Chapter 118: Psoriasis

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UPDATE SUMMARY

Update Summary

March 1, 2023

The following sections, tables, and figures were updated:

- Added section comparing efficacy among IL-17 inhibitors
- Added apremilast, janus kinase inhibitors, and bimekizumab place in therapy, dosing, side effects, and monitoring requirements
- Updated epidemiology of psoriasis rates in pediatric patients
- Added section on psoriasis severity, topical products, and systemic treatment options in pediatric patients

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 17, Psoriasis.

KEY CONCEPTS

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1. Patients with psoriasis have a lifelong illness that may be visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients.

2. Psoriasis is a progressive T-lymphocyte–mediated systemic inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Genetic predisposition and precipitating "trigger" factors play a role in the "march of psoriasis." This march of innate and adaptive immune responses results in clinical expressions (eg, keratinocyte proliferation) and is linked to systemic psoriatic comorbidities.

3. Diagnosis of psoriasis is usually based on recognition of the characteristic psoriatic lesion and not based on laboratory tests.

4. Treatment goals for patients with psoriasis use "treat to target" strategies to reduce disease morbidity and improve quality of life. They serve to minimize signs such as plaques and scales, alleviate symptoms such as pruritus, reduce the frequency of flare-ups, improve the patient's quality of life ensure appropriate treatment of associated comorbid conditions, such as metabolic syndrome, psoriatic arthritis, or clinical depression, and minimize treatment-related morbidity.

5. Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies.

6. Nonpharmacologic alternatives such as stress reduction and the liberal use of moisturizers may be beneficial and should always be considered and initiated when appropriate.

7. Pharmacologic alternatives for psoriasis include topical agents, phototherapy, and systemic agents (both traditional/nonbiologic and biologic agents).

8. Pharmacologic therapy is generally guided by the severity of disease and its impact on the patient's quality of life, advancing from topical agents to phototherapy to systemic agents as needed.

9. Rotational therapy (ie, rotating systemic drug interventions) is a means to minimize drug-associated toxicities. However, continuous treatment has replaced rotational or sequential therapy and is now the standard of care for many dermatologists. Rotational and sequential therapy are used in pediatrics. Sequential therapy may be needed for biologics.

10. Some biologic agents have proven efficacy for psoriasis; however, there are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. Biologics are often used for moderate-to-severe psoriasis and may be first-line therapy especially if comorbidities exist.

BEYOND THE BOOK

BEYOND THE BOOK

What does psoriasis look like? Search online for images of the skin manifestations of the various types of psoriasis (as described in Table 118-1). In particular, for plaque psoriasis (the most common phenotype), search for images of scalp, trunk/limb, hands, and nail involvement (oil spots). This activity is useful to enhance students understanding of the ASSESS step in the patient care process.

INTRODUCTION

Psoriasis is a chronic disease that waxes and wanes. It is never cured, and it is now known to be associated with multiple comorbidities including heart

disease, diabetes, and metabolic syndrome. The signs and symptoms of psoriasis may subside totally (go into remission) and then flare up again (exacerbation). Triggers include stress, seasonal changes, and some drugs. Disease severity may vary from mild to disabling. Psoriasis imposes a burden of disease that extends beyond the physical dermatologic manifestations.

1 Patients with psoriasis often have a lifelong illness that may be visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients. Thus, management of this condition is necessarily long-term and multifaceted, and management modalities may change according to the severity of the illness at the time.

EPIDEMIOLOGY

Psoriasis is the most common immune-mediated inflammatory disease worldwide. In the United States, psoriasis affects about 8 million people, or approximately 3% of the population.[1] The prevalence in countries varies between 0.09% and 11.4%, with differing reasons for the wide range.[2] Climate, sun exposure, and ethnicity are thought to affect prevalence, but correlation between latitude and prevalence is weak.[3]

According to the largest population-based survey—the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP)—the prevalence of psoriasis ranges from 1.4% in Spain to 3.3% in Canada, with the United States at 2.2% and the overall prevalence of psoriasis at 1.9%.[4] Lower frequencies of between 0.4% and 0.7% are seen for people of African and Asian descent.[3] Of interest is the fact that psoriasis is seldom seen in North and South American aboriginal Indians. It affects males and females equally.[5] Psoriasis can present at any age.[4] The majority of patients (approximately 75%) have onset before the age of 40 years,[5] but psoriasis has been observed at birth and as late as the ninth decade of life.[5]

Prevalence increases are roughly linear over the life course (about 0.12% at age 1 year to 1.2% at age 18).[3] Many studies report two peak ages of onset: at 20 to 30 years and again at 50 to 60 years of age.[4,5]

ETIOLOGY

2 Psoriasis is a T-lymphocyte–mediated systemic inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Genetic predisposition coupled with some precipitating factor triggers an abnormal immune response, resulting in the initial psoriatic skin lesions. This has been called the “march of psoriasis”[6,7] to reflect the innate and adaptive immune responses that are present. This march leads to expressions of psoriasis with keratinocyte proliferation being central to the clinical presentation of psoriasis and is likely responsible for various comorbidities as a consequence of the chronic inflammation associated with psoriasis.[3,6] For example, there is an association between psoriasis and cardiovascular disease, which is an ongoing, two-way interplay.[6,7] The concept is that systemic inflammation enhances insulin resistance, causing endothelial dysfunction, leading to atherosclerosis and coronary events.[8]

Genetics

Dermatologists have recognized the familial tendencies of psoriasis for many years. Approximately 30% of patients have a first-degree relative with psoriasis, and the risk of psoriasis increases with the number of affected relatives.[4] Monozygotic twins have a concordance rate in the 80% range. Rates of family history in a psoriasis family range between 36% and 91%.[9,10] A study using the founder population of Newfoundland and Labrador noted that more than 80% of the patients had a positive family history.

The bimodal distribution of this disease (prevalence peaking at 20-30 years and again at 50-60 years) may represent two distinct forms of psoriasis, with early-onset psoriasis much more likely to possess a genetic marker highly associated with psoriasis.[4]

There are psoriasis susceptibility genes and variants that reside on various chromosomes. The psoriasis susceptibility locus 1 (*PSORS1*) on chromosome 6p is a key gene locus, accounting for up to 50% of disease heritability.[3] In 2009, studies of the Newfoundland and Labrador population confirmed that major histocompatibility complex antigen HLA-Cw6 and tumor necrosis factor (TNF)-α as major psoriasis susceptibility genes, along with interleukin (IL)-23 loci that had previously been reported.[5,11] The findings have been confirmed in multiple populations worldwide.[12]

Roughly 40 additional loci are thought to be associated with psoriasis.[3] Corresponding genes to these loci are involved in pathogenesis pathways in the immune system (adaptive and innate). There is a general role for T cells and a specific role for TH17 lymphocytes in psoriasis pathogenesis and as indicators of psoriasis risk.[3]

Predisposing Factors and Precipitating Factors

Injury to the skin, infection, drugs, smoking, alcohol consumption, obesity, and psychogenic stress have been implicated in the development of psoriasis. Examples of these precipitating factors include a horsefly bite causing skin trauma and resulting in new-onset psoriasis (known as the *Koebner phenomenon*),[13] a viral or streptococcal infection, or the use of β-adrenergic blockers.[14] Factors exacerbating preexisting psoriasis include drugs[14] (eg, lithium, nonsteroidal anti-inflammatory drugs [NSAIDs], antimalarials such as chloroquine, β-adrenergic blockers, fluoxetine, and withdrawal of corticosteroids), and psoriatic patients commonly have exacerbations during times of stress.[3,14,15] Smoking cigarettes has been shown in two international studies to be a risk factor for psoriasis.[16] Lifestyle intervention to mitigate risk factors has been recommended.[17]

PATHOPHYSIOLOGY

Psoriasis is a common chronic inflammatory disease that involves both adaptive and innate immunity.[3] It is an immune-mediated disease in which the skin inflammatory changes are dependent on immune cells and their cytokines.[4] The interaction between dermal dendritic cells, activated T cells of the TH-1, TH-17 lineage in concert with a multitude of cytokines and growth factors are responsible for the epidermal hyperplasia and dermal inflammation that is seen in the skin of patients with psoriasis. Cross-talk between the innate and adaptive immune system mediated by cytokines including TNF-α, interferon-gamma, and interleukin-1 is a major research focus.[3]

Comorbidities

It is well documented that psoriasis patients have significantly associated comorbidities.[3,4,6,7,16] Approximately 75% of patients will have at least one comorbid condition, and many will have multiple comorbidities.[4] Psoriatic arthritis (PsA) is one of the most common and well-known extracutaneous manifestations of the disease.[4,16] Other associated comorbidities include metabolic syndrome, other immune-mediated disorders such as Crohn's disease, multiple sclerosis, and some psychological illnesses (anxiety, depression, and alcoholism).[18] Also, malignancies such as cutaneous T-cell lymphoma are associated with psoriasis, and melanoma and nonmelanoma skin cancer are associated with psoriasis treatments.

The National Psoriasis Foundation published a clinical consensus on psoriasis comorbidities with recommendations for screening and addressing issues such as cardiovascular risk, metabolic syndrome, and obesity.[19] The importance of screening for comorbidities in psoriasis patients cannot be overemphasized: nearly half of the psoriatic patients older than 65 years have at least three comorbidities (with two-thirds of this patient population having two or more comorbidities).[20] The presence of specific comorbidity in a patient with psoriasis may influence the choice of pharmacotherapy.

PsA usually develops after the onset of psoriasis,[5] typically 10 years later,[18] with a range of 5 to 12 years.[4] However, 10% to 15% of patients report that the PsA appeared first.[5] The prevalence of PsA in psoriatic patients is about 30%[3,18] but varies by disease severity.[18] In one US study, the prevalences were 14% for patients with mild psoriasis, 18% for those with moderate psoriasis, and 56% for patients with severe psoriasis.[21] PsA most commonly presents as polyarticular peripheral arthritis but can vary widely with peripheral and/or axial, monoarticular, or polyarticular patterns.[4] The severity of PsA also varies widely and does not necessarily correlate with the severity of skin findings.[4] TNF-α and HLA-Cw6 are linked to both PsA and psoriasis.[22] Although immunomodulating treatments for psoriasis (such as methotrexate or TNF-α inhibitors) are useful for PsA, NSAIDs effective for joint symptoms of PsA may exacerbate psoriasis.

Metabolic syndrome is a cluster of risk factors including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance or glucose intolerance, prothrombotic state, and a proinflammatory state.[19] Patients with psoriasis are at increased risk of developing metabolic syndrome.[3,19] The syndrome is a strong predictor of cardiovascular diseases, stroke, and diabetes.[19,23,24] Patients with this syndrome are three times as likely to have a myocardial infarction (MI) or stroke, twice as likely to die from the MI or stroke, and five times as likely to develop type 2 diabetes.[19] A 2010 retrospective analysis of pooled data from three clinical trials (M02-528, CHAMPION, and REVEAL) showed that patients with psoriasis have a 28% and

12% increased 10-year risks of coronary heart disease (CHD) and stroke, respectively.[24]

Psychiatric/psychologic comorbidities include depression, suicidal ideation and suicide, anxiety, and poor self-esteem.[16] A recent meta-analysis reported that more than 25% of psoriasis patients had depressive symptoms and more than 10% were clinically depressed.[16,25] In comparison to control subjects, psoriasis patients had significantly more depression symptoms with an odds ratio (OR) of 1.57% (95% CI 1.40–1.76) for clinical depression (using the International Classification of Diseases codes) and had an OR of 4.24 (95% CI 1.53–11.76) for antidepressant use.[16,25]

Patients with psoriasis also have a decreased life expectancy and increased rates of mortality. Psoriasis is an independent risk factor for atherosclerosis, especially for younger patients with severe disease.[19] A 2006 study found that a relative risk (RR) of death for a 30-year-old person with severe psoriasis was 3.10, after controlling for traditional cardiovascular risk factors (eg, age, gender, hypertension, dyslipidemia, diabetes mellitus, smoking, body mass index [BMI], C-reactive protein [CRP], and family history of cardiovascular disease).[19,26] Three epidemiological meta-analyses identified increased cardiovascular mortality risk (relative risk: 1.39, 1.37, 1.2) and stroke (relative risk 1.56, 1.59, and 1.21) for psoriatic patients.[3] Only patients with severe psoriasis are associated with a higher cardiovascular disease risk.[16] Moderate-to-severe psoriasis may be associated with an increased risk of chronic kidney disease.[16]

Systemic treatment of psoriasis with anti-inflammatory agents—in particular, methotrexate and some biologic therapies—may have protective effects against cardiovascular death, MI, and stroke/cerebrovascular disease.[27,28] However, the use of systemic retinoids does not.[28]

Types of Psoriasis

Plaque psoriasis, also known as *psoriasis vulgaris*, is the most common type of psoriasis (Table 118-1) and is seen in about 90% of psoriasis patients. Plaque psoriasis presents as shown in the Clinical Presentation box.

TABLE 118-1

Phenotypic Classifications of Psoriasis

Plaque (psoriasis vulgaris)
Flexural and/or intertriginous (inverse psoriasis)
Seborrheic
Scalp
Acrodermatitis of Hallopeau
Palm and/or soles
Generalized pustular psoriasis
Guttate
Erythrodermic

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Psoriasis

Signs and Symptoms of Plaque Psoriasis	Description (from Reference 16)
Lesions (plaques)	Erythematous
	Red-violet in color
	At least 0.5 cm in diameter
	Well demarcated—clearly distinguished from normal skin
	Typically covered by silver, flaking scales—scale removal is accompanied by fine points of bleeding (the "Auspitz sign")
	Lesions may develop at sites of trauma or injury (the "Koebner phenomenon")
Skin involvement	Either as single lesions at predisposed areas (eg, knees, elbows)
	Or
	Generalized over a wide BSA
	Mild psoriasis: ≤5% BSA involvement
	Moderate psoriasis: PASI ≥8 (higher in trials of biologics)
	Severe psoriasis: The rule of tens: PASI ≥10 or DLQI ≥10 or BSA ≥10% (in some phototherapy trials, BSA ≥20% used as lower limit)
	Categories in the European consensus: Mild psoriasis: BSA ≤10 and PASI ≤10 and DLQI ≤10. Moderate-to-severe psoriasis: (BSA >10 or PASI >10) and DLQI >10
Pruritus	More than 50% of patients with psoriasis have associated pruritus
	May be severe in some patients and may require treatment to minimize excoriations from constant scratching
Other associated concerns	This condition may also be physically debilitating or socially isolating with significant quality-of-life issues for the patient
	Potential comorbidities: PsA, depression, hypertension, obesity, diabetes mellitus, Crohn's disease, anxiety, alcoholism

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, psoriasis area and severity index; PsA, psoriatic arthritis.

Up to 30% of patients with psoriasis have associated PsA[3] but this varies by disease severity.[18] Although nail involvement (psoriatic onychodystrophy) can occur with any type of psoriasis, it is seen in up to 90% of patients with PsA.[16] Fingernails are involved in about 50% of all patients with psoriasis

and toenails are involved in 35% of patients.[16]

DIAGNOSTIC CONSIDERATIONS

3 The diagnosis of psoriasis is based on recognition of the characteristic psoriatic lesion and not on laboratory tests. Diagnostic testing is rarely performed as a biopsy may be suggested but is not diagnostic of psoriasis.

Psoriasis is traditionally classified into mild, moderate, or severe disease. In 2011, a European consensus (19 countries) formalized the definition of disease severity and treatment goals and defined plaque psoriasis severity as two main categories: mild versus moderate-to-severe. This became the basis for defining treatment goals in the 2015 European guidelines.[29,30] Both classification systems are in use today. In 2017, the Medical Board of the National Psoriasis Foundation (NPF) used a consensus-building (Delphi) process to establish treatment goals/targets in psoriasis (discussed later).[31] In clinical practice, assessment of the severity of disease includes both an objective evaluation of the extent and symptoms as well as a subjective evaluation of the impact of disease on the patient's quality of life.[16] Assessment typically includes measures of symptom and involvement such as body surface area (BSA), Psoriasis Area and Severity Index (PASI), or Physician's Global Assessment (static PGA), as well as quality-of-life measures such as the Dermatology Life Quality Index (DLQI) or the Short Form (SF-36) Health Survey.[4,16]

Classification of psoriasis as mild, moderate, moderate-severe, or severe disease is generally based on skin lesions and BSA or PASI measurements (see Clinical Presentation box). Practically, to give a rough estimate of BSA involvement, palm size is approximately 1% BSA, head and neck involvement is approximately 10% BSA, both upper limbs approximately 20% BSA, trunk involvement (front and back) approximately 30% BSA, and both lower limbs approximately 40% BSA. The DLQI and other indicators of the disease's impact on a patient's quality of life may also play a role. In 2020, an international group using a Delphi consensus process suggested that in lieu of severity, patients with psoriasis should be classified as either candidates for topical therapy or candidates for systemic therapy[32]; however, this classification differs from the 2021 AAD/NPF treatment guidelines that are discussed later in this chapter.

TREATMENT

Treatment of psoriasis is based on managing the underlying pathophysiology. Agents that modulate the abnormal immune response, such as topical corticosteroids (TCS) and biologic agents, are important treatment strategies for psoriasis. Topical therapies that affect cell turnover, such as retinoids, are also effective for psoriasis. In addition, nonpharmacologic therapies are effective adjuncts and should be considered for all patients with psoriasis. A treatment regimen should always be individualized, taking into consideration severity of disease, patient responses, and tolerability to various interventions. Furthermore, if comorbidities exist, they must be taken into treatment considerations and managed early. Optimal psoriasis care needs to maintain a focus on the patient's overall health-related quality of life.

Desired Outcomes

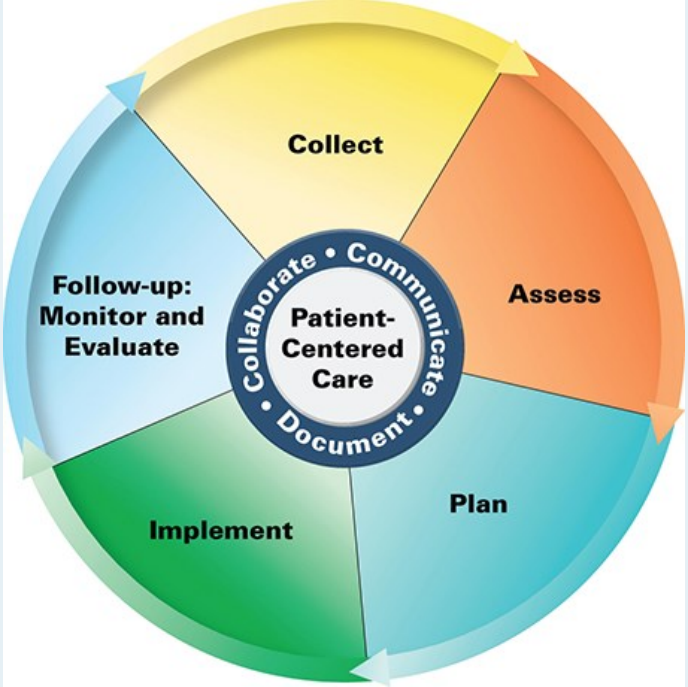
4 Goals of treatment[15]:

- Minimizing or eliminating the visible signs of psoriasis, such as plaques and scales
- Alleviating pruritus and minimizing excoriations
- Reducing the frequency of flare-ups
- Ensuring appropriate treatment of associated comorbid conditions such as PsA, hypertension, dyslipidemia, diabetes, or clinical depression, and ensuring follow-up care for other conditions by appropriate healthcare providers
- Screening for and managing lifestyle factors which may trigger exacerbations (eg, stress, smoking, obesity)[32]
- Minimizing nonspecific triggers such as mild trauma (scratching, piercings, tattoos), sunburn, chemical irritants, environmental/workplace factors[3]

- Optimizing the patient's overall health-related quality of life
- Providing guidance or counseling as needed (eg, stress-reduction techniques, smoking cessation programs)
- Avoiding or minimizing adverse effects from treatments used (topical, phototherapy, and/or systemic)
- Providing cost-effective therapy

PATIENT CARE PROCESS

Patient Care Process for Management of Psoriasis



Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Patient description of history of psoriasis, subjective complaints of itch, and other symptoms
- Signs associated with severity of psoriasis (eg, areas of involvement)
- Signs associated with severity of itch (eg, excoriations, sleep disturbances)
- Signs of other comorbid illnesses (PsA, depression, anxiety, poor self-esteem, Crohn's disease, and metabolic syndrome–associated diseases, eg, dyslipidemia, hypertension, and obesity)
- Signs of secondary skin infections
- Symptoms of stress or distress (personal and family/caregiver)

Assess

- Type of psoriasis (plaque psoriasis being most common)
- Severity of psoriasis—classified into mild, moderate, or severe disease. Mild psoriasis: ≤5% BSA involvement. Moderate psoriasis: PASI ≥8 (higher in trials of biologics). Severe psoriasis: the rule of tens: PASI ≥10 or DLQI ≥10 or BSA ≥10% (in some phototherapy trials, BSA ≥20% used as lower limit). Categories in the European consensus: Mild psoriasis: BSA ≤10 and PASI ≤10 and DLQI ≤10. Moderate-to-severe psoriasis: (BSA >10 or PASI >10) and DLQI >10. Both classifications are in use in North America.
- Severity of itch
- Ability/willingness to pay for medical treatment options
- Emotional concerns for patient and caregiver (if any) and the level of disease-associated stress

Plan

- Determine an appropriate treatment approach, that is, topical or phototherapy or systemic therapy or a combination of treatments
- Determine specific therapeutic agents/treatments of choice
- Recommend the most appropriate therapies (nonpharmacologic and pharmacologic) for this patient's psoriasis
- Manage the itch with appropriate nonpharmacologic and pharmacologic therapies

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Provide information about prevention of future flare-ups

Follow-up: Monitor and Evaluate

- Contact patient/caregiver in 1 to 3 weeks (or as recommended based on the specific drug therapy) to follow-up about the efficacy of recommended therapies and any issues with the treatment regimen
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed)
- Reinforce preventive measures including continuation of maintenance therapy
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a psychologist for stress reduction therapy)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Evaluation of Therapeutic Outcomes

Successful management of psoriasis should include not only clearance of skin lesions, which may take weeks to months depending on the severity of disease, but also control of associated conditions such as itching, and, importantly, comorbidities, including dyslipidemia, hypertension, PsA, and clinical depression as discussed earlier. The ultimate goal is to provide enough control of this chronic disease and its comorbidities (if present) so that the patient's quality of life is optimized.

The 2011 European consensus defined induction and maintenance phases and provided separate treatment goals for induction and maintenance.[29,30] The induction phase is defined as the first 16 weeks of treatment for drugs with a rapid induction to remission (such as adalimumab or infliximab),

extending the phase to 24 weeks of treatment for less rapidly effective drugs (such as methotrexate or etanercept).[30] To be considered successful therapy, a treatment regimen should result in a reduction of PASI greater than or equal to 75%, or PASI of 50% to 75% coupled with a DLQI less than 5.[30] Otherwise, treatment modifications should be considered. Treatment goals should be assessed at 10 to 16 weeks and then every 8 weeks thereafter.[30]

In 2017, the NPF-led US consensus recommended earlier treatment response targets: An acceptable treatment response at 3 months after starting new therapies (ie, induction phase) is either BSA 3% or less, or BSA improvement of 75% or more from baseline; the target response at 3 months after starting new therapies is BSA 1% or less.[31] During the maintenance phase, evaluation should occur every 6 months with the target response being BSA 1% or less at every 6 months of maintenance evaluation.[31]

It is important to treat beyond clearing visible skin lesions. Psoriasis is a dermatological inflammatory disorder where the goal is to manage both skin lesions and associated diseases. Comorbidities and trigger factors must be managed as early as possible.

General Approach to Treatment

5 Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies. Nonpharmacologic management strategies are important and should be used for all patients with psoriasis, regardless of the severity of disease. Pharmacologic therapies are always tailored to the individual patient with psoriasis, and different treatment strategies would be used depending on psoriatic disease severity, presence or absence of comorbid illnesses, and any special considerations such as hepatic or renal dysfunction.

Nonpharmacologic Management Strategies

6 Nonpharmacologic alternatives may be beneficial and should always be considered and initiated when appropriate.[15] These include stress-reduction strategies, moisturizers, oatmeal baths, and skin protection using sunscreens.[33]

In particular, stress reduction has been shown to improve both the extent and severity of psoriasis, and includes methods such as guided imagery and stress-management clinics. Liberal use of nonmedicated moisturizers, applied ad lib, helps to maintain skin moisture, reduces skin shedding, controls associated scaling, and may reduce pruritus. Oatmeal baths further reduce pruritus and with regular use may minimize the need for systemic antipruritic drugs.

Sunscreens, preferably with a sun protection factor (SPF) of 30 or more, should be regularly used because sunburns can trigger an exacerbation of psoriasis. Irritation to the skin should be minimized—harsh soaps or detergents should not be used. Cleansing should be done with tepid water and preferably with lipid-free and fragrance-free cleansers.[15,33]

For patients with comorbidities such as dyslipidemia, obesity, or cardiovascular disease, cessation of nicotine and alcohol consumption, diet management and increasing physical activity can be important interventions.[6,32]

Pharmacologic Therapies

7 Pharmacologic alternatives for psoriasis are topical agents, phototherapy, and systemic agents, including biologic agents (formerly referred to as biologic response modifiers or BRMs).

Drug Treatments of First Choice

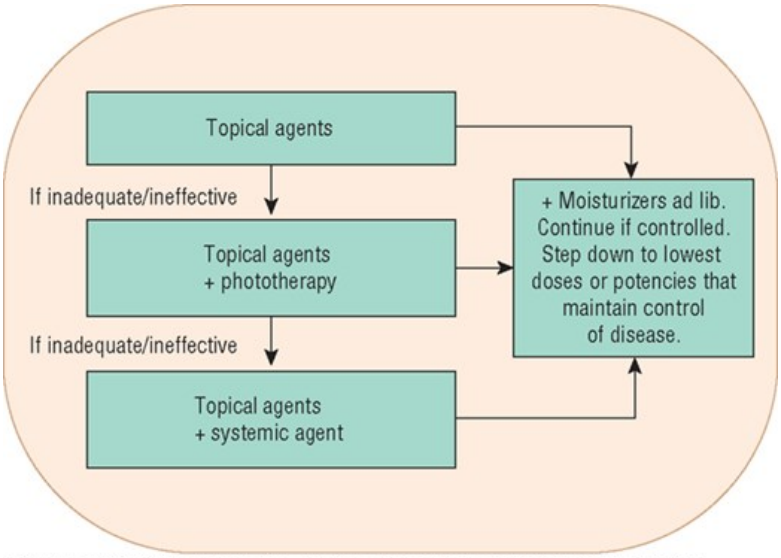
8 9 For limited or mild-to-moderate disease, topical treatments are the mainstay of care.[34] Phototherapy and photochemotherapy are used in moderate-to-severe cases.[35] For patients presenting with extensive or moderate-to-severe disease, systemic therapies with or without the use of topical treatments are the usual standard of care.[36,37] Newer systemic treatments such as biologic agents may be the treatments of choice, especially for patients with comorbidities such as PsA or if traditional systemic treatments (such as methotrexate or cyclosporine) are contraindicated.[37] See the "Systemic Therapy with Biologic Agents" section about guidelines for transitioning from traditional nonbiologic systemic agents to biologics.

Once the disease is under control, therapy is reduced in intensity to the least potent, least toxic agent(s) that maintain(s) control. Rotational therapy (ie, rotating systemic drug interventions) may minimize drug-associated toxicities; however, continuous treatment has replaced rotational or sequential therapy and is now the standard of care for many dermatologists. Sequential therapy may be needed for biologics.

Different treatment algorithms are used, depending on the severity of the plaque psoriasis (Figs 118-1 and 118-2). The European consensus categorizes psoriasis as mild or moderate-to-severe with mild disease treated topically and moderate-to-severe disease treated systemically. The Canadian Psoriasis Guidelines Addendum Committee[16] and the British Association of Dermatologists have recommendations for first and alternate choices for biologics (if used)—see the "Systemic Therapy with Biologic Agents" section for details.

FIGURE 118-1

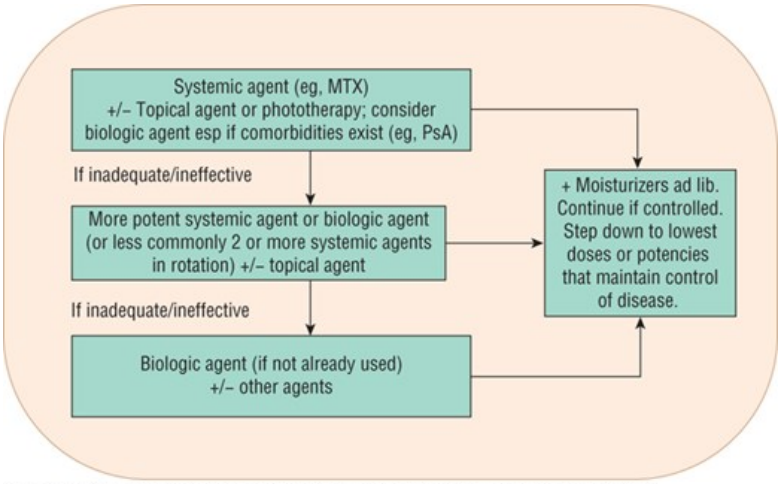
Treatment algorithm for mild-to-moderate psoriasis.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

FIGURE 118-2

Treatment algorithm for moderate-to-severe psoriasis. (See section "Systemic Therapy with Biologic Agents" for details: choosing a biologic and guidelines for transitioning from traditional systemic therapies to biologics.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Published Guidelines or Treatment Protocols

There are treatment guidelines for both Canada (the Canadian Dermatology Association [CDA])[16] and the United States (American Academy of Dermatology [AAD]).[38–41] In addition, the National Psoriasis Foundation (NPF) has guidelines for use of cyclosporine and methotrexate[42,43] and jointly with AAD for use of topical and alternative medicines in management of psoriasis.[40] In 2011, a 19-country European conference provided a consensus document focusing on disease severity and treatment goals, which ultimately resulted in updated European treatment guidelines in 2015.[29] In 2016, the CDA provided a guideline addendum which updated each chapter of the 2009 guidelines, and in particular, provided more information on use of biologics for treatment of psoriasis.[16] This was followed by new biologics guidelines from the British Association of Dermatologists (BAD) in 2017,[44] and updated joint AAD-NPF biologics guidelines in 2019.[45] AAD-NPF also provided psoriasis guidelines with special attention paid to comorbidities in 2019.[46] As mentioned earlier, the NPF provided guidance about psoriasis treatment targets in 2017 via a consensus study (Delphi method).[31] These guidelines represent the current standards of care.

Topical Therapies

Approximately 80% of patients with psoriasis have mild-to-moderate disease, and the majority of these patients can be treated with topical therapies alone.[40] Individualized approaches are essential because of the wide variation in patients' presentations, their psychosocial health, and their personal opinions as to what would be acceptable treatment.[14,16] Traditional topical therapies include corticosteroids, vitamin D_3 analogs, retinoids, anthralin, and coal tar. In addition, topical calcineurin inhibitors may be useful for difficult-to-treat sites such as the intertriginous areas or the face. Topical biologic agents are being developed and marketed. Topical agents are also used as adjunctive therapy for patients with more extensive disease, who are being treated concurrently with phototherapy or systemic agents.

To determine the quantity of topical agents required, the fingertip unit[47,48] can be used. One fingertip unit is approximately 500 mg,[40,47] which is sufficient to cover one hand (front and back) or about 2% BSA.[48] The trunk (front and back) is about 30% BSA; to cover the entire trunk once, about 15 fingertip units, or 7,500 mg (7.5 g), would be required.

In the United States, the current (2021) treatment guidelines recommend TCS of varying strengths as first-line treatment for limited psoriasis,[40,49] used either as monotherapy or in conjunction with nonsteroidal topical agents; and potency can be enhanced with different vehicles, and as needed by occlusion.[49] Case-based discussions illustrating the guidelines were published in 2010.[49]

In a 2012 systematic review of topical and phototherapies for psoriasis by dermatologists in France, nine recommendations based on evidence and expert opinion are offered. However, quality literature was limited, and the recommendations relating to optimal steroid use and optimal first-line treatment for psoriasis did not reach 80% consensus.[47]

Corticosteroids

TCS have been the mainstay of therapy for the majority of patients with psoriasis for over half a century. They are generally well tolerated, although adverse effects can occur, including systemic ones on occasion. Table 118-2 provides a summary of TCS formulations—including ointments, creams, gels, foams, lotions, sprays, shampoos, tape, and solutions—and potencies.

TABLE 118-2

Topical Corticosteroid Potency Chart

Potency Rating	Corticosteroid—Topical Preparations
Class 1: Superpotent	Betamethasone dipropionate 0.05% ointment (Diprolene and Diprosone ointment)
	Clobetasol propionate 0.05% lotion/spray/shampoo/foam (Clobex lotion/spray/shampoo, OLUX and OLUX-E foam)

	Clobetasol propionate 0.05% cream, gel, solution (scalp), ointment (Cormax, Temovate, Dermovate)
	Diflorasone diacetate 0.05% ointment (Florone, Psorcon, ApexiCon)
	Halobetasol propionate 0.05% cream, lotion, ointment (Ultravate)
	Flurandrenolide tape 4 µg/cm^2 (Cordran)
Class 2: Potent	Amcinonide 0.1% ointment (Cyclocort, Amcort)
	Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream)
	Desoximetasone 0.25% cream, gel, ointment (Topicort)
	Diflorasone diacetate 0.05% ointment (ApexiCon, Florone, Psorcon)
	Fluocinonide 0.05% cream, gel, ointment (Lidex)
	Halcinonide 0.1% cream (Halog)
Class 3: Upper mid-strength	Amcinonide 0.1% cream (Cyclocort)
	Betamethasone valerate 0.1% ointment (Betnovate/Valisone)
	Diflorasone diacetate 0.05% cream (Psorcon, Florone, ApexiCon)
	Fluticasone propionate 0.005% ointment (Cutivate)
	Mometasone furoate 0.1% ointment (Elocon)
	Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Class 4: Mid-strength	Betamethasone valerate 0.12% foam (Luxiq)
	Betamethasone dipropionate 0.05% spray (Sernivo)
	Clocortolone pivalate 0.1% cream (Cloderm)
	Desoximetasone 0.05% cream and gel (Topicort LP)
	Fluocinolone acetonide 0.025% ointment (Synalar)
	Fluocinolone acetonide 0.2% cream (Synalar-HP)
	Hydrocortisone valerate 0.2% ointment (Westcort)
	Mometasone furoate 0.1% cream, lotion, solution (Elocon)
	Triamcinolone acetonide 0.1% ointment (Kenalog)
Class 5: Lower mid-strength	Betamethasone dipropionate 0.05% lotion (Diprosone)

	Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone)
	Desonide 0.05% lotion, ointment, gel (DesOwen, Tridesilon)
	Fluocinolone acetonide 0.01% shampoo (Capex)
	Fluocinolone acetonide 0.01%, 0.025%, 0.03% cream (Synalar)
	Flurandrenolide 0.05% cream and lotion (Cordran)
	Fluticasone propionate 0.05% cream and lotion (Cutivate)
	Hydrocortisone butyrate 0.1% ointment, lotion, cream (Locoid, Locoid Lipocream)
	Hydrocortisone probutate 0.1% cream (Pandel)
	Hydrocortisone valerate 0.2% cream (Westcort)
	Prednicarbate 0.1% cream and ointment (Dermatop)
	Triamcinolone acetonide 0.1% cream, ointment and lotion (Kenalog)
Class 6: Mild (low potency)	Alclometasone dipropionate 0.05% cream and ointment (Aclovate)
	Betamethasone valerate 0.05% cream and ointment (Valisone)
	Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon)
	Desonide 0.05% foam (Verdeso)
	Fluocinonide acetonide 0.01% cream and solution (Synalar)
	Fluocinonide acetonide 0.01% FS oil (Derma-Smoothe)
Class 7: Least Potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

Data from References 50–53.

The most important distinction between corticosteroids is their potency differences. Various potency classification systems are available and Table 118-2 is a compilation with 7 potency classes similar to the 2021 AAD-NPF classification.[40] A comparison of potency classification systems was recently published.[54] Superpotent (class I) TCS provides rapid onset of efficacy but has the greatest risk of adverse effects. Their use should be limited in scope (body area) and duration (2-4 weeks). Clobetasol-17-propionate and betamethasone dipropionate were effective in clearing or markedly improving psoriasis in 75% to 80% of patients in about 3 weeks.[55] Lowest potency TCS should be used on the face and skin folds.

Salt forms of corticosteroids affect potency. For example, betamethasone dipropionate is superpotent to high potency (formulation dependent), whereas betamethasone valerate is medium to lower-mid potency (formulation dependent).

The choice of vehicle affects corticosteroid potency: Ointments, being the most occlusive, enhance drug penetration and provide the most potent formulations. However, patients may prefer a less greasy formulation, such as a cream or lotion for daytime use, although they may be willing to apply the more effective ointment-based corticosteroid during the night.[40] Providing additional occlusion will increase drug penetration of a topical preparation, resulting in enhanced potency. For example, flurandrenolide cream and lotion are potency class 5, but flurandrenolide tape was found to

have higher efficacy than diflorasone diacetate ointment (potency class 1).[40,56]

Despite their widespread use, there have been few large-scale, randomized placebo-controlled corticosteroid trials and even fewer head-to-head comparisons with other therapies. The most comprehensive review to date is the analysis of topical psoriasis therapies done in 2002 but recent studies aren't included so this review was already somewhat out of date when published.[16,57] This systematic review found that all TCS treatments considered were efficacious and significantly better than placebo; and that the highest potency corticosteroids were the most efficacious, followed by vitamin D_3 analogs.[16] The French group in 2012 found variable efficacy in their systematic review, noting that recommendations about topical steroid use should be mostly based on expert opinion, and that maintenance intermittent treatment may prolong remission.[58] In addition, TCS used in combination with other agents—topical, systemic, or biologic—may be mutually beneficial. For example, the concomitant use of a second agent may provide a steroid-sparing effect; or the TCS may enhance the efficacy of the second agent. Specifics are discussed in various sections below.

Corticosteroids have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects.[34,40] These are mediated through a variety of mechanisms. Mechanisms of action include binding to intracellular corticosteroid receptors and regulation of gene transcription (in particular, those which code for proinflammatory cytokines).[34,40]

Appropriate use of TCS should include an assessment of disease severity and disease location as well as knowledge of the patient's preference and age. Lower potency TCS should be used for infants and lesions on the face, intertriginous areas, and areas with thin skin. For other areas of the body in adults, mid- to high-potency agents are generally recommended as initial therapy.[40] The highest potency TCS are generally reserved for patients with thick plaques or recalcitrant disease, such as plaques on palms and soles. The use of potency class 1 corticosteroids should be limited to a duration of 2 to 4 weeks,[40] recognizing that the risk of cutaneous and systemic side effects increases with continued use.

Cutaneous adverse effects include skin atrophy, acne, contact dermatitis, hypertrichosis, folliculitis, hypopigmentation, perioral dermatitis, striae, telangiectases, and traumatic purpura.[16,40] Systemic adverse effects have been reported not only with superpotent corticosteroids but also with extended or widespread use of mid-potency agents.[40] Systemic adverse effects include hypothalamic–pituitary–adrenal (HPA) axis suppression and less commonly Cushing's syndrome, osteonecrosis of the femoral head, cataracts, and glaucoma.[40]

Tachyphylaxis can occur with prolonged use, although its clinical significance is difficult to verify.[16] It is recommended that the frequency of use be gradually reduced once clinical response is seen, although there are no established tapering regimens.[40] The French group recommended twice-weekly maintenance therapy.[47] Other approaches include transitioning to weaker potency agents or combination with other nonsteroidal topical therapies.[40] Pulse dosing has also been used to minimize tachyphylaxis and adverse effects.[59]

Vitamin D_3 Analogs

Topical vitamin D_3 analogs include calcipotriol (calcipotriene), calcitriol (the active metabolite of vitamin D), and tacalcitol. Calcipotriol and calcitriol are currently available in the United States and Canada and tacalcitol is available in the United Kingdom. Calcitriol is only available in ointment form; however, calcipotriol is available in ointment, cream, foam, solution, and gel suspension formulations.[34] Other analogs currently under study include maxacalcitol and becocalcidiol. Their mechanisms of action include binding to vitamin D receptors, which results in inhibition of keratinocyte proliferation and enhancement of keratinocyte differentiation.[16] They also have immunosuppressive properties such as inhibiting proinflammatory cytokine production (eg, IL-2 and IFN-gamma) leading to inhibition of T-lymphocyte activity.[16]

Topical calcitriol can be used as first-line monotherapy or in combination regimens for patients with mild plaque psoriasis.[16] The efficacy of calcitriol has been established in large, randomized, double-blind clinical trials.[16] The efficacy of calcipotriol for patients with mild psoriasis is also well established in randomized double-blind placebo-controlled trials. In head-to-head comparison studies with other topical agents, calcipotriol was found to be more effective than anthralin (dithranol)[60] and comparable or slightly more effective than potency class 3 (upper mid-strength) TCS ointments such as betamethasone valerate 0.1% ointment.[16,61,62] In an analysis of topical psoriasis therapies done in 2002,[57] calcipotriol was found to be as effective as all but the most potent TCS.[16,57] Combination therapy with a TCS is particularly effective[63] and is also discussed later in the chapter.

Vitamin D_3 analogs are generally well tolerated and have a good safety profile in comparison with other topical therapies.[63] They have been considered the safest long-term topical treatments.[3] Cutaneous adverse effects most commonly include a mild irritant contact dermatitis; others include burning, pruritus, edema, peeling, dryness, and erythema.[16,40] These adverse effects may be mitigated with continued use.[40] Systemic adverse effects, including hypercalcemia and parathyroid hormone suppression, are rare unless patients are using more than the recommended maximum of 5-mg calcipotriol (100 g of calcipotriol 50 µg/g cream or ointment) per week[16,40] or if there is underlying renal disease or impaired calcium metabolism.[40] When applied sparingly over a BSA <30%, the risk of hypercalcemia is remote.[47]

Calcipotriol is inactivated by ultraviolet A (UVA) light, thus it should be applied after rather than before UVA light exposure.[40] Calcipotriol can be inactivated by acidic substances and thus should not be used with salicylic acid in treating psoriasis.[34] It may also be partially degraded by hydrocortisone valerate.[34] However, calcipotriol is stable with other TCS[63] and stable combinations available in the United States include: calcipotriol and betamethasone dipropionate ointment and suspension (Taclonex) and calcipotriol and betamethasone dipropionate foam (Enstilar).[34] The combination of calcipotriol with betamethasone dipropionate in either ointment or foam results in enhanced efficacy when compared with either agent used alone.[34]

Retinoids

Tazarotene is a topical retinoid that acts through the following mechanisms: normalizing abnormal keratinocyte differentiation, diminishing keratinocyte hyperproliferation, and clearing the inflammatory infiltrate in the psoriatic plaque.[16,40] It is effective in clearing psoriatic plaque lesions and achieving remission.

In a placebo-controlled trial of tazarotene 0.1% and 0.05% gels for patients with plaque psoriasis, tazarotene provided a 50% or greater improvement in 63% (0.1% gel) and 50% (0.05% gel) of patients, respectively, after 12 weeks of use.[64] The therapeutic benefit is maintained for 12 weeks after cessation of therapy.[64] Later clinical trials with tazarotene 0.1% and 0.05% creams versus a placebo vehicle provided similar findings.[65] The 2012 systematic review similarly found that about 50% of patients experienced a 50% or more improvement with no difference in formulations.[47] In comparison to other agents, tazarotene 0.1% gel has similar efficacy to calcipotriol 0.005% ointment (in a small study) but is less effective than clobetasol propionate 0.05% cream.[16] It may be combined with TCS to enhance efficacy and reduce irritation.[34] Fixed combinations are marketed, for example, halobetasol propionate and tazarotene lotion 0.01%/0.045% (Duobrii) received FDA approval in April 2019.

Adverse effects of tazarotene include a high incidence of irritation at the site of application, a dose-dependent effect.[16] This results in burning, itching, and erythema, which can occur in lesional and perilesional skin.[40] Irritation may be reduced by using the cream formulation, lower concentration, alternate-day application, or short-contact (30-60 minutes) treatment.[40] Ad lib use of moisturizers is also beneficial. Tazarotene is also potentially photosensitizing, due to thinning of the epidermis that can occur with continued use.[40]

Tazarotene is contraindicated in pregnancy and should not be used in women of childbearing age unless effective contraception is being used. (All retinoids are potentially teratogenic including topically applied agents. See under section “Retinoids” for further details.)

Anthralin

Anthralin is not as commonly used as other topical therapies currently available for psoriasis; however, there are situations where its use is appropriate and efficacious. It has a direct antiproliferative effect on epidermal keratinocytes,[16,34] normalizing keratinocyte differentiation.[40] Although the exact mechanism of action is unknown, it may have a direct effect on mitochondria[40,66] and reduce the mitotic activity of epidermal cells.[34] It also prevents T-lymphocyte activation.[40] Small placebo-controlled studies demonstrated efficacy for anthralin used continuously or as short contact (1 minute of treatment).[40]

Short-contact anthralin therapy (SCAT) is usually the preferred regimen, where the anthralin ointment is applied only to the thick plaque lesions for 2 hours or less and then wiped off.[15,40] To minimize irritation, it can be applied for 5 to 10 minutes daily initially then titrating up the application time to 20 to 30 minutes or more as tolerated.[34] Because lesions are generally well demarcated, zinc oxide ointment or a nonmedicated stiff paste should be

applied to the surrounding normal skin to protect it from irritation and burning. Anthralin should be used with caution, if at all, on the face and intertriginous areas because of the risk of severe skin irritation.[40]

Concentrations for SCAT range from 1% to 4% or as tolerated; concentrations for continuous anthralin therapy vary from 0.05% to 0.4%. Aside from significant and often severe skin irritation, other adverse effects include folliculitis and allergic contact dermatitis, but these are uncommon.

Anthralin powder causes skin irritation. People who handle the dry anthralin powder should avoid skin contact (eg, by wearing gloves while compounding).[15]

Coal Tar

Coal tar was one of the earliest agents used to treat psoriasis. It is keratolytic and may have antiproliferative and anti-inflammatory effects.[15,34] Coal tar formulations include crude coal tar and tar distillates (liquor carbonis detergens—LCD) in ointments, creams, and shampoos. Because of limited efficacy coupled with patient acceptance and compliance issues, coal tar preparations are less commonly used today, especially in North American and European[47] countries.

A 2007 comparative study in Thailand reported that betamethasone valerate was significantly more effective than coal tar.[16,67] Although coal tar may have similar efficacy as calcipotriol,[16] it has a slower onset of action.[16] In addition, coal tar has an unpleasant odor and will stain clothing; thus, it may be cosmetically unappealing to patients. LCD 15% solution was shown to be cosmetically acceptable, well tolerated, and effective when compared with calcipotriol 0.005% cream.[16,68]

Adverse effects include folliculitis, acne, local irritation, and phototoxicity.[16] It is carcinogenic in animals, but for human, no convincing data have emerged regarding carcinogenicity with topical use.[40]

Coal tar concentrations as used in psoriasis treatments (0.5%-5%) are considered safe by the FDA.[69] However, occupational exposure to coal tar, especially in high concentrations such as coal tar used in industrial paving, was reported to increase the risk of lung cancer, scrotal cancer, and skin cancer.[40] The risk of teratogenicity when used in pregnancy is likely to be small, if it exists.[40,69]

Salicylic Acid

Salicylic acid has keratolytic properties and has been used in various formulations including shampoos or bath oils for patients with scalp psoriasis. In combination with TCS, it enhances steroid penetration, thus increasing efficacy.[34] It should not be used in combination with ultraviolet B (UVB) light phototherapy because of a filtering effect that may reduce UVB efficacy.[34] It should not be used with calcipotriol as it inactivates calcipotriol upon contact.[34] Systemic absorption and toxicity can occur, especially when applied to more than 20% BSA[34] or when used for patients with renal impairment.

Avoid the use of salicylic acid in children. However, it may be used for limited and localized plaque psoriasis in pregnancy.[40]

Calcineurin Inhibitors

Topical calcineurin inhibitors such as pimecrolimus 1% cream (Elidel) are marketed for the treatment of inflammatory skin diseases such as atopic dermatitis.[70–72] They are not FDA-approved for psoriasis but are used off-label. Pimecrolimus was found effective for plaque psoriasis when used under occlusion[71] and also effective for patients with moderate-to-severe inverse psoriasis (intertriginous areas are affected).[72] Because this cream is less irritating than calcipotriol and also avoids steroid adverse effects such as skin atrophy, it may be a useful alternative for patients with lesions in intertriginous areas or on the face.[34]

Janus Kinase (JAK) Inhibitors

Tofacitinib (topical and systemic) and ruxolitinib (topical) are nonbiologic JAK inhibitors. Tofacitinib is currently used off-label for plaque psoriasis

(topical and oral) but is indicated for psoriatic arthritis (oral use), rheumatoid arthritis, ankylosing spondylitis, and ulcerative colitis. If used systemically, the dosage must be adjusted for moderate-to-severe renal impairment and moderate hepatic impairment, Tofacitinib is not recommended in severe hepatic impairment. Ruxolitinib is currently indicated for atopic dermatitis.

Combination Topical Therapies

Combining agents from different drug classes may be particularly useful in enhancing efficacy or minimizing toxicity.[40] Refer to the "Combination Therapies" section for further information.

Phototherapies and Photochemotherapy

Phototherapy has been used for treating psoriasis for years and is still an important treatment modality today. It has been known for centuries that some skin diseases improve with sun exposure, and clinical studies with phototherapies have been reported since the late 19th century.[38] Phototherapy consists of using nonionizing electromagnetic radiation, either UVA or UVB, as light therapy to treat psoriatic lesions.[73]

UVB is given alone as either broadband or narrowband UVB (NB-UVB), currently with NB-UVB being the preferred method. UVB is also given as photochemotherapy with topical agents such as crude coal tar (Goeckerman regimen)[73] or anthralin (Ingram regimen) for enhanced efficacy.[38]

UVA is generally given with a photosensitizer, such as oral psoralens, to enhance efficacy—this regimen is known as PUVA (photochemotherapy with oral methoxypsoralen and ultraviolet A light).[73]

With respect to comparative efficacy, NB-UVB is more efficacious than broadband UVB, but may be slightly less effective than PUVA.[38,74] PUVA is effective in the majority of patients, with the potential for long remissions.[38] A meta-analysis showed that more patients are still clear at 6 months with PUVA versus with NB-UVB.[74] However, because of greater availability of UVB treatment centers, more evidence available now of the efficacy of UVB treatments for psoriasis (in particular, NB-UVB), and especially the increasing concerns about PUVA toxicities (including skin cancers), phototherapy for psoriasis currently uses UVB or NB-UVB where available. Failure of NB-UVB may justify PUVA therapy.[73]

UVB interferes with protein and nucleic acid synthesis, leading to decreased proliferation of epidermal keratinocytes.[38] UVA has similar effects on epidermal keratinocytes. However, because of deeper penetration into the dermis, it also has effects on dermal dendritic cells, fibroblasts, endothelial cells, mast cells, and skin-infiltrating inflammatory cells including granulocytes and T lymphocytes.[38]

Adverse effects of phototherapy include erythema, pruritus, xerosis, hyperpigmentation, and blistering, especially with higher dosages. It should be used with caution for patients with photosensitivity concerns, and drug interactions include photosensitizing medications such as tetracyclines. Patients must be provided with eye protection during UVB, NB-UVB, or PUVA treatments, and for 24 hours[73] or the remainder of the day[38] after PUVA treatments. In addition, patients receiving PUVA therapy may experience gastrointestinal symptoms such as nausea or vomiting, which may be minimized by taking the oral psoralens with food or milk.[38] For patients also receiving oral retinoids plus PUVA (RE-PUVA), the UVA dose should be reduced by one-third.[38] Long-term PUVA use can lead to photoaging and the development of PUVA lentigines. Psoralens bind to proteins in the lens of the eye; thus, there is a potential for increased cataract formation.

Furthermore, although UVB has a theoretical risk of photocarcinogenesis, the risk is significantly higher with PUVA and is dose related.[38,73] A meta-analysis reported a 14-fold increase in the incidence of squamous cell carcinoma (SCC) in patients receiving high-dose PUVA when compared with low-dose PUVA, with SCC of the male genitalia particularly elevated.[38,75] PUVA may also increase the risk of basal cell carcinoma and possibly melanoma,[38] which may occur 15 years after the first treatment.[73] Thus, the use of phototherapy or photochemotherapy is contraindicated in patients with a history of melanoma or multiple nonmelanoma skin cancers.

Targeted phototherapy using excimer lasers that selectively target psoriatic lesions without affecting normal skin is an option being studied and early results are promising, although blistering and burning of treated lesions are more common, and long-term safety has not been established.[38]

Systemic Therapies

Systemic therapies are the mainstay of treatment for patients with moderate-to-severe psoriasis, with topical therapies remaining as useful adjuncts. However, as discussed below under combination therapies, topical calcipotriol and betamethasone dipropionate ointment may provide sufficient disease control for some patients.[16,76] Conversely, a subset of patients with limited disease may have debilitating symptoms and the use of systemic therapies would be warranted.[39] This may include disease involving "sensitive areas" with significant impact on quality of life (QoL).[54] Systemic therapies include the following traditional agents: acitretin, cyclosporine, methotrexate, mycophenolate mofetil (MMF), and hydroxyurea; as well as the biologic agents, specifically adalimumab, alefacept, etanercept, infliximab, ustekinumab, secukinumab, and newer agents certolizumab, ixekixumab, brodalumab, guselkumab, tildrakizumab, risankizumab, and others at various stages of development.

Acitretin

In the 1980s, etretinate became the first oral retinoid, or vitamin A acid derivative, available for the treatment of psoriasis. It has since been replaced by acitretin, its active metabolite.

Retinoids may be less effective than methotrexate or cyclosporine when used as monotherapy, although the initial response may be more rapid than methotrexate for patients with severe inflammatory forms of psoriasis. Acitretin is more commonly used in combination with topical calcipotriol or phototherapy.[16,39] Its efficacy is dose dependent.[39] Although low-dose acitretin (25 mg/day) is safer and better tolerated than higher-dose (50 mg/day) therapy,[16] low-dose acitretin is not recommended as monotherapy for psoriasis.

Common adverse effects of acitretin include hypertriglyceridemia and mucocutaneous adverse effects such as dryness of the eyes, nasal and oral mucosa, chapped lips, cheilitis, epistaxis, xerosis, brittle nails, and burning or sticky skin.[16,39] Less commonly, "retinoid dermatitis" may occur. Ophthalmologic changes include photosensitivity, decreased color vision, and impaired night vision.[29] GI side effects including hepatitis and jaundice are rare with liver enzyme elevations usually being transient.[29] Periungual pyogenic granulomas are sometimes seen after long-term use of acitretin.[39] Rarely, skeletal abnormalities—such as disseminated idiopathic skeletal hyperostosis (DISH) syndrome—may occur.[16]

All retinoids are teratogenic and are absolutely contraindicated in pregnancy, including topical retinoids. Acitretin should not be used for women of childbearing age unless they are able and willing to use effective birth control not only for the duration of acitretin therapy but also for at least 2 years after discontinuing the agent.[16,29,39] Blood donation (men and women) is not permitted during and for at least a year after treatment.[29] Ethanol should be avoided during therapy and for 2 months after drug discontinuation because it causes the transesterification of acitretin to etretinate, which has a much longer elimination half-life.

Cyclosporine

Cyclosporine is a systemic calcineurin inhibitor. The more bioavailable microemulsion formulation, Neoral, was approved by the FDA in 1997 for the treatment of psoriasis and rheumatoid arthritis.[42]

Cyclosporine is efficacious for both inducing remissions and as maintenance therapy for patients with moderate-to-severe plaque psoriasis. It is also effective in treating pustular, erythrodermic, and nail psoriasis.[42] The 2009 Canadian Guidelines recommended that cyclosporine be normally reserved for intermittent use in periods up to 12 weeks for most patients with psoriasis, for treatment failures, in crisis management, and as a bridge to other therapies such as biologics.[16] Other recommendations are for periods of 1 year or up to 2 years.[42] Risk of toxicity increases with treatment duration: intermittent short-course therapy (<12 weeks) is preferable since this significantly reduces the risk of nephrotoxicity as compared to continuous therapy.[16,29,42]

In comparative randomized controlled trials (RCTs), cyclosporine was significantly more effective than etretinate[77] and similar or slightly better in efficacy than methotrexate.[16,42,78] After inducing remission, maintenance therapy using low doses (1.25-3.0 mg/kg/day) may prevent relapse.[42] The dose should always be titrated to the lowest effective dose for maintenance. In one placebo-controlled study, the relapse rate was 42% for patients on 3.0 mg/kg/day versus 84% for patients on placebo.[79] For patients discontinuing cyclosporine, a gradual taper of 1 mg/kg/day each week may prolong the time before relapse, as compared with abrupt discontinuation.[39,42] Abrupt discontinuation resulted in a dramatic rebound of psoriasis in a few cases.[16] Because more than half of patients discontinuing cyclosporine will relapse within 4 months, patients should be provided with appropriate

alternative treatments shortly before or after discontinuing cyclosporine therapy.[42]

Adverse effects of cyclosporine include cumulative renal toxicity, hypertension, and hypertriglyceridemia. The latter two are particularly significant for patients with prior elevation of diastolic blood pressure or triglycerides.[16] Hypertriglyceridemia can occur in up to 15% of patients with psoriasis who are treated with cyclosporine, although this effect is generally reversible upon cessation of therapy.[39] The cyclosporine-induced blood pressure elevation is dose-related, based on a Cochrane systematic review.[80]

The risk of SCC and other nonmelanoma skin cancers increases with duration of treatment[16] and with prior PUVA treatments.[39] Thus, although continuous therapy for up to 2 years may be efficacious,[42] it should be used only in a subset of patients[16] in whom renal function is monitored with annual determinations of glomerular filtration rate (GFR) and monthly measurements of blood pressure and creatinine clearance, with more frequent measurements during the initial 6 weeks of treatment.[16]

Baseline blood pressure, serum creatinine, serum urea nitrogen, triglycerides, complete blood count, uric acid, potassium, and magnesium should be obtained before initiating therapy, every 2 weeks for the first 12 weeks of therapy, and monitored monthly thereafter during therapy.[16,42] If the serum creatinine increases to 25% above the patient's baseline on two occasions (2 weeks apart), the cyclosporine dosage needs to be decreased by 25% to 50%, and serum creatinine rechecked as often as every other week for 1 month. If the serum creatinine does not return to within 10% of the patient's baseline value, a further dose decrease of 25% to 50% should be considered. If the value continues to be greater than 10% above the patient's baseline value, consider discontinuing cyclosporine therapy.[42] (*Note*: A 25% above-baseline cutoff for dosage reduction is the manufacturer's recommendation; the NPF consensus guidelines continue to recommend a 30% cutoff.)[42] Age-appropriate malignancy screening should also be done, and patients should be seen for dental examinations at least yearly because of the risk of gingival hyperplasia.[42]

As a cytochrome P450 isoenzyme 3A4 (CYP3A4) substrate, cyclosporine has significant drug interactions. Serum concentration monitoring is not routinely needed for patients with psoriasis because doses used are lower than in transplant recipients, although monitoring may be advisable for patients taking interacting drugs.

Drugs that can increase cyclosporine concentrations include calcium channel blockers (verapamil, diltiazem, and nicardipine), amiodarone, thiazide diuretics, macrolide antibiotics, allopurinol, oral contraceptives, ezetimibe, selective serotonin reuptake inhibitors (fluoxetine, sertraline), fluoroquinolones (ciprofloxacin, norfloxacin), antifungals (ketoconazole, itraconazole, fluconazole, voriconazole), and cimetidine.[42] Grapefruit juice will also increase cyclosporine concentrations.

Drugs that can reduce cyclosporine concentrations include anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, valproic acid), rifampin, efavirenz, and St. John's wort.[42]

Conversely, cyclosporine may also affect the drug levels of some drugs. Concurrent use of potentially interacting drugs should be avoided when possible.

The combination of cyclosporine with some topical agents may be beneficial. Refer to the "Combination Therapies" section for details. Cyclosporine should not be used with PUVA due to reduced efficacy and the increased risk of cutaneous malignancies.[42]

Methotrexate

For decades, methotrexate has been the mainstay of systemic therapy for patients with moderate-to-severe psoriasis. It has direct anti-inflammatory benefits due to its effects on T-cell gene expression and also has cytostatic effects.[16] It is more efficacious than acitretin and similar or slightly less efficacious than cyclosporine.[16,43]

Although it also has a significant adverse-effect profile, methotrexate is generally considered a safer alternative than cyclosporine unless there are preexisting contraindications such as liver disease. In some head-to-head clinical studies, more patients dropped out of the cyclosporine treatment arms due to adverse effects.[39,43] While biologic agents are undoubtedly more efficacious, they are much more costly, and some insurance companies require an inadequate response or intolerance to methotrexate (the gold standard) as a prerequisite for approving their use.[43] In a recent placebo-

controlled comparative study with adalimumab (CHAMPION), the efficacy of methotrexate was 36% versus 80% for adalimumab and 19% for placebo.[81] Adalimumab also provided a more rapid response; however, the duration of remission is unclear.

Initial doses of 7.5 to 15 mg once weekly may be increased to 20 to 25 mg once weekly if the response is inadequate at 8 to 12 weeks, with appropriate adverse effect monitoring. Low-dose methotrexate (7.5 to 10 mg once weekly in combination with a biologic agent is also recommended.[29] Methotrexate can be used continuously for years or decades with sustained benefits.[16] Methotrexate inhibits folate biosynthesis; and the use of folate supplementation during prolonged methotrexate therapy as seen in dermatology remains controversial. Although some experts recommend folate supplementation for all patients receiving methotrexate for psoriasis, others add folate only when patient issues occur, such as gastrointestinal adverse effects or early bone marrow toxicity (as manifested by an increased mean corpuscular volume) that can be caused by megaloblastic anemia.[39,43] Lack of folate supplementation has also been listed as a risk factor for hepatotoxicity from methotrexate use.[43] One small placebo-controlled study suggested that folate supplementation may result in a slight decrease in efficacy of treatment,[82] but the study methodology has been questioned.[39,43]

The most significant adverse effect is cumulative liver toxicity, and the total lifetime dose of methotrexate must be monitored. Traditionally, patients received a pretreatment liver biopsy and subsequent biopsies when a cumulative dose of 1.5 g is reached. Liver biopsy is the gold standard for assessing histological changes and provides an invasive marker of liver fibrosis. It is recognized that pretreatment liver biopsies may not be practical or appropriate in all cases.[16,43] It has also been recommended that a baseline liver biopsy be delayed for 2 to 6 months so that medication efficacy and tolerability can first be established[43] (ie, intention to continue with methotrexate use). Risk factors for hepatotoxicity from methotrexate include the following: a history of or current alcohol consumption, persistent abnormal liver chemistry studies, history of liver disease including chronic hepatitis B or C, family history of inheritable liver disease, history of significant exposure to hepatotoxic drugs or chemicals, diabetes mellitus, obesity, and hyperlipidemia.[39,43] For patients without preexisting risk factors for hepatotoxicity, it is recognized that they would likely have a low risk of fibrosis and would not require a baseline liver biopsy; furthermore, consideration can be made to continue methotrexate treatment for these patients without biopsies at all, to perform a liver biopsy after 3.5 to 4.0 g total cumulative dose, or to switch therapy to an alternate drug at that point.[39,43]

Currently, liver biopsies are reserved for select high-risk patients. Noninvasive blood serology (FIB-4, Fibrosure, Fibrometer or Hepascore) and LFT monitoring should be performed at baseline prior to starting methotrexate to assess the risk for hepatotoxicity. The additional use of type III serum procollagen as additional monitoring would be ideal, but this is not readily available in the US.[39] The procollagen type III N-terminal peptide (P3NP or PIIINP) serum level is the 2015 European recommendation for MTX monitoring - prior to starting MTX and every 3 months thereafter.[29] As a precaution, a systematic review and meta-analysis of the diagnostic accuracy of noninvasive markers of liver fibrosis in patients with psoriasis taking methotrexate concluded that the clinical utility of LFTs, P3NP, and liver ultrasound is poor, and that if these tests are used in isolation, a significant proportion of patients with liver fibrosis may remain unidentified.[83]

Other adverse effects include significant nausea, pulmonary toxicity, pancytopenia, acute myelosuppression, megaloblastic anemia, and a small but significant increase in lymphoma.[16] Although rare, pancytopenia can occur anytime with the use of low-dose weekly methotrexate and even after single doses of methotrexate.[39] Informing patients about the early symptoms of pancytopenia (dry cough, nausea, fever, dyspnea, cyanosis, stomatitis/oral symptoms, and bleeding) may aid early detection.[29] Methotrexate is an abortifacient and is teratogenic and is absolutely contraindicated in pregnancy. After methotrexate therapy is discontinued, it is recommended that men continue effective birth control for 3 months (since one cycle of spermatogenesis is 74 days), and women should be on effective birth control for at least one ovulatory cycle.[16,39]

Use of folic acid has been shown to reduce hepatic laboratory abnormalities and gastrointestinal side effects in patients with rheumatoid arthritis and also likely reduces hematologic side effects.[39]

Significant drug interactions include serum albumin binding interactions with salicylates, phenytoin, sulfonamides/trimethoprim, ciprofloxacin, and thiazide diuretics, potentially increasing toxicity. Drugs that can reduce methotrexate renal elimination (such as acidic drugs, including salicylates or vitamin C) will also increase serum methotrexate levels and hence increase toxicity. In addition, drugs with hepatotoxic potential may pose an additive risk with methotrexate use.[39]

Janus Kinase (JAK) Inhibitors: Tofacitinib

Tofacitinib is a potent and selective inhibitor of the JAK family of kinases. It inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2.[84] Inhibition of JAK1 and JAK3 blocks signaling through common receptors for cytokines including IL2, IL4, IL7, IL9, IL15, and IL21.[84] JAK1 inhibition also attenuates signaling by other proinflammatory cytokines (ie, IL6 and Type I interferons).[84]

Tofacitinib is both a topical agent (see above) and an oral agent with a recommended dosage of 5 mg twice daily (or 11 mg of the tofacitinib XR once daily) taken with or without food; the XR tablets must be swallowed whole and cannot be split, crushed, or chewed.[84] There are potential drug interactions with CYP450 substrates—potent CYP3A4 inhibitors (eg, ketoconazole) or modest CYP3A4 plus potent CYP2C19 inhibitions (eg, fluconazole) may increase tofacitinib exposure and potent CYP3A4 inducers (eg, rifampin) may reduce tofacitinib exposure.[84]

Oral Phosphodiesterase Inhibitors: Apremilast

Apremilast is an oral phosphodiesterase inhibitor that downregulates inflammatory responses and may modulate cytokine levels. It is effective for psoriasis, particularly for palmar-plantar or scalp psoriasis, and also for psoriatic arthritis. Apremilast has a good safety profile, with gastrointestinal symptoms being most common (70%–80% occurring within the first 2 weeks of therapy). Depression occurs in about 1% of patients, and it is recommended that patients receive appropriate discussion and counseling before apremilast is initiated to prevent worsening of depression or suicidality.[39] Dose reduction is needed in renal impairment. Weight loss may also occur.

Systemic Therapy with Biologic Agents

10 Biologic agents have exploded onto the treatment scenario for many immune conditions, including psoriasis. More and more biologic agents have proven efficacy for psoriasis and have been or approved for use, with many more being used off-label or in various stages of development. Currently available biologic agents include *tumor necrosis factor-α (TNF-α) inhibitors* (etanercept, infliximab, adalimumab, certolizumab), ustekinumab, *IL-17 inhibitors* (secukinumab, ixekixumab, brodalumab), *IL-23 inhibitors* (guselkumab, tildrakizumab, risankizumab), and others. They are recommended for consideration as first-line therapies alongside conventional systemic agents for moderate-to-severe disease. There are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. In addition to biologic agents, there are biosimilars to established biologic agents (eg, Amjevita is a biosimilar to adalimumab [Humira]).

General Concerns and Precautions

What precautions are needed when using biologics for treating psoriasis? In general, because of their immunomodulatory effects, there is an increased risk of infection with most of these agents, including serious infections such as sepsis, new-onset or reactivation of tuberculosis, and opportunistic infections such as histoplasmosis, cryptococcosis, aspergillosis, candidiasis, and pneumocystis. The use of live or live-attenuated vaccines during therapy is generally contraindicated. Because biologics are relatively new on the market, the risks of rare but serious adverse effects or those with a longer latency period may still be unrecognized or unreported. Further, clinical trial experience is limited for some biologics, and adequate postmarketing or long-term data are not available. Likewise, safety data on vulnerable populations such as children or women planning a pregnancy are usually absent.[85] There may be more safety data with earlier biologics which had approval for use in rheumatoid arthritis; however, it is the newer classes of biologics which are showing most promise. A 2018 publication concisely addresses the adverse reactions known to-date of biologics used in dermatology—both as indicated and off-label use.[86] In 2020, a Canadian panel of experts (psoriasis, pediatric dermatology, consensus process) considered efficacy and safety of biologics and provided recommendations for use of three biologics in children with moderate-to-severe plaque psoriasis, including a treatment algorithm.[86]

A more recently recognized concern about using biologics is that their efficacy may not be sustainable for much more than three years, that is, there is a loss of effect over time. For example, the British Association of Dermatologists (BAD) Biologic Interventions Register (BAD-BIR) has registered a 53% overall probability of drug survival by year 3, that is, about 50% failure.[85] BAD-BIR currently has more than 10,000 registrations including children.[85] Current data also suggest that failure of one biologic may negatively impact the efficacy of the next, as seen in psoriasis studies.[85] From experience with biologics for rheumatoid diseases, it appears that, after three biologic agents are used, other agents are less likely to be efficacious—there may be a similar phenomenon with their use in psoriasis.

Place in Therapy and Transitioning from Other Therapies

Biologics are often considered for patients with moderate-to-severe psoriasis when other systemic agents are inadequate or relatively contraindicated, or if comorbidities such as active PsA exists. Biologic agents are sometimes recommended for first-line therapy, alongside conventional systemic agents, for patients with moderate-to-severe psoriasis; however, in practice, drug access due to cost considerations may be a limiting factor. The availability of biosimilars may mitigate this to some extent. British Association of Dermatologists (BAD) recommends biologics in methotrexate and cyclosporine failure/intolerance/contraindication; when psoriasis has significant impact on physical, psychological, or social functioning and (a) the psoriasis is extensive (BSA >10 or PASI >=10) or (b) the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (eg, nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures, and genitals).[44]

Are there guidelines for transitioning from traditional systemic therapies to biologics? BAD provides some transitioning strategies in their 2017 guidelines[44]: (1) In stable disease, aim to allow 1 month to elapse between the last dose of any current standard systemic immunosuppressive therapy (except MTX) and the planned date of biologic initiation; (2) start a biologic with no drug washout period in patients taking MTX, or on other therapies where a drug washout period would lead to unstable disease; (3) when standard systemic immunosuppressant therapy cannot be stopped (eg, if a disease flare would be severe or hazardous), rationalize the use of therapy and stop as soon as possible (eg, when a minimum response has been achieved).[44]

Biologics may be appropriate/preferred as first-line therapy if comorbidities exist. For example, biologics such as infliximab or adalimumab would be an appropriate treatment option for patients with both plaque psoriasis and active PsA. Biologics currently available for the treatment of psoriasis and/or PsA include adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekixumab, risankizumab, secukinumab, tildrakizumab, ustekinumab, and others at various stages of development.[37]

Tumor Necrosis Factor-α Inhibitors: Adalimumab, Certolizumab, Etanercept, and Infliximab

The regulation of TNF-α production is associated with various inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, PsA, and psoriasis.[16,37,41,44,45] Elevated TNF-α levels are seen in both the affected skin and serum of patients with psoriasis; and these elevated levels have a significant correlation with psoriasis severity.[41] The biologic agents adalimumab, certolizumab, etanercept, and infliximab are TNF-α inhibitors; this class of agents is effective for psoriasis and PsA.[16,37,41,44,45,87,88]

There are safety concerns common to TNF-α inhibitors, mainly from observations made through their use in rheumatoid arthritis and inflammatory bowel disease and more recently in psoriasis.[87–89] One concern is an increased risk of bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic, or other opportunistic infections—most commonly upper respiratory tract infections, and less commonly serious infections including sepsis, new-onset or reactivation tuberculosis, and opportunistic infections.[16,41,87–90] There have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, and blastomycosis infections, sometimes with fatal outcomes when these infections were not consistently recognized and promptly treated in the patients taking TNF-α inhibitors.[90]

A second concern is the development or worsening of autoimmune diseases such as peripheral and central demyelinating disorders including multiple sclerosis and drug-induced lupus-like syndromes.[16,41,89] Although there is no definitive causal relationship, it is recommended that anti-TNF agents be avoided in patients with established demyelinating diseases (eg, multiple sclerosis), and treatment discontinued in patients with suspected demyelination during therapy.[89] A third concern is the potential increased risk of malignancies such as lymphoma,[16,89,90] melanoma, and nonmelanoma skin cancer.[41] A fourth concern is the potential for other cutaneous adverse effects including vasculitis, granulomatous reactions, cutaneous infections, psoriasiform eruptions, and infusion or injection site reactions.[88] Flares of pustular psoriasis have been reported primarily for patients undergoing treatment for nondermatologic conditions such as rheumatoid arthritis.[16] A fifth concern is the risk of hematologic toxicity including neutropenia (more commonly reported)[89,90] and rare reports of other hematologic events including pancytopenia and aplastic anemia.[90]

There is also a sixth concern about chronic heart failure (CHF): worsening congestive heart failure (CHF) and new-onset CHF have been reported during the use of these agents. TNF-α inhibitors are contraindicated in patients with preexisting moderate-to-severe CHF (NYHA class III/IV),[29,41,90] and those with milder CHF should have their TNF-α inhibitors withdrawn at the onset of new symptoms or worsening of preexisting CHF.[41]

Although the above are safety concerns common to adalimumab, certolizumab, etanercept, and infliximab, their safety profiles are not identical. For example, the risk for tuberculosis (TB) is lowest with etanercept and may be highest with infliximab.[16] Nonetheless, they are contraindicated in patients with active TB.[29] Patients should be evaluated for active or latent TB prior to therapy and considered for a yearly PPD.[16,41] CBC and LFTs are also recommended prior to and periodically during therapy.[29] In addition, pretreatment C-reactive protein (CRP), hepatitis serology (HBV, HCV), and HIV testing have been recommended.[29] They are safe to use in pregnancy.[41] However, some manufacturers have cautioned that, since these agents cross the placenta, infants exposed in utero may be at higher risk of infections and live vaccines would therefore be contraindicated for several months after birth.[90]

Adalimumab is a human monoclonal antibody that provides rapid and efficacious control of psoriasis.[16,41] Adalimumab is indicated for adults with psoriasis, particularly when psoriatic arthropathy is a consideration.[44] Clinical trials in patients with moderate-to-severe psoriasis have shown dramatic results. A 2006 12-week RCT with open-label extension to 52 weeks showed significant improvement within 1 week of therapy, with complete or nearly complete clearance in some patients, and clinical benefits were maintained for at least 1 year with continuous therapy for most patients.[16,91] There is evidence that some patients may achieve/maintain PASI 90 through at least 160 weeks of treatment.[16]

A pivotal 2008 52-week RCT (REVEAL) with an initial 16-week double-blind placebo-controlled (DBPC; period A) phase followed by a 17-week open-label phase (period B) followed by a 19-week DBPC phase (period C) showed a 71% PASI 75 response for adalimumab-treated patients versus 7% for placebo-treated patients at week 16. All patients received open-label adalimumab from weeks 17 through 32. At week 33, patients achieving PASI 75 were rerandomized to adalimumab or placebo; patients achieving PASI 50 but <75 were continued on open-label adalimumab; and therapy for patients with PASI <50 was discontinued. At week 52, 5% of patients rerandomized to adalimumab lost adequate response versus 28% of patients rerandomized to placebo. Adalimumab was continued at 40 mg every other week. The study showed that adalimumab can produce rapid and dramatic results which can be sustained on continued use, in patients with moderate-to-severe psoriasis.[92]

An additional 3-year open-label extension study for patients in REVEAL showed that in patients with sustained initial PASI 75 responses, adalimumab efficacy was maintained for more than 3 years of continuous therapy, and maintenance was best at PASI 100. Some patients with PASI <75 in REVEAL also achieved long-term PASI 75 responses.[87]

For comparative studies, as discussed in the "Methotrexate" section, a head-to-head study showed that adalimumab was significantly more efficacious than methotrexate.[81] For patients who have an inadequate response to other psoriasis treatments (including etanercept), adalimumab is a good alternative.[16]

Adalimumab is given as 80 mg subcutaneously in the first week, then 40 mg the following week, and thereafter 40 mg every other week continuously.[16,29,41,90] More frequent dosing has been explored.[16] For PsA, adalimumab is given as 40 mg subcutaneously every other week, with concomitant use with other medications (analgesics, DMARDs, glucocorticoids, methotrexate, and NSAIDs) allowed, according to product labeling.

Adverse effects in adalimumab clinical trials including the 3-year extension were similar to those already described for this class of biologics.[90]

Etanercept was one of the earliest biologics available on the market for use in inflammatory diseases. It has demonstrated efficacy for rheumatoid arthritis. It was approved for use in PsA in the United States in June 2002 and approved in 2004 for use in moderate-to-severe psoriasis. It is also approved for treatment of juvenile rheumatoid arthritis and ankylosing spondylitis. Thus, as opposed to some of the other biologics approved for psoriasis, etanercept has been extensively used in rheumatology for both adults and children.

The dosing of etanercept in psoriasis differs from its other indications, reflective of the dosing regimens found to be effective for psoriasis in clinical trials. Etanercept is used continuously, given as 50 mg subcutaneously twice weekly for the first 12 weeks, followed by 25 mg twice weekly[16] or 50 mg once weekly.[29,41] Significant improvement was seen in about 50% of patients in clinical trials by week 12 and more than 50% of participants by week 24; with continuing therapy, weaker responders continued to improve for up to 1 year.[16,41,93] Continuing therapy using 50 mg twice weekly regimens is being explored and may provide greater benefit.[16] Etanercept was efficacious in children and adolescents (aged 4-17 years) with plaque psoriasis dosed at 0.8 mg/kg (maximum 50 mg) once weekly.[94] The dosing of etanercept for active PsA is 50 mg by subcutaneous injection once weekly. In patients with moderate-to-severe psoriasis with active PsA, etanercept 50 mg twice weekly for 12 weeks followed by 50 mg once weekly for an

additional 12 weeks can be considered, according to product labeling.

Infliximab also received approval for rheumatologic diseases before psoriasis and was on the market before adalimumab. Infliximab is more efficacious than etanercept. A 2011 open-label study showed that psoriatic patients with an inadequate response to etanercept had rapid and sustained improvement when switched to infliximab.[95] Unlike etanercept or adalimumab, infliximab is a chimeric antibody with both murine and human components; thus, antibodies to the drug can develop, resulting in infusion reactions[41,45] and loss of clinical efficacy.[45] The standard dosing regimen is the same for plaque psoriasis and PsA: three IV infusions of 5 mg/kg given over a 6-week induction period, followed by regular infusions every 8 weeks.[41] This 8-week gap between infusions is longer than with other agents, thus increasing the risk of infusion reactions and loss of efficacy due to antibody development in comparison to other biologics.[45]

Clinical response is seen rapidly. In a pivotal phase III RCT, 76% and 70% of patients achieved PASI 75 by week 10 (after 3 doses of infliximab at 5 mg/kg and 3 mg/kg respectively), and PASI 90 was achieved by 45% and 37%, respectively[45,96]; however, the response dropped to about 50% by week 50.[96,97] Combining infliximab with other therapies may enhance response. Methotrexate can reduce the immunogenicity of infliximab, which minimizes the risk of antibody development to infliximab and a consequent loss of clinical response.[45] Enhanced clinical response has been seen in psoriasis and PsA.[45] Thus, the joint AAD-NPF guidelines recommend that the addition of methotrexate to infliximab should be considered strongly for all patients.[45] They caution that the long-term safety of this combination is currently unknown.[45] Infliximab has been combined with TCS and a vitamin D analog to augment efficacy but rigorous evidence supporting this combination is currently lacking.[45]

In addition to antibody development and infusion reactions, serious adverse events, including fatal cases of hepatosplenic T-cell lymphomas, have been reported rarely with infliximab use.[41] Cutaneous adverse effects include nonmelanoma skin cancers; however, these were mostly seen in patients with prior exposure to UV therapy, including NB-UVB and PUVA.[89] Other rare instances of cholecystitis and autoimmune hepatitis, which may be a class effect for TNF-α inhibitors, have also been reported.[16]

Certolizumab pegol is a humanized antigen-binding fragment of a monoclonal antibody that is further conjugated with a polyethylene glycol moiety. This binds to TNF-α, blocking its interaction with TNF receptors.[45] A phase II RCT showed PASI 75 achieved in 75% and 83% of patients by week 10, on doses of 200 mg or 400 mg every other week, respectively, versus 7% for the placebo group.[45,98] Recommended certolizumab dosing is 400 mg (as 2 × 200-mg subcutaneous injections) every 2 weeks, with a dose-reduced regimen for patients under 90 kg (198 lb): 400 mg (as 2 × 200-mg subcutaneous injections) initially and at weeks 2 and 4, followed by 200 mg every other week.[45,99] Recommended initial certolizumab dosing in active PsA is 400 mg (as 2 × 200-mg subcutaneous injections) once and then repeat at weeks 2 and 4. Maintenance dosing for active PsA is 200 mg subcutaneously every other week or 400 mg every 4 weeks, according to product labeling.

IL-12/IL-23 Inhibitors: Ustekinumab

Ustekinumab is an IL-12/23 monoclonal antibody approved for the treatment of moderate-to-severe plaque psoriasis and/or active PsA alone or in combination with methotrexatein adults 18 years or older.[16,26] It has a higher drug survival rate than TNF-α inhibitors, that is, longer duration of efficacy with continued treatment.[45] There is evidence that some patients may maintain PASI 90 through at least 244 weeks of treatment.[16] One study found that patients who had not used a biologic before (ie, biologic-naïve) or were using methotrexate concomitantly had longer survival.[45,100] Ustekinumab was significantly more efficacious than etanercept but less efficacious than the IL-17 inhibitors secukinumab or ixekizumab in clinical trials.[41] Ustekinumab has demonstrated long-term efficacy and safety for up to 5 years.[16] In addition, it is effective for difficult-to-treat areas, including hand and foot (either palmoplantar plaque or pustular), nail, and scalp psoriasis.[41]

Ustekinumab selectively targets IL-12 and IL-23, two cytokines that play a role in the pathogenesis of psoriasis.[29,45] It binds to their shared p40 protein subunit, thus preventing interaction with their cell surface IL-12Rβ1 receptor.[101] This shared binding may allow ustekinumab to exert its clinical effects in both psoriasis and PsA through interruption of the TH1 and TH17 cytokine pathways, central to both disease conditions.[101]

Ustekinumab can provide a rapid response that is seen within 2 weeks of initiating treatment.[45,102,103] Two large randomized placebo-controlled trials (PHOENIX 1[97] and PHOENIX 2[98]) demonstrated clinical efficacy of ustekinumab, with approximately 70% of patients achieving 75% skin clearance after

two doses and maintaining the response for 1 year with continued treatment. The improvements were dramatic. Ustekinumab is effective in treating difficult-to-treat areas, such as hand and foot (palmoplantar plaque or pustular), nail, and scalp psoriasis.[45] In active PsA, ustekinumab demonstrated a greater proportion of ACR20 response at week 24 when compared to placebo in adult patients, according to product labeling. There was also a greater proportion of patients on ustekinumab with no or less radiographic progression at week 24 when compared with placebo.

The impact of ustekinumab on patients' health-related QoL was evaluated in the PHOENIX 2 trial.[104] Patients showed a significant improvement not only in skin-related QoL, but also in symptoms of anxiety and depression (as assessed by the Hospital Anxiety and Depression Scale).[103] The subset of patients with PsA in PHOENIX 1 and PHOENIX 2 also showed significant improvement in QoL, anxiety, and depression.[105]

Weight-based dosing rather than fixed-dose was found to be clinically significant for efficacy in PHOENIX 1 and PHOENIX 2—heavier patients required a higher dose.[106] Serum ustekinumab concentrations were also affected by weight.[106] Clinical response is related to serum ustekinumab levels achieved.[101] Manufacturer-recommended dosing is 45 mg for patients weighing 100 kg (220 lb) or less, and 90 mg for those of higher weights. Ustekinumab is administered subcutaneously at weeks 0 and 4, then every 12 weeks thereafter as maintenance therapy.[16,101] This dosing regimen is the same for active PsA alone or in combination with methotrexate. In cases where a loss of response is detected in the patient, the dose can be increased from 45 mg every 12 weeks to 90 mg every 8 weeks to improve response.[16]

Cumulative 3-year safety data from PHOENIX 1 and 2 have been published[107,108] and there is 5-year safety data.[89] Common adverse effects include upper respiratory infections, headache, fatigue, pruritus, back pain, injection site reactions, and arthralgia, with the most common events being headache and nasopharyngitis.[107] Ustekinumab does not exacerbate atopic diseases.[107] Serious adverse effects include those seen with other biologics, including serious tubercular, fungal, viral infections, and cancers. No evidence of a dose-response to infection rates was seen.[108] Serious infections and malignancy rates did not increase with long-term ustekinumab treatment for up to 3 years.[107,108] In addition, a reversible posterior leukoencephalopathy syndrome (RPLS) has been reported.[88,89] Regarding major adverse cardiovascular events (MACE), 5-year follow-up of clinical trials did not show an increased risk with ustekinumab.[89,109]

Recommended monitoring parameters (pretreatment and every 3–6 months thereafter) include complete blood count, liver enzymes, serum creatinine, and renal status. In addition, pretreatment CRP and testing for hepatitis B and C and human immunodeficiency virus have been recommended.[29] Contraindications include clinically important active infection (including untreated latent TB) and hypersensitivity to the drug or excipients.

IL-17 Inhibitors: Secukinumab, Ixekizumab, Brodalumab, and Bimekizumab

IL-17 is a proinflammatory cytokine. It is a key cytokine in the pathogenesis of psoriasis—binding to receptors on keratinocytes leads to increased inflammation and recruitment of inflammatory cell types, resulting in the characteristic psoriatic plaques.[37]

IL-17 inhibitors are useful in blocking this process. These agents have comparable efficacies, and some adverse effects are similar, such as an increased risk of infection—in particular mucocutaneous *Candida* infection.[45] Patients with a history of or active inflammatory bowel disease (IBD) may experience worsening or reactivation, and IL-17 inhibitors should be avoided in these patients.[45] Neutralizing antibodies to specific IL-17 inhibitors have been reported, and their presence may be associated with lower serum concentrations of the biologic and reduced efficacy.[45]

Secukinumab is a fully human IgG1κ monoclonal antibody that selectively binds and inhibits IL-17A, thus inhibiting the release of chemokines and other proinflammatory mediators. It was approved in the United States and Canada in 2015 for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[45,110] The approval was based on the results of four RCTs (including ERASURE and FIXTURE)[111] that included more than 2,000 patients. Secukinumab was shown to induce a rapid response with clinically significant greater PASI rates by week 12, and continued treatment was associated with sustained high responses through week 52.[111]

The CLEAR study compared secukinumab to ustekinumab in participants with plaque psoriasis and found greater efficacy at week 16 with secukinumab.[112] Secukinumab showed greater efficacy at 300 mg than at 150 mg in several RCTs and is equally safe.[45] Thus, the recommended dosing regimen for plaque psoriasis is 300 mg (as two subcutaneous injections of 150 mg) at weeks 0, 1, 2, and 3, followed by 300 mg as a maintenance dose

starting at week 4.[45,110] However, a 150-mg dose may be acceptable for some patients.[45,111] The 300-mg dose may be more effective in treating head, neck, nail, palmoplantar, erythrodermic, and generalized pustular psoriasis.[45,113–116] A loading dose may be considered for active PsA. If a loading dose is given, subsequent dosing includes 150 mg subcutaneously every week up to week 4 and then every 4 weeks thereafter. If a loading dose is not given, 150 mg subcutaneously every 4 weeks is recommended, with consideration of increasing the dose to 300 mg every 4 weeks if the disease persists, according to product labeling. Adverse effects from clinical trials commonly included nasopharyngitis, headache, upper respiratory tract infection, diarrhea, and uncommonly included neutropenia and detection of anti-secukinumab antibodies.[45,110,111]

Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17A.[45] Binding to IL-17A prevents it from binding to its target IL-17 receptor, thus reducing/attenuating the expression of cytokines including interferon-gamma, IL-17, IL-22, and Il-23.[37] It is indicated for moderate-to-severe psoriasis; pivotal clinical trials include UNCOVER-1, UNCOVER-2, UNCOVER-3, and IXORA-S.[37,45] UNCOVER-3 was a phase 3 RCT that showed that ixekizumab was superior to etanercept after a 12-week induction phase.[34,117] The percentages of patients achieving PASI 75, PASI 90, and PASI 100 were 84%, 65%, and 35% with ixekizumab versus 53%, 26%, and 7% with etanercept, respectively.[45,117] Placebo responses were 7%, 3.1%, and 0%, respectively.[117] IXORA-S was a phase 3 RCT comparing efficacy of ixekizumab with ustekinumab at the label doses. At week 12, patients achieving PASI 90 were 73% with ixekizumab versus 42% with ustekinumab.[45,118] Ixekizumab is also efficacious for palmoplantar (nonpustular), nail, scalp, erythrodermic, inverse, and generalized pustular psoriasis.[45]

Recommended dosing for ixekizumab in patients with plaque psoriasis is an initial dose of 160 mg (self-administered subcutaneously) followed by 80 mg every 2 weeks until week 12, followed by a maintenance phase of 80 mg every 4 weeks thereafter.[37,45] Dosing for active PsA is 160 mg (as two 80 mg injections) subcutaneously at week 0, then 80 mg every 4 weeks. If the patient has plaque psoriasis with active PsA, dosing for plaque psoriasis as described above is recommended. Adverse events from clinical trials include nasopharyngitis, URTI, injection site reactions, with the most serious being cellulitis (0.4%); MACE was rare (one patient with a stroke).[37] Neutralizing anti-ixekizumab antibodies develop over time and are associated with reduced drug concentrations and loss of efficacy.[45]

Brodalumab is a fully human IgG2 anti-IL-17RA monoclonal antibody that binds to the IL-17 receptor A and blocks the biologic activities of cytokines including IL-17A, IL-17F, IL-17A/F, IL-17A/F heterodimer, IL-17C, and IL-17E (also known as IL-25).[37,45] Pivotal clinical trials include IMAGINE-1, IMAGINE-2, and IMAGINE-3. In both IMAGINE-2 and IMAGINE-3, brodalumab at 210-mg doses had higher PASI 90 and PASI 100 response rates than ustekinumab.[37,45] Brodalumab is also efficacious in erythrodermic, nail, scalp, generalized pustular psoriasis, and PsA.[45] Recommended dosing is 210 mg subcutaneously self-injected on weeks 0, 1, and 2 then 210 mg every 2 weeks.[45]

The most frequent adverse effects in clinical trials of brodalumab were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, and infections were seen in 25% of patients (mostly URTI, nasopharyngitis, UTI, bronchitis, influenza, and nonserious skin and mucosal *Candida* infections).[37] The most serious potential risk is suicidal ideation or behavior which occurred in 34 of 4,464 patients treated with brodalumab (ie, a rate of 0.37 per 100 participant-years).[37] Thus, brodalumab has a black box warning, and it is contraindicated in patients with suicidal ideation, recent suicidal behavior, or history of suicidal ideation. In addition, brodalumab is only available through a risk evaluation and mitigation strategy (REMS) program,[37,45] the SILIQ REMS.[45]

Bimekizumab is a humanized IgG1/k monoclonal antibody that binds selectively to IL-17A, IL-17F, and IL17-AF cytokines, inhibiting their interaction with IL-17RA and IL-17RC receptors. It was approved for moderate-to-severe plaque psoriasis by Health Canada in February 2022 but had failed FDA preapproval inspection at the time of this writing. Bimekizumab has also received approval for use in psoriasis from other countries such as Japan. The Canadian approval is supported by three phase 3 trials with significant Canadian participation; these evaluated the efficacy and safety of bimekizumab compared with placebo (BE READY), ustekinumab (BE VIVID) and adalimumab (BE SURE).

Bimekizumab dosing is weight dependent, since adult patients weighing 120 kg or more are predicted to have at least 30% lower drug plasma concentrations than those weighing 90 kg. Bimekizumab is given as two 160 mg subcutaneous injections (320 mg dose) every 4 weeks for 16 weeks, followed by differential dosing based on weight: every 8 weeks thereafter EXCEPT in patients weighing 120 kg or more, for whom 320 mg every 4 weeks may be considered after week 16 if complete skin response has not been achieved.

Significant adverse reactions to bimekizumab include infections and antibody development (45%; neutralizing 16%). Recently, the two-year safety

profile for bimekizumab based on pooled data from four phase 2 and phase 3 trials suggests that bimekizumab is well tolerated.[119]

IL-23 Inhibitors: Guselkumab, Tildrakizumab, Risankizumab

Acting through a transcription pathway, IL-23 induces a population of T-helper cells (designated as TH17 cells) with a unique inflammatory gene signature that is important in the pathogenesis of psoriasis and other autoimmune diseases.[120] IL-23 inhibitors block/bind to the p19 subunit of IL-23.[45] Neutralizing antibodies to specific IL-17 inhibitors have been reported and their presence may be associated with lower serum concentrations of the biologic and reduced efficacy.[45] In patients on these agents who are not responding adequately, dose escalation may be needed or other modalities (eg, TCS, vitamin D analogs, methotrexate, or UVB) added.[45]

Guselkumab is a fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23.[45] A phase 3 RCT (VOYAGE 2) comparing guselkumab with adalimumab and placebo found greater efficacy at week 16 (PASI 90 was 70% vs 47% for adalimumab and 2.4% for placebo).[121] Furthermore, 66% of adalimumab nonresponders switched to guselkumab reached PASI 90 at week 48.[45,121] The recommended guselkumab dose for active PsA and plaque psoriasis is 100 mg subcutaneously at weeks 0 and 4, and every 8 weeks thereafter.[45] The agent has also been shown to be effective for scalp, nail, and plaque-type palmoplantar psoriasis.[45]

Tildrakizumab is a humanized IgG1 monoclonal antibody designed to selectively block IL-23 by binding to the p19 subunit.[45] A phase 3 RCT (reSURFACE 2) comparing two doses of tildrakizumab (200 mg and 100 mg) to etanercept and placebo found greater efficacy at week 12 with either dose of tildrakizumab than with etanercept (66% of patients on tildrakizumab 200 mg achieving PASI 75 and 61% for tildrakizumab 100 mg, compared with 48% for etanercept and 6% with placebo).[122] PASI 90 was achieved by 37% (200-mg dose), 39% (100-mg dose), 21% (etanercept), and 1% (placebo) of participants.[45,122] The recommended dose is 100 mg subcutaneously administered *only by a healthcare provider* at weeks 0 and 4, and every 12 weeks thereafter.[45]

Risankizumab is a humanized IgG1 monoclonal antibody that selectively inhibits IL-23 by binding to the p19 subunit; it is more efficacious than ustekinumab.[45,123,124] The agent received FDA and Health Canada approvals in April 2019 for treatment of moderate-to-severe plaque psoriasis. The approval decisions were supported by positive results from four phase 3 RCTs: ultIMMa-1, ultIMMa-2, IMMhance, and IMMvent.[123,124] From clinical trials, at week 12, PASI 90 for risankizumab was about 75% (90 mg and 180 mg doses pooled) versus about 40% to 45% for ustekinumab (weight-based dosing).[45,123] Recommended dosing is risankizumab 75 mg subcutaneously for 2 doses (totaling 150 mg) at weeks 0 and 4, followed by 150 mg as two injections every 12 weeks thereafter.

Switching Between Biologic Agents

Switching between biologic agents to possibly improve efficacy, safety, and/or tolerability is a useful consideration. Biologics that develop neutralizing antibodies may have reduced efficacy over time (secondary failure),[45] and sustainability for more than 3 years is currently a treatment target for a biologic agent—and 3 years is not that long a time for a chronic disease such as psoriasis.

Switching to another biologic even within its own class of biologics may restore efficacy. However, not all switches result in improvement, and there are no recommendations for specific switches in the US guidelines, nor recommendations for the duration interval between discontinuing one biologic and starting another.[45]

BAD provided some general recommendations in its 2020 guidelines: Consider using a 1-month washout period, or the length of the treatment cycle (whichever is longer), between the last dose of the current biologic therapy and the planned date of a new biologic initiation.[44] BAD also recommended taking into consideration the pharmacology of the agents, the patient's clinical circumstances, and the patient's views on the risks and benefits of transitioning option(s).[44]

Combination Therapies

Combination therapies may be beneficial in the management of plaque psoriasis: generally to either enhance efficacy or minimize toxicity. As shown in Figs. 118-1 and 118-2, combinations can include two topical agents, a topical agent plus phototherapy, a systemic agent plus topical therapy, a systemic

agent plus phototherapy, two systemic agents used in rotation, or a biologic agent with either a systemic agent or a topical agent.

The combination of a TCS and a topical vitamin D_3 analog is particularly useful. This was shown in several studies to be efficacious and safe, with less skin irritation than monotherapy with either agent, and the combination product containing calcipotriol and betamethasone dipropionate ointment has demonstrated efficacy in RCTs for patients with relatively severe psoriasis.[16,40] The combination may also be steroid sparing.[40]

The combination of retinoids with phototherapy has also been shown to increase efficacy. Because retinoids may be photosensitizing and increase the risk of burning after ultraviolet (UV) light exposure, doses of phototherapy should be reduced to minimize adverse effects. An RCT with tazarotene and broadband UVB not only showed significant enhancement of UVB efficacy but also reduced the number of UVB treatment sessions needed for response.[38,40,125] The combination of acitretin and broadband UVB reduced the number of needed treatments, compared with UVB alone.[16,126] Acitretin with NB-UVB (RE-UVB) was highly effective for patients with difficult-to-control psoriasis.[40,127] The combination of acitretin and PUVA (RE-PUVA) also showed greater efficacy than monotherapy with either agent.[38,128] RE-PUVA can be used to achieve clearance with up to a twofold reduction in total UV exposure.[16] Phototherapy has also been used with other topical agents, such as UVB with coal tar (Goeckerman regimen)[73] to increase treatment response because coal tar is also photosensitizing.

Cyclosporine and calcipotriol/betamethasone dipropionate in combination is superior to cyclosporine alone.[29] Cyclosporine may also be successfully used with SCAT; however, it should not be used with PUVA due to reduced efficacy and the potential increased risk of cutaneous malignancies.[42]

The combination of MTX and UVB is synergistic.[39,43] MTX in combination with biologics is beneficial. MTX has been effectively used in conjunction with etanercept, infliximab, adalimumab, ustekinumab, and others. MTX in combination with adalimumab or infliximab is widely used in rheumatology, and low-dose MTX (eg, 7.5-10 mg once per week) is likely sufficient to reduce the formation of anti-biologic-antibodies and increase the respective trough levels of adalimumab or infliximab.[29] Infliximab given concurrently with MTX or azathioprine may result in a lower incidence of infusion reactions to infliximab.[41]

Biologics used in combination with nonbiologic therapies are being explored and recommended, sometimes with just a theoretical rationale (ie, without RCT backup yet). In particular, the concept of increasing biologic survival with the addition of an immunosuppressive agent that reduces the development of neutralizing biologic antibodies is gaining acceptance as experience and clinical evidence accumulate with their use. Newer biologics whose use is associated with neutralizing antibodies are often used together with an immunosuppressive agent such as MTX.[45]

Other Drug Treatments

Selective Phosphodiesterase-4 (PDE4) Inhibitors: Crisaborole, Apremilast

A relatively new approach to management of inflammatory skin conditions such as psoriasis and atopic dermatitis (AD) is targeted inhibition of phosphodiesterase 4 (PDE4).[129] PDE4 inhibition causes an increase in intracellular cyclic AMP (cAMP), which leads to multiple effects, including reduced production of proinflammatory mediators.[129]

Apremilast is an oral tablet approved in the United States and Canada for patients with active PsA or moderate-to-severe psoriasis. It has shown efficacy and safety in 2 Phase III RCT (ESTEEM 1 and ESTEEM 2) for patients with psoriasis.[130] Recommended dosing is 10 mg on day 1, 10 mg twice daily on day 2, 10 mg in the morning and 20 mg in the evening on day 3, 20 mg twice daily on day 4, 20 mg in the morning, and 30 mg in the evening on day 5, then 30 mg twice daily thereafter. Dosing if renally impaired (CrCl <30 mL/min [0.5 mL/s]) is 10 mg in the morning on days 1 to 3; titrate using morning doses only (skip evening doses) to 20 mg on days 4 and 5, with the maintenance dose of 30 mg once daily in the morning thereafter.

Apremilast may be taken without regard to food; however, it should not be crushed, chewed, or split. There are drug interactions: the levels/effects of apremilast may be decreased by bosentan, CYP3A4 inducers (moderate and strong); dabrafenib, deferasirox, ivosidenib, lorlatinib, pitolisant, sarilumab, siltuximab, tocilizumab, and St. John's wort.[131]

Crisaborole is a topical PDE4 inhibitor approved for atopic dermatitis.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a systemic agent occasionally used for patients with resistant cases of moderate-to-severe psoriasis.[16] This is not an approved indication in either Canada or the United States (off-label use).

A few reports and small studies are available describing the efficacy of MMF when used as monotherapy or adjuvant therapy.[132] In addition, one small study evaluated the switch for eight patients with severe psoriasis from cyclosporine to MMF after a washout period of 2 to 4 weeks. On cyclosporine, seven of these patients had deteriorating renal function and hypertension, and one experienced loss of efficacy.[133] After the switch to MMF, there was a significant loss of psoriasis control in five of the eight patients, but also a significant improvement in renal function for six patients.[132,133]

Conversely, another small study evaluated the sequential use of MMF followed by cyclosporine in eight patients with moderate-to-severe psoriasis.[134] There was significant improvement with MMF in all patients, and all patients further improved when switched to cyclosporine.[134]

MMF has some uncommon but significant adverse effects, including increased incidence of opportunistic infections such as cytomegalovirus, cryptococcosis, candidiasis, and *Pneumocystis jirovecii*.[3,132] Cases of progressive multifocal leukoencephalopathy have also been reported.[132] There may be an associated risk of malignancy.[135]

Hydroxyurea

Hydroxyurea is an antimetabolite usually used for cancer treatments, but it has also been used in the systemic treatment of psoriasis for more than 30 years.[16,39] It is still occasionally tried for patients with recalcitrant severe psoriasis, although biologics may be a better option for these patients.

Hydroxyurea has been compared with MTX for patients with moderate-to-severe psoriasis.[136] Weekly regimens showed greater efficacy for MTX with a faster clearance rate, although hydroxyurea was also efficacious. The authors concluded that weekly doses of hydroxyurea may be an alternative to MTX for patients experiencing intolerable MTX side effects or who have reached the recommended cumulative MTX dose.[136]

Adverse effects of hydroxyurea include significant bone marrow suppression, lesional erythema, localized tenderness, and reversible hyperpigmentation.[16,136]

Complementary and Alternative Medicines

The use of complementary and alternative medicine (CAM) among patients with psoriasis is common, with a prevalence of 43% to 69% in various studies.[137] Most of these patients use herbs, special diets, or dietary supplements in conjunction with their usual antipsoriatic medications and not as replacements. Most patients do not discuss CAM use with their physicians.[137]

A 2009 systematic review of RCTs found that, although there is a large body of literature on CAM use in psoriasis, the quality of most studies was relatively low.[137] CAM agents and interventions with documented clinical efficacy in psoriasis include *Mahonia aquifolium*, fish oil, climatotherapy (Dead Sea salts), and stress reduction techniques.

Mahonia aquafolium (Oregon grape, Mountain grape, or barberry but *not* European barberry) is an evergreen native to southern British Columbia, western Oregon, and northern Idaho. The rhizome and root contain berberine as the primary active constituent. Berberine is an alkaloid that inhibits keratinocyte growth and reduces keratinocyte proliferation, and it also has antibacterial and antifungal activities. In at least two clinical trials, *Mahonia aquifolium* was efficacious in reducing disease severity: in one randomized placebo-controlled study, a *Mahonia aquifolium* 10% preparation applied topically twice daily resulted in a significant improvement in the PASI score and the Quality of Life Index (QLI), compared with placebo.[138] Adverse effects in clinical trials included rash, burning sensation, redness, and itching.

Fish oil contains two important long-chain polyunsaturated fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are omega-3 fatty acids. They act as substrates competing with arachidonic acid for cyclooxygenase and lipoxygenase, thus reducing the production of proinflammatory molecules in psoriatic plaques.[137] Several randomized placebo-controlled and/or comparative trials for patients with psoriasis have demonstrated efficacy of fish oils. One study comparing EPA plus etretinate to etretinate monotherapy found significantly greater efficacy with the combination of EPA plus etretinate.[139]

Climatotherapy refers to the practice of traveling to the Dead Sea and sunbathing and/or bathing in the sea—the beneficial effects are likely from the high salinity of the sea and UV rays.[137] Several studies have demonstrated efficacy, including two studies using saline spa baths. One study used highly concentrated (25%-27%) saline spa baths plus UVB compared with UVB alone, and the other used low concentrated (4.5%-12%) saline spa bath plus UVB again compared with UVB alone. In both studies, the clinical response was significantly better with the saline spa bath plus UVB combination.[137,140,141]

Stress-reduction techniques have inconsistently shown some benefit. One randomized study demonstrated that both meditation or meditation and imagery were efficacious as adjunctive treatments for patients with scalp psoriasis.[142] A second randomized study for patients with psoriasis receiving either UVB or PUVA therapy showed that the addition of a mindfulness-based stress-reduction audiotape played during light treatments reduced response times for patients receiving UVB but not PUVA therapy.[143] This confirmed the belief that psychological stress plays a role in psoriasis. More recently, in a case-control study of risk factors during the year before the onset of psoriasis, stressful life events were found to be significant.[144,145]

Personalized Pharmacotherapy

Despite the availability of good quality evidence and clinical practice guidelines, patients with psoriasis are still often undertreated or inappropriately managed.[30] A 2007 study in the United States involving 1,657 patients from National Psoriasis Foundation surveys found that 40% of patients with psoriasis were receiving no current treatment; of those, 27% had psoriasis involving >10% BSA.[146] In addition, those receiving care may be undertreated.[146] Early access to care and adherence may also be issues.

Patient-specific therapies that take into consideration comorbid illnesses, adherence, and pharmacoeconomic issues in addition to the patient's psoriatic manifestations and responses to treatments are important, and will ultimately improve the quality of care. Treatment goals need to be patient-specific and defined for both short-term and long-term management time frames.[30] Without optimizing patient care, the concern is that patients with poorly managed psoriasis may follow a "diminished" life course compared with the course they might have taken if they did not have psoriasis, as the disease has significant psychological, social, and economic impacts in addition to its physical manifestations.[147]

To this end, a current focus is defining frameworks,[147] specific treatment goals,[29,30] and targets[31] for implementation of practice guidelines, as described earlier in this chapter. The reader is encouraged to review the noted references for further information.

Special Populations

Psoriasis in Children

Psoriasis affects approximately 1% of children, with the most common onset during adolescence. One third of patients with psoriasis had onset of symptoms during the pediatric years.[148] Pediatric psoriasis is more often attributable to direct precipitating factors such as skin trauma, infections, drugs, or stress.[16,149] Compared with adults, plaque lesions in children are often smaller, thinner, and less scaly, which can make diagnosis more difficult. Face and flexures are more commonly involved than for adults. Psoriatic diaper rash can occur up to age 2. PsA is rare.[16]

Disease severity in clinical practice is most often defined using the percentage of BSA that is affected: less than 3%, mild; 3%-10%, moderate; and more than 10%, severe. The 2020 AAD-NPF guidelines of care for psoriasis in pediatric patients state that BSA should not be the sole predictor of disease severity, and that the impact on the child's QoL should be taken into consideration. For example, a child with psoriasis limited to the face or scalp may not have severe disease based on BSA definitions, but if the skin involvement has led to social withdrawal, shame, or bullying by others, it could be considered severe based on impact beyond the skin. A 2020 Canadian consensus concurs that children with psoriasis may experience stigmatization, social isolation affecting emotional and/or social development, and changes in their school functioning. Stigmatization may result in depression, anxiety, eating disorders, and risk-taking behaviour. A Children's Dermatology Life Quality Index (CDLQI) derived from the DLQI used in adults to assess QoL for patients age 4 through 16 years is available in written and cartoon form.[86,148]

Psoriasis in children is associated with cardiovascular risk factors and metabolic syndrome.[16] Cardiovascular risk factors include being overweight, obesity, hyperlipidemia, hypertension, high blood glucose, and diabetes.[16] Obesity and excessive waist circumference (central adiposity) are higher in

children with severe psoriasis, and in general, are higher in childhood psoriasis than in adults.[16,150] Adolescent girls who are overweight are at increased risk of later developing moderate-to-severe psoriasis, suggesting that obesity precedes the onset of psoriasis.[16,151]

Thus, nonpharmacologic management strategies in children also include minimizing cardiovascular risk factors and the development of the metabolic syndrome. The importance of maintaining a healthy lifestyle with good eating habits, exercise, and weight balance is crucial information to communicate to the child/adolescent and caregivers.

Topical treatment is the standard of care for children with psoriasis.[16,152] Vitamin D3 analogues (calcipotriene, calcipotriol, and calcitriol) have a corticosteroid-sparing function; this is an important advantage for pediatric patients. Calcipotriol with or without TCS has been recommended as treatment of first choice[16,152] because it produces minimal adverse effects.[16] Since children's skin is thinner and better hydrated than that of adults, they are at higher risk of drug absorption leading to systemic adverse effects. If a TCS is needed, the lowest potency TCS that provides control should be used, and it should be tapered as the lesions improve.

Combination products with calcipotriol and betamethasone dipropionate are effective and have FDA approval for use in children 12 years and older. Calcipotriol/betamethasone dipropionate ointment applied once daily for up to 4 weeks at a time has been recommended by AAD-NPF as a safe and effective treatment for children 12 years and older with mild-to-moderate plaque psoriasis, and the suspension has been recommended for once-daily use up to 8 weeks for mild-to-moderate scalp psoriasis. Due to the expense of combination products, individual products are often prescribed for simultaneous use in various regimens (e.g. once daily for the first 2 weeks, then reduced to weekends for topical corticosteroids and weekdays for the vitamin D analogue). To minimize corticosteroid use, combination therapy can be transitioned to topical vitamin D monotherapy when the condition improves.[148]

If long-term calcipotriol is used, monitoring of ionized calcium is recommended because of the risk of hypercalcemia.[16] Topical calcineurin inhibitors have been recommended as first-line therapy for psoriasis of the face, genitalia, and body folds. Rotational therapy with topical vitamin D analogues, topical calcineurin inhibitors, emollients, tar-based therapies, and topical corticosteroids should be considered in children as steroid-sparing regimens.[148,152]

For treatment-resistant or moderate-to-severe psoriasis, anthralin has been suggested, before considering short-term UVB in adolescents.[16,152] NB-UVB is recommended as a treatment option for moderate-to-severe pediatric plaque and guttate psoriasis.[148]

Systemic therapies (traditional nonbiologic and biologic) are appropriate for children with moderate-to-severe and recalcitrant psoriasis[16,86,148,152] or in the presence of comorbidities such as psoriatic arthritis.[148] In general, the goal with all systemic therapies in children is to control or clear the disease, provide maintenance disease stability for several months, then taper to the lowest effective dose and ultimately transition off systemic therapies if possible. If not possible, long-term maintenance at the lowest effective dose using the least toxic therapy is the preferred approach. MTX can provide near to complete clearance and has been recommended as the systemic treatment of choice in the Canadian guidelines[16] and recommended as effective systemic therapy in the AAD-NPF guidelines. MTX can be safely used to control severe childhood psoriatic episodes and then withdrawn as lesions improve.[16] Folate supplementation is recommded. Regular monitoring for liver and blood toxicity is required.[16] Other nonbiologic systemic agents such as cyclosporine and acitretin may also be used in children.[86,148]

Biologic agents recommended in the 2020 AAD-NPF guidelines for use in children include etanercept, adalimumab, infliximab, and ustekinumab.[148] Etanercept has been recommended as a third-line option in the 2016 Canadian guidelines.[16] A 2020 Canadian consensus summarizing the most recent evidence on the use of biologics for moderate-to-severe plaque psoriasis in pediatrics provides an algorithm that includes the biologics etanercept and adalimumab.[86] A randomized controlled trial in 211 children and adolescents (4-17 years) with moderate-to-severe plaque psoriasis showed that etanercept significantly reduced disease severity; however, four serious adverse events occurred (ovarian cyst requiring removal, gastroenteritis, gastroenteritis-associated dehydration, and left basilar pneumonia).[153] Etanercept has been studied in children with polyarticular juvenile rheumatoid arthritis without new safety concerns emerging.[16] Ustekinumab and adalimumab's safety profiles are also continuing to be evaluated.[16]

Biologics can be safely combined with topical corticosteroids, with or without a topical vitamin D analogue, to augment effectiveness for the treatment of moderate-to-severe plaque psoriasis in children.[148]

Phototherapy should be used with caution, especially for younger children, because of long-term carcinogenic risks and phototoxicities. For older children and adolescents with severe, extensive, or treatment-resistant disease, UVB (in particular, NB-UVB) may be a treatment option.[16]

Psoriasis in Pregnancy

Hormonal changes in pregnancy can improve symptoms for patients with plaque psoriasis. In one study, 55% of patients showed improvements during pregnancy.[16,154] For patients with more than 10% BSA involvement who reported improvement, lesions decreased by more than 80% during pregnancy.[154] This appeared to correlate with high estrogen but not progesterone levels.[154] Thus, some pregnant women may require minimal treatment for their psoriasis.

Some antipsoriatic drugs have significant teratogenic risks, making them contraindicated in pregnancy. Thus, women of childbearing potential must use effective birth control during therapy, and may need to continue effective contraception after discontinuing therapy for a period of time, as discussed in detail throughout this chapter. In addition, some drugs may carry known teratogenic risks in animal studies or have limited available data for use in pregnancy in humans.

UVB has been considered the safest treatment for extensive psoriasis during pregnancy. It is recommended for patients with widespread disease not controlled by topical agents. One problem with this therapy is an increased potential for reactivation of herpes simplex, which may be transmitted to the infant at delivery.[16]

For more detailed information about antipsoriatic drugs in pregnancy, a systematic, drug-by-drug review of case reports and case-control studies is available.[155] The 2009 Canadian Guidelines provides a drug-by-drug summary of recommendations for topical agents, phototherapy, and systemic agents in pregnancy.[16] The 2015 European S3 Guidelines provides a discussion about most appropriate treatments for women with a wish for pregnancy in the near future, and which treatments to avoid.[29]

Psoriasis in Older Adults

Age-related changes in organ function/drug clearance and greater drug sensitivity increase the risk of adverse drug events for elderly patients with psoriasis.

MTX is hepatotoxic and should be used with caution in older adults. Cyclosporine has nephrotoxic potential and may also increase blood pressure. Both drugs have significant drug interactions, and polypharmacy, common in older patients, makes management of interactions challenging.

In addition, older patients may have preexisting comorbidities, such as hyperlipidemia and metabolic syndrome, and this may further limit drug selection. Adalimumab is equally efficacious in patients aged 65 years or older who may have higher incidences of hypertension, hyperlipidemia, depression, obesity, and diabetes.[156] Adverse-effect profiles were similar between subgroups (various weights and comorbidities) with no significant differences in serious adverse events.[156] Ustekinumab requires no dosage adjustments for renal or hepatic impairments and geriatric dosing is the same as for adults younger than 65 years, with the dose based on weight. Secukinumab also requires no dosage change in older adults and those with renal/hepatic impairment.

Topical psoriasis treatments are often prescribed for older adults as first-line therapy[16]; however, even with topicals, adverse effects—including systemic ones—can occur with greater frequency in these patients.[16]

Psoriasis in Patients with a History of Solid Tumors

As discussed throughout this chapter, many antipsoriatic therapies carry significant cancer risks. PUVA, systemic therapies such as cyclosporine, and some biologics are associated with increased risks of oncologic disorders.

A systematic review of the risk of malignancy associated with therapies for moderate-to-severe psoriasis confirmed the following[135]: PUVA is associated with an increased risk of cutaneous SCC and malignant melanoma; UVB is a much safer therapeutic modality than PUVA; cyclosporine increases risks of lymphoma, internal malignancies, and skin cancers; methotrexate may be associated with increased melanoma and Epstein-Barr virus–associated lymphomas; MMF may be associated with lymphoproliferative disorders; and the malignancy risk may be increased for biologic

agents, especially the TNF-α inhibitors.[135]

The 2009 Canadian guidelines recommend that TNF-α inhibitors be used with caution for patients with a history of malignancy or existing malignancies, and the T-cell modulator alefacept (now voluntarily withdrawn from the US and Canadian markets) is contraindicated for these patients.[16] There are currently registry safety databases (PSOLAR,[157] BADBIR,[158] PsoBest[159,160]) for biologics; over time, these will provide biologic-specific and updated safety information.[160] Known risks in general include the development of neoplasms such as nonmelanoma skin cancer.[89]

Coronavirus Disease 2019 Risk in Patients Receiving Biologics for Psoriasis

During the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there was concern around increased risk of infection in patients receiving ongoing biologic therapy for psoriasis.

A study exploring the incidence of COVID-19 in 1,830 patients with psoriasis who were receiving various biologics (etanercept, ustekinumab, ixekizumab, secukinumab, and guselkumab) found a COVID-19 incidence rate (IR) of 9.7 (95% CI 3.9-20.1) per 10,000 person-months in patients with psoriasis versus an IR of 11.5 (95% CI 11.4-11.7) per 10,000 person-months in the general population. This study was conducted in northeast Italy (the Veneto region comprising Verona, Padua, and Vicenza) with data collected between February 20, 2020, and June 1, 2020, during the height of an initial wave of the COVID-19 pandemic in this region. Only six cases of COVID-19 occurred among 1,830 patients with psoriasis compared with 19,154 cases among 4,905,854 people in the general population. Of the six COVID-19–positive patients with psoriasis, four were hospitalized with interstitial pneumonia with no deaths. These results were contrary to the expectation that the incidence and severity of COVID-19 would be higher in patients with psoriasis as they had a higher prevalence of known comorbidities (hypertension, cardiovascular diseases, diabetes) than those in the general population.[161]

Pharmacoeconomic Considerations

10 The wide gap in costs of agents for psoriasis makes economics and availability of insurance or other coverage important considerations in formulating a therapeutic plan.

The biologics are often considered for patients with moderate-to-severe psoriasis when less-expensive traditional systemic agents are inadequate or relatively contraindicated. Biologics have also been recommended as first-line therapy, alongside conventional systemic agents, for patients with moderate-to-severe psoriasis; however, in practice, drug access secondary to cost considerations can limit use. These agents may be needed early, though, for some patients with comorbidities, such as PsA.

A pharmacoeconomic analysis of biologics in the treatment of psoriasis suggests that the cost-to-benefit ratio for biologics may be favorable.[162] This analysis was performed in 2009 when available biologics were fewer and more expensive than today. More recent analyses indicate wide variations when clinical outcomes are factored into costs of recently marketed agents.[163]

CONCLUSION

Psoriasis is a lifelong illness with no known cure. Significant comorbidities may coexist. Treatment should be patient-specific, with consideration given to disease severity, patient risk factors, age, and comorbidities. Newer treatment modalities, including numerous biologics, are now parts of the armamentarium available in the management of this disease.

ABBREVIATIONS

BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BMI	body mass index

BRM	biologic response modifier (This term has been replaced by “biologic agents.”)
BSA	body surface area
CAM	complementary and alternative medicine
CDA	Canadian Dermatology Association
CHD	coronary heart disease
CHF	chronic heart failure
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CYP3A4	cytochrome P450 isoenzyme 3A4
DBPC	double-blind placebo-controlled
DHA	docosahexaenoic acid
DISH	disseminated (or diffuse) idiopathic skeletal hyperostosis
DLQI	Dermatology Life Quality Index
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HLA-C	major histocompatibility complex antigen
HPA	hypothalamic–pituitary–adrenal
IL	interleukin
MACE	major adverse cardiovascular events
MMF	mycophenolate mofetil
MI	myocardial infarction
NPF	National Psoriasis Foundation
NSAIDs	nonsteroidal anti-inflammatory drugs
NB-UVB	narrowband ultraviolet B (311-nm ultraviolet B light)
OR	odds ratio

PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PUVA	psoralens with ultraviolet A light
QoL	quality of life
QLI	Quality of Life Index
RCT	randomized controlled trial
RE-PUVA	retinoid plus PUVA (as combination therapy)
RE-UVB	retinoid plus NBUVB (as combination therapy)
RPLS	reversible posterior leukoencephalopathy syndrome
RR	relative risk
SARS-COV2	severe acute respiratory syndrome coronavirus
SCAT	short-contact anthralin therapy
SCC	squamous cell carcinoma
SF-36	Short Form Health Survey
SPF	sun protection factor
TB	tuberculosis
TNF-α	tumor necrosis factor-α
UV	ultraviolet
UVA	ultraviolet A (315-400 nm ultraviolet A light)
UVB	ultraviolet B, or broadband UVB (28-315 nm ultraviolet B light)

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SELF-ASSESSMENT QUESTIONS

1. Which of the following may precipitate new-onset psoriasis?
   A. Corticosteroids
   B. Azathioprine
   C. β-Adrenergic blocker
   D. Thiazide diuretics
2. Which of the following may exacerbate preexisting psoriasis?
   A. β-Adrenergic blocker
   B. Lithium
   C. Nonsteroidal anti-inflammatory drugs
   D. All of the above
3. Comorbidities associated with psoriasis include all of the following except:
   A. Psoriatic arthritis
   B. Crohn's disease
   C. Multiple sclerosis
   D. Multiple myeloma

4. A 33-year-old man has been diagnosed with mild plaque psoriasis. Presenting clinical signs and symptoms may include all of the following except:
   A. Hypopigmentation
   B. Pruritus
   C. Erythema
   D. Silvery scales on lesions
5. True or false: Psoriasis is an independent risk factor for atherosclerosis.
   A. True
   B. False
6. True or false: Psoriasis is usually diagnosed based on a skin biopsy.
   A. True
   B. False
7. Appropriate nonpharmacologic therapy for a 33-year-old person with mild plaque psoriasis includes all of the following except:
   A. Moisturizer applied ad lib
   B. Oatmeal baths
   C. Tanning beds
   D. Stress management clinics
8. Initial pharmacologic therapy for a 33-year-old person with mild plaque psoriasis should be:
   A. Betamethasone dipropionate 0.05% ointment for 2 months
   B. Calcipotriol 50 µg/g cream for 2 months
   C. Methotrexate 5 mg/week for 2 months
   D. PUVA treatments for 2 months
9. SCAT therapy refers to:
   A. Steroid + plus calcipotriol use
   B. Steroid + pluscoal tar use
   C. Anthralin use
   D. Tazarotene use
10. A 28-year-old person is in the first trimester of pregnancy. She has severe plaque psoriasis that did not improve when she became pregnant. In fact, the stress of pregnancy has resulted in a flare-up of her psoriasis. Appropriate treatment for this person's psoriasis would be:
    A. Methotrexate
    B. NB-UVB

C. Topical tazarotene

D. Acitretin

11. Moderate-to-severe psoriatic lesions in a 33-year-old person fail to clear with topical therapy or NB-UVB. The NB-UVB treatments were continued and acitretin was added. Appropriate counseling for this patient includes all of the following except:

A. Effective birth control for the duration of acitretin therapy.

B. Effective birth control for at least 2 years after discontinuing acitretin.

C. Ineligible to donate blood.

D. No more than two alcoholic drinks per day.

12. Moderate-to-severe psoriatic lesions in a 48-year-old person are being treated with methotrexate. Although rare, pancytopenia can occur anytime—even after single doses of methotrexate. The patient should be counseled about the early signs and symptoms of pancytopenia, which include:

A. Stomatitis/oral symptoms

B. Fever

C. Dyspnea/cyanosis

D. All of the above

13. Initial biologic selection for a patient with moderate-to-severe psoriasis who also has active psoriatic arthritis (as recommended by both the Canadian Psoriasis Guidelines Addendum Committee and the British Association of Dermatologists) is:

A. Methotrexate

B. Adalimumab

C. Tildrakizumab

D. Tofacitinib

14. The systemic treatment of choice for children with severe psoriasis is currently:

A. Acitretin

B. Methotrexate

C. Cyclosporine

D. Prednisone

15. Precautions about the use of apremilast include all of the following except:

A. Take with food

B. Do not crush, split or chew the tablet

C. Drug interaction with St. John's wort

D. Dose reduction in renal impairment

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Of these options, only beta-blockers are precipitating factors for psoriasis.
2. **D.** All of the listed options can exacerbate psoriasis.
3. **D.** Multiple myeloma is not associated with psoriasis.
4. **A.** The psoriatic plaques are red-violet and sharply demarcated from normal skin. Hypopigmentation is not consistent with psoriasis.
5. **A.** This is true. Psoriasis is an independent risk factor for atherosclerosis, especially for younger patients with severe disease. This leads to increased cardiovascular mortality risk.
6. **B.** This is false. Psoriasis is diagnosed based on clinical presentation: recognition of the characteristic psoriatic lesion, and not on laboratory tests.
7. **C.** Tanning beds are inappropriate for treatment of psoriasis.
8. **B.** The patient has mild psoriasis, which can be appropriately treated with calcipotriol topically as initial therapy. The betamethasone dipropionate 0.05% ointment is too potent, and systemic therapy with methotrexate or phototherapy is inappropriate as initial therapy for mild plaque psoriasis.
9. **C.** SCAT therapy refers to Short Contact (20 minutes to 2 hours) Anthralin Therapy, using a much higher anthralin concentration and is meant for thicker plaques such as may be found on knees and elbows.
10. **B.** NB-UVB is safe to use in pregnancy. The other three listed choices are teratogenic.
11. **D.** This person should avoid alcohol during therapy and for 2 months after drug discontinuation, as alcohol causes transesterification of acetretin to etretinate, which has a much longer elimination half-life.
12. **D.** Early signs and symptoms of pancytopenia may be nonspecific and includes all the above.
13. **B.** A TNF or IL-17 antagonist is recommended as first-line biologic therapy in patients with moderate-to-severe psoriasis who also have active PsA. Adalimumab is a TNF inhibitor and is the best option to use for comorbid active PsA. Methotrexate is not a biologic agent. Tildrakizumab is an IL-23 antagonist and is not indicated for active PsA. Tofacitinib is an oral JAK inhibitor approved for active PsA, however, is not a biologic agent. There are no IL-17 antagonists available as answer options.
14. **B.** Methotrexate has been recommended as the systemic treatment of choice and can be safely used to control severe childhood psoriatic episodes and then withdrawn as lesions improve. Regular monitoring for liver and blood toxicities is required.
15. **A.** Apremilast may be taken without regard to food.