Treatment of psoriasis in adults

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INTRODUCTION

Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are not severe enough to directly affect general health and are treated in the outpatient setting. Rare, life-threatening presentations can occur that require intensive inpatient management.

This topic reviews the treatment of psoriatic skin disease. The epidemiology, clinical manifestations, and diagnosis of psoriatic skin disease are discussed in detail separately, as are psoriatic arthritis and the management of psoriasis in pregnant women, children, and special populations. (See "Psoriasis: Epidemiology, clinical manifestations, and diagnosis" and "Treatment of psoriatic arthritis" and "Pathogenesis of psoriatic arthritis" and "Clinical manifestations and diagnosis of psoriatic arthritis" and "Management of psoriasis in pregnancy" and "Psoriasis in children: Management of chronic plaque psoriasis" and "Treatment selection for moderate to severe plaque psoriasis in special populations".)

APPROACH

Psoriasis is a chronic disease that can have a significant effect on quality of life. Therefore, management of psoriasis involves addressing both psychosocial and physical aspects of the disease.

Numerous topical and systemic therapies are available for the treatment of the cutaneous manifestations of psoriasis. Treatment modalities are chosen on the basis of disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and

evaluation of individual patient response [1]. Although medication safety plays an important role in treatment selection, this must be balanced by the risk of undertreatment of psoriasis, leading to inadequate clinical improvement and patient dissatisfaction [2,3].

The desired outcome of treatment differs for individual patients and is dependent upon factors such as patient preferences regarding the preferred amount of disease control and tolerance of specific treatments. A reasonable goal for patients who desire maximum resolution of skin disease is minimal to no skin involvement achieved with a well-tolerated treatment regimen. A panel of psoriasis experts convened by the National Psoriasis Foundation identified the acceptable response for plaque psoriasis after three months of treatment as either less than 3 percent body surface area involvement or 75 percent improvement compared with baseline and the target response after six months as 1 percent body surface area [4]. However, the values and preferences of some patients support tolerance of a greater degree of skin involvement and a less aggressive approach to therapy.

Psychosocial aspects — Psoriasis can be a frustrating disease for the patient and the provider. The clinician needs to be empathetic and spend adequate time with the patient. It may be helpful for the clinician to touch the patient's psoriasis lesions with an ungloved hand, when appropriate, to communicate physically that the skin disorder is neither repulsive nor contagious.

Clinicians should lay out reasonable aims of treatment, making it clear to the patient that the primary goal of treatment is control of the disease. Although treatment can provide patients with high degrees of disease improvement, there is no cure for psoriasis.

Educating the patient about psoriasis is important and referral to an organization such as the National Psoriasis Foundation is often helpful.

Psoriasis may affect patients' perceptions of themselves and this can potentially initiate or exacerbate psychologic disorders such as depression [5,6]. Patients with limited skin disease may still have significant psychosocial disability [7]. Some patients with psoriasis may benefit from counseling and/or treatment with psychoactive medications.

Choice of therapy — For most patients, the initial decision point around therapy will be between local (topical) and full body (phototherapy or systemic) therapy. However, even patients on systemic therapy will likely continue to need some topical agents. Topical therapy may provide symptomatic relief and can help minimize required doses of systemic medications.

For purposes of treatment planning, patients may be grouped into mild (or limited) disease and extensive (moderate to severe) disease categories. Mild skin disease can often be managed with topical agents, while patients with moderate to severe disease may need

phototherapy or systemic therapy. The location of the disease and the presence of psoriatic arthritis also affect the choice of therapy. Psoriasis of the hand, foot, or face can be debilitating functionally or socially and may deserve a more aggressive treatment approach. The treatment of psoriatic arthritis is discussed separately. (See "Treatment of psoriatic arthritis".)

Moderate to severe psoriasis is typically defined as involvement of more than 5 to 10 percent of the body surface area (the entire palmar surface, including fingers, of one hand is approximately 1 percent of the body surface area [8]) or involvement of the face, palm or sole, or disease that is otherwise disabling. Patients with more than 5 percent body surface area affected are generally candidates for phototherapy or systemic therapy, since application of topical agents to a large area is not usually practical or acceptable for most patients. Attempts to treat extensive disease with topical agents alone are often met with failure, can add cost, and lead to frustration in the patient-clinician relationship. However, topical agents are useful adjuncts for resistant, localized lesions in patients who are getting phototherapy or systemic agents for extensive involvement.

There is ample evidence of efficacy of the newer systemic therapies ("biologics"); however, cost is a major consideration with these agents. Established therapies such as methotrexate and phototherapy continue to play a role in the management of moderate to severe plaque psoriasis. (See 'Biologic agents' below.)

The management of patients with extensive or recalcitrant disease is a challenge even for experienced dermatologists. However, the availability of biologic medications has reduced the challenge considerably.

The concept that many patients with psoriasis in the United States do not receive sufficient treatment to control the disease is suggested by an analysis of surveys performed by the National Psoriasis Foundation between 2003 and 2011 [2]. Among the 5604 survey respondents with psoriasis, 52 percent expressed dissatisfaction with their treatment. Many survey respondents received no treatment, including 37 to 49 percent of respondents with mild psoriasis, 24 to 36 percent of respondents with moderate psoriasis, and 9 to 30 percent of respondents with severe psoriasis; selection bias and the particular population that was surveyed may have contributed to the high observed rate of undertreatment. Further studies will be useful for clarifying the reasons for these observations and for determining the value of interventions to increase the accessibility of treatment.

Widespread pustular disease requires aggressive treatment, which may include hospitalization. Therapeutic approaches to generalized pustular psoriasis and psoriatic arthritis are discussed separately. (See "Pustular psoriasis: Management" and "Treatment of psoriatic arthritis".)

Limited disease — Limited plaque psoriasis can respond well to topical corticosteroids and emollients. Alternatives include vitamin D analogs (eg, calcipotriene and calcitriol), tar, and topical retinoids (tazarotene). For facial or intertriginous areas, topical tacrolimus or pimecrolimus may be used as alternatives or as corticosteroid-sparing agents, though improvement may not be as rapid as with potent topical corticosteroids. Localized phototherapy is another option for recalcitrant disease.

Combinations of potent topical corticosteroids (table 1) and either calcipotriene, calcitriol, tazarotene, or UVB phototherapy are commonly prescribed by dermatologists. Calcipotriene in combination with class I topical corticosteroids is highly effective for short-term control. Calcipotriene alone can then be used continuously and the combination with potent corticosteroids used intermittently (on weekends) for maintenance. Examples of commercially available combination products include calcipotriene-betamethasone and halobetasol-tazarotene. With proper adherence, considerable improvement with topical therapies may be seen in as little as one week, though several weeks may be required for full benefits.

Because adherence to topical treatment can be a major hurdle, keeping the treatment regimen simple and using treatment vehicles that the patient finds acceptable is often beneficial [9].

Moderate to severe disease — Severe psoriasis requires phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, apremilast, or biologic immune modifying agents. Biologic agents used in the treatment of psoriasis include the anti-tumor necrosis factor (TNF) agents adalimumab, etanercept, infliximab, and certolizumab pegol; the anti-interleukin (IL) 12/IL-23 antibody ustekinumab; the anti-IL-17 antibodies secukinumab and ixekizumab; the anti-IL-17 receptor antibody brodalumab; and the anti-IL-23/IL-39 antibodies guselkumab, tildrakizumab, and risankizumab. Improvement usually occurs within weeks. Patients with severe psoriasis generally require care by a dermatologist.

Intertriginous psoriasis — In general, intertriginous (inverse) psoriasis should be treated with class VI and VII low potency corticosteroids (table 1) due to an increased risk of corticosteroid-induced cutaneous atrophy in the intertriginous areas. Very short-term use of more potent topical corticosteroids may also be acceptable and can help reduce the complexity of the treatment regimen when patients are prescribed high-potency topical corticosteroids for use on other parts of the body.

Topical calcipotriene or calcitriol and the topical calcineurin inhibitors tacrolimus or pimecrolimus are additional first-line treatments [10,11]. These agents may be used alone or in combination with topical corticosteroids as corticosteroid-sparing agents for long term maintenance therapy. Calcipotriene, tacrolimus, and pimecrolimus are more expensive

options than topical corticosteroids. Some concerns have been raised about the safety of the calcineurin inhibitors. (See 'Calcineurin inhibitors' below and "Psoriasis: Epidemiology, clinical manifestations, and diagnosis", section on 'Inverse (intertriginous) psoriasis'.)

Scalp psoriasis — The presence of hair on the scalp can make topical treatment of psoriasis challenging because patients may find certain products messy or difficult to apply. Recognizing the patient's preference for a drug vehicle may help to improve adherence to therapy. For many patients, solution, shampoo, lotion, gel, foam, or spray vehicles are preferable to thicker creams or ointments for use on the scalp.

Topical corticosteroids are the primary topical agents used for psoriasis on the scalp [12]. Support for the use of these agents is evident in a systematic review of randomized trials that found that very potent or potent topical corticosteroids are more effective treatments for scalp psoriasis than topical vitamin D analogs [13]. Combining a corticosteroid and vitamin D analog may offer additional benefit; in the systematic review, combination treatment with a potent topical corticosteroid and a vitamin D analog appeared slightly more effective than potent topical corticosteroid monotherapy. However, in clinical practice, complicating the treatment regimen with more than one topical product may reduce the likelihood of consistent adherence to the treatment regimen. Thus, we usually prescribe a topical corticosteroid alone as initial therapy. Commercial betamethasone dipropionate-calcipotriene combination products are available but are more expensive than most generic topical corticosteroid preparations.

Other topical therapies used for psoriasis (eg, tazarotene, coal tar shampoo, anthralin) and intralesional corticosteroid injections also may be beneficial for scalp involvement, though data on efficacy specifically in scalp disease are limited [12]. Salicylic acid can be a helpful adjunctive treatment because of its keratolytic effect, but prescribing it alongside a separate topical corticosteroid makes the treatment regimen more complicated and, therefore, could adversely affect adherence to treatment. Phototherapy (eg, excimer laser) and systemic agents are additional treatment options for patients who cannot achieve sufficient improvement with topical agents [12].

Guttate psoriasis — The management of guttate psoriasis is reviewed separately. (See "Guttate psoriasis", section on 'Treatment'.)

Generalized pustular psoriasis — The management of generalized pustular psoriasis is reviewed separately. (See "Pustular psoriasis: Management".)

Localized pustular psoriasis — Localized pustular psoriasis (palms and soles) is difficult to treat. Approaches include potent topical corticosteroids and topical bath psoralen plus ultraviolet A phototherapy (PUVA). (See "Psoralen plus ultraviolet A (PUVA) photochemotherapy".)

Data are limited on the use of systemic retinoids for localized pustular psoriasis. However, these drugs appear to be particularly effective in the treatment of pustular psoriasis, and we consider them first-line therapy. Acitretin is the retinoid that is used most often for this indication. Acitretin is a potent teratogen and should not be used in women who might become pregnant. Pregnancy is contraindicated for three years following acitretin therapy (see 'Acitretin' below). Methotrexate, cyclosporine, apremilast, and the array of biologics for psoriasis can also be used.

Nail psoriasis — Although nail involvement alone is uncommon, many patients with psoriasis have disease that involves the nails. The management of nail psoriasis is reviewed in detail separately. (See "Nail psoriasis", section on 'Treatment'.)

Erythrodermic psoriasis — Erythrodermic psoriasis is an uncommon, severe version of psoriasis characterized by widespread skin involvement. The management of this condition is reviewed in detail separately. (See "Erythrodermic psoriasis in adults".)

Children — The immediate and long-term adverse effects of therapies for psoriasis are of particular concern in the pediatric population. Although many agents used in the treatment of adult psoriasis have also been used for children, high-quality studies on the efficacy and safety of therapies for psoriasis in children are limited. The management of psoriasis in children is reviewed separately. (See "Psoriasis in children: Management of chronic plaque psoriasis".)

Concomitant psoriatic arthritis — Patients with psoriasis should be assessed periodically for signs and symptoms of psoriatic arthritis. The concomitant presence of psoriatic arthritis and moderate to severe psoriasis favors the selection of treatments that are effective for both skin and joint disease. (See "Clinical manifestations and diagnosis of psoriatic arthritis" and "Treatment of psoriatic arthritis".)

Special populations — The treatment of psoriasis in pregnant women and patients with hepatitis B, hepatitis C, human immunodeficiency virus infection, latent tuberculosis, or malignancy is reviewed separately. (See "Treatment selection for moderate to severe plaque psoriasis in special populations" and "Management of psoriasis in pregnancy".)

There is an association between psoriasis and inflammatory bowel disease. Biologics such as infliximab, adalimumab, and ustekinumab can be effective for both diseases. Etanercept and the anti-IL-17 biologics secukinumab, brodalumab, and ixekizumab are effective for psoriasis, but not for inflammatory bowel disease, and should be used with caution in patients with inflammatory bowel disease because these drugs may exacerbate inflammatory bowel disease [14].

Referral — Referral to a dermatologist should be considered in the following settings:

- Confirmation of the diagnosis is needed.
- The response to treatment is inadequate as measured by the clinician, patient, or both.
- There is significant impact on quality of life.
- The primary care clinician is not familiar with the treatment modality recommended such as PUVA, phototherapy, or immunosuppressive medications.
- The patient has widespread severe disease.
- In cases of psoriatic arthritis, referral and/or collaboration with a rheumatologist is indicated. (See "Treatment of psoriatic arthritis".)

TOPICAL THERAPIES

Patient adherence may be the largest barrier to treatment success with topical therapies [9]; early patient follow-up (within a week of initiating treatment) may improve adherence. Published guidelines for the treatment of psoriasis with topical therapies are available [15].

Emollients — Hydration and emollients are valuable and inexpensive adjuncts to psoriasis treatment. Keeping psoriatic skin soft and moist minimizes the symptoms of itching and tenderness. Additionally, maintaining proper skin hydration can help prevent irritation and thus the potential for subsequent Koebnerization (development of new psoriatic lesions at sites of trauma).

The most effective are ointments such as petroleum jelly or thick creams, especially when applied immediately after a hydrating bath or shower. In practice, however, whichever moisturizer the patient finds most appealing may be the best choice.

Corticosteroids — Topical corticosteroids remain the mainstay of topical psoriasis treatment despite the development of newer agents [16]. The mechanism of action of corticosteroids in psoriasis is not fully understood. Corticosteroids exert anti-inflammatory, antiproliferative, and immunosuppressive actions by affecting gene transcription.

The inherent potency of a topical corticosteroid is frequently reported using a I to VII scale based on vasoconstrictive assays (table 1). Although ointments are sometimes thought to be inherently more effective because of their occlusive properties, this is not uniformly correct. In practice, the efficacy/potency of a topical corticosteroid is dependent on many factors, including application site, plaque thickness, how well the vehicle delivers the active drug molecule, how well that drug molecule activates corticosteroid receptors, and, perhaps most importantly, compliance.

To minimize adverse effects and maximize compliance, the site of application needs to be considered in choosing the appropriately potent corticosteroid:

- On the scalp or in the external ear canal, potent corticosteroids in a solution vehicle (eg, fluocinonide 0.05% or clobetasol propionate 0.05%) are frequently indicated. Clobetasol 0.05% shampoo, foam, or spray can also be used for scalp involvement. Patients who use scalp oils or ointments for general hair care (a common practice among individuals with Afro-textured hair) may prefer an oil or ointment vehicle for scalp involvement.

- On the face and intertriginous areas, a low-potency ointment or cream (eg, over-the-counter hydrocortisone 1% or prescription-strength 2.5%) is often sufficient.

- For thick plaques on extensor surfaces, potent preparations (eg, betamethasone 0.05% or clobetasol propionate 0.05%) are often required.

The typical regimen consists of twice daily application of topical corticosteroids. Most patients will show a rapid decrease in inflammation with such therapy, but complete normalization of skin or lasting remission is unpredictable.

Topical corticosteroids generally can be continued as long as the patient has thick active lesions. Skin atrophy from topical corticosteroids usually is not a problem unless the medication is continuously applied after the skin has returned to normal thickness or if areas without psoriasis are exposed. Once clinical improvement occurs, the frequency of application should be reduced [17]. For patients in whom lesions recur quickly, topical corticosteroids can be applied intermittently (eg, on weekends only) to maintain improvement. The addition of noncorticosteroid topical treatments to the treatment regimen can also facilitate the avoidance of long-term daily topical corticosteroids. (See 'Limited disease' above.)

The risks of cutaneous and systemic side effects associated with chronic topical corticosteroid use are greater with high-potency formulations compared with lower-potency formulations. Data support limiting the continuous application of class I topical corticosteroids to two to four weeks; thus, close clinician supervision should be employed if longer treatment durations are required, as often occurs in psoriasis (table 1) [17]. Data are less clear regarding treatment durations for less potent topical corticosteroids. Side effects of topical corticosteroids, including the potential for suppression of the hypothalamic axis, are discussed separately. (See "Pharmacologic use of glucocorticoids" and "Topical corticosteroids: Use and adverse effects".)

The cost of topical corticosteroids varies widely. The price of a 60 gram tube of a potent corticosteroid brand name product can be hundreds of dollars. There are generic preparations in each potency class that have reduced the cost somewhat, though generic

prices in the United States are rising [18]. Examples of available generics include, in order of increasing potency, hydrocortisone 2.5%, triamcinolone 0.1%, fluocinonide 0.05%, betamethasone dipropionate 0.05%, and clobetasol 0.05%.

Different formulations have been developed in an effort to enhance the delivery of topical corticosteroids. The main advantage of these newer preparations is likely greater patient acceptance, which may translate into greater adherence; the main disadvantage is cost. Betamethasone valerate in a foam had superior efficacy for scalp psoriasis and was preferred, on average, by patients when compared with betamethasone valerate lotion [19]. The foam becomes a liquid on contact with skin and is also well tolerated by patients with trunk and extremity psoriasis [20]. A clobetasol propionate spray is also available; like foams, sprays are easy to apply to large areas [21]. Placement of a corticosteroid solution in a spray bottle may be helpful for patients who desire a spray but are unable to obtain a commercially available product.

Topical vitamin D analogs — Topical vitamin D analogs for the treatment of psoriasis include calcipotriene (calcipotriol), calcitriol, and tacalcitol. Although topical vitamin D analogs are effective as monotherapy for some patients, a systematic review found that combination therapy with a topical corticosteroid is more effective than either treatment alone [22].

Until 2009, calcipotriene was the only topical vitamin D analog available in the United States. Calcipotriene is obtainable as a cream, solution, ointment, or foam, or as a combination ointment, suspension, or foam with betamethasone dipropionate. Topical calcitriol ointment has been prescribed in Europe for years, and is now available in the United States. When compared with calcipotriene, calcitriol appears to induce less irritation in sensitive areas of the skin (eg, skin folds) [23].

Calcipotriene — Calcipotriene (calcipotriol) is an established therapy in psoriasis. The precise mechanism is not clear, but a major effect is the hypoproliferative effect on keratinocytes [24]. An immune modulating effect has been postulated for calcipotriene, but has not been shown to be significant in psoriasis to date [25].

In a systematic review of randomized controlled trials, calcipotriene was at least as effective as potent (not super-potent) topical corticosteroids, calcitriol, short contact dithranol, tacalcitol, coal tar and combined coal tar 5%, allantoin 2%, and hydrocortisone 0.5% [26]. Only potent topical corticosteroids appeared to have comparable efficacy at eight weeks. Skin irritation is the main adverse event associated with calcipotriene.

Combined use of calcipotriene and superpotent corticosteroids increases clinical response and tolerability in clinical trials compared with either agent used alone [27-29]. One regimen employed daily use of both calcipotriene ointment and halobetasol ointment for two weeks,

followed by weekend use of the halobetasol ointment and weekday use of calcipotriene [27]. This regimen produced six-month remission maintenance in 76 percent compared with 40 percent with weekend halobetasol alone. A similar regimen with calcipotriene ointment and clobetasol propionate foam also appears to be effective [30].

In addition, a randomized trial found that an ointment preparation that combines calcipotriene with betamethasone dipropionate (0.064%) was effective with once-daily usage and more effective than once-daily therapy with either betamethasone or calcipotriene [31]. Patients who use topical corticosteroids in combination with calcipotriene must be monitored for adverse effects as with corticosteroid monotherapy. Other vehicle options for this combination include oil, foam, and cream [32]. Cost can be a limiting factor for combination agents. (See 'Corticosteroids' above.)

Thus, topical calcipotriene may be used as an alternative or adjunct to topical corticosteroid therapy. It is applied twice daily when used as monotherapy. No controlled trials guide how best to use topical corticosteroids in conjunction with calcipotriene. Once daily use of each may be adequate. Acidic products can inactivate topical calcipotriene, and some topical corticosteroids may be acidic. A reasonable approach to combination therapy is to have patients apply topical calcipotriene and topical corticosteroids each once daily at different times of day. However, the potential impact on adherence from complicating the treatment regimen should be kept in mind.

Other than skin irritation, side effects of topical calcipotriene are usually minimal; the risk of hypercalcemia is low when the drug is used appropriately [33]. However, topical calcipotriene is more expensive than many generic potent corticosteroids.

Calcitriol — The mechanism of action of calcitriol is thought to be similar to that of calcipotriene and involves the drug's ability to inhibit keratinocyte proliferation and stimulate keratinocyte differentiation [34]. In addition, calcitriol inhibits T cell proliferation and other inflammatory mediators [34]. In two randomized trials with a total of 839 patients with mild to moderate plaque psoriasis, calcitriol 3 mcg/g ointment was more effective than vehicle [35]. At the end of the study periods (up to eight weeks), 39.6 and 32.7 percent of the calcitriol groups versus 21.2 and 12 percent of the vehicle groups exhibited at least marked global improvement.

In a systematic review, calcipotriene and calcitriol were equally effective [22]. However, on sensitive or intertriginous areas of the skin, calcitriol appears to be less irritating than calcipotriene. An intraindividual randomized trial of 75 patients compared treatment with calcitriol 3 mcg/g ointment to calcipotriene 50 mcg/g ointment for mild to moderate psoriasis on facial, hairline, retroauricular, and flexural areas [23]. Perilesional erythema, perilesional edema, and stinging or burning sensations were less common in the areas

treated with calcitriol. A 52-week, open-label study of the safety of calcitriol ointment did not reveal an adverse effect on calcium homeostasis [36].

Similar to calcipotriene, calcitriol ointment is more expensive than many generic potent topical corticosteroids. The drug is applied twice daily.

Tar — The use of tar is a time-honored modality for treating psoriasis, although newer (and less messy) treatment options have reduced its popularity. The precise mechanism of action of tar is not known but may involve aryl hydrocarbon receptors [37]. Tar has apparent anti-inflammatory and antiproliferative effects [38].

Tar can be helpful as an adjunct to topical corticosteroids. There are no commercially available corticosteroid/tar combinations. Tar products are available without a prescription in the form of shampoos, creams, lotions, ointments, and oils. Newer products include a solution and a foam. Some patients may prefer the less messy formulations.

Tar can also be compounded into creams and ointments. A commonly used compound is 2% or 3% crude coal tar in triamcinolone cream 0.1% applied twice daily to individual plaques. An alternative is 4 to 10% LCD (liquor carbonis detergens, a tar distillate) in triamcinolone cream or ointment, used similarly.

Topical tar preparations, including shampoos, creams, and other preparations, can be used once daily. Patients should be warned that tar products have the potential to stain hair, skin, and clothing. It may help to use them at night and wear inexpensive night clothes (eg, old pajamas) as tar products tend to be messy. Patients may also find the odor of tar products unpleasant.

For shampoos, the emphasis should be on making sure the product reaches the scalp. Tar shampoo should be left in place for 5 to 10 minutes before rinsing it out.

Tazarotene — Tazarotene is a topical retinoid that was safe and effective in two randomized, vehicle-controlled trials that included 1303 patients with psoriasis [39]. The 0.1% cream was somewhat more effective than 0.05% cream, but with a slightly higher rate of local side effects. In another study, once-daily administration of tazarotene gel, 0.05% or 0.1%, compared favorably with twice-daily administration of topical fluocinonide 0.05% [40]. Absorption of tazarotene was minimal over the 12-week course of the study, suggesting that systemic toxicity is unlikely during long-term therapy. A small uncontrolled study of short contact tazarotene found that a 20 minute application followed by washing appeared to be less irritating than traditional use, and seemed to have similar efficacy [41]. Irritation limits use of tazarotene by itself; the irritation is reduced by concomitant treatment with a topical corticosteroid [42].

Treatment with tazarotene is often combined with topical corticosteroid therapy to minimize skin irritation. A combination product containing halobetasol propionate and tazarotene is available. In two phase 3 trials, 418 patients with moderate to severe plaque psoriasis were randomly assigned in a 2:1 ratio to once-daily application of either halobetasol propionate 0.01% plus tazarotene 0.045% lotion or vehicle for eight weeks [43]. At week 8, 36 and 45 percent of patients in the halobetasol propionate plus tazarotene groups achieved at least a two-grade improvement in the Investigator's Global Assessment score and clear or almost clear disease status. In contrast, only 7 and 13 percent of patients in the vehicle groups achieved this endpoint. Halobetasol propionate 0.01%-tazarotene 0.045% lotion is commercially available; it may cost more than $800 for 100 g.

Calcineurin inhibitors — Topical tacrolimus 0.1% and pimecrolimus 1% are effective in the treatment of psoriasis in sensitive areas [44-47]. Facial and intertriginous areas may be well suited to these treatments, which can allow patients to avoid or minimize chronic topical corticosteroid use:

- In an eight-week, randomized trial in 167 patients ages 16 and older, twice-daily treatment of intertriginous and facial lesions with tacrolimus 0.1% ointment resulted in more patients achieving clearance of lesions or excellent improvement compared with placebo (65 versus 32 percent) [48].

- In an eight-week, randomized trial in 57 adults with moderate to severe inverse psoriasis, twice-daily treatment with pimecrolimus 1% cream resulted in more patients clearing or almost clearing lesions compared with placebo (71 versus 21 percent) [49].

Topical tacrolimus and pimecrolimus are generally well tolerated when used to treat facial and intertriginous psoriasis [48,49]. However, corticosteroid therapy may be more effective, at least compared with pimecrolimus. This was suggested in a four-week randomized trial in 80 patients with intertriginous psoriasis that compared various therapies applied once daily [50]. Betamethasone valerate 0.1% was more effective than pimecrolimus 1%.

In 2005, the US Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults [51], and in 2006 placed a "black box" warning on the prescribing information for these medications [52]. No definite causal relationship has been established; however, the FDA recommended that these agents only be used as second-line agents for atopic dermatitis. Subsequent studies have found no evidence of an increased risk of lymphoma [53,54]. (See "Treatment of atopic dermatitis (eczema)", section on 'Topical calcineurin inhibitors'.)

Tapinarof — Tapinarof is a topical aryl hydrocarbon receptor-modulating agent that may improve psoriasis through modulation of T helper type 17 (Th17) cytokines, such as

interleukin (IL) 17A and IL-17F; normalization of the skin barrier; and antioxidant activity. The FDA approved tapinarof 1% cream for the treatment of plaque psoriasis in adults in 2022 [55]. The drug is applied to affected areas once daily:

- In two identical phase 3 trials (PSOARING 1 and PSOARING 2), a total of 1025 adults with chronic plaque psoriasis involving 3 to 20 percent of the total body surface area were randomly assigned in a 2:1 ratio to either tapinarof 1% cream or vehicle applied once daily [56]. At week 12, patients in the tapinarof groups were more likely to achieve the primary endpoint of a Physician Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) and at least a two-point decrease in the five-point PGA scale than patients in the placebo group (35.4 versus 6 percent [adjusted difference 29.4 percentage points; relative rate 5.8, 95% CI 2.9-11.5] in PSOARING 1 and 40.2 versus 6.3 percent [adjusted difference 33.9 percentage points; relative rate 6.1, 95% CI 3.3-11.4] in PSOARING 2). Seventy-five and 90 percent improvement in the Psoriasis Area and Severity Index (PASI 75 and PASI 90, respectively) rates were also greater in the tapinarof groups than in the vehicle groups.

  Local adverse effects appear to be the most common adverse effects of tapinarof. In the PSOARING 1 and PSOARING 2 trials, folliculitis, contact dermatitis, and headache occurred more frequently in the tapinarof groups than in the vehicle groups [56].

Roflumilast — Roflumilast is a topical phosphodiesterase 4 inhibitor. In 2022, the FDA approved roflumilast 0.3% cream for the treatment of plaque psoriasis, including psoriasis in intertriginous areas, in people 12 years of age and older [57]. The cream is applied to affected areas once daily and is expected to become commercially available in 2022:

- In a phase 2, randomized trial (n = 331), adults with chronic plaque psoriasis affecting 2 to 20 percent of the body surface area were randomly assigned to roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle applied once daily to affected areas for 12 weeks [58]. At week 6, patients in the roflumilast 0.3% and roflumilast 0.15% groups were more likely to achieve clear or almost clear status on the Investigator's Global Assessment than patients in the placebo group (28, 23, and 8 percent achieved clear or almost clear status, respectively). Adverse effects considered by the investigators to be related to the intervention (application site reactions and gastrointestinal adverse effects) occurred with similar frequency in the roflumilast and placebo groups. Efficacy of roflumilast has also been evaluated in unpublished phase 3 trials [59,60].

Anthralin — Topical anthralin (also known as dithranol) is an effective treatment for psoriasis and has been utilized since the early 20th century [61-63]. The mechanism of action of anthralin in psoriasis is not well understood, but may involve anti-inflammatory effects and normalization of keratinocyte differentiation [17].

Skin irritation is an expected side effect of anthralin that can limit the use of this therapy. This side effect and the ability of anthralin to cause permanent red-brown stains on clothing and temporary staining of skin have contributed to a decline in the use of anthralin therapy.

In order to minimize irritation, anthralin treatment is usually prescribed as a short-contact regimen that is titrated according to patient tolerance. For example, treatment may begin with concentrations as low as 0.1% or 0.25% applied for 10 to 20 minutes per day, with weekly step-wise increases in duration to reach a total contact time up to one hour [64]. Then, weekly, serial increases in the concentration of anthralin can be performed (eg, 0.5, 1, and 2%) based upon patient tolerance and lesion response. Additionally, application to surrounding unaffected skin should be avoided. Petrolatum or zinc oxide may be applied to uninvolved surrounding skin as a protectant prior to application. After the desired contact period has elapsed, anthralin should be washed off the treated area [17].

In the United States, anthralin is commercially marketed only as a 1% or 1.2% cream or a 1% shampoo. Thus, in the outpatient setting in the United States, the initial treatment regimen often consists of 1% or 1.2% anthralin applied for 5 to 10 minutes per day. Subsequently, the application time is titrated up to 20 to 30 minutes as tolerated.

Benefit from anthralin therapy is often evident within the first few weeks of therapy. When administered by patients in the outpatient setting, anthralin is less effective than topical vitamin D or potent topical corticosteroid therapy [22,65,66].

ULTRAVIOLET LIGHT

Ultraviolet (UV) irradiation has long been recognized as beneficial for the control of psoriatic skin lesions. UV radiation may act via antiproliferative effects (slowing keratinization) and anti-inflammatory effects (inducing apoptosis of pathogenic T cells in psoriatic plaques). In choosing UV therapy, consideration must be given to the potential for UV radiation to accelerate photodamage and increase the risk of cutaneous malignancy.

Office-based phototherapy and photochemotherapy require the supervision of a dermatologist trained in these treatment modalities. Despite high efficacy and safety, the use of office-based phototherapy has declined in the United States because of administrative issues and the development of new systemic medications [67].

The American Academy of Dermatology and the National Psoriasis Foundation have issued joint guidelines for the treatment of psoriasis with phototherapy [68].

Conventional modalities — Therapeutic doses of UV light can be administered as narrowband ultraviolet B (UVB) phototherapy, broadband UVB phototherapy, or oral or bath psoralen plus ultraviolet A (PUVA) photochemotherapy. Narrowband UVB and broadband

UVB involve the delivery of 311 nm and 290 to 320 nm of UVB radiation, respectively. Photochemotherapy (PUVA) involves treatment with a photosensitizer (either oral or bath psoralen) followed by ultraviolet A (UVA) radiation (320 to 400 nm). (See "UVB therapy (broadband and narrowband)" and "Psoralen plus ultraviolet A (PUVA) photochemotherapy".)

Phototherapy is typically administered three times per week during the treatment phase. Upon achievement of a satisfactory response, the frequency of treatment may be tapered to the lowest frequency required to maintain improvement. Treatment protocols for phototherapy are reviewed separately. (See "UVB therapy (broadband and narrowband)", section on 'Dosimetry and treatment protocols' and "Psoralen plus ultraviolet A (PUVA) photochemotherapy", section on 'Treatment protocols'.)

Selection among modalities of phototherapy is based upon consideration of efficacy, safety, availability, and ease of therapy. Narrowband UVB is generally preferred over PUVA photochemotherapy based upon greater ease of administration (administration of psoralens not required) and a less severe side effect profile. Randomized trials comparing the efficacy of narrowband UVB with PUVA have yielded inconsistent findings, though it appears that oral PUVA may provide a faster and more sustained response [69]. There are few data on the comparative efficacy of oral and bath PUVA for psoriasis. A small, open, randomized trial of 74 patients with moderate to severe psoriasis did not find a significant difference in efficacy between the two treatments [70]. (See "UVB therapy (broadband and narrowband)", section on 'Short- and long-term adverse effects' and "Psoralen plus ultraviolet A (PUVA) photochemotherapy", section on 'Adverse effects'.)

Narrowband UVB is generally considered more effective than broadband UVB phototherapy, contributing to acceptance of narrowband UVB as the preferred form of UVB phototherapy for psoriasis, provided it is available [68]. Although greater efficacy of narrowband UVB over broadband UVB for plaque psoriasis is supported by some studies [71,72], this has not been confirmed in high-quality, randomized trials [69].

Home phototherapy — An alternative to office-based phototherapy is the use of a home UVB phototherapy unit prescribed by the treating clinician [73]. This option may be preferred by patients who are not in close proximity to an office-based phototherapy center, whose schedules do not permit frequent office visits, or for whom the costs of in-office treatment exceed those of a home phototherapy unit. Home units cost about $3000, but may prove cost-effective in the long term, particularly when compared with biologic therapies. Insurance coverage of these units varies.

For some dermatologists, uncertainty regarding the safety of home units has led to a reluctance to prescribe them. Some have expressed concern for the potential for improper or excessive usage of these devices [74]. In contrast, a randomized trial of 196 subjects found that narrowband UVB administered via home units was as safe and effective as office-

based treatments [74]. Home phototherapy units that are equipped with electronic controls that allow only a prescribed number of treatments are available and may help to mitigate clinician concerns.

Commercial tanning beds can improve psoriasis and are occasionally used for patients without access to medical phototherapy [75,76]. However, data are limited on this mode of treatment, and clinicians and patients should be cognizant that there is significant variability in the UV output of tanning beds [77].

Excimer laser — The excimer laser, a laser that emits UVB light, is an alternative for the treatment of localized areas of psoriasis. The 308 nm excimer laser allows treatment of only involved skin; thus, considerably higher doses of UVB can be administered to psoriatic plaques at each treatment session when compared with traditional phototherapy. (See "Targeted phototherapy".)

Uncontrolled trials suggest that laser therapy results in faster responses than conventional phototherapy [78,79]. As an example, one study of excimer laser therapy involved 124 patients with stable mild to moderate plaque psoriasis, of whom 80 completed the entire protocol [78]. Treatments were scheduled twice weekly. After 10 or fewer treatments, 84 and 50 percent of patients achieved the outcomes of 75 percent or better and 90 percent or better clearing of plaques, respectively. This number of treatments was far fewer than that typically required of phototherapy (25 or more). Side effects of laser therapy included erythema and blistering; in contrast to whole body phototherapy burns, the localized phototherapy burns were generally well tolerated because of the limited areas treated, and no patient discontinued therapy because of adverse effects.

A common sequela of excimer laser therapy is the induction of UV-induced hyperpigmentation (tanning) in treated areas, which can be cosmetically distressing for some patients. Hyperpigmentation slowly resolves after the discontinuation of treatment.

Like 311 nm UVB, the excimer laser represents a therapeutic advance toward specific wavelength therapies for psoriasis. While both the excimer laser and narrowband UVB are approved for use in psoriasis, inconsistencies in third party coverage for these treatments limit their utilization.

Cancer risk — A concern with PUVA is an increased risk of nonmelanoma skin cancer and melanoma. Ongoing monitoring is indicated in patients who have received prolonged courses of PUVA. In general, phototherapy is contraindicated in patients with a history of melanoma or extensive nonmelanoma skin cancer. (See "Psoralen plus ultraviolet A (PUVA) photochemotherapy", section on 'Skin cancer'.)

Folate deficiency — Folate deficiency has been associated with health disorders such as neural tube defects in fetuses of affected pregnant women, anemia, and hyperhomocysteinemia (a risk factor for cardiovascular disease). In an in vitro study, exposure of plasma to UVA led to a 30 to 50 percent decrease in the serum folate level within 60 minutes [80]. However, folate deficiency secondary to UVA exposure has not been proven to occur in vivo. In a small randomized trial of healthy subjects, no difference in serum folate levels was identified between subjects irradiated with UVA for six sessions and untreated subjects [81]. In addition, an observational study of 35 psoriasis patients found that narrowband UVB had no effect on serum folate levels after 18 treatment sessions [82].

Saltwater baths — Exposure to natural sunlight improves psoriasis. Bathing in sea water in combination with sun exposure (climatotherapy) has also been used as a therapy for psoriasis, as has the use of salt water baths with artificial UV exposure (balneophototherapy). (See 'Ultraviolet light' above.)

In a large, open, randomized trial, treatment with UVB after a saltwater bath had greater efficacy than UVB after a tap-water bath, and similar efficacy to bath PUVA [83]. Although the raters of disease severity were intended to be blinded, raters knew treatment assignment in nearly 60 percent of cases. Additionally, less than half the patients were considered to have met the study's prespecified criteria for having been eligible and treated per protocol. In per-protocol analyses, no difference was found between saltwater and tap-water baths, and bath PUVA was superior to UVB after a saltwater bath.

Additional studies are required to demonstrate that combining saltwater baths with phototherapy is superior to tap-water baths plus phototherapy or to phototherapy alone.

SYSTEMIC THERAPIES

A variety of systemic medications are used for the treatment of psoriasis [84-86], particularly for patients with more than 5 percent body surface area involvement or less extensive, but debilitating, disease. The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) have released guidelines for systemic treatments, including guidelines dedicated to systemic nonbiologic therapy and biologic therapy [87,88]. In addition, European S3-Guidelines on the systemic treatment of psoriasis have been published [89,90]. In 2020, the British Association of Dermatologists released updated guidelines for biologic therapy [91]. (See 'Society guideline links' below.)

Options for systemic therapy include immunosuppressive or immunomodulatory drugs such as methotrexate, cyclosporine, apremilast, biologic agents, and deucravacitinib. Systemic retinoids, which improve psoriasis through effects on epidermal proliferation and

differentiation as well as immunomodulation, are also used for the treatment of this condition [84].

Biologic agents include the most effective therapies for moderate to severe psoriasis. Network meta-analyses support their efficacy and demonstrate varying degrees of efficacy among the individual biologic treatments [92-98]. In a network meta-analysis of Psoriasis Area and Severity Index (PASI) response data from randomized trials assessing the efficacy of biologic treatments (etanercept, adalimumab, certolizumab pegol, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, tildrakizumab, guselkumab, and risankizumab) or oral nonbiologic treatments (apremilast, dimethyl fumarate, acitretin, cyclosporine, fumaric acid esters, and methotrexate) for psoriasis, risankizumab, brodalumab, ixekizumab, and guselkumab had the highest PASI 75, 90, and 100 response rates (ie, achieved at least 75, 90, or 100 percent improvement in PASI) after 10 to 16 weeks [93]. There were no statistically significant differences in efficacy among these four treatments. PASI 90 rates ranged from 67 to 72 percent. These four treatments had the highest PASI 75, 90, and 100 rates in a traditional meta-analysis that assessed long-term responses (after 44 to 60 weeks) [93].

Although knowledge of the relative efficacies of systemic treatments for psoriasis is useful, consideration of factors such as drug side effects, patient preference, drug availability, and treatment cost (eg, the high cost of biologic agents compared with conventional therapies) also play an important role in treatment selection.

Impact of COVID-19 pandemic — The coronavirus disease 2019 (COVID-19) pandemic has led organizations, including the AAD and NPF, to issue guidance regarding the use of biologic agents or other systemic immunomodulatory drugs during the pandemic [99,100]. Our understanding of the impact of COVID-19 on psoriasis (and of psoriasis treatment on COVID-19) is rapidly evolving. Use of systemic immunomodulatory therapies during this period is reviewed separately. (See "COVID-19: Cutaneous manifestations and issues related to dermatologic care", section on 'Therapeutic considerations during the pandemic'.)

Methotrexate — The folic acid antagonist methotrexate has been used successfully in the treatment of psoriasis for over 50 years [101]. It is also effective for the treatment of psoriatic arthritis and psoriatic nail disease. Initial thoughts on the mechanism of action centered around the antiproliferative effects of methotrexate on DNA synthesis in epidermal cells; subsequent evidence supports the concept that it is the immunosuppressive effects of methotrexate on activated T cells that controls psoriasis [102]. (See "Treatment of psoriatic arthritis", section on 'Methotrexate'.)

Methotrexate has multiple contraindications [87]. Absolute contraindications include pregnancy, nursing, alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes, bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia, or hypersensitivity to methotrexate. Relative contraindications include

liver and renal function abnormalities and active infection. In addition, concomitant treatment with certain drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], certain antibiotics) can increase risk for methotrexate toxicity.

Methotrexate appears to be less effective than at least some of the biologic agents (see 'Biologic agents' below). In one trial, 271 patients with moderate to severe plaque psoriasis were randomized to receive oral methotrexate (7.5 to 25 mg per week), adalimumab (40 mg every other week), or placebo [103]. After 16 weeks, the proportion of patients achieving PASI 75 with methotrexate was more than that with placebo but less than with adalimumab (36, 19, and 80 percent, respectively). A placebo-controlled randomized trial evaluating subcutaneous methotrexate (17.5 to 22.5 mg per week) in patients with moderate to severe plaque psoriasis found a similar efficacy rate. After 16 weeks, 37 of 91 patients (41 percent) in the methotrexate group achieved PASI 75 compared with 3 of 29 patients (10 percent) in the placebo group [101].

Methotrexate is usually administered in an intermittent low-dose regimen such as **once weekly**. Similar regimens are in use in patients with rheumatoid arthritis. Administration can be oral, intravenous, intramuscular, or subcutaneous; the usual dose range is between 7.5 and 25 mg per week. Treatment is usually started at 10 to 15 mg weekly. Older patients and other patients with decreased kidney function are at increased risk for hematologic toxicity and can be given a single test dose of 5 mg with blood work one week later, followed by upward titration and close monitoring for toxicity. Dose can then be escalated every four to eight weeks depending on tolerance, efficacy, and toxicity. Subcutaneous methotrexate can be used and may be helpful when doses higher than 15 mg/week are needed, as hepatic metabolism may limit the bioavailability of higher methotrexate doses. Unlike cyclosporine, which is generally used for only a limited duration of treatment because of cumulative renal toxicity, methotrexate can be used for long-term therapy. (See "Use of methotrexate in the treatment of rheumatoid arthritis" and 'Cyclosporine' below.)

Folic acid, 1 mg daily, protects against some of the common side effects seen with low-dose methotrexate such as stomatitis [104]. Folate does not appear to protect against pulmonary toxicity, and it is uncertain whether it protects against hepatic toxicity; monitoring for bone marrow suppression and hepatotoxicity are necessary during therapy. Concurrent use of other medications that interfere with folic acid metabolism, such as sulfa antibiotics, can increase the toxicity of methotrexate. (See "Major side effects of low-dose methotrexate".)

Hepatotoxicity — For patients with one or more risk factors for hepatotoxicity from methotrexate, use of a different systemic drug should be considered.

Risk factors for hepatotoxicity from methotrexate include [87]:

- History of more than moderate alcohol consumption

- Persistent abnormal liver function test findings
- History of liver disease, including chronic hepatitis B or C
- Family history of inherited liver disease (eg, hemochromatosis)
- Diabetes mellitus
- Obesity
- History of exposure to hepatotoxic drugs or chemicals
- Hyperlipidemia

Previously, the AAD and NPF advised obtaining blood liver function tests every one to three months as well as consideration of a liver biopsy after a cumulative methotrexate dose of 3.5 to 4 g in the absence of risk factors for hepatotoxicity and after every 1 to 1.5 g in the presence of risk factors for hepatotoxicity [84,105]. The 2020 AAD-NPF joint guidelines for the management of psoriasis with nonbiologic therapies support less frequent blood liver function tests and incorporate use of newer noninvasive monitoring techniques, including serologic panels of markers of fibrosis and transient elastography [87]. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations" and "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography".)

Acitretin — Systemic retinoids (derivatives of vitamin A) are utilized for patients with severe psoriasis, including pustular and erythrodermic forms, and in patients with HIV-associated psoriasis. The retinoid of choice in psoriasis is acitretin. In a pilot study, 6 of 11 patients with psoriasis and HIV infection achieved good to excellent results with acitretin therapy, with four achieving complete clearing of their skin disease [106]. The usual dose range of acitretin is 25 mg every other day to 50 mg daily. The onset of effect is relatively slow; the full benefit of acitretin may not be evident for three to six months [87].

Acitretin can be used in combination with UVB or psoralen plus ultraviolet A (PUVA) therapy. Used in this way, patients have higher response rates with better tolerance and less UV exposure [107,108].

Monitoring for hypertriglyceridemia and hepatotoxicity are required with retinoid therapy. Common side effects include cheilitis and alopecia. Acitretin is teratogenic; it is only indicated in men and in women of nonreproductive potential. Pregnancy is contraindicated for **three years** after discontinuing the drug [109].

Cyclosporine — The T cell suppressor cyclosporine is effective in patients with severe psoriasis [110,111]. Usual doses are in the range of 3 to 5 mg/kg per day orally. Improvement is generally observed within four weeks. Lower doses (1 to 3 mg/kg per day) are more appropriate if a modified microemulsion form of cyclosporine that is more steadily absorbed is prescribed.

Contraindications to cyclosporine therapy include prior PUVA treatment, abnormal renal function, uncontrolled hypertension, malignancy, and hypersensitivity to cyclosporine [87]. Caution is indicated in the setting of major infections or poorly controlled diabetes. Cyclosporine also has multiple drug interactions.

The use of cyclosporine in psoriasis is based upon multiple studies supporting its status as a highly and rapidly effective treatment [84,112-114]. In a placebo-controlled randomized trial, after eight weeks of treatment with 3, 5, or 7.5 mg/kg of cyclosporine per day, 36, 65, and 80 percent of patients, respectively, were rated as clear or almost clear of psoriasis [112]. All three regimens were superior to placebo, and patients who received the 5 mg dose were least likely to require dose alterations due to side effects or lack of efficacy.

A few randomized trials have compared the efficacy of cyclosporine and methotrexate, utilizing varying treatment regimens and providing different results. Although a 16-week randomized trial in 88 patients failed to find a significant difference in the effects of cyclosporine (3 to 5 mg/kg per day) and methotrexate (15 to 22.5 mg per week) on moderate to severe plaque psoriasis [115], a subsequent 12-week randomized trial of 84 patients with moderate to severe plaque psoriasis found greater efficacy with cyclosporine (3 to 5 mg/kg per day) over methotrexate (7.5 to 15 mg per week) [116]. A smaller trial of patients with severe psoriasis found superior efficacy of methotrexate over cyclosporine (3 to 4 mg/kg per day), but utilized much higher doses of methotrexate than are typically prescribed in clinical practice (0.5 mg/kg per week) [117].

Close monitoring is required since renal toxicity and hypertension are common and often limit the long-term use of cyclosporine in patients with psoriasis. (See "Cyclosporine and tacrolimus nephrotoxicity".)

An investigational oral calcineurin inhibitor, ISA247, was efficacious in randomized trials in patients with moderate to severe plaque psoriasis, and may have less nephrotoxicity than cyclosporine [118].

Apremilast — Apremilast, a phosphodiesterase 4 inhibitor, is another oral agent for the treatment of plaque psoriasis [119-122]. Phosphodiesterase 4 inhibition reduces production of multiple cytokines involved in the pathogenesis of psoriasis. Apremilast is costly, priced closer to biologics than to methotrexate. The drug can also be effective for psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Apremilast'.)

Apremilast is indicated for the treatment of plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

The initial approval for moderate to severe psoriasis was supported by the findings of two 16-week, multicenter, randomized trials in which 1257 adults with moderate to severe

psoriasis were randomly assigned to receive 30 mg of apremilast twice daily or placebo [123]. In the first trial, 33 percent of 562 patients treated with apremilast achieved PASI 75 compared with only 5 percent of 282 patients in the placebo group. Results of the second trial were similar; 29 percent of 274 adults treated with apremilast achieved PASI 75 compared with 6 percent of 137 patients in the placebo group. Although apremilast represents an alternative systemic agent for the treatment of psoriasis, reported treatment success rates with apremilast are lower than those frequently reported for biologic agents [124].

The use of a 30 mg twice daily dose of apremilast is further supported by a phase 2 randomized trial of 352 adults with moderate to severe plaque psoriasis that found lower efficacy with reduced doses. Among patients treated with 30 mg twice daily, 20 mg twice daily, 10 mg twice daily, and placebo, PASI 75 was achieved by 41, 29, 11, and 6 percent of patients, respectively [121].

Randomized trial data also support apremilast therapy for patients with mild to moderate psoriasis. In the ADVANCE trial, 595 adults with mild to moderate chronic plaque psoriasis that could not be controlled with one or more topical therapies were randomly assigned to either apremilast (30 mg twice daily) or placebo [125]. At week 16, 22 percent of patients in the apremilast group achieved the primary endpoint (a static Physician Global Assessment score of 0 or 1 [clear or almost clear skin] and at least a two-point reduction from baseline) compared with only 4 percent of patients in the placebo group. Moreover, a higher proportion of patients achieved PASI 75 at week 16 in the apremilast group than in the placebo group (33 versus 7 percent, respectively).

Apremilast is associated with a short-term risk of diarrhea, especially when treatment is started, occurring in roughly 15 to 20 percent of patients. Tolerability of apremilast is improved by slowly ramping up the dose when treatment is initiated. The recommended dose titration schedule for adults is as follows:

- Day 1 – 10 mg in morning
- Day 2 – 10 mg in morning and 10 mg in evening
- Day 3 – 10 mg in morning and 20 mg in evening
- Day 4 – 20 mg in morning and 20 mg in evening
- Day 5 – 20 mg in morning and 30 mg in evening
- Day 6 and thereafter – 30 mg twice daily

In adult patients with severe renal impairment, the recommended final dose is 30 mg once daily. At the start of therapy, only the morning dose of the above titration schedule is given.

Examples of other reported side effects of apremilast include nausea, upper respiratory infection, headache, drug interactions, and weight loss. Periodic monitoring of weight is

recommended [123]. Advising patients, their caregivers, and families to be alert for worsening depression, suicidal thoughts, or other mood changes during treatment also is suggested based upon the possibility of a slight increase in risk for depression [123].

Use of apremilast should be avoided in patients with known hypersensitivity reactions to apremilast or to excipients in the formulation [126]. Hypersensitivity reactions, such as angioedema and anaphylaxis, have rarely been reported during postmarketing surveillance [126].

Biologic agents — Biologic agents are important treatment options for moderate to severe plaque type psoriasis [127-131]. The available biologics for psoriasis have excellent short-term and long-term efficacy and favorable tolerability. Examples of biologic therapies include etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab, and certolizumab pegol.

Itolizumab, a biologic agent marketed in India, is not available in the United States.

There is a concern that all TNF-alpha inhibitors have the potential to activate latent infections such as tuberculosis, and increased rates of infection have been seen in patients with rheumatoid arthritis treated with etanercept, infliximab, and adalimumab. In addition, risk for herpes zoster may be increased in patients receiving biologic therapy in combination with methotrexate [132]. Anti-IL-17 biologic drugs (eg, ixekizumab, secukinumab, brodalumab) have been associated with a slight increase in risk for candidal infections [133].

An analysis of data from adults with psoriasis in a large registry of patients eligible to receive or receiving conventional systemic or biologic therapy (Psoriasis Longitudinal Assessment and Registry [PSOLAR]) found a higher risk of serious infections with adalimumab and infliximab compared with nonbiologic systemic and no systemic therapies [134]. Serious infection rates among patients treated with infliximab, adalimumab, etanercept, and ustekinumab were 2.49, 1.97, 1.47, and 0.83 per 100 patient-years, respectively. Among patients who had never received a biologic therapy or methotrexate and patients who had never received a biologic therapy but had received methotrexate, rates were 1.05 and 1.28 per 100 patient-years, respectively.

Another publication from the PSOLAR registry provides some reassurance regarding the use of biologic therapy for psoriasis [135]. Compared with treatment with nonbiologic agents, biologic therapy did not appear to be a significant predictor of death, major adverse cardiovascular events (MACE), or malignancy. Patients were not randomized to the different treatment arms in the PSOLAR registry, and therefore selection bias could account for differences (or lack of differences) between groups.

Potential side effects of TNF-alpha inhibitors are reviewed in greater detail separately. (See "Tumor necrosis factor-alpha inhibitors: Bacterial, viral, and fungal infections" and "Tumor necrosis factor-alpha inhibitors and mycobacterial infections" and "Tumor necrosis factor-alpha inhibitors: Risk of malignancy" and "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects".)

TNF-alpha inhibitors — Biologic tumor necrosis factor (TNF)-alpha inhibitors utilized for psoriasis include etanercept, infliximab, adalimumab, and certolizumab pegol.

Etanercept — The TNF-alpha inhibitor etanercept is of benefit in psoriasis [136-140]. It is approved by the US Food and Drug Administration (FDA) for adults with psoriatic arthritis and for patients age four years or older with chronic moderate to severe plaque psoriasis. Standard dosing for etanercept for adults is subcutaneous injection of 50 mg twice weekly for the initial three months of therapy, followed by a 50 mg injection once weekly for maintenance therapy. Standard pediatric dosing is 0.8 mg/kg weekly, with a maximum dose of 50 mg per week. Etanercept is also an effective treatment for psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Resistant to nonbiologic DMARDs'.)

A randomized trial of etanercept in 652 adult patients with active but stable plaque psoriasis involving at least 10 percent of the body surface area found three doses of subcutaneous etanercept (25 mg weekly, 25 mg twice weekly, 50 mg twice weekly) significantly superior to placebo [137]. After 12 weeks, there was at least a 75 percent improvement in the PASI score in 14, 34, 49, and 4 percent, respectively. After 24 weeks, such an improvement was seen in 25, 44, and 59 percent, respectively (no patients received placebo for more than 12 weeks). Etanercept was well tolerated with adverse events and infections occurring at similar rates in all four groups.

A 12-week randomized trial found similar benefits with subcutaneous etanercept 50 mg twice weekly, and that, compared with placebo, patients receiving etanercept had significant improvements in measures of fatigue and depression [141]. In another randomized trial, etanercept was effective for moderate to severe plaque psoriasis in children and adolescents [142]. The long-term safety of etanercept for psoriasis is supported by a 96-week study of etanercept 50 mg twice weekly [143].

The formation of anti-etanercept antibodies has been reported to occur in 0 to 18 percent of patients treated with the drug for psoriasis [144]. However, in contrast to antibodies against infliximab and adalimumab in patients treated for psoriasis with those agents, the formation of anti-etanercept antibodies does not appear to reduce treatment efficacy [144].

Etanercept-szzs (GP2015) is an etanercept biosimilar that has similar efficacy and safety in patients with moderate to severe plaque psoriasis [145].

Infliximab — The TNF-alpha inhibitor infliximab is of benefit in patients with moderate to severe plaque psoriasis and appears to generally be well tolerated [146-149]. In addition, the findings of a systematic review suggest that the onset of action of infliximab is faster than several other commercially available biologic agents [150]. Standard dosing for infliximab for adults is intravenous infusion of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks thereafter. Infliximab is also an effective treatment for psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Resistant to nonbiologic DMARDs'.)

Infliximab was efficacious for psoriasis in a multicenter randomized trial in 249 patients with severe plaque psoriasis. Compared with placebo, more patients treated with infliximab 3 mg/kg or 5 mg/kg (given intravenously at weeks 0, 2, and 6) achieved PASI 75 at week 10 (6 percent versus 72 and 88 percent, respectively) [148]. The duration of response appeared to be longer with the higher dose. More patients treated with infliximab had serious adverse events (12 versus 0), including four cases that the authors felt were reasonably related to treatment: squamous cell carcinoma, cholecystitis, diverticulitis, and pyelonephritis with sepsis.

The efficacy of infliximab (5 mg/kg given at weeks 0, 2, 6, 14, and 22) was compared with methotrexate (15 to 20 mg per week) in a 26-week open-label randomized trial in patients with moderate to severe psoriasis (RESTORE1 trial) [151]. At week 16, patients who did not achieve at least 50 percent improvement were able to switch to the alternative therapy. The trial found that patients treated with infliximab (n = 653) exhibited greater improvement (78 versus 42 percent achieved PASI 75 by week 16) and were much less likely than patients in the methotrexate group (n = 215) to require switching to the alternative therapy (1 versus 29 percent) [151]. In addition, patients who were transitioned from methotrexate to infliximab fared better than those who switched to methotrexate from infliximab; 73 versus 11 percent achieved PASI 75.

Maintenance therapy with infliximab also appears to be effective [149,152,153]. A randomized trial using the dosing schedule above with infliximab 5 mg/kg through six weeks but then adding maintenance dosing of infliximab 5 mg/kg every eight weeks through 46 weeks found that 61 percent of patients achieved PASI 75 at week 50 [149]. Infliximab was generally well tolerated. The use of maintenance therapy was further supported by a 50-week randomized trial; patients treated with continuous therapy (3 or 5 mg/kg infusion every eight weeks after induction therapy at zero, two, and six weeks) maintained the response to treatment better than patients who received intermittent "as needed" therapy (3 or 5 mg/kg infusions separated by at least four weeks when PASI improvement fell below 75 percent) [152].

In addition to experiencing better maintenance of response, there are some data that suggest that patients who receive continuous maintenance therapy with infliximab may be

less likely to experience serious infusion-related reactions than patients who receive intermittent maintenance therapy. In trials comparing the two modes of maintenance therapy, slightly higher rates of infusion-related reactions have been observed among recipients of intermittent maintenance therapy [152,153]. A 128-week randomized trial (RESTORE2 trial) designed to compare the long-term efficacy of continuous maintenance therapy (5 mg/kg of infliximab every eight weeks after induction) and intermittent maintenance therapy (reinduction with up to four 5 mg/kg infusions of infliximab over 14 weeks if more than a 50 percent loss in PASI improvement occurred) was terminated early (at week 124) due to an observation of a higher proportion of serious infusion-related reactions in the intermittent therapy group (8 of 219 [4 percent] versus 1 of 222 patients [<1 percent]) [153]. The reason for this observation was unclear. Whether other regimens of intermittent maintenance therapy would be less likely to yield infusion reactions remains to be seen.

Studies in psoriasis, inflammatory bowel disease, and rheumatoid arthritis have suggested that the production of antibodies to infliximab may contribute to the loss of response to infliximab in some patients with these diseases [144,154-156]. Anti-infliximab antibodies occur in 5 to 44 percent of patients who receive infliximab for psoriasis [144,157]. (See "Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases", section on 'Anti-drug antibodies'.)

Infliximab-dyyb (CT-PI3) is a biosimilar to infliximab. In a randomized trial that included patients with various infliximab-responsive diseases, including psoriasis, switching to infliximab-dyyb was not inferior to continued originator infliximab therapy [158]. (See "Overview of biologic agents and kinase inhibitors in the rheumatic diseases", section on 'Biosimilars for biologic agents'.)

Adalimumab — Adalimumab, a humanized monoclonal antibody with activity against TNF-alpha, was originally used for patients with rheumatoid arthritis and is also effective for psoriatic arthritis (see "Treatment of psoriatic arthritis"). Adalimumab is approved by the FDA for treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. Standard dosing for adalimumab for adults is an initial subcutaneous injection of 80 mg of adalimumab followed by 40 mg given every other week, beginning one week after the initial dose. (See "Treatment of psoriatic arthritis", section on 'Resistant to nonbiologic DMARDs'.)

Examples of studies supporting the efficacy of adalimumab include:

- A randomized trial in 147 patients with moderate to severe plaque psoriasis compared adalimumab by subcutaneous injection 40 mg every other week, 40 mg weekly, and placebo [159]. After 12 weeks, more patients treated with adalimumab every other week or weekly achieved PASI 75 (53 and 80 percent, respectively) versus 4 percent with

placebo. In an open-label extension of the study, improvements were sustained for 60 weeks.

- In a randomized trial in 490 patients with moderate to severe psoriasis who had achieved PASI 75 after 32 weeks of adalimumab, continuing adalimumab resulted in a higher percentage of patients maintaining their response at 52 weeks (95 versus 72 percent) [160].

- Therapy with adalimumab was more effective than methotrexate in a randomized trial involving 271 patients with moderate to severe psoriasis [103]. (See 'Methotrexate' above.)

- In a randomized trial, adalimumab was more effective than placebo for the treatment of moderate to severe chronic plaque psoriasis involving the hands or feet [161]. After 16 weeks, disease was cleared or almost cleared in 15 out of 49 patients in the adalimumab group (31 percent) compared with 1 out of 23 patients in the placebo group (4 percent).

Adalimumab may be an effective alternative for patients who fail to respond to etanercept [162-164]. In a multicenter, open-label study, patients who did not improve with 50 mg of etanercept twice weekly (n = 50) or who worsened following a dose reduction of etanercept to 50 mg once weekly (n = 35) were treated with 40 mg of adalimumab every other week [162]. After 12 weeks, psoriasis was cleared or almost cleared in 34 percent (95% CI 20-48) of patients who had failed etanercept and 31 percent (95% CI 15-48) of patients who had disease recurrence on the lower dose of etanercept. Treatment success rates approached 50 percent when adalimumab (40 mg weekly or every other week) was given for an additional 12 weeks.

Formation of antibodies against adalimumab is reported to occur in 6 to 50 percent of patients treated with adalimumab for psoriasis and may reduce the response to therapy [144,157,165]. (See "Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases", section on 'Anti-drug antibodies'.)

Further study is necessary to determine whether assessing serum levels of adalimumab during treatment will be useful for improving responses to therapy [166].

Drugs biosimilar to adalimumab include adalimumab-atto and adalimumab-adbm [167,168]. In a randomized trial that compared adalimumab-atto with adalimumab in 350 adults with moderate to severe plaque psoriasis, the two drugs had similar efficacy and safety after 16 weeks of treatment [169].

Certolizumab pegol — Certolizumab pegol is a pegylated humanized antibody Fab fragment with specificity for TNF-alpha. In 2018, the FDA approved the drug for the

treatment of adults with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Standard dosing for certolizumab is 400 mg every other week. An optional regimen for patients who weigh ≤90 kg is 400 mg at weeks 0, 2, and 4, followed by 200 mg every other week. A potential advantage of certolizumab pegol is minimal transfer across the placenta; unlike other anti-TNF biologics, certolizumab pegol does not bind the neonatal Fc receptor because it lacks the IgG Fc. The drug is also effective for psoriatic arthritis.

Support for the use of certolizumab comes from phase 3 randomized trials [170,171]. In the CIMPASI-1 and CIMPASI-2 trials, adults with moderate to severe chronic plaque psoriasis (234 adults in CIMPASI-1 and 227 adults in CIMPASI-2) were randomly assigned to 400 mg of certolizumab pegol every two weeks, 200 mg of certolizumab pegol every two weeks (after loading dose of 400 mg at weeks 0, 2, and 4), or placebo every two weeks [170]. Patients who achieved at least PASI 50 continued treatment through 48 weeks. At week 16, more patients in the certolizumab pegol 400 mg and certolizumab pegol 200 mg groups achieved PASI 75 than in the placebo group. PASI 75 response rates in CIMPASI-1 were 76, 67, and 7 percent, respectively. In CIMPASI-2, response rates were 83, 81, and 12 percent, respectively. Responses to certolizumab pegol were maintained over 48 weeks. The most common adverse effects among patients receiving certolizumab were nasopharyngitis and upper respiratory infection. In total, serious treatment-emergent adverse effects occurred in 18 patients who received certolizumab pegol 400 mg, 11 patients who received certolizumab pegol 200 mg, and 1 patient in the placebo groups.

A separate phase 3 trial (CIMPACT) randomly assigned 559 adults with moderate to severe chronic plaque psoriasis to certolizumab 400 mg, certolizumab 200 mg, or placebo every two weeks for 16 weeks or etanercept 50 mg twice weekly for 12 weeks [171]. The trial found both the 400 and 200 mg dose regimens more effective than placebo, with greater response to the 400 mg dose. At 12 weeks, certolizumab 400 mg was more effective than etanercept, and certolizumab 200 mg was noninferior to etanercept for achieving PASI 75. As in the CIMPASI trials, nasopharyngitis and upper respiratory infections were the most common adverse effects.

Inhibitors of the IL-17 pathway — Inhibitors of the interleukin (IL) 17 pathway utilized for the treatment of psoriasis include secukinumab, ixekizumab, brodalumab, and bimekizumab. Bimekizumab is not available in the United States.

Secukinumab — Secukinumab, an anti-IL-17A monoclonal antibody, is an effective treatment for moderate to severe plaque psoriasis [172-181]. Standard dosing for plaque psoriasis is 300 mg given subcutaneously once weekly at weeks 0, 1, 2, 3, and 4 followed by 300 mg every four weeks. Doses of 150 mg are sufficient for some patients. Secukinumab is

also effective for psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Secukinumab'.)

Two 52-week phase 3 placebo-controlled trials (ERASURE trial and FIXTURE trial) support the efficacy of secukinumab for moderate to severe plaque psoriasis [172]. In both trials, secukinumab was given as a 300 mg or 150 mg dose once weekly for five weeks, then once every four weeks. In the ERASURE trial (n = 738), PASI 75 at week 12 was achieved by 82 percent of patients in the 300 mg secukinumab group and 72 percent of patients in the 150 mg secukinumab group compared with only 5 percent of patients in the placebo group. In the FIXTURE trial (n = 1306), which incorporated similar doses of secukinumab, secukinumab was superior to both etanercept (50 mg twice weekly for 12 weeks, then once weekly) and placebo. After 12 weeks, PASI 75 was achieved by 77 percent of patients in the 300 mg secukinumab group, 67 percent of patients in the 150 mg secukinumab group, 44 percent of patients in the etanercept group, and 5 percent of patients in the placebo group. Placebo-controlled, randomized trials evaluating the efficacy of secukinumab administered with an autoinjector or prefilled syringe in moderate to severe psoriasis also support the drug's efficacy [173,174].

Secukinumab has greater efficacy for moderate to severe plaque psoriasis than ustekinumab with a similar degree of safety. In a prospective trial (CLEAR trial), 676 adults with moderate to severe plaque psoriasis were randomly assigned to secukinumab (300 mg given at baseline, week 1, week 2, and week 3, then every 4 weeks) and ustekinumab (45 mg or 90 mg given at baseline, week 4, and then every 12 weeks) [175]. After 16 weeks, PASI 90 occurred in 79 percent of patients in the secukinumab group compared with 58 percent of patients in the ustekinumab group. The rates of adverse effects were similar in the two groups. An analysis of additional data from the CLEAR trial revealed that with continued treatment, the greater efficacy of secukinumab persists for at least 52 weeks [176]. At week 52, 76 percent of patients in the secukinumab group achieved PASI 90 compared with 61 percent of patients in the ustekinumab group. Safety was comparable between the two groups.

Secukinumab improved psoriasis faster but had less long-term efficacy than guselkumab and risankizumab in randomized trials. These trials are discussed below. (See 'Guselkumab' below and 'Risankizumab' below.)

Whether the dose frequency of secukinumab should be increased following insufficient responses to standard dosing is unclear. A randomized trial that included 325 patients with suboptimal responses to secukinumab (achievement of PASI 75 but not PASI 90 after 16 weeks of standard dosing) did not find a statistically significant difference in the proportion of patients who achieved PASI 90 at week 32 between patients who switched to secukinumab every two weeks and patients who continued secukinumab every four weeks (64 versus 57

percent, respectively; odds ratio [OR] 0.64, 95% CI 0.39-1.07) [182]. However, patients in the every-two-week secukinumab group had a lower absolute PASI score at week 32 and were more likely to achieve minimal disease activity on the Investigator's Global Assessment [182].

A reduced dose interval may be beneficial for heavier patients. In a randomized trial, 331 adults who weighed ≥90 kg and had moderate to severe psoriasis were assigned to receive 300 mg of secukinumab either every two weeks or every four weeks. Patients who did not achieve PASI 90 at week 16 were reallocated to continue secukinumab every four weeks or switch to secukinumab every two weeks [181]. At week 16, patients treated with secukinumab every two weeks were more likely to achieve PASI 90 than patients treated every four weeks (73 versus 56 percent, respectively, odds ratio estimate 2.3, 95% CI 1.4-3.8). The two-week dose interval remained more effective than the four-week dose interval at week 52 (PASI 90 achieved in 76 versus 52 percent of patients, respectively). Adverse events were comparable in the two groups.

Ixekizumab — In March 2016 the FDA approved ixekizumab, a humanized monoclonal antibody against IL-17A, for the treatment of moderate to severe plaque psoriasis in adults. Phase 3 trials support the efficacy of ixekizumab [183-188]. Standard dosing for ixekizumab is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12. Subsequently, 80 mg are given every four weeks. Ixekizumab is also effective for psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Ixekizumab'.)

In the UNCOVER-2 (n = 1224) and UNCOVER-3 (n = 1346) trials, patients with moderate to severe plaque psoriasis were randomly assigned to receive 80 mg of ixekizumab every two weeks after a 160 mg starting dose, 80 mg of ixekizumab every four weeks after a 160 mg starting dose, etanercept (50 mg twice weekly), or placebo in a 2:2:2:1 ratio [183]. At week 12, more patients treated with ixekizumab every two weeks or ixekizumab every four weeks achieved PASI 75 than patients treated with etanercept or placebo. In UNCOVER-2, PASI 75 rates were 90, 78, 42, and 2 percent, respectively. PASI 75 rates in UNCOVER-3 were 87, 84, 53, and 7 percent, respectively. In a third phase 3 trial (UNCOVER-1, n = 1296) that compared the same two- and four-week dose regimens for ixekizumab to placebo, PASI 75 rates at week 12 were 89, 83, and 4 percent, respectively [184].

The 12-week induction periods in the UNCOVER trials were followed by 48-week extension periods. In UNCOVER-1 and UNCOVER-2, patients who responded to ixekizumab at week 12 (clear or minimal psoriasis on static Physician Global Assessment) were randomly reassigned to receive 80 mg of ixekizumab every four weeks, 80 mg of ixekizumab every 12 weeks, or placebo. At the week 60 time point, 74, 39, and 7 percent of patients, respectively, still had clear or minimal psoriasis. Patients in UNCOVER-3 continued ixekizumab at a dose of 80 mg every four weeks after the induction period at the discretion of the investigator and patient. At week 60, clear or minimal psoriasis rates among patients initially treated with ixekizumab

every two weeks and every four weeks were 75 and 73 percent, respectively. The rates of serious adverse effects were similar in the ixekizumab and placebo groups. Overall, neutropenia, candidal infection, and inflammatory bowel disease occurred in 12, 3, and less than 1 percent of all patients exposed to ixekizumab during weeks 0 to 60, respectively. Neutropenia was generally transient and did not result in cessation of ixekizumab.

A randomized trial suggests ixekizumab may induce faster improvement compared with guselkumab. This trial is discussed below. (See 'Guselkumab' below.)

Brodalumab — Brodalumab, an anti-IL-17 receptor A monoclonal antibody, has high efficacy for psoriasis. In February 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies [189]. Recommended dosing is 210 mg given at weeks 0, 1, and 2 and then every two weeks. In the United States, use of the drug will require participation in a Risk Evaluation and Mitigation Strategy program due to concerns regarding risk for suicidal ideation and completed suicides in treated patients. However, a causal relationship between brodalumab treatment and suicidal ideation and behavior has not been confirmed. An analysis of data from five clinical trials did not find evidence of causality [190].

Data from phase 3 randomized trials support the efficacy of brodalumab for moderate to severe plaque psoriasis [191,192]. In two identically designed trials (AMAGINE-2 [n = 1831] and AMAGINE-3 [n = 1881]), patients were assigned in a 2:2:1:1 ratio to receive brodalumab 210 mg every two weeks; brodalumab 140 mg every two weeks; standard dosing of ustekinumab on day 1, week 4, and then every 12 weeks (45 mg dose if body weight ≤100 kg, 90 mg dose if body weight >100 kg); or placebo. At week 12, more patients receiving 210 mg of brodalumab or 140 mg of brodalumab achieved PASI 75 compared with patients in the placebo group (86, 67, and 8 percent, respectively [AMAGINE-2], and 85, 69, and 6 percent, respectively [AMAGINE-3]). In addition, the rate of complete clearance of skin disease (PASI 100) at week 12 was higher among patients given 210 mg of brodalumab compared with patients receiving ustekinumab (44 versus 22 percent, respectively [AMAGINE-2], and 37 versus 19 percent, respectively [AMAGINE-3]). A statistically significant benefit of the 140 mg dose of brodalumab over ustekinumab for achieving PASI 100 was evident in AMAGINE-3 at week 12 but not in AMAGINE-2. Mild to moderate *Candida* infections were more frequent in the brodalumab groups than in the ustekinumab and placebo groups, and neutropenia occurred more frequently in the brodalumab and ustekinumab groups than in the placebo group. In addition, two suicides occurred in patients receiving brodalumab in crossover and open-label phases of AMAGINE-2.

Bimekizumab — Phase 3, randomized trials support the efficacy of bimekizumab, a monoclonal immunoglobulin G1 (IgG1) antibody that inhibits IL-17A and IL-17F [193-196].

Bimekizumab is available in Canada, the United Kingdom, and some countries in the European Union [197-199]. Standard adult dosing for moderate to severe plaque psoriasis is 320 mg given every four weeks for the first 16 weeks, followed by 320 mg given every eight weeks. Discontinuation of bimekizumab is reasonable if patients have no response within 16 weeks. Patients weighing ≥120 kg who have an inadequate response after 16 weeks may benefit from maintaining the four-week treatment interval [197-199]. Bimekizumab is under study for psoriatic arthritis [200].

In the BE READY trial (n = 435), adults with moderate to severe plaque psoriasis were randomly assigned to receive either bimekizumab (320 mg every four weeks) or placebo in a 4:1 ratio [194]. At week 16, 317 of 349 patients (91 percent) in the bimekizumab group achieved PASI 90 compared with only 1 of 86 patients (1 percent) in the placebo group. Patients in the bimekizumab group who achieved PASI 90 were reallocated (1:1:1) to receive bimekizumab 320 mg every four weeks, bimekizumab 320 mg every eight weeks, or placebo over the subsequent 40 weeks. Patients who continued bimekizumab every four or eight weeks were more likely to achieve PASI 90 at week 56 than patients in the placebo group (87, 91, and 16 percent, respectively). The most common treatment-emergent adverse events for bimekizumab were nasopharyngitis, oral candidiasis, and upper respiratory tract infections.

> The BE VIVID trial (n = 567) compared the efficacy and safety of bimekizumab, ustekinumab, and placebo. Adults with moderate to severe plaque psoriasis were randomly assigned (4:2:1) to receive bimekizumab (320 mg every four weeks), ustekinumab (weight-based dosing of 45 or 90 mg at weeks 0 and 4, then every 12 weeks), or placebo (every four weeks) for 16 weeks [193]. At week 16, patients in the placebo group transitioned to bimekizumab, and patients in the active treatment groups continued treatment until week 52. Patients in the bimekizumab group (n = 321) were more likely to achieve PASI 90 at week 16 than patients in the ustekinumab (n = 163) and placebo (n = 83) groups (PASI 90 achieved in 85, 50, and 5 percent of patients, respectively). The most common treatment-emergent adverse events for bimekizumab were nasopharyngitis, oral candidiasis, and upper respiratory tract infection, with candidiasis occurring more frequently in the bimekizumab group than in the ustekinumab group. Over 52 weeks, five major cardiac adverse events occurred in patients with pre-existing cardiovascular risk factors in the bimekizumab group, and none occurred in the ustekinumab group. Oral candidiasis rates were higher than for other drugs blocking the IL-17 pathway, and one case of inflammatory bowel disease was recorded. Additional study may be useful for clarifying safety.

Trials comparing bimekizumab with adalimumab or secukinumab also support greater efficacy of bimekizumab. In a 56-week, phase 3 trial (BE SURE trial), adults with moderate to severe plaque psoriasis were randomly assigned to bimekizumab (320 mg every four weeks for 56 weeks), bimekizumab (320 mg every four weeks for 16 weeks and then every eight

weeks until week 56), or adalimumab (80 mg followed by 40 mg one week later and then 40 mg every two weeks until week 24) [196]. Patients in the adalimumab group were subsequently given bimekizumab (320 mg every four weeks from week 24 to 56). At week 16, 275 of 319 patients (86 percent) receiving bimekizumab achieved PASI 90 compared with 75 of 159 patients (47 percent) receiving adalimumab (adjusted risk difference 28.2 percentage points, 95% CI 19.7-36.7). Responses were maintained through week 56 with both dosing regimens for bimekizumab.

> In a 48-week, phase 3 trial (BE RADIANT trial), adults with moderate to severe plaque psoriasis were randomly assigned to bimekizumab (320 mg every four weeks) or secukinumab (300 mg weekly to week 4 and then once every four weeks) [195]. At week 16, patients receiving bimekizumab were rerandomized to receive bimekizumab once every four weeks or eight weeks. At week 16, 230 of 373 patients (62 percent) in the bimekizumab group achieved PASI 100 compared with 181 of 370 patients (49 percent) in the secukinumab group (adjusted risk difference 12.7 percentage points, 95% CI 5.8-19.6). Bimekizumab maintained superior efficacy at 48 weeks (PASI 100 in 67 versus 46 percent of patients). The study was not adequately powered to detect differences between the two bimekizumab maintenance treatment groups.

Inhibitors of IL-23 and related cytokines — Antipsoriatic drugs with anti-interleukin (IL) 23 activity include ustekinumab, guselkumab, tildrakizumab, and risankizumab.

Ustekinumab — Ustekinumab is a human monoclonal antibody that targets IL-12 and IL-23. Ustekinumab is indicated for the treatment of adults and children 12 years and older with moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. Dosing of ustekinumab is weight based. Standard dosing for ustekinumab for adults ≤100 kg is 45 mg given at weeks 0, 4, and every 12 weeks thereafter. A 90 mg dose given in the same regimen is recommended for adults who weigh more than 100 kg. Ustekinumab can also improve psoriatic arthritis. (See "Treatment of psoriatic arthritis", section on 'Ustekinumab'.)

Phase 3 trials have confirmed the efficacy of ustekinumab [201-205]. Examples of phase 3 trial data on ustekinumab therapy include:

- In a randomized trial where 766 patients had moderate to severe plaque psoriasis, more patients treated with ustekinumab 45 or 90 mg achieved at least PASI 75 at week 12 than those treated with placebo (67 and 66 versus 3 percent) [201]. Ustekinumab was administered monthly by subcutaneous injection for the first two doses and then every 12 weeks. Responders who were kept on therapy generally maintained improvements in psoriasis out to at least 76 weeks. Serious adverse events were seen at similar rates in the ustekinumab and placebo arms.

- In a second similarly designed trial where 1230 patients had moderate to severe plaque psoriasis, more patients treated with ustekinumab 45 or 90 mg achieved PASI 75 at week 12 than those treated with placebo (67 and 76 versus 4 percent) [202]. Patients who achieved a partial response at week 28 were randomly assigned to continue every 12 week dosing or escalate to every 8 week dosing. More frequent dosing did not enhance response rates at one year in patients receiving 45 mg but did enhance PASI 75 rates in those receiving 90 mg (69 versus 33 percent with continued 12 week dosing). Serious adverse events were again seen at similar rates in the ustekinumab and placebo arms.

The utility of therapeutic drug monitoring for optimization of response to ustekinumab is under investigation. A prospective cohort study of 491 adults treated with ustekinumab for psoriasis found an association between higher serum ustekinumab levels measured 1 to 12 weeks after the start of treatment and achievement of a PASI 75 response after six months of treatment (OR 1.38, 95% CI 1.11-1.71) [206]. However, other outcome measures of PASI response assessed in the study did not demonstrate a similar correlation. Drug monitoring of ustekinumab levels is neither required nor a standard component of ustekinumab treatment.

Trial data on the use of ustekinumab in adolescents with psoriasis are limited. A randomized trial of 110 adolescents (ages 12 to 17 years) with moderate to severe psoriasis (CADMUS) found ustekinumab effective in this population [205]. The response to ustekinumab (0.75 mg/kg if weight ≤60 kg, 45 mg if weight >60 but ≤100 kg, and 90 mg if weight >100 kg) given at weeks 0, 4, and every 12 weeks was similar to the response observed in the adult population.

The efficacy of ustekinumab appears to persist over time. In one of the phase 3 randomized trials above [201], ustekinumab maintained a high level of efficacy over three years [207]. In addition, treatment appears to be well tolerated [208,209].

A randomized trial reported superior efficacy of ustekinumab over etanercept for the treatment of psoriasis [210]. In this trial, 903 patients with moderate to severe psoriasis received 90 mg of ustekinumab at weeks 0 and 4, 45 mg of ustekinumab at weeks 0 and 4, or 50 mg of etanercept twice weekly. After 12 weeks, PASI 75 was observed in 73.8, 67.5, and 56.8 percent of patients in the 90 mg ustekinumab, 45 mg ustekinumab, and etanercept groups, respectively. In addition, some patients who did not respond to etanercept benefited from treatment with ustekinumab. Twelve weeks after crossover to 90 mg of ustekinumab (administered at weeks 16 and 20), 48.9 percent achieved PASI 75. The incidence of serious adverse effects was similar between treatment groups.

Data are limited on the best methods for transitioning patients from other therapies to ustekinumab. In a randomized trial (TRANSIT trial) performed in 490 patients with moderate

to severe plaque psoriasis who had insufficient responses to methotrexate, measures of the efficacy and safety of ustekinumab after 12 weeks were similar among patients who immediately discontinued methotrexate at the start of ustekinumab therapy and patients who gradually withdrew methotrexate during the first four weeks after starting ustekinumab [211]. Standard doses of ustekinumab were given; patients weighing 100 kg or less and patients weighing more than 100 kg were assigned to 45 and 90 mg doses, respectively. The findings of this study suggest that tapering of methotrexate during the transition to ustekinumab treatment may not be necessary. While there are not extensive data on the use of ustekinumab with methotrexate in patients with psoriasis, ustekinumab is FDA approved as a treatment with or without concomitant methotrexate in patients with psoriatic arthritis. (See "Treatment of psoriatic arthritis".)

Because of its immunomodulatory mechanism of action, there is concern that ustekinumab may increase the risk for infections and malignancy. However, five-year safety data showed no dose-related or cumulative sign of increased risk of severe infection or malignancy [208]. Uncommon adverse effects that may or may not be drug-related, such as reversible posterior leukoencephalopathy syndrome and a lymphomatoid drug eruption, have occurred in two separate patients [212,213]. The development of noninfectious pneumonia (eg, interstitial pneumonia, eosinophilic pneumonia, organizing pneumonia, hypersensitivity pneumonitis) has also been infrequently reported in the setting of ustekinumab therapy [214].

Although ustekinumab was effective for psoriatic arthritis in randomized trials, concern has been raised about whether psoriatic arthritis may worsen in certain patients during ustekinumab therapy. A case series documents four patients with psoriasis in whom psoriatic arthritis flared during ustekinumab therapy [215]. (See "Treatment of psoriatic arthritis".)

Reports of major adverse cardiovascular events (MACE) during phase 2 and 3 studies for ustekinumab and briakinumab, another anti-IL-12/23 agent, led to the performance of a meta-analysis of placebo-controlled, randomized trials evaluating the relationship between anti-IL-12/23 therapy and MACE in patients with chronic plaque psoriasis [216]. More MACE were reported in patients who received active treatment with ustekinumab or briakinumab than in those who received placebo (10 out of 3179 patients versus 0 out of 1474 patients). Although the difference in events was not statistically significant, the trial lengths were short (12 to 20 weeks), and the meta-analysis may have been underpowered to detect a significant difference.

A review of pooled data from phase 2 and 3 trials with up to five years follow-up did not reveal an increased risk for MACE [208]. In addition, analysis of data from a large,

observational study of patients receiving or eligible to receive systemic therapy for psoriasis (PSOLAR) did not find an association between ustekinumab therapy and MACE [135].

Anti-ustekinumab antibodies may occur in 4 to 6 percent of patients treated with ustekinumab for psoriasis; however, an effect of anti-ustekinumab antibody formation on treatment efficacy remains to be confirmed [144].

Guselkumab — Guselkumab is a human IgG1 lambda monoclonal antibody that binds to the p19 subunit of IL-23. IL-39 also contains this p19 subunit. The mechanism of action in psoriasis is thought to involve inhibition of IL-23 signaling. Recommended dosing for guselkumab is 100 mg at weeks 0, 4, and then every 8 weeks. Guselkumab is also effective for psoriatic arthritis. Guselkumab was effective for psoriasis in phase 3 randomized trials [217-219]. In the 48-week VOYAGE 1 trial, 837 adults with moderate to severe plaque psoriasis were randomly assigned in a 2:1:2 ratio to guselkumab (100 mg at weeks 0, 4, then every 8 weeks), placebo (given at weeks 0, 4, and 12) followed by guselkumab (100 mg at weeks 16 and 20, then every 8 weeks), or adalimumab (80 mg at week 0, 40 mg at week 1, then 40 mg every 2 weeks) [218]. At week 16, more patients treated with guselkumab achieved PASI 90 than patients in the adalimumab or placebo groups (73, 50, and 3 percent, respectively). Guselkumab remained more effective than adalimumab after 48 weeks. Adverse effects were comparable among the treatment groups.

The initial 24 weeks of the 48-week phase 3 VOYAGE 2 trial (n = 992) involved random assignment of adults with moderate to severe plaque psoriasis in a 2:1:1 ratio to guselkumab, placebo followed by guselkumab, or adalimumab groups, with dosing regimens similar to those in VOYAGE 1 [219]. As in VOYAGE 1, guselkumab was more effective than adalimumab and placebo at week 16. At week 28, patients either continued (or started) guselkumab or transitioned to placebo followed by guselkumab upon loss of response. Guselkumab-treated patients who had achieved at least PASI 90 were rerandomized to one of these groups. Among the rerandomized patients, continued therapy was associated with greater maintenance of response than withdrawal; 89 versus 37 percent maintained PASI 90 through week 48 in the continued therapy and withdrawal groups, respectively.

In another phase 3 trial (the NAVIGATE trial), guselkumab was effective in patients with moderate to severe plaque psoriasis who had inadequate responses to ustekinumab [217].

Guselkumab showed greater long-term efficacy than secukinumab in a phase 3 trial (ECLIPSE trial) in which 1048 adults with moderate to severe plaque psoriasis were randomly assigned to either guselkumab (100 mg at weeks 0 and 4, then every 8 weeks) or secukinumab (300 mg at weeks 0, 1, 2, 3, and 4, then every 4 weeks) [220]. In the trial, 84 percent of patients in the guselkumab group achieved the primary trial endpoint of a PASI 90 response at week 48 compared with 70 percent of patients in the secukinumab group, despite a more rapid initial

response in the secukinumab group. Although both treatments were generally well tolerated and had similar numbers of adverse events, there were three occurrences of Crohn disease in the secukinumab group compared with none in the guselkumab group and six diagnoses of nonmelanoma skin cancer in the guselkumab group compared with two in the secukinumab group. The findings of this trial support the selection of guselkumab over secukinumab when a high likelihood of greater long-term control of psoriasis is desired. However, factors such as tolerance of treatment risks, cost, and drug availability also influence the selection of a biologic therapy for psoriasis.

In a 24-week trial (IXORA-R trial) in which 1027 adults with moderate to severe plaque psoriasis were randomly assigned to treatment with either ixekizumab (160 mg at week 0, then 80 mg every two weeks until week 12, then 80 mg every four weeks) or guselkumab (100 mg at weeks 0 and 4 and then every eight weeks), ixekizumab was associated with faster improvement [221,222]. At week 12, 215 of 529 patients (41 percent) treated with ixekizumab, compared with 126 of 507 patients (25 percent) treated with guselkumab, achieved PASI 100 [221]. At week 24, responses to the ixekizumab and guselkumab were comparable for achieving PASI 100 (50 versus 52 percent) [222]. Longer-term efficacy was not assessed.

Upper respiratory tract infections, tinea and herpes simplex virus infections, arthralgia, diarrhea, and gastroenteritis are the most common adverse effects of guselkumab.

Tildrakizumab — Tildrakizumab is a human IgG1 kappa monoclonal antibody that binds to the p19 subunit of IL-23. In 2018, the FDA approved tildrakizumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Recommended dosing is 100 mg given subcutaneously at weeks 0 and 4 and then every 12 weeks.

Phase 3 trials (reSURFACE 1, reSURFACE 2) support superiority of tildrakizumab compared with placebo and etanercept [223]. In reSURFACE 1, 772 adults with moderate to severe plaque psoriasis were randomly assigned to receive tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo at weeks 0 and 4 and then every 12 weeks. After 12 weeks, 62, 64, and 6 percent of patients in the 200 mg, 100 mg, and placebo groups, respectively, achieved PASI 75. The reSURFACE 2 trial randomly assigned 1090 patients to similar groups plus an etanercept group. After 12 weeks, 66, 61, 6, and 48 percent of patients in the tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, and etanercept groups, respectively, achieved PASI 75. Rates of serious adverse effects were similar among the groups in both reSURFACE 1 and reSURFACE 2. One patient in the tildrakizumab 100 mg group died of an unclear cause during reSURFACE 2.

Risankizumab — Risankizumab is a humanized monoclonal antibody directed against the p19 subunit of IL-23 and IL-39 [224]. In 2019, the FDA approved risankizumab for the

treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Recommended dosing for risankizumab is 150 mg at week 0 and week 4, then every 12 weeks. Risankizumab is also effective for psoriatic arthritis.

Risankizumab had greater efficacy than ustekinumab and placebo in phase 3 trials. In the 16-week blinded phase of the 52-week UltIMMA-1 (n = 506) and UltIMMa-2 (n = 491) trials, patients with moderate to severe plaque psoriasis were randomly assigned to risankizumab (150 mg), ustekinumab (45 or 90 mg based upon weight), or placebo in a 3:1:1 ratio [225]. Doses in this phase were given at zero and four weeks. In UltIMMa-1, 75, 42, and 5 percent of patients, respectively, achieved PASI 90 at 16 weeks. In UltIMMa-2, 75, 48, and 2 percent achieved this endpoint, respectively. Overall, the proportion of adverse effects was similar among the three groups; however, infections were more frequent in the risankizumab and ustekinumab groups than in the placebo group.

Risankizumab was more effective for plaque psoriasis than adalimumab in a randomized trial. In a phase 3 trial (IMMvent trial) in which 605 adults with moderate to severe chronic plaque psoriasis were randomly assigned to either risankizumab (150 mg at weeks 0 and 4, then every 12 weeks) or adalimumab (80 mg at week 0, then 40 mg at week 1 and every other subsequent week), 72 percent of patients in the risankizumab group achieved PASI 90 by week 16 compared with 47 percent of patients given adalimumab [226]. Risankizumab was also more effective than adalimumab in a second phase in which 109 intermediate responders to adalimumab were rerandomized to either risankizumab or continuation of adalimumab (66 versus 21 percent achievement of PASI 90 at week 44, respectively). Adverse effect rates were similar between risankizumab and adalimumab groups.

An open-label, efficacy-assessor, blinded trial (IMMerge trial) that compared risankizumab (150 mg at weeks 0 and 4, then every 12 weeks) versus secukinumab (300 mg at weeks 0, 1, 2, 3, and 4, then every four weeks) in 327 adults with moderate to severe plaque psoriasis suggests greater long-term efficacy for risankizumab [227]. While secukinumab appeared to improve psoriasis more quickly, risankizumab was noninferior to secukinumab at 16 weeks (PASI 90 in 74 versus 66 percent; noninferiority margin of 12 percent) and more effective than secukinumab at week 52 (PASI 90 in 87 versus 57 percent).

Other — Itolizumab, a monoclonal antibody against the T cell costimulator CD6, is a biologic agent that is available for the treatment of psoriasis in India. Itolizumab is not available in the United States.

The findings of a phase 3 trial support the superiority of itolizumab compared with placebo for the treatment of moderate to severe plaque psoriasis [228]. However, response rates in the phase 3 trial were lower than those reported in phase 3 trials of infliximab, adalimumab, and ustekinumab therapy [149,160,201,202]. The efficacy of itolizumab has not been directly compared with other biologic agents.

Tyrosine kinase inhibitor

Deucravacitinib — Deucravacitinib is an oral selective inhibitor of tyrosine kinase 2 (TKY2), a kinase that mediates signaling of cytokines involved in the pathogenesis of psoriasis, such as IL-23. In 2022, the FDA approved deucravacitinib for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Standard dosing for deucravacitinib is 6 mg taken once daily [229].

Two 52-week, phase 3 trials (POETYK PSO-1 and POETYK PSO-2) support efficacy of deucravacitinib [230,231]:

- In POETYK PSO-1 (n = 666) and POETYK PSO-2 (n = 1020), adults with moderate to severe plaque psoriasis were randomly assigned (in a 2:1:1 ratio) to deucravacitinib (6 mg once daily), placebo, or apremilast (30 mg twice daily after completion of a five-day dose titration). In both trials, patients in the deucravacitinib groups were more likely to achieve PASI 75 at week 16 than patients in the placebo or apremilast groups. In POETYK PSO-1, week 16 PASI 75 rates in the deucravacitinib, placebo, and apremilast groups were 58, 13, and 35 percent, respectively [230]. In POETYK PSO-2, this endpoint was achieved by 53, 9, and 40 percent of patients, respectively [231]. Sustained efficacy was also demonstrated through 52 weeks among patients who received deucravacitinib continuously.

  Overall rates of adverse events were similar among the three treatment groups in both trials, with nasopharyngitis and upper respiratory tract infection the most common adverse effects in patients treated with deucravacitinib. Serious adverse events were infrequent. In POETYK PSO-1, pericarditis and cholecystitis were the only severe adverse effects that occurred in more than one patient, with each occurring in two patients treated with deucravacitinib. In POETYK PSO-2, rates of herpes zoster, serious infections, acne, and folliculitis were slightly higher in the deucravacitinib group compared with the other groups.

Other immunosuppressive agents — Other immunosuppressive agents are sometimes used in selected cases of severe psoriasis [111]. These drugs include hydroxyurea, 6-thioguanine, and azathioprine, which have a place in the treatment of psoriasis when other systemic modalities cannot be used, and tacrolimus, which is similar to cyclosporine and requires larger studies before it can be considered an accepted alternative [84]. Daclizumab, which is used for prevention of renal transplant rejection, and the cancer chemotherapeutic drug paclitaxel are also under investigation for use in severe psoriasis [232,233]. Abatacept, a drug used for psoriatic arthritis, has modest benefit in psoriasis [234].

Fumaric acid esters — Fumaric acid esters (fumarates) have been used to treat psoriasis in Northern Europe [235]. A systematic review of randomized trials found evidence to support superior efficacy of fumaric acid esters compared with placebo for psoriasis; however, the quality of the evidence was low overall [236]. In a randomized trial of 60 patients with moderate to severe psoriasis, reductions in disease severity after treatment with fumaric acid esters were similar to those observed with methotrexate therapy [237]. Additional trials of fumarates are being performed.

Lymphopenia is an occasional side effect of treatment with fumaric acid esters. In 2013, two cases of progressive multifocal leukoencephalopathy (PML) were reported in patients who continued to receive long-term fumaric acid ester therapy despite the development of severe lymphopenia [238,239]. These patients did not have other known causes of immunodeficiency. PML in the setting of fumaric acid therapy for psoriasis has also been reported in patients without severe lymphocytopenia [240,241].

TONSILLECTOMY

An association between psoriasis (especially guttate psoriasis) and streptococcal infection has contributed to investigations of the role of tonsillectomy for the treatment of psoriasis. (See "Guttate psoriasis", section on 'Pathogenesis'.)

A systematic review that evaluated data on tonsillectomy for guttate or plaque psoriasis from controlled and observational studies (including case reports and case series) found that the majority of reported patients experienced improvement in psoriasis after tonsillectomy (290 of 410 patients) [242]. Lengthening of psoriasis remissions and improvement in response to treatments for psoriasis were also documented. However, data were insufficient to recommend the routine use of tonsillectomy for psoriasis because most of the patient data were derived from case reports and case series and publication bias may have contributed to the favorable results. Further study is necessary to confirm the effects of tonsillectomy on psoriasis.

Given the limitations of the available data, tonsillectomy should be reserved for select patients with recalcitrant psoriasis that clearly exhibits exacerbations related to episodes of tonsillitis [242]. Tonsillectomy is not a benign procedure; infection, hemorrhage, laryngospasm, bronchospasm, temporomandibular joint dysfunction, vocal changes, and rarely airway compromise are potential adverse effects [242]. Relapse after tonsillectomy is also possible.

Because of the potential morbidity associated with tonsillectomy, a method to determine which patients are most likely to benefit from the procedure would be of value. Homozygous HLA-Cw*0602 carriage appeared to correlate with greater benefit from tonsillectomy in a

prospective cohort study of 28 patients with moderate to severe chronic plaque psoriasis and a history of psoriasis exacerbations in association with sore throat and/or streptococcal throat infections [243]. Among the 4 HLA-Cw*0602 homozygotes, 17 HLA-Cw*0602 heterozygotes, and 7 HLA-Cw*0602 negative patients, the Psoriasis Area and Severity Index scores fell by 82, 42, and 31 percent, respectively, during the 24-month follow-up period. Additional study is necessary to determine whether HLA-Cw6*0602 carriage is a reliable predictor of the response to tonsillectomy.

DIET

There has been uncertainty regarding the role of dietary interventions in the treatment of psoriasis. In 2018, based upon a systematic review of the literature, the Medical Board of the National Psoriasis Foundation released dietary recommendations for adults with psoriasis [244]. The authors found high-quality evidence to support weight reduction with a hypocaloric diet as an adjunct to standard medical therapy for overweight or obese adults (body mass index [BMI] ≥25) with psoriasis as well as a gluten-free diet in individuals with psoriasis and confirmed celiac disease. In addition, the board suggested a three-month trial of a gluten-free diet as an adjunct to standard medical therapy in adults with psoriasis who test positive for serologic markers of gluten sensitivity. Universal screening of individuals with psoriasis for gluten sensitivity was discouraged in favor of limiting screening to individuals with a first-degree relative with celiac disease or active gastrointestinal symptoms. There was insufficient evidence of efficacy to recommend supplements, including fish oil, vitamin D, selenium, and vitamin B12, for psoriasis.

Additional study is also necessary to explore the effects of specific dietary patterns on psoriasis [244]. A French web-based questionnaire cohort study found an inverse association between psoriasis severity and the degree of adherence to the Mediterranean diet (a diet high in fruits, vegetables, legumes, cereals, bread, fish, fruit, nuts, and extra-virgin olive oil) [245]. However, data are insufficient to confirm a beneficial effect of this diet. (See "Healthy diet in adults", section on 'Mediterranean diet'.)

EMERGING THERAPIES

There are multiple therapies under investigation for the treatment of psoriasis. These therapies are designed to mediate psoriasis through a variety of mechanisms:

- **Therapies targeting the Th17 pathway** – Interleukins (ILs) in the T helper type 17 (Th17) pathway (IL-23 and IL-17) play a pivotal role in the pathogenesis of psoriasis and continue to be targets for drug development. A phase 2 trial suggests efficacy of vunakizumab, a humanized monoclonal IL-17 antibody [246].

- **Small molecules** – Other potential therapies include various small molecules that target the interruption of cellular signaling; such signaling is critical to propagation of the inflammatory response. Examples of small molecules that are being studied for the treatment of psoriasis include molecules that block Janus kinases (JAKs) [247-250], lipids [251], a protein kinase C inhibitor [252], a selective tyrosine kinase 2 (TYK2) inhibitor [253], and crisaborole, a topical phosphodiesterase 4 inhibitor:

  - Oral tofacitinib, a small molecule JAK inhibitor approved and marketed for the treatment of psoriatic arthritis, was effective for moderate to severe plaque psoriasis in randomized trials [248,249,254-256]. In a phase 3 trial that randomly assigned 1106 adults with moderate to severe plaque psoriasis to treatment with tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, etanercept (50 mg twice weekly), or placebo, tofacitinib 10 mg twice daily was superior to placebo and noninferior to etanercept for achieving 75 percent improvement in the Psoriasis Area and Severity Index (PASI 75) score [254]. By week 12, 64, 40, 59, and 6 percent of patients treated with tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, etanercept, and placebo achieved this endpoint, respectively. Tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily were effective for chronic plaque psoriasis in other phase 3 trials [255]. The best results are achieved with 10 mg twice-daily dosing.

    The onset of effect of tofacitinib can be fairly rapid, with responses evident by week 4, and there are data to support the efficacy of tofacitinib through two years [256]. Treatment is generally well tolerated [257]. Tofacitinib may increase risk for infection. Elevations of cholesterol and creatine phosphokinase levels also may occur during therapy [254,255].

    In addition, a phase 2 randomized trial found that a topical formulation of tofacitinib was more effective for plaque psoriasis than vehicle [248].

  - Baricitinib, another oral reversible inhibitor of JAK1/JAK2 tyrosine kinases, has been evaluated for the treatment of moderate to severe psoriasis in a phase 2, dose ranging, randomized trial [258]. In this study, 271 patients were randomly assigned to treatment with daily doses of baricitinib 2, 4, 8, or 10 mg, or placebo. At 12 weeks, more patients in the baricitinib 8 and 10 mg groups than those in the placebo group achieved PASI 75 (43, 54, and 17 percent, respectively). Adverse effects were more common among patients receiving the highest baricitinib doses and included infections, lymphopenia, neutropenia, anemia, and elevation of creatine phosphokinase.

  - Targeting of the sphingosine 1-phosphate receptor 1 (S1PR1), a receptor involved in the movement of lymphocytes from secondary lymphoid tissues into the circulation,

may be an additional effective method to treat psoriasis. Ponesimod, a selective modulator of S1PR1 also studied for the treatment of multiple sclerosis, induces internalization of S1PR1, thereby inhibiting sphingosine 1-phosphate (S1P)-induced egress of lymphocytes. In a phase 2 randomized trial that evaluated ponesimod in 326 patients with moderate to severe chronic plaque psoriasis, patients treated with ponesimod were significantly more likely than patients treated with placebo to achieve PASI 75 after 16 weeks [259].

- In small, uncontrolled studies, treatment with a glucagon-like peptide 1 (GLP-1) analog (exenatide or liraglutide) seemed to promote modest improvement in psoriasis in patients with both psoriasis and type 2 diabetes [260,261]. However, a placebo-controlled randomized trial (n = 20) found liraglutide ineffective for plaque psoriasis [262].

- In case reports, treatment with topical crisaborole, a phosphodiesterase 4 inhibitor, has been associated with improvement in facial psoriasis, intertriginous psoriasis, and palmoplantar psoriasis manifesting as erythematous plaques, papules, and deep-seated pustules on the palms and soles [263,264].

- **Topical calcineurin inhibitor** – Historically, poor efficacy of topical cyclosporine for plaque psoriasis has been attributed to poor topical absorption. In a small randomized trial, a novel formulation of topical cyclosporine using liposomal carriers to improve penetration of the stratum corneum was effective for limited chronic plaque psoriasis [265].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psoriasis" and "Society guideline links: COVID-19 – Index of guideline topics".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th

grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Psoriasis (The Basics)" and "Patient education: Topical corticosteroid medicines (The Basics)")
- Beyond the Basics topics (see "Patient education: Psoriasis (Beyond the Basics)")

The National Psoriasis Foundation is a nonprofit organization that provides useful information to patients with psoriasis and their clinicians. Membership includes access to a newsletter that provides information on current areas of research and new treatments. Brochures on various forms of psoriasis treatment (topical, phototherapy, systemic agents) and specific fact sheets on each biologic treatment are available from the Foundation and its website.

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SUMMARY AND RECOMMENDATIONS

- **Overview** – Numerous topical and systemic therapies are available for the treatment of psoriasis. Treatment modalities are chosen on the basis of disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and evaluation of individual patient response. (See 'Approach' above.)
- **Psychosocial aspects** – Psoriasis can have negative psychosocial effects. Clinicians should address the psychosocial needs of patients with psoriasis. The National Psoriasis Foundation provides extensive resources to help patients with psychosocial problems and to educate patients on their treatment options. (See 'Psychosocial aspects' above.)
- **Limited plaque psoriasis**:

- We suggest that patients with limited plaque psoriasis be initially treated with topical corticosteroids and emollients (**Grade 2B**). (See 'Limited disease' above.)

- Alternatives include tar, topical retinoids (tazarotene), topical vitamin D, and anthralin. For facial or intertriginous areas, topical tacrolimus or pimecrolimus may be used as alternatives or as corticosteroid-sparing agents.

- Improvement can be anticipated within one or two months. Combination regimens may be required, including localized phototherapy. Patient adherence may be the largest barrier to treatment success with topical therapies; early follow-up (one week after starting treatment) may improve compliance. (See 'Topical therapies' above and 'Ultraviolet light' above.)

- **Moderate to severe plaque psoriasis**:

  - We suggest that most patients with moderate to severe plaque psoriasis be initially treated with phototherapy if feasible and practical (**Grade 2B**). Financial considerations or time constraints may make systemic therapy preferable to phototherapy for some patients. (See 'Moderate to severe disease' above.)

  - Topical therapies are generally also required as adjuvant therapy and for symptomatic relief. (See 'Topical therapies' above.)

  - In patients with contraindications to phototherapy or who have failed phototherapy, we suggest treatment with a systemic agent (**Grade 2B**). Systemic agents include retinoids, methotrexate, cyclosporine, apremilast, biologic immune modifying agents, and deucravacitinib.

  - Improvement from phototherapy or systemic therapies should be observed within weeks. Patients on systemic treatment will generally require care by a dermatologist. (See 'Moderate to severe disease' above.)

- **Psoriatic arthritis** – Treatment of psoriatic arthritis is discussed in detail separately. (See "Treatment of psoriatic arthritis".)

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