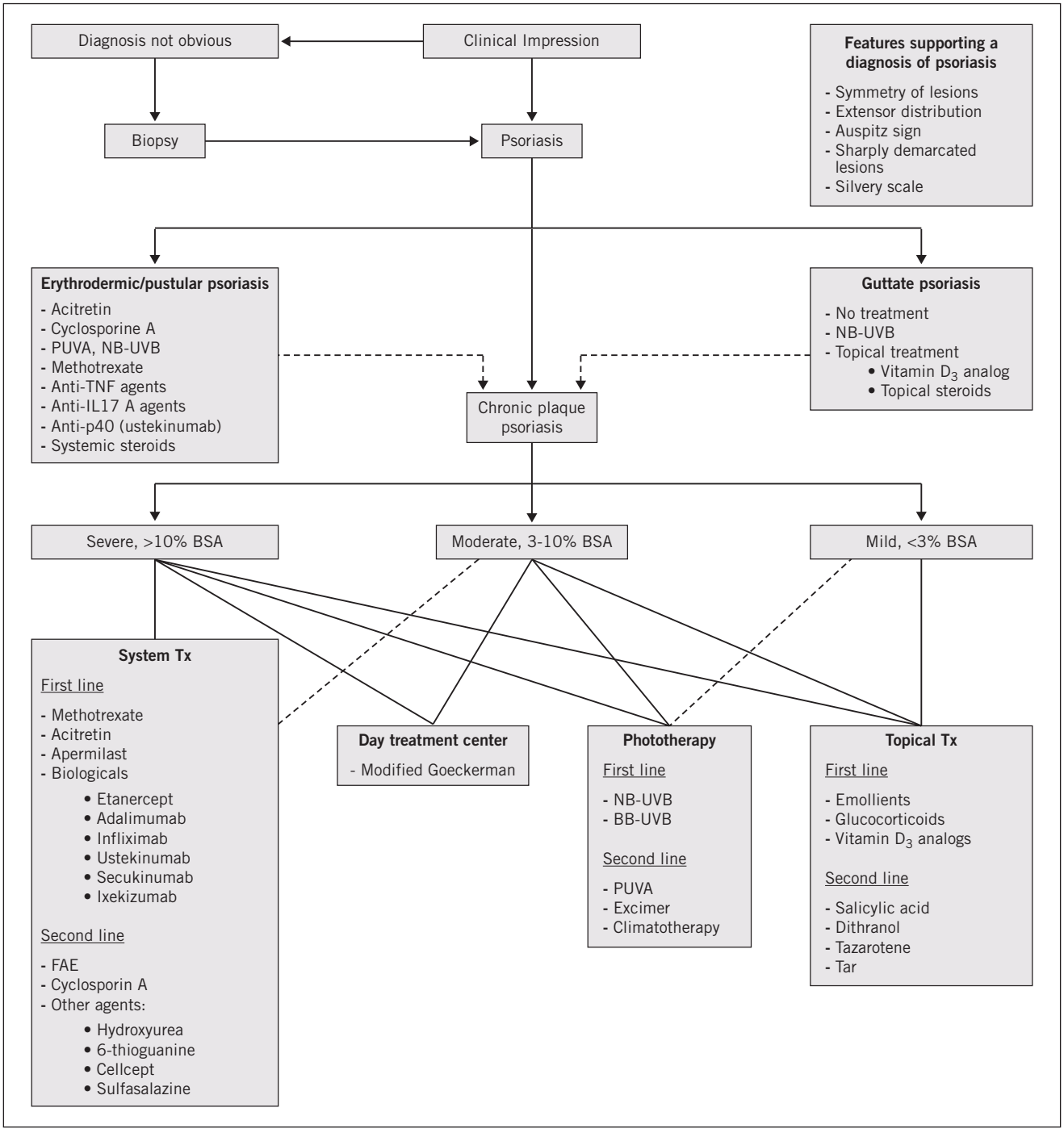

FIGURE 7. Psoriasis treatment algorithm

Adapted with permission from Kang S, Amagai M, Bruckner AL, et al. *Fitzpatrick's Dermatology*. 9th ed. New York, NY: McGraw-Hill Education; 2019.

Phototherapy This therapy can be used as monotherapy or given concomitantly with topical agents. Phototherapy is appropriate for patients who require more than topical medication alone or who wish to avoid systemic medications. Narrow-band ultraviolet B (NB-UVB) has proven to be the most efficacious phototherapy treatment for patients with psoriasis.[10] NB-UVB eliminates the harmful ultraviolet light by emitting wavelengths in a minimal range, 311 to 313 nm.[10] NB-UVB phototherapy takes place two to three times per week. The patient receives the

maximum benefits from phototherapy while avoiding the danger of severe burning. Broadband ultraviolet B (BB-UVB) phototherapy, an early type of phototherapy, is less effective than NB-UVB for the management of psoriasis.[10]

Second-line phototherapy treatments include psoralen and long-wave UV radiation (PUVA), excimer laser, and climatotherapy.[1] PUVA uses a photosensitizing agent, psoralen, to increase the influence of UVA light in target cells. The excimer laser uses a high-intensity UVB light dose targeting psoriasis plaques. Climatotherapy refers to the practice of relocating patients to geographic areas with climates conducive to disease control.

Goeckerman therapy This therapy uses UVB phototherapy combined with topical coal tar to treat psoriasis. The powerful and quick clinical response observed with the Goeckerman regimen, the extended period of disease control, and the limited adverse reaction profile makes it a viable option for patients with resistant disease.[10] A disadvantage is that it is an outpatient treatment regimen that requires proximity to a capable treatment center.

Systemic therapy Topical therapies used as monotherapy or combined with phototherapy may be inadequate for patients with moderate-to-severe disease, when lesions are diffuse or in an active phase with sudden exacerbations. In such cases, systemic treatment with immunosuppressants cannot be combined with UV light because of the increased risk of skin cancer. For these patients, first-line therapy includes methotrexate, acitretin, apremilast, and biologics. All of these treatments must be closely monitored.

Methotrexate This drug inhibits DNA synthesis by competing as a substrate for dihydrofolate reductase, making it beneficial in treating pustular psoriasis and psoriatic arthritis. The usual dosage is 7.5 to 25 mg once a week.[11] Prescribe concomitant folic acid supplementation to reduce the incidence of adverse reactions. Infection and reactivation of latent tuberculosis (TB), lymphoma, as well as hepatitis are possible during methotrexate treatment because of the agent's immunosuppressive nature.[11] Initial laboratory monitoring includes baseline complete blood cell (CBC) count, liver function tests (LFTs), hepatitis B and C serologies, and screening for latent TB. Additional follow-up is advised for patients with compromised renal function.[12] Ongoing monitoring includes yearly screening for latent TB, and CBC count and LFTs every 3 to 6 months if laboratory studies remain normal.[11] Common toxicities of methotrexate include fatigue, anorexia, nausea, and stomatitis.[11] Methotrexate is contraindicated in patients with cirrhosis, leukopenia, anemia, significant thrombocytopenia, and in those who are pregnant or nursing.[11]

When the PASI is used, PASI-75 represents the percentage of patients who have attained 75% or more reduction in their PASI score from baseline. PASI-100 represents patients with a complete resolution of disease. The efficacy of methotrexate is 45% PASI-75 after 16 weeks of treatment.[13]

TABLE 1. Dosages of biologic agents for psoriasis

Adapted with permission from Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.

Agent	Loading dose	Maintenance dose
Etanercept	50 mg subcutaneous twice weekly for 12 weeks	50 mg subcutaneous once weekly
Infliximab	5 mg/kg IV administered in weeks 0, 2, and 6	5 mg/kg IV administered every 8 weeks (time interval and dosage can be increased based on patient response)
Adalimumab	80 mg subcutaneous (2 x 40 mg) followed by 40 mg 1 week later	40 mg subcutaneous every 2 weeks
Certolizumab	400 mg subcutaneous. For patients weighing less than 90 kg (198 lb), 400 mg initially and at weeks 2 and 4	400 mg subcutaneous every other week (200 mg for patients weighing less than 90 kg)
Usetekinumab	45 mg subcutaneous initially and 4 weeks later for patients weighing 100 kg (220.5 lb) or less; 90 mg initially and 4 weeks later for patients weighing more than 100 kg	45 mg subcutaneous every 12 weeks for patients weighing 100 kg or less; 90 mg every 12 weeks for patients weighing more than 100 kg
Secukinumab	300 mg subcutaneous at weeks 0, 1, 2, 3, and 4	300 mg subcutaneous every 4 weeks
Ixezumab	160 mg subcutaneous followed by 80 mg in weeks 2, 4, 6, 8, 10, and 12	80 mg subcutaneous every 4 weeks
Brodalumab	210 mg subcutaneous in weeks 0, 1, and 2	210 mg subcutaneous every 2 weeks
Guselkumab	100 mg subcutaneous in weeks 0 and 4	100 mg subcutaneous every 4 weeks
Tildrakizumab	100 mg subcutaneous initially and 4 weeks later	100 mg subcutaneous every 12 weeks
Risankizumab	150 mg subcutaneous in weeks 0 and 4	150 mg subcutaneous every 12 weeks

TABLE 2. Summary of biologic therapies

Adapted with permission from Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.

	TNF-alpha inhibitors	IL-12/-23 inhibitors	IL-17 inhibitor	IL-23 inhibitors
Baseline monitoring	• CBC count with differential • CMP • Hepatitis B and C serologies • HIV (clinician discretion) • Latent TB screen	• CBC count with differential • CMP • Hepatitis B and C serologies • HIV (clinician discretion) • Latent TB screen	• CBC count with differential • CMP • Hepatitis B and C serologies • HIV (clinician discretion) • Latent TB screen • Evaluation for IBD	• CBC count with differential • CMP • Hepatitis B and C serologies • HIV (clinician discretion) • Latent TB screen
Ongoing monitoring	• Yearly skin cancer screening • Yearly latent TB screening • Infliximab: liver function tests every 3 months until stable, then every 6 to 12 months • Follow-up in 4 to 6 months	• Yearly skin cancer screening • Yearly latent TB screening • CBC count and CMP (clinician discretion) • Follow-up in 4 to 6 months	• Yearly skin cancer screening • Yearly latent TB screening • Assess for exacerbation or new-onset IBD • Brodalumab: assess for suicidal ideation • Follow-up in 4 to 6 months	• Yearly skin cancer screening • Yearly latent TB screening • Follow-up in 4 to 6 months
Adverse reactions	• Multiple sclerosis (rare) • Hepatotoxicity • Drug-induced reversible lupus erythematosus • Exacerbation or new-onset heart failure • Cytopenia	Hypersensitivity reaction	• Increased liver transaminases • IBD (small risk) • Neutropenia (rare) • Suicidal ideation (brodalumab) • *Candida* infection	Increased liver transaminases
Contraindications	• Untreated hepatitis B infection • History of lymphoreticular malignancy • Active TB infection • Allergy to the drug • Significant heart failure or preexisting multiple sclerosis	• Untreated hepatitis B infection • History of lymphoreticular malignancy • Active TB infection • Allergy to the drug	• Active history of IBD • Presence of suicidal ideation (brodalumab) • Allergy to the drug	Allergy to the drug
Use in pregnancy/ lactation	Safe	No data	No human data	No data

Acitretin This oral retinoid is not an immunosuppressant but a vitamin A derivative. Its mechanism of action is not completely recognized, yet acitretin regulates epidermal differentiation and proliferation while maintaining anti-inflammatory and immunomodulatory effects.[11] The dosage for patients with psoriasis ranges from 10 mg to 50 mg daily, with titration upward balancing tolerability toward the desired clinical result. Although acitretin is not as effective as other systemic agents, it often is used in patients with psoriasis who also are taking HIV treatments.[11] Initial recommended laboratory tests are fasting lipid profile, renal and hepatic function tests, and a pregnancy test in women of childbearing age.[12] Ongoing monitoring should consist of appropriate monthly pregnancy testing for women, and for all patients, fasting lipid profile and hepatic enzyme testing for the first 3 months, repeated every 3 months. The efficacy of acitretin is 23% PASI-75 after 8 weeks of treatment.[14]

Apremilast This oral drug inhibits phosphodiesterase-4, resulting in increased cyclic adenosine monophosphate levels and a downregulation of inflammatory responses.[15] The initial dosage of 10 mg daily is titrated up by 10 mg per day over the first 5 days to minimize adverse gastrointestinal reactions, and then maintained at 30 mg twice daily.[12] Common adverse reactions are diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache.[15] Depression was reported in about 1% of patients.[1] Talk to patients about depression and recommend counseling for patients with preexisting

or worsening depression or suicidality. The efficacy of apremilast is 33% at 16 weeks of treatment.[15]

Biologics TNF, made by activated macrophages, plays a key part in the pathogenesis of many inflammatory conditions. Etanercept is a recombinant human TNF-alpha receptor protein fused with IgG1 that binds to TNF-beta and neutralizes its activity.[16] Infliximab is a chimeric monoclonal antibody with high specificity, affinity, and avidity for TNF-alpha.[17] Adalimumab is a fully human recombinant monoclonal antibody that targets TNF-alpha explicitly.[18] Adverse reactions associated with TNF-alpha include multiple sclerosis, hepatotoxicity, drug-induced lupus erythematosus, exacerbation of heart failure, and cytopenia.[12] Baseline screening includes screening for latent TB, CBC count with differential, complete metabolic profile (CMP), and hepatitis B and C serologies.[12] Ongoing monitoring includes assessment for infections, yearly skin cancer screening and testing for latent TB, CBC count with differential and CMP.[12] The efficacy of etanercept is 59% PASI-75, infliximab 50% PASI-75, and adalimumab 71% PASI-75.[16-18]

Ustekinumab is a human monoclonal antibody that binds to the P40 subunit of interleukin 12 (IL-12) and IL-23, thereby subduing the IL-12- and IL-23-mediated inflammation affiliated with psoriasis.[19] Overall, IL-12/23 is well received, although hypersensitivity reactions can occur. Baseline monitoring includes screening for latent TB, CBC count, CMP, and hepatitis B and C serologies. Ongoing annual monitoring includes skin screening and testing for latent TB, screening for adverse reactions, CBC count with differential, and CMP. The efficacy of ustekinumab is 78% PASI-75.[19]

Secukinumab is a human recombinant monoclonal antibody that binds IL-17A, and ixekizumab is a humanized monoclonal antibody that specifically targets IL-17A.[20,21] Adverse reactions to these IL-17 inhibitors include elevated liver transaminases, a small risk of irritable bowel disease (IBD), rare cases of neutropenia, and incidences of suicidal ideation and completed suicide behavior with brodalumab, another IL-17 inhibitor.[12] IL-17 inhibitors are well tolerated overall, and are associated with a greater risk of *Candida* infection.[12] Baseline monitoring includes screening for latent TB, CBC count, CMP, hepatitis B and C serologies, and evaluation for a history of IBD. Ongoing monitoring includes yearly skin screening and testing for latent TB, assessment for infections and exacerbation or development of IBD, and frequent evaluation for suicidal ideation in patients treated with brodalumab. The efficacy of secukinumab is 82% PASI-75, 59% PASI-90, and 29% PASI-100, and for ixekizumab it is 87% PASI-75, 68% PASI-90, and 38% PASI-100.[20,21]

Lastly, guselkumab, tildrakizumab, and risankizumab are humanized monoclonal antibodies that selectively block IL-23. Adverse reactions to these drugs include elevated liver transaminase levels, but overall they are well tolerated. Baseline monitoring includes screening for latent TB, CBC count, CMP, and serologic testing for hepatitis B and C. Ongoing monitoring includes yearly skin cancer screening and testing for latent TB, assessment for increased liver transaminases and infections, and hepatitis B and C serologies. At 16 weeks, the efficacy of guselkumab is 70% PASI-90, tildrakizumab 39% PASI-90, and risankizumab 77% PASI-90.[22-24]

See **Table 1** for dosages of biologic agents for psoriasis treatment, and **Table 2** for a summary of monitoring events for biologic therapies.

CONCLUSION

Psoriasis vulgaris is an autoimmune-mediated, multisystem inflammatory disease believed to be stimulated by a multitude of genetic and environmental factors. Prompt recognition, diagnosis, and initiation of treatment in patients with psoriasis improve clinical outcomes and quality of life. Clinicians should discuss disease severity, treatment efficacy and safety, and quality of life assessment with patients. Educating them about the cause of psoriasis and its management regimen enhances shared decision-making, strengthens the relationship between the patient and clinician, and improves patient adherence and satisfaction. **JAAPA**

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