CLINICAL

DISEASE STATE SPOTLIGHT:

Psoriasis and Psoriatic Arthritis: Update in Management

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Psoriasis and psoriatic arthritis are complex, chronic diseases with a high morbidity burden. Fortunately, a wide range of topical and systemic therapies is available, including a new class of highly effective immunosuppressive and biologic agents. However, the newer therapies must be closely monitored due to their potential to cause serious adverse drug effects. Managing these treatment challenges can go a long way toward ensuring optimal outcomes for patients.

Psoriasis affects as many as 7.5 million Americans.[1] Dysregulation of T-cells and other immune cells in the skin, along with known triggers (trauma to the skin, sunburn, chemical irritants, and drugs), play a critical role in disease development.[2,3] Diagnosis is usually made based on clinical examination with a focus on appearance and location of lesions. Disease severity is classified as mild-moderate if less than 5% of body surface area (BSA) is affected with no involvement of genitals, hands, feet, and face; moderate-severe disease affects 5% or greater of BSA or hands, feet, face, or genitals.[3] The Psoriasis Area and Severity Index (PASI) is commonly used in clinical trials to evaluate disease severity, and medication efficacy is most often reported as the proportion of patients achieving a 75% reduction in PASI (PASI-75). Other severity scales include the Psoriasis Global Assessment (PGA) and Lattice System-Physicians Global Assessment (LS-PGA). Up to 30% of people with psoriasis develop psoriatic arthritis, an inflammatory form of arthritis characterized by swelling, stiffness, and pain in and around the joints, particularly the distal joints in the fingers and toes.[1,4]

The various types of psoriasis are summarized in Table 1.[3,5,6] Clinical findings in individual patients often overlap categories, but determining the primary type of disease can help guide choice of therapy.

Pharmacologic Treatment

Topical Therapy

Topicals may be used as monotherapy for limited disease, or in combination with topical or systemic agents or phototherapy.[7] American Academy of Dermatology (AAD) guidelines strongly recommend combination topical therapy with a corticosteroid and vitamin D analog or retinoid (tazarotene).[8] Generally, potent topical agents should only be used continuously for short-term periods to achieve disease control, and intermittently for long-term management. Treatment of psoriasis localized to trunk, limbs, and scalp includes a potent corticosteroid alone or in combination with a vitamin D analog (calcipotriene), or monotherapy with a very potent corticosteroid. Treatment of face and flexures includes calcineurin inhibitors (tacrolimus or pimecrolimus) and weak topical corticosteroids.

Table 1. Characteristics of Psoriasis Types[3,5,6]

Type	Characteristics	Location	Notes
Chronic plaque	Well-defined, sharply demarcated, erythematous plaques; irregular, round to oval shapes and silvery lamellar scales	Scalp, trunk, buttocks, limbs (especially elbows and knees)	Most common form (80%-90% of patients)
Erythrodermic	• Generalized erythema; varying degrees of scaling • May have systemic symptoms—chills, night sweats, arthralgia, pedal edema, fever	Nearly entire body surface area	• Most severe form of psoriasis; may be life-threatening • Can develop acutely or gradually from other forms of psoriasis
Guttate	Dewdrop-like salmon-pink papules, usually with a fine scale	Trunk and proximal extremities	• Uncommon (<2% of patients) • Usually in younger patients (age <30 y) • May be preceded by upper respiratory tract infection with group A Ð-hemolytic streptococci
Intertriginous (inverse)	Erythematous plaques with minimal scale	Skinfolds or flexural areas such as breasts, groin, axillae, genitals, perineal, perirectal, or intergluteal areas, or cubital fossa	Friction and moisture hinder plaque growth
Nail	Pitting, onycholysis, subungual hyperkeratosis, nail plate dystrophy	Fingernails and/or toenails	Can occur with all other psoriasis types
Pustular	• Acute generalized: widespread pustules (pus-filled blisters) on an erythematous background; skin lesions can progress quickly and be potentially life-threatening • Localized: pustular disease with or without plaque disease	Varies; may be generalized or localized (palms/soles or fingers/toes)	Most cases of generalized disease are caused by recessive genetic mutations

Nonbiologic Systemic Therapy

Systemic therapies are generally reserved for more extensive disease (>10% BSA), debilitating symptoms, or limited disease that does not respond to topical agents.[9] Systemic therapies for psoriasis and psoriatic arthritis are summarized in Table 2.[3,9-17] Historically, immunosuppressive agents (methotrexate or cyclosporine) or acitretin were the cornerstone of systemic therapy.[9] Although these agents were effective in controlling disease, poor tolerance and toxicity limited their use as long-term monotherapy.[7]

In recent years, better understanding of the pathophysiology and molecular pathways in psoriasis has led to the development of several novel therapies with improved safety profiles compared with traditional systemic therapy.[2] Most notably, small molecule agents (apremilast and tofacitinib), which selectively inhibit intracellular signaling pathways, are emerging as alternative targeted therapy options for patients who do not respond to conventional or targeted antibody treatments.[11] The remainder of this review focuses on newer nonbiologic and biologic therapies.

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that impedes production of proinflammatory cytokines, increases anti-inflammatory cytokines, and reduces in vivo epidermal thickness.[10] Two Phase III trials (ESTEEM 1

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Table 2. Systemic Therapies for Psoriasis and Psoriatic Arthritis[3,9-17]

	Drug Class	Agent	Route	Onset of Effect	Expected PASI-75 for Psoriasis, %	Adverse Drug Events	Comments
Nonbiologic	Immunosuppressant	Methotrexate	PO	Weeks to months	35.5-41.9	Hepatotoxicity, CBC abnormalities, GI symptoms, infection, alopecia	• Daily folic acid recommended • Improved tolerability when used in combination with other systemic therapies or phototherapy
		Cyclosporine		Several weeks	60-70	Nephrotoxicity, HTN, malignancy, HA, GI symptoms, gingival hyperplasia, infection	Effective as short-term rescue medication, bridge to safer long-term therapies, or in rotation with other agents
		Azathioprine		Weeks to months	Poorly characterized	Myelosuppression, malignancy, infection, GI symptoms, pancreatitis, hepatitis	Poor-quality data
		Mycofenolate mofetil		Several months	20	GI symptoms, CBC abnormalities, urinary symptoms, infection, electrolyte abnormalities, HTN, HA, peripheral edema	Poor efficacy Low risk for long-term toxicity
		Tacrolimus		Unclear	Poorly characterized	Tremor, HA, nausea, diarrhea, HTN, renal impairment	Poor-quality data
	DMARD	Sulfasalazine		Several weeks	<40	Anorexia, HA, GI symptoms, oligospermia, rash, anemia	
		Leflunomide		Unclear	17	GI symptoms, HA, dizziness, hepatotoxicity	
	Antimetabolite	Hydroxyurea		Several months	40-50 50-80 35.5-41.9	Myelosuppression, hepatotoxicity, GI symptoms • Hydroxyurea: dermatologic reactions, temporary impairment of renal tubular function • 6-thioguanine: HA, herpes zoster, taste changes, herpes zoster	Response poorly sustained
		6-thioguanine					
	JAK inhibitor	Tofacitinib		Several weeks	39.5-66.7	Infection, lymphopenia, neutropenia, increased LFTs, lipid abnormalities, herpes zoster	• Safety concerns with higher dose • Registry for exposure reporting in pregnancy • Avoid concomitant use with other immunosuppressants
	Oral retinoid	Acitretin		Several months	20-40	Dry skin, eyes, and mouth; chapped lips; alopecia; paronychia; paresthesias; HA; nausea; lipid abnormalities; hepatotoxicity	• More effective for • palmoplantar, pustular, • or erythrodermic psoriasis, or in combination with phototherapy or biologics • Safe in combination with other oral agents and topicals • Long half-life
	PDE4 inhibitor	Apremilast[a]		Weeks to months	30	HA, nausea, diarrhea, URI	• Titrated over 6 d upon initiation • Registry for exposure reporting in pregnancy
Biologic	IL-17A receptor antagonist	Secukinumab	SC		67-87	Diarrhea, risk for infection, neutropenia	May cause Crohn's disease flare
	IL-12/23 inhibitor	Ustekinumab[a]	SC		59-76	HA, fatigue, risk for infection, malignancy, posterior leukoencephalopathy syndrome	Weight-based dosing
	TNF inhibitor	Adalimumab[a]	SC		53-80	Injection site reactions, CBC abnormalities, infection, lupus, demyelinating disorders, malignancy, new or worsening heart failure, hepatitis B reactivation	–
		Etanercept[a]	SC		30-59		–
		Infliximab[a]	IV	Several weeks	60-88		Administered as an IV infusion in a physician's office
		Golimumab[b]	SC	Unclear	75-83		–
		Certolizumab[b]	SC		N/A		

[a] Approved for psoriasis and psoriatic arthritis.

[b] Only approved for psoriatic arthritis.

CBC, complete blood count; **DMARD,** disease-modifying antirheumatic drug; **GI,** gastrointestinal; **HA,** headache; **HTN,** hypertension; **IL,** interleukin; **JAK,** Janus kinase; **LFT,** liver function test; **N/A, n**ot applicable; **PASI-75,** 75% reduction in Psoriasis Area and Severity Index; **PDE4,** phosphodiesterase 4; **PO,** by mouth; **SC,** subcutaneous; **TNF,** tumor necrosis factor; **URI,** upper respiratory tract infection

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and ESTEEM 2) compared apremilast 30 mg twice daily with placebo for moderate-severe plaque psoriasis.[18,19] After 16 weeks, 28.8% and 33.1% of patients in the apremilast groups achieved PASI-75, versus less than 6% in the placebo groups. Currently, there is an ongoing study comparing apremilast with etanercept and placebo.[20] Overall, success rates for apremilast are lower than those for older agents, including cyclosporine, anti–tumor necrosis factor (TNF) agents, and ustekinumab.[12]

Tofacitinib, a Janus kinase (JAK) inhibitor with relative specificity for JAK1 and JAK3, blocks signaling transduction of cytokines and halts the activity of helper and cytotoxic T-cells.[11] Combined results from 2 Phase III trials that compared off-label tofacitinib 5 and 10 mg twice daily with placebo for chronic plaque psoriasis demonstrated superior efficacy with tofacitinib after 16 weeks of therapy.[21] Best results were achieved with 10 mg twice daily dosing, which resulted in about 59% of patients in both trials achieving PASI-75, versus 6.2% and 11.4% in the placebo groups. In another Phase III trial of adults with moderate-severe plaque psoriasis, tofacitinib 5 and 10 mg twice daily were compared with etanercept 50 mg twice weekly and placebo.[22] Tofacitinib 10 mg twice daily was superior to placebo and noninferior to etanercept for achieving PASI-75.

Biologic Systemic Therapy

Compared with traditional systemic therapies, biologics target specific inflammatory cosignaling molecules and offer improved safety profiles, decreased incidence of cumulative toxicity, and fewer drug interactions. A 2013 meta-analysis of 41 clinical trials that compared several biologics with placebo found significantly increased PASI response rates with ustekinumab and infliximab.[23] A subsequent meta-analysis of 48 trials of systemic therapies for moderate-severe psoriasis identified infliximab, adalimumab and ustekinumab as the most efficacious treatments for induction therapy, and superiority of adalimumab and infliximab over methotrexate.[12]

Ustekinumab is the first interleukin (IL)-12/23 inhibitor with demonstrated efficacy in patients with moderate-severe plaque psoriasis. Two Phase III trials (PHOENIX 1 and PHOENIX 2) found that 66.4% and 75.7% of patients randomized to ustekinumab 90 mg achieved PASI-75 after 12 weeks of therapy, compared with less than 4% in the placebo groups.[24,25] Pooled data from 4 studies demonstrated the safety of ustekinumab for up to 5 years.[26]

Two trials (ERASURE and FIXTURE) demonstrated efficacy of secukinumab, the first anti-IL 17A monoclonal antibody, in patients with moderate-severe plaque psoriasis.[13] After 12 weeks, PASI-75 was achieved in 82% of patients randomized to secukinumab 300 mg once weekly, compared with less than 5% in the placebo group. Compared with etanercept 50 mg twice weekly, a higher proportion of patients achieved PASI-75 at 12 weeks with secukinumab 300 mg (44% and 77%, respectively). A Phase III randomized controlled trial (CLEAR) that compared secukinumab with ustekinumab in patients with moderate-severe plaque psoriasis demonstrated greater efficacy with secukinumab and similar safety profiles.[27]

Overall, there is limited guidance for choosing between systemic therapies for psoriasis. Guidelines do not include the newer agents (apremilast, tofacitinib, golimumab, secukinumab and ustekinumab); however, recommendations for ustekinumab are provided in several more recent consensus statements from The National Psoriasis Foundation.[3,9,28-30]

Nonpharmacologic Treatment

Nonpharmacologic care of psoriasis may include moisturizers, oatmeal baths, sunscreen, and stress reduction.[31] Routine skin care should include emollient moisturizers and ointments to maintain skin hydration, maximize function of the epidermal moisture barrier, and reduce shedding, scaling, and pruritus.[5,31] A thin protective layer of petrolatum applied to skinfold areas affected by intertriginous psoriasis may also be helpful.[5] Phototherapy with narrowband UVB or psoralen-UVA 2 to 3 times weekly depletes dermal and epidermal inflammatory cells, and improves psoriasis lesions.[32]

Psoriatic Arthritis

The AAD has developed guidelines for the management of psoriatic arthritis, with an emphasis on biologic medications.[4] Mild disease can be managed with physical therapy, trigger avoidance, and nonsteroidal anti-inflammatory medications. Intraarticular corticosteroid injections may also be effective if only a few joints are involved. Moderate-severe psoriatic arthritis requires oral disease-modifying antirheumatic drug (DMARD) therapy. The standard of care for more aggressive or extensive disease is the combination of methotrexate and a TNF inhibitor (only adalimumab, etanercept, and infliximab are mentioned). These guidelines do not address recently approved drugs for psoriatic arthritis.[4]

Approval of the newer agents was based on placebo-controlled trials. There are few data to guide treatment choices between the available agents, but some comparative studies have been published. One randomized, single-center trial in 100 patients with psoriatic arthritis and inadequate response to DMARD therapy compared the effect of adding etanercept, adalimumab, or infliximab.[33] After 12 months, a similar proportion of patients in each group met the criteria for response (70%-75%), but patients who received etanercept had significantly fewer tender joints compared with the other therapies. Swollen joints were similar between treatment groups. Adalimumab had the lowest overall adverse event rate (6%), followed by etanercept (17%) and infliximab (23%). An indirect comparison of Phase III placebo-controlled trials with etanercept, infliximab, adalimumab, and golimumab did not find any significant differences in response after 24 weeks.[34] However, this analysis identified a higher incidence of injection site reactions (by about 26%) with etanercept versus the other agents. Similarly, another indirect analysis found no significant differences between adalimumab, etanercept, and infliximab in efficacy or serious adverse events at 12 to 16 weeks.[35] No direct or indirect comparisons with apremilast are available.

Therapeutic Monitoring and Preventive Care

Patients with psoriasis have an increased risk for cardiovascular disease, lymphoma, and depression.[3] All biologic agents for psoriasis or psoriatic arthritis (except ustekinumab) have a boxed warning regarding the risk for serious infections such as tuberculosis, invasive fungal infections, and opportunistic bacterial and viral infections.[14] Therefore, patients receiving these therapies should undergo baseline and yearly screening for latent tuberculosis.[3,36,37] Screening for latent tuberculosis can also be considered before initiating methotrexate or cyclosporine. There is also a risk for lymphoma and other malignancies and autoimmune conditions (lupus) with the use of biologics.[29] Treatment with adalimumab, etanercept, infliximab, or golimumab warrants liver function and complete blood count testing at baseline and periodically thereafter.[3,14,36]

Alteration of the immune system by immunologic and biologic therapies may prevent an adequate immune response to vaccines.[3,29,38] Guidelines recommend that pneumococcal, hepatitis A and B, influenza, and tetanus-diphtheria vaccines should be given before initiation of immunosuppressants; other vaccines can be given if immunity is lacking or if risk factors for the disease are present.[38] Annual influenza vaccination is also recommended for all patients.[36,38] If possible, live and live attenuated vaccines should be avoided in patients who are receiving immunosuppressive therapy. Administration of live vaccines (eg, measles-mumps-rubella, varicella, nasal influenza, oral typhoid, and rotavirus) should be completely avoided in patients being treated with biologic agents because of the theoretical risk for infection. If these vaccines are needed, they should be given 2 to 4 weeks before starting therapy or more than 4 medication half-lives after discontinuation.[3,38]

Conclusion

As noted, psoriasis and psoriatic arthritis present significant management challenges. Immunosuppressive and biologic agents, in particular—although very effective—must be closely monitored due to serious safety concerns. Moreover, the availability of new therapies that are currently in development, including biosimilar biologic agents; the IL-17 inhibitors ixekizumab and brodalumab; and new topical agents such as JAK inhibitors, PDE4 inhibitors, cysteine protease inhibitors, and lymphocyte migration inhibitors, will continue to change therapeutic approaches for these conditions.[39-42]

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