Guidelines of care for the management of psoriasis and psoriatic arthritis

Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions

Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In the first 5 parts of the American Academy of Dermatology Psoriasis Guidelines of Care, we have presented evidence supporting the use of topical treatments, phototherapy, traditional systemic agents, and biological therapies for patients with psoriasis and psoriatic arthritis. In this sixth and final section of the Psoriasis Guidelines of Care, we will present cases to illustrate how to practically use these guidelines in specific clinical scenarios. We will describe the approach to treating patients with psoriasis across the entire spectrum of this fascinating disease from mild to moderate to severe, with and without psoriatic arthritis, based on the 5 prior published guidelines. Although specific therapeutic recommendations are given for each of the cases presented, it is important that treatment be tailored to meet individual patients’ needs. In addition, we will update the prior 5 guidelines and address gaps in research and care that currently exist, while making suggestions for further studies that could be performed to help address these limitations in our knowledge base. (J Am Acad Dermatol. 10.1016/j.jaad.2010.11.055.)

Key words: adalimumab; alefacept; biologics; case studies; clinical guidelines for psoriasis; combination therapy; comorbidities; dermatology; etanercept; gaps in knowledge; gaps in research; golimumab; guidelines; inflammation; infliximab; methotrexate; narrowband; phototherapy; psoralen plus ultraviolet A; psoriasis; psoriatic arthritis; skin disease; systemic therapy; therapeutic recommendations; topical treatments; traditional systemic therapy; tumor necrosis factor-alfa; ustekinumab.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or deemed inclusive of all proper methods of care nor exclusive of other methods of care directed toward obtaining the same results. The ultimate judgment regarding the propriety of any

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Funding sources: None.

The authors’ conflict of interest/disclosure statements appear at the end of the article.

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Published online February 7, 2011. 0190-9622/$36.00 © 2010 by the American Academy of Dermatology, Inc. doi:10.1016/j.jaad.2010.11.055
Specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

**SCOPE**

This sixth and final section of the psoriasis guidelines will cover the approach to the treatment of patients across the entire clinical spectrum of psoriasis including limited skin disease, moderate to severe skin disease, and concurrent psoriatic arthritis (PsA).

**METHOD**

A work group of recognized psoriasis experts was convened to determine the scope and structure of this final guideline. Work group members completed a disclosure of commercial support.

An evidence-based model was used and evidence was obtained using a search of the PubMed/MEDLINE database spanning the years 1960 through 2010. Only English-language publications were reviewed. The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician, Family Medicine, Journal of Family Practice*, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.1

Evidence was graded using a 3-point scale based on the quality of methodology as follows:

I. Good-quality patient-oriented evidence.
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, expert opinion, or case studies.

Clinical recommendations were developed on the best available evidence tabulated in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, or case studies.

In those situations where documented evidence-based data are not available, we have used expert opinion to generate our clinical recommendations. Prior guidelines on psoriasis were also evaluated. This guideline has been developed in accordance with the American Academy of Dermatology (AAD) “Administrative Regulations for Evidence-based Clinical Practice Guidelines,” which include the opportunity for review and comment by the entire AAD membership and final review and approval by the Council of Science and Research and the AAD Board of Directors. The American Academy of Dermatology strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and updated for all work group members throughout guideline development, and guidelines are subject to extensive peer review by the AAD Clinical Guidelines and Research Committee, AAD members, the AAD Council on Science and Research, and the AAD Board of Directors.

**INTRODUCTION**

Psoriasis is a chronic inflammatory disease affecting approximately 2% of the population and affected patients frequently remain undiagnosed or untreated.2-4 Skin disease with multiple different phenotypic variations and degrees of severity is its most prominent feature. Approximately 80% of patients with psoriasis have mild to moderate disease, whereas 20% have moderate to severe disease.2 The severity of psoriasis is defined not only by extent of body surface area (BSA) involvement (<5% being considered mild, ≥5% but <10% moderate, and ≥10% severe), but also by involvement of the hands, feet, facial, or genital regions, by which, despite involvement of a smaller BSA, the disease may interfere significantly with activities of daily life (Guidelines, Section 1).2 Moreover, even limited disease can have a substantial psychological impact on one’s personal well-being (Guidelines, Section 1).2 PsA, which can progress to

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**Abbreviations used:**

AAD: American Academy of Dermatology
BB: broadband
BSA: body surface area
FDA: Food and Drug Administration
IL: interleukin
LFT: liver function test
MTX: methotrexate
NB: narrowband
NSAIDs: nonsteroidal anti-inflammatory drugs
PASI: Psoriasis Area and Severity Index
PASI-75: 75% improvement from baseline in Psoriasis Area and Severity Index score
PsA: psoriatic arthritis
PUVA: psoralen plus ultraviolet A
SCC: squamous cell carcinoma
TNF: tumor necrosis factor
UV: ultraviolet
significant deforming disease, has been reported to occur in up to 42% of individuals with psoriasis (Guidelines, Section 2). Although PsA is considered more common in patients with more extensive skin disease, deforming PsA may occur in patients with little to no cutaneous involvement. Patients’ perception of the physical and mental burden that the disease imposes on their life may be greater than that of cancer, arthritis, hypertension, heart disease, diabetes, and depression. Psoriasis is also associated with considerable morbidity and comorbid conditions. Psoriasis and Crohn’s disease share common genetic susceptibility factor(s), with the incidence of Crohn’s disease among psoriatics being 3.8 to 7.5 times that of the general population. In addition, there may be a link of psoriasis with multiple sclerosis. Patients with psoriasis also have an increased incidence of lymphoma, heart disease, obesity, type 2 diabetes, and the metabolic syndrome. Depression and suicide, smoking, alcohol consumption, and household income are also more common in patients with psoriasis. Patients with severe psoriasis have an increased risk for mortality, largely attributable to cardiovascular death, and die on average about 5 years younger than patients without psoriasis. The basis for the relationship between these associations is complex, with the effects of chronic systemic inflammation, psychosocial issues, and potential adverse effects of therapies likely to be important.

Both genetic and environmental factors contribute to the development of psoriasis. In the skin, scaling, thickened plaques, and erythema can be attributed to hyperproliferation of epidermal keratinocytes and to a dysregulated interplay among the epidermis and dermis, the cutaneous microvasculature, and the immune system. The complexity of this process, coupled with intriguing questions raised by the genetics of the disease, environmental provocateurs, and disease associations, has attracted the interest of investigators from a variety of disciplines. As a result, there has been considerable progress in defining many of the genetic and immunologic features of the disease.

Since the AAD Guidelines of Psoriasis and Psoriatic Arthritis were first developed, new information regarding the pathogenesis of psoriasis has been elucidated. Although interferon-gamma-producing TH1 T-helper cells have long been implicated in the pathogenesis of psoriasis, recent reports have shown the important central role that the TH17 subset of T-helper cells also plays in psoriasis. In addition to interleukin (IL)-17, TH17 cells secrete other cytokines including IL-22, which promotes proliferation of keratinocytes, stimulates production of keratinocyte-derived cytokines and chemokines, and augments the production of antimicrobial peptides.

Identification of these molecules and further definition of their precise role in the immunopathogenesis of psoriasis will certainly contribute to the next generation of antipsoriatic drugs, a number of which are already in early stages of clinical development and trials.

With our increased understanding of the immunopathogenesis of psoriasis, multiple biologic agents have been introduced during the past 8 years that target specific molecules necessary for the development of psoriatic plaques (Guidelines, Section 1). Biologics that have received regulatory approval for psoriasis and/or PsA include two that interfere with T-cell function (alefacept and efalizumab), 3 monoclonal antibodies that inhibit tumor necrosis factor (TNF)-alpha (infliximab, adalimumab, and golimumab), one soluble receptor that inhibits IL-12 and IL-23 p40 (briakinumab), and one monoclonal antibody directed at the p40 subunit common to IL-12 and IL-23 (ustekinumab). In addition, a second biologic agent that similarly inhibits IL-12 and IL-23 p40 (briakinumab) is in late stage clinical trials. Since the AAD clinical guidelines for psoriasis and PsA were first published in 2008, efalizumab has been withdrawn from the market because of the findings of progressive multifocal leukoencephalopathy in 3 patients; golimumab has been approved by the Food and Drug Administration (FDA) for PsA; and ustekinumab is currently undergoing phase III clinical trials for PsA.

Despite the introduction of these current and future biologic agents, topical medications, phototherapy, photochemotherapy, and traditional systemic drugs continue to play an essential role in the therapeutic armamentarium of psoriasis (Guidelines, Sections 3, 4, and 5). Topical therapies are the mainstay for mild disease either as monotherapy or in combination, and are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease (Guidelines, Section 3). Phototherapy, photochemotherapy, and traditional systemic agents are generally used for individuals with moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated. Phototherapy and photochemotherapy (Guidelines, Section 5) are effective and economical without many of the potential toxicities of traditional and biologic systemic therapies. However, inconvenience, lack of availability, and reimbursement issues do limit their feasibility, with home ultraviolet (UV) phototherapy an attractive alternative for the appropriate patient. In general, traditional systemic therapies are generally used for individuals with moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated.
agents (methotrexate [MTX], acitretin, cyclosporine, and others) (Guidelines, Section 4) have been available far longer than biologics (MTX was approved for psoriasis in 1971), with short- and long-term toxicity profiles that are well known from clinical practice in spite of the absence of formal long-term studies in patients with psoriasis. Traditional systemic agents are given orally (MTX may also be given by injection) and are also less expensive than injectable biologic agents.

Because of the clinical importance of the disease and the variety of treatment options available to patients with psoriasis and PsA, the AAD has recently published 5 of 6 parts of a set of guidelines that provide recommendations for its treatment. Treatment options for psoriasis must be tailored to the individual patient, taking into account efficacy, side effects, availability, ease of administration, comorbidities, family history, and coexisting diseases.

In this sixth and final section of the guidelines, the approach to psoriatic patients with limited disease, with moderate to severe psoriasis, and with PsA will be illustrated with case presentations and conclusions based on the previous 5 sections of the AAD Psoriasis Guidelines of Care.

CASE PRESENTATIONS

In the following section, we present cases that will illustrate how to use these psoriasis and PsA guidelines for practical use in specific clinical scenarios. We will initially discuss the treatment of patients who are candidates for topical therapy, defined as those with limited disease typically affecting less than 5% of the BSA and usually not involving the face, genitals, hands, or feet. Patients who are candidates for UV-based therapy (UVB or psoralen plus UVA [PUVA]) or systemic therapy (which includes oral agents and biologic agents) have more significant disease, typically affecting 5% or more of the BSA. Candidates for UV therapy or systemic therapy may also present with less than 5% BSA affected but have concurrent PsA requiring a systemic therapy or have psoriasis in vulnerable areas such as the face, genitals, hands or feet (palmoplantar), scalp, or intertriginous areas that are either unresponsive to topical therapy or causing major quality-of-life issues as to warrant these therapies from the onset. Finally, we will discuss the important role of the dermatologist in the early diagnosis and treatment of patients with PsA.

TREATMENT OF PATIENTS WITH LIMITED DISEASE

Because at least 80% of patients with psoriasis have limited disease, it is important to address the clinical approach to the treatment of these patients using the published AAD guidelines. We will also address several important clinical scenarios that require special attention, including inverse/intertriginous psoriasis, genital psoriasis, scalp psoriasis, and the treatment of women of childbearing potential. Although no example is given in the cases below, it is important to assess all patients, even those with limited psoriasis, for the presence of PsA. This assessment should always include questions regarding the onset of joint symptoms, particularly the presence of morning stiffness lasting a minimum of 30 minutes, with appropriate examination for tender, swollen, or deformed joints. The presence of PsA indicates a need for more active intervention rather than purely topical therapies or UV-based therapies.

Case 1

A 25-year-old woman with a several-year history of psoriasis presents for evaluation. Recently she has noted significant worsening with the onset of colder weather. Previous treatments include coal tar and 2.5% hydrocortisone cream with limited response. She believes that her psoriasis is “ruling her life” because she goes to great lengths to avoid clothing that exposes her psoriasis. She also has started to avoid athletic activities she previously enjoyed, such as tennis, because of concerns of exposing her psoriasis to others and what their reactions may be. Her psoriasis now involves multiple areas of her body including the trunk and all 4 limbs.

The patient is married, with no children to date. She is anxious to control her psoriasis so that she can regain her feeling of self-confidence and then consider conception within 1 year. She is currently using oral contraceptive pills, does not smoke, and drinks one to two glasses of red wine daily. There are no joint symptoms. The patient works as an exercise instructor, wearing long sleeves, leotards, and sports bras, which on occasion irritate her skin and exacerbate her psoriasis.

Cutaneous examination shows multiple erythematous, well-demarcated plaques with overlying silvery scale involving the elbows, knees, periumbilical area, and back (Fig 1). In addition, there are erythematous, minimally indurated, and nonscaling plaques in the right and left inframammary region, the vulva, and the supragluteal area. No satellite papules or pustules are present. BSA involved with psoriasis is 4%. The scalp, nails, and mucosal surfaces are uninvolved. There is no evident joint swelling, tenderness, or enthesitis (inflammation in the enthesis, the location where tendon, ligament, or joint capsule fibers insert into the bone).
Discussion

Psoriasis has many clinical phenotypes with traditional plaques being by far the commonest presentation. Inverse psoriasis affects intertriginous areas such as the breasts, groin, axillae, and intergluteal clefts. Patients frequently present with more than one subtype of psoriasis, as in this case. Secondary candidiasis needs to be considered when psoriasis presents in body folds where moisture is trapped and may complicate the diagnosis and treatment. In this case, the lack of satellite pustules associated with the patient’s intertriginous plaques makes secondary candidal infection unlikely.

The majority of patients with psoriasis have limited involvement, typically defined as less than 5% BSA; these patients can be effectively treated with topical agents, which have the advantage of being targeted directly to the skin lesions and are generally effective, safe, and well tolerated. Disadvantages of topical therapy include the time required for application, the need for long-term maintenance treatment, and incomplete clearance of lesions, all making adherence to topical regimens a challenge. To encourage the safe and effective use of topical treatments on a long-term basis, it is imperative that patients have individually tailored medical regimens with appropriate education such as verbal and written instructions.

Topical corticosteroids of varying strengths are a first-line treatment for limited psoriasis (Tables II and III, Guidelines, Section 3). They can be enhanced with different vehicles, and as needed by occlusion. Caution must be exercised when using occlusive methods, however, as this may result in a significant increase in potency—for example, 0.1% flurandrenolide functions as a class 5 topical corticosteroid when used as a cream but as a class 1 topical corticosteroid when used as a tape (Guidelines, Section 3). Limitations of topical corticosteroids include the potential for inducing skin atrophy and systemic absorption, especially with the use of higher potency corticosteroids over larger BSA. Although successful treatment of psoriasis often requires the use of more potent topical corticosteroid preparations, care must be taken to balance this need with the risk of these side effects. In many cases, as in this patient, the use of a low-potency topical corticosteroid for standard plaque psoriasis offers little benefit. Efforts to maintain long-term efficacy and to minimize the risks of topical corticosteroids frequently require innovative rotational and combination strategies.

Tachyphylaxis to the action of topically applied corticosteroids and other topical agents has been commonly described. However, in a 12-week study of continuous treatment with topical corticosteroids, none of the patients exhibited tachyphylaxis. A more recent explanation for the perceived “tachyphylaxis” observed in the clinical setting is poor patient adherence rather than the long-held view of down-regulation of receptor function as the major cause.

The vitamin D analogs, calcipotriene, calcipotriol, and calcitriol, are other first-line topical agents with proven efficacy in the treatment of psoriasis (Table V, Guidelines, Section 3). They inhibit keratinocyte
proliferation and enhance keratinocyte differentiation. Although these agents are less effective than class 1 topical corticosteroids, they are often used in combination with topical corticosteroids to enhance efficacy and reduce the risk of atrophy, especially over the long term. In this situation, both the topical corticosteroid and the vitamin D analog are initially used twice daily with a gradual shift to weekend only use of the topical corticosteroid while maintaining 5 days a week therapy with the vitamin D agent. This strategy minimizes the amount and frequency of the potent topical corticosteroids used, thereby reducing the risk of cutaneous atrophy. When treating extremity and/or truncal noninverse psoriasis, another approach is to use the combination calcipotriene/betamethasone dipropionate single product, which is efficacious when used once daily, with or without the prior short-term use of a class 1 corticosteroid, thus simplifying the treatment regimen and potentially improving patient compliance with therapy.

Since publication of part 3 of the guidelines in April 2009,52 calcitriol, the active metabolite of vitamin D, has become available for use in the United States. This formulation is less irritating than other vitamin D analogs and hence better tolerated on sensitive skin areas such as the face and flexures (Guidelines, Section 3).52 A maximum of 100 g of vitamin D analogs per week should be used to avoid hypercalcemia (Table V, Guidelines, Section 5).

Topical tazarotene, a retinoid, is an additional corticosteroid-sparing agent (Table VI, Guidelines, Section 3).52 The major limitation of topical tazarotene is irritation, which can be minimized by applying it sparingly to the lesion, avoiding the perilesional areas and/or in combination with a topical corticosteroid, producing not only a synergistic effect but also a longer duration of treatment benefit and remission (Guidelines, Section 3).52 Other topical preparations such as tar, anthralin, and salicylic acid used extensively in the past, have now taken on more secondary roles. Tar and anthralin are particularly challenging to use as they stain skin and clothing.

Another approach for the treatment of limited disease is the 308-nm monochromatic xenon-chloride (excimer) laser and other phototherapeutic appliances that deliver UV radiation to localized areas of skin. This therapy allows for selective targeting of localized psoriatic lesions and resistant areas such as the scalp and skin folds, while leaving surrounding nonlesional skin unaffected (Table V, Guidelines, Section 5).54

Topical tacrolimus may also be considered a first line of therapy for intertriginous psoriasis.

Emollients and ointments are widely used in the treatment of psoriasis but there is limited evidence that they are beneficial. One study showed that the use of a water-in-oil cream or lotion combined with betamethasone dipropionate cream increased efficacy while achieving control with fewer applications of the steroid cream.64 The steroid-sparing effects of such emollients and their potential benefits as monotherapy have been attributed to their ability to restore normal hydration and water barrier function to the epidermal layer of the psoriatic plaque.52 Regardless of their efficacy or their mechanism of action, emollients moisturizers and ointments are an important part of the routine skin care that dermatologists recommend for patients with psoriasis.

Topical treatment of inverse/intertriginous psoriasis and genital psoriasis

Inverse psoriasis, as in this first patient, can involve the axillae; inframammary areas; abdominal, inguinal, and gluteal folds; groin; genitalia; perineum; and perirectal area. Psoriasis in these locations tends to be erythematous, less indurated, and well demarcated with minimal scale. Genital psoriasis, frequently not alluded to by patients, causes a significant psychological impact in affected patients. In a study examining the stigmatization experience in patients with psoriasis, involvement of the genitalia was found to be the most relevant, regardless of the overall psoriasis severity.53 Despite major advances in other aspects of psoriasis research, there has been very little emphasis in recent times on the identification and treatment of genital psoriasis in routine dermatologic practice, where patients with psoriasis are often neither questioned nor examined for this manifestation and its psychosexual implications.

The warm, moist environment of the flexural areas brings unique treatment challenges and advantages. In general, penetration of medications is facilitated by the local, ambient humidity, but as a consequence, irritation and risk of atrophy by more potent topical corticosteroids is significantly increased.54

Although the traditional topical medications used to treat psoriasis vulgaris can also be used in inverse psoriasis and genital psoriasis, care is needed to minimize the risks of irritation and toxicity. This includes techniques such as using lower potencies of topical corticosteroids, diluting calcipotriene with a moisturizer (although depending on the ingredients in the moisturizer this maneuver could affect the stability of calcipotriene as its combination with some topical corticosteroids, salicylic acid, or ammonium lactate lotion leads to instability55), or using calcitriol, a less irritating vitamin D analog. Calcineurin inhibitors (topical tacrolimus and topical pimecrolimus), although marginally effective in plaque type psoriasis, are helpful in the treatment of inverse psoriasis and
When calcipotriol ointment was compared with comparing different topical agents with each other. 

Comparison studies of topical therapies 

Topical treatment of scalp psoriasis 

Psoriasis frequently manifests initially on the scalp. Topical treatment of scalp psoriasis mirrors the treatment of plaque psoriasis on other areas of the body, with the major difference being the presence of hair making the use of ointments and cream-based products particularly difficult and messy. Thus, the recent availability of shampoo, gel, solution, oil, foam, and other formulations has allowed for easier use to and more acceptable scalp therapies.  

Scalp psoriasis remains one of the most frustrating, difficult to manage, and resistant forms of the disease. This is not easily explained by poor penetration because the normal scalp has a weak barrier function (similar to the axilla) compared with normal-appearing skin. Koebnerization of the scalp as a result of repetitive scratching frequently leads to unilateral fixed, well-circumscribed hypertrophic plaques. This causes further difficulties in control with resistance to therapy also aggravated by poor adherence to treatment frequently related to time restraints, frustration, and lack of clinical response. 

Risks unique to women of childbearing potential from topical psoriasis therapies 

Although this young female patient is not actively considering conception, pregnancy considerations must be borne in mind when young women present for treatment of their psoriasis. Although the true risk of systemic absorption from topical psoriasis medications has been inadequately studied, all of the topical psoriasis medications are labeled pregnancy category C, and tazarotene, category X. Women who are either pregnant or actively trying to conceive should therefore be carefully counseled about the risks and benefits of topical agents, while bearing in mind that a significant proportion of patients are likely to experience spontaneous improvement of their psoriasis during pregnancy. 

Comparison studies of topical therapies 

There are a relatively small number of studies comparing different topical agents with each other. When calcipotriol ointment was compared with betamethasone valerate ointment (a class 3 topical corticosteroid) in a randomized double-blind, 6-week, bilateral comparison trial, there was a 69% reduction in the mean Psoriasis Area and Severity Index (PASI) score of patients treated with calcipotriol ointment compared with 61% reduction in patients treated with betamethasone valerate ointment (P < .001). In another 4-week study of 1603 patients, 48% of patients treated with a combination of calcipotriene 0.005% and betamethasone propionate 0.064% ointment once to twice daily achieved an end point of absent to mild disease, compared with 16% of those treated with calcipotriene ointment alone or 26% of those treated with betamethasone ointment alone. Vitamin D analogs have a slower onset of action than topical corticosteroids, but tend to yield longer disease-free periods. Thus, one randomized double-blind study found that 48% of patients treated with calcitriol ointment remained in remission 8 weeks posttreatment as compared with 25% of patients treated with betamethasone dipropionate (a class 1 topical corticosteroid) ointment. A systematic review of calcipotriol ointment revealed that it is more effective for mild to moderate chronic plaque psoriasis than either coal tar or short contact anthralin, and that only potent topical corticosteroids have comparable or greater efficacy after 8 weeks of treatment. These authors noted that although calcipotriol ointment is more irritating than topical corticosteroids, calcipotriol has less potential long-term toxicities compared with topical corticosteroids. When two strengths of tazarotene gel (0.05% and 0.1%) were compared with twice daily fluocinonide 0.05% cream (a class 2 topical corticosteroid) in a 12-week, multicenter, investigator-masked, randomized, parallel-group trial, there was no significant difference in the efficacy of these therapies. Tazarotene did demonstrate significantly better maintenance of effect after discontinuation of therapy. In a multicenter, investigator-blinded study evaluating tazarotene 0.1% gel plus mometasone furoate 0.1% cream (a class 4 topical corticosteroid) once daily compared with calcipotriene 0.005% ointment twice daily, patients in the tazarotene plus mometasone group achieved greater reductions in BSA involvement than those treated with calcipotriene alone. In a 6-week randomized, double-blind study of 50 patients with intertriginous and facial psoriasis, tacrolimus ointment (0.1%) was more effective than calcitriol ointment. In a 4-week, randomized, double-blind placebo-controlled trial of 80 patients with intertriginous psoriasis, patients were randomized to receive one of 3 active treatments or vehicle control. Betamethasone ointment 0.1% ointment...
produced an 86% mean reduction in PASI score, calcipotriol 0.005% ointment resulted in a 62% mean reduction in PASI score, with pimecrolimus cream being less efficacious (a 40% mean reduction in PASI score). The control group had a 20% mean reduction in PASI score.76

**Improving adherence to topical treatment**

Suboptimal treatment outcomes often result from incorrect use of topical medications and poor patient compliance. Up to 40% of patients report nonadherence to topical medication regimens, citing frustration with medication efficacy, inconvenience, time constraints, unclear instructions, and fear of side effects as the primary reasons.77 In this regard, a Danish study found that one third of all psoriasis prescriptions are not filled.78 Studies using electronic monitors have also shown that adherence with topical therapy decreases quickly over time.79

Patient education can greatly facilitate adherence to topical treatment and thereby improve treatment outcomes. It is important that patients are made aware of the limitations of topical treatment and that their expectations are matched with realistic outcomes. Disappointment stemming from unrealistic treatment goals may lead to poor patient motivation.80 Although some patients expect complete clearance of their disease and are motivated to pursue continuous intense treatment regimens, others are content with treatment of only their most visible lesions for practical and social reasons. Therefore, it is essential that practitioners ascertain patients treatment goals and that treatment regimens be tailored to these goals.

A wide range of vehicles exist for delivery of topical treatments (Guidelines, Section 3).52 Vehicle preferences can affect adherence to topical regimens and preferences often differ among patients with different skin types and racial or ethnic background. Although ointments enhance penetration of the active agent and prevent evaporation of skin moisture leading to increased efficacy, many patients prefer to use less greasy, more cosmetically elegant vehicles. Other patients are content to use a non-ointment base by day and an ointment at night. Different vehicles may also be more suitable for different locations such as solutions, foams, shampoos, and sprays for the scalp and other hairy areas. Expert opinion supports the concept that many African American patients prefer oil-based preparations for the scalp, because such preparations are more compatible with their routine hair and scalp care. The most appropriate vehicle for an individual patient is the one he or she is most likely to use. Specific instructions for application of topical medications, written if possible, with simple and practical dosing regimens are likely to improve compliance.80

**Short-term use of systemic agents in patients with limited disease**

Although there are no studies addressing the potential short-term use of systemic agents for patients with limited disease, it is the opinion of this group that under certain circumstances, such as an important event, such as an upcoming wedding or a graduation, that consideration be given for the short-term use of systemic agents to gain rapid control.

**Conclusions—treatment of limited disease**

Topical therapies, either as monotherapy or in combination with phototherapy, systemic therapy, and biologic therapy, are the mainstay of therapy for the vast majority of patients with psoriasis. Careful selection of medication options must take into account body site, thickness and scaling of the lesions, age of the patient, costs, and vehicle preferences of the patient, and is critical to meeting the needs of the individual patient. For the majority of patients with limited disease, topical treatments are safe, effective, and convenient. Provided patients are fully counseled and educated on the multiple nuances of this form of therapy.

In our patient, a full discussion was initially held with her relating to her expectations and the range of therapeutic options available. A potent topical corticosteroid ointment was initially prescribed for use on her elbows, knees, and back plaques, with slow reduction in frequency of use during a 4-week period and the introduction of a vitamin D agent once adequate clearing was obtained. In addition, a medium-potency topical corticosteroid ointment was used for 2 weeks for her intertriginous psoriasis, followed by maintenance therapy with topical tacrolimus ointment.64 At follow-up 6 weeks later, this patient’s psoriasis was much improved and she was pleased with her initial progress. With appropriate counseling and continued adherence to the treatment plan longer-term adequate control of this patient’s disease is possible. Fig 2 is an algorithm to approach the treatment of patients with limited psoriasis.

**TREATMENT OF PATIENTS WHO REQUIRE MORE THAN TOPICAL THERAPY AND ARE THEREFORE CANDIDATES FOR UV-BASED OR SYSTEMIC THERAPY**

Patients who are candidates for UV-based or systemic therapy (including oral and biologic agents) have more significant disease, typically affecting more than 5% of the BSA. Some candidates for these
therapies may have less than 5% BSA affected but have psoriasis in vulnerable areas such as the face, genitals, hands and feet (palmoplantar disease), scalp, or intertriginous areas and have disease that adversely affects their quality of life.

In this section, we present clinical scenarios and then use our previously published guidelines to develop the most appropriate approach. We will address the use of both UVB phototherapy and photochemotherapy with PUVA, and the treatment of patients with palmoplantar disease, erythrodermic psoriasis, and multiple comorbidities. In daily practice as compared with clinical trials, in which patients are frequently excluded for a variety of pre-existing or current illnesses or cancer, there are numerous scenarios that may arise making it important for the clinician to become familiar and comfortable using multiple different therapeutic modalities.

**UV-based therapies (phototherapy and photochemotherapy)**

**Ultraviolet B.** Case 2. A 51-year-old postmenopausal woman with a 25-year history of psoriasis presented for evaluation of worsening disease. She had been treated in the past with multiple topical medications with only partial control. Two years before presentation, she was given the diagnosis of multiple sclerosis and is currently well controlled with glatiramer acetate. Like many psoriatics with significant disease, she imbibes excess alcohol (12-18 beers each weekend). There is no history of arthritis, diabetes, or hypertension.

Cutaneous examination reveals 15% BSA involvement with erythematous patches and plaques with silvery scales on the trunk, and upper and lower extremities (Fig 3, A). Mildly erythematous patches with fine scales are noted on the face, with thick plaques covered by micaceous scales evident on the scalp. Mild palmar and plantar involvement is also observed (Fig 3, B).

**Discussion**

In view of the significant BSA involvement, history of worsening of psoriasis, along with the history of alcohol excess and multiple sclerosis, narrowband (NB)-UVB is an attractive treatment option, while recognizing its limitations in improving scalp psoriasis, a significant problem in our patient. NB-UVB is well tolerated, cost effective, and can be used safely in patients with demyelinating disease, in which the use of TNF-alfa-inhibiting biologic agents is contraindicated.

Although also being appropriate for patients with large BSA involvement, NB-UVB can be administered in an outpatient setting or in a day hospital. In darker-skinned individuals and in patients with very thick lesions, PUVA photochemotherapy is likely to be more efficacious because of the better penetration of UVA compared with UVB (Guidelines, Section 5). NB-UVB has many advantages over PUVA, including a lower long-term photocarcinogenic risk, the lack of need for oral medication before each treatment session or photoprotective eyewear between treatments, and safety in pregnancy (Guidelines, Section 5). Remission duration with NB-UVB is, however, shorter than with PUVA. A limiting factor of UV-based therapy is the need for 2 to 3 visits per week to a phototherapy center; once clearance has been achieved, home NB-UVB phototherapy for maintenance therapy is an attractive alternative. If the patient fails to obtain an adequate response after approximately 20 to 30 treatments with NB-UVB given 2 to 3 times weekly, PUVA, traditional systemic agents, or biologic agents should be considered. Because of the history of significant alcohol intake, MTX would be contraindicated in this patient (Guidelines, Section 4). 

Acitretin is teratogenic and thus is contraindicated for use in treatment of psoriasis in women of...
childbearing potential. It could be considered as a reasonable option for this postmenopausal woman either as monotherapy or in combination with NB-UVB. With combination therapy lower doses of acitretin and fewer NB-UVB sessions are usually needed to obtain clearing. Fewer mucocutaneous side effects are seen with lower acitretin doses. Up to 16% of patients treated with acitretin develop elevated liver function tests (LFT) findings (Guidelines, Section 4) \(^5\); therefore, patients need to be regularly monitored for LFT abnormalities. This is particularly true for patients such as ours with a history of excessive alcohol consumption. Acitretin therapy hastens the resolution of scaling and decreases the thickness of psoriatic plaques, hence improving the efficacy of NB-UVB and reducing the total number of phototherapy treatments \(^6\) needed. Acitretin may also be effective in palmoplantar psoriasis. Patients being treated with acitretin and UVB combination therapy should have their UVB exposure times increased cautiously, because epidermal thinning caused by acitretin therapy will make the patient’s skin more susceptible to UV-induced erythema. In patients who are already on phototherapy or photochemotherapy when acitretin is added, it is appropriate to decrease the UV dose by 20% to 30% before resuming the graduated increases in UV dose.

It is important to discuss this patient’s psoriasis treatment with her neurologist because of her diagnosis of multiple sclerosis. Because her multiple sclerosis is being treated with the nonimmunosuppressive agent glatiramer acetate, there is less concern about using an immunosuppressive agent to treat her psoriasis. If there is a suboptimal response to an adequate course of NB-UVB and acitretin, a trial of oral cyclosporine might be appropriate. Cyclosporine is not a standard treatment for multiple sclerosis, but one that has been successfully and safely used in some patients. Because of its renal and hypertensive side effects, cyclosporine should generally only be used as a short-term “interventional” therapy (Guidelines, Section 4) \(^5\). Should the above-mentioned therapeutic interventions prove unsuccessful, it might be reasonable to consider a trial of either alefacept or ustekinumab, as neither is contraindicated in patients with multiple sclerosis. Treatment with TNF-alfa inhibitors is contraindicated in patients with multiple sclerosis (Guidelines, Section 1). \(^2\) Unfortunately there are no data regarding the safety of alefacept in a patient with multiple sclerosis making this a less attractive option. There is a study demonstrating that, although ustekinumab was not efficacious for the treatment of multiple sclerosis, it was well tolerated and no patients in the study experienced worsening of their multiple sclerosis. \(^9\) The superior efficacy of ustekinumab in a significant proportion of patients compared with alefacept for the treatment of psoriasis, along with its safety profile would thus support using ustekinumab as the next therapeutic option in this patient. It is important, however, to take into consideration the cost-benefit ratio of using biologics. \(^84\)

**PUVA photochemotherapy.** Case 3. A 34-year-old Asian American man presented with 2-year history of generalized plaque type psoriasis involving 30% BSA and including the palms and soles. In the past, he was treated with multiple topical medications with little improvement. A 3-month course of aggressively dosed NB-UVB phototherapy also yielded only moderate improvement. He was then treated with PUVA initially 3 times per week and after 8 weeks, there was excellent improvement of his psoriasis with the exception of recalcitrant lesions on the palmar and plantar surfaces (Fig 4). Hand and
foot PUVA using “soak” PUVA was used in conjunction with oral PUVA therapy. With this combination regimen, the patient experienced almost complete clearing of his psoriasis after 12 weeks. Over the ensuing 3 to 4 months, the frequency of PUVA therapy was gradually decreased. Thereafter, monthly treatment with PUVA maintained almost complete clearing during a 7-year period without the development of any skin cancers, although he did develop multiple PUVA lentigines.

Discussion

Since the advent of NB-UVB and the availability of biologic agents, there has been a significant decrease in the use of PUVA. PUVA must, however, still be considered a valuable treatment option, because of its high efficacy, systemic safety, and potential for long-term remissions. It is important to note that UVA light penetrates deeper into the dermis than does UVB. When PUVA was studied in a randomized, double-blind, placebo-controlled trial, 86% of patients achieved 75% improvement from baseline in PASI score (PASI-75) after 12 weeks of therapy.85 Several small studies have suggested similar efficacies of NB-UVB and PUVA in the treatment of psoriasis.86-88 Although one open study of 54 patients demonstrated similar rates of clearing for NB-UVB used thrice weekly and PUVA used twice weekly,89 another open study of 100 patients demonstrated that oral 8-methoxypsoralen PUVA used twice weekly demonstrated better rates of clearing than NB-UVB used twice weekly.90 A double-blind, randomized, single-center study that compared NB-UVB with PUVA for the treatment of 93 patients with psoriasis demonstrated that PUVA treatment achieves clearance in more patients with fewer treatment sessions than does NB-UVB, and that PUVA results in longer remission times than does NB-UVB.91 Even though PUVA is less convenient than NB-UVB in the early stages of therapy, once psoriasis is brought under control, patients may find PUVA a more convenient and attractive option during the maintenance phase with less frequent treatments required for maintenance of control and a longer remission period as compared with NB-UVB.

The major drawback of PUVA therapy is concern regarding its potential to increase skin cancer risk and accelerate photoaging. Although there is good evidence for an increased risk of cutaneous squamous cell carcinoma (SCC) in PUVA-treated patients,92 this has only been demonstrated for Caucasians, with no evidence that PUVA increases the risk of any form of skin cancer in non-Caucasians.93 However, the published studies in non-Caucasians have a follow-up period of 10 years or less, whereas the photocarcinogenic risk in Caucasian patients has been observed after 25 years of follow-up.92 A meta-analysis of several PUVA trials revealed a 14-fold increased incidence of SCC in patients who received high-dose PUVA (200 treatments or 2000 J/cm²) compared with those who received low-dose PUVA (100 treatments or 1000 J/cm²).94 A history of treatment with PUVA also puts patients at significantly greater risk for the development of SCC if they are subsequently treated with cyclosporine. For example, the risk of SCC in patients with a history of PUVA and any use of cyclosporine is similar to the risk of SCC in patients with psoriasis who have received greater than 200 PUVA treatments.95 Thus, the use of cyclosporine in patients with a history of significant PUVA use should be avoided, at least in fair-skinned Caucasians. Because oral retinoids may suppress the development of nonmelanoma skin cancers96,97 their use in combination with PUVA appears prudent.

Whether exposure to PUVA increases the risk of developing melanoma is an area of significant controversy. Several European studies of patients with psoriasis treated with PUVA, including the largest one from Sweden that examined the fair-skinned Caucasian Swedish population, have not shown an increased risk for developing melanoma.93,98,99 A long-term US study of PUVA-treated patients found that after a latency period of 15 years, exposure to more than 200 PUVA treatments increases the risk of melanoma by 5-fold.100 These results contrast with other US studies that have not shown this risk.101,102 The risk of melanoma in the US PUVA cohort is increased in patients who have been exposed to the highest dosages but these findings also have been the subject of debate and controversy.103 Other potential side effects of PUVA include photoaging, phototoxicity, gastrointestinal symptoms associated

Fig 4. Recalcitrant psoriasis of the plantar surfaces.
with the ingestion of methoxsalen, PUVA itch, and, rarely, bullous lesion formation. Although there is a theoretical increased risk of cataract formation with systemic PUVA, a 25-year prospective study showed that exposure to PUVA did not increase the risk of developing cataracts among patients using appropriate eye protection.\textsuperscript{104}

The use of broadband (BB)-UVB has largely been superseded by NB-UVB treatment, although BB-UVB is still available in many phototherapy units. Patients treated with NB-UVB have superior response rates and demonstrate more rapid clearing of disease than patients treated with BB-UVB.\textsuperscript{105} We have presented data showing that long-term treatment with PUVA increases the risk of SCC and may increase the risk of melanoma (based on the results of one large US-based study). Based on these findings, it would be reasonable for clinicians to try to minimize the number of PUVA treatments to decrease the long-term risk of skin cancer.

**Palmoplantar psoriasis.** Case 4. A 66-year-old man presented with a 15-year history of psoriasis involving the face, scalp, genitalia, and groin, with significant involvement of the palms and soles (Fig 5). The patient’s scalp psoriasis is well controlled using topical clobetasol solution applied twice daily on the weekends. His face and suprapubic area psoriasis have responded well to tacrolimus ointment 0.1% twice daily and fluticasone ointment twice weekly as needed. His palms and soles, however, are completely refractory to treatment with multiple different potent topical corticosteroids under occlusion, calcipotriene ointment, and combination topical therapy also used under occlusion. A 3-month course of topical PUVA also produced only minor improvement. This patient has a history of depression treated with lithium, hyperlipidemia treated with atorvastatin, asthma, and hay fever.

Physical examination revealed erythematous scaly and fissured hyperkeratotic psoriatic patches and plaques involving approximately 40% of both the palmar and plantar surfaces (Fig 6). The patient’s quality of life was significantly impacted with limitations in the use of his hands and significant pain with walking. Laboratory studies revealed a normal blood cell count, and lipid and liver panel results. Acitretin (25 mg daily) was initiated. Within 2 months, there was substantial improvement in both the palmar and plantar psoriasis, leading to a significant improvement in this patient’s quality of life. Reduction of his acitretin dosage to 25 mg on alternate days was then possible and the mucocutaneous side effects

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Fig 5. Large confluent plaques involving the scalp (A) and temple (B). After three days of topical clobetasol solution twice daily, there was significant improvement. Thick, indurated large scaly plaques are present in the suprapubic area (C).
associated with acitretin therapy thus diminished. An attempt to reduce his lithium dose was unsuccessful because of a worsening of his depression.

Discussion

Although palm and sole psoriasis affects a small (<5) percent of the total cutaneous surface, it is frequently debilitating, painful, and interferes with simple functions such as walking or buttoning one's clothing. The impact of palm and sole psoriasis on quality of life is out of proportion to the small percent of BSA affected. Quality of life measurements demonstrate the emotional and physical impact of psoriasis limited to the palms and soles, justifying the use of systemic therapies in such patients.\textsuperscript{106} Thus, when intensive topical therapy under occlusion or photochemotherapy is insufficient to achieve adequate improvement and long-term control, therapy with oral or biologic medications should be given strong consideration. Both MTX and cyclosporine are effective in a significant proportion of patients, however, the potential hepatotoxicity and bone-marrow toxicity of the former and the nephrotoxicity of the latter must be considered. Palm and sole psoriasis is often responsive to oral retinoids.\textsuperscript{107} Although elevations in both triglycerides and cholesterol can be a complication of retinoid therapy, these should not necessarily be a contraindication to retinoid therapy, as elevated triglycerides can be appropriately managed with fibrates, alone or combined with statins, and elevated cholesterol can be managed with statins. Caution needs to be exercised when statins and fibrates are given simultaneously because of the risk for rhabdomyolysis. Other treatment options include targeted phototherapy (with 308-nm excimer laser or similar light sources) or PUVA, particularly soak PUVA in which patients soak their palms and soles for 15 to 30 minutes in a methoxsalen solution before UVA exposure. Topical PUVA usually requires treatments two or three times per week for several months for adequate clearing and maintenance of control of palmoplantar psoriasis. As discussed in our prior case, oral PUVA has been associated with the development of cutaneous malignancies after long-term treatment. Cutaneous malignancy on the palms or soles after topical PUVA therapy is, however, very rare. Using oral acitretin in combination with topical PUVA also reduces the number of treatments necessary for clearing\textsuperscript{106,107} and potentially decreases the risk of development of skin malignancies associated with PUVA therapy.\textsuperscript{54}

Biologics may also be effective in the treatment of palm and sole psoriasis.\textsuperscript{108} Although double-blind placebo-controlled trials of palm and sole psoriasis have been performed individually for 3 different biologic agents—efalizumab, adalimumab, and infliximab—the results of these studies have yet to be formally published. Paradoxically, the development of psoriasis of the palms and soles, particularly of the pustular variety, and less frequently other areas of the body, has been reported infrequently in patients without a history of psoriasis who have rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, or PsA under treatment with TNF-alfa antagonists.\textsuperscript{109}

Of interest in this case is the patient's treatment with lithium, which can exacerbate psoriasis. There is evidence that inositol supplementation may benefit lithium-induced psoriasis.\textsuperscript{110} Switching from lithium to an alternative psychiatric medication or lowering the dose of lithium was recommended for this patient. Unfortunately, when the lithium dose was lowered, his depression flared and his psychiatrist was unwilling to consider an alternative medication to control his otherwise recalcitrant depression. The patient was therefore continued on a relatively low dose of oral acitretin (25 mg every other day) with intermittent courses of topical PUVA required to maintain adequate control of his psoriasis and improvement in his quality of life. Fig 7 is an algorithm to approach the treatment of patients with palmoplantar psoriasis.

Recalcitrant psoriasis and multiple comorbidities. Case 5. A 37-year-old obese woman presents with widespread plaque psoriasis for more than 20 years for which a wide variety of therapies have been used. In addition to topical steroids and vitamin D analogs, she had received more than 300 PUVA treatments and 2 years of NB-UVB with her last phototherapy treatment being 3 years previously. The NB-UVB was not effective in adequately controlling her psoriasis. Medical history is significant for hypertension, dyslipidemia, and noninsulin-
dependent diabetes mellitus, features consistent with the diagnosis of metabolic syndrome. She has had one basal cell carcinoma and one SCC involving her trunk, excised 4 and 2 years ago, respectively. Her menstrual cycles are regular and she is sexually active but not considering pregnancy. She reports drinking one ounce of alcohol daily for the past 12 years. Her current medications include metformin, rosuvastatin, fenofibrate, olmesartan, and an oral contraceptive. She has mildly elevated liver enzymes thought to be caused by a combination of her obesity (steatohepatitis) and her alcohol intake. On examination, she has hundreds of PUVA lentigines and several actinic keratoses involving sun-exposed areas of her arms, hands, and face. Thick psoriatic plaques are found on her trunk, extremities, and scalp involving 35% of her BSA. There is no onychodystrophy and no signs or symptoms of PsA are present (Fig 8).

Discussion

This is a complex patient with several important comorbidities that potentially reduce her therapeutic options. In addition, given her obesity, noninsulin-dependent diabetes mellitus, dyslipidemia, and extensive burden of inflammation, she is at increased risk for infection, myocardial infarction, and even potential early demise. Her lack of response to long-term treatment with both types of UV-based therapy along with the extent of her psoriasis and her skin cancer history render treatment with UV light a poor choice.

Acitretin, an oral retinoid, is problematic for several reasons. First and foremost, the patient is a female of childbearing potential. Because there are no safe levels for oral retinoids in the face of pregnancy, the FDA has placed a 3-year postdosing moratorium on pregnancy with acitretin. Therefore and in a practical sense, female patients of childbearing potential should never receive oral acitretin. Because systemic isotretinoin has a much shorter half-life than acitretin, its safe and relatively effective use in female psoriasis patients of childbearing potential has been reported. There are additional concerns with acitretin therapy in this patient. For example, up to 16% of acitretin-treated patients will develop elevations in their serum transaminase levels and between 25% and 50% develop elevations in their serum triglycerides (Guidelines, Section 4). These issues are additional important relative contraindications to the use of acitretin as a treatment for this patient’s psoriasis. Another consideration is the efficacy of acitretin. When used as monotherapy, it is the expert opinion of the authors that acitretin may need to be given in doses exceeding 25 mg/d to obtain significant improvement while recognizing that acitretin-induced mucocutaneous side effects, elevations of liver enzymes, and lipids are dose dependant. Although acitretin combined with phototherapy leads to a better response than monotherapy, this patient’s extensive phototherapy and skin
cancer history make this combination approach far less attractive.

Cyclosporine, a highly effective oral medication, is another therapeutic option. Because of its nephrotoxicity, cyclosporine is traditionally used as a “rescue” medication in psoriasis and rarely used as a maintenance therapy, being approved in the United States for only up to 1 year of continuous therapy at a time. In addition to nephrotoxicity, cyclosporine has other potential systemic side effects that are relevant to this patient. Her history of hypertension, dyslipidemia, and mild elevations in liver enzymes must be considered before initiating treatment (Guidelines, Section 4). In this patient, cyclosporine has a high probability of exacerbating her known hypertension. Her extensive UVB and PUVA treatment and skin cancer history increase significantly her likelihood of developing eruptive SCC and basal cell carcinoma should cyclosporine be added to her regimen. Cyclosporine is metabolized by the cytochrome P450 3A4 system and therefore the potential for drug interactions must be considered. This patient is being treated with rosuvastatin for her dyslipidemia and this presents risk of increased cyclosporine serum levels in this patient. Although these are all relative and not absolute contraindications to treatment with cyclosporine, the knowledge that cyclosporine is best used only as a rescue medication and not as a long-term therapy makes cyclosporine an unattractive option for this patient.

MTX, the most commonly used systemic agent worldwide for moderate to severe psoriasis, is another possible option. Dermatologists are well trained in its use and usually adopt a dose strategy designed to maintain the minimal effective dose for each patient. Important factors to consider include clinical response, side effects such as nausea or fatigue, and alterations in the blood cell count or liver enzymes (Guidelines, Section 4). Because this patient is overweight, and likely has steatohepatitis, a known risk factor for increased hepatotoxicity from MTX, MTX is a less attractive option. In addition, her moderate alcohol intake and current medications may also increase the likelihood of liver toxicity from MTX. Lastly, MTX is a pregnancy category X drug and contraception must be practiced at all times (Guidelines, Section 4). Although these issues are relative but not absolute contraindications to treatment with MTX, given the extent of her disease, the sum of these issues makes MTX, like systemic acitretin and cyclosporine, an unattractive option.

Biologic therapies offer significant advantages to patients with complex medical histories on multiple medications. In general, there are no relevant drug interactions with the biologics and they are considered to have fewer significant safety issues as compared with the traditional systemic agents (Guidelines, Section 1). Given this patient’s medical and dermatologic history, a TNF-alfa antagonist is the rational first choice for several reasons. There are no known drug interactions with the TNF-alfa antagonists and they have no known deleterious effect on renal function or blood pressure. Although there are data from rheumatoid arthritis studies suggesting that TNF-alfa inhibitors may increase total cholesterol and high-density lipoprotein cholesterol, similar elevations have not been demonstrated in patients with psoriasis treated with TNF-alfa inhibitors and the significance of these findings is not known. Although significant elevations of liver enzymes occurred in 4.9% of patients during the phase III clinical trials of infliximab and in a smaller percentage of patients treated with adalimumab, the relevance of these findings in clinical practice is unclear, and the elevations are, in the majority of cases, self-correcting. Isolated case reports described the sudden development of SCC when TNF-alfa antagonists are used in patients with psoriasis and a history of significant UVB or PUVA exposure. In addition there appears to be an increased risk of nonmelanoma skin cancers in patients with rheumatoid arthritis who have been treated with TNF-alfa inhibitors. Although there are no data evaluating the potential long-term (>5 years) effects of TNF-alfa antagonists in patients with psoriasis, a study of 1430 patients with rheumatoid arthritis treated with TNF-alfa antagonists have a decrease in mortality from all causes (adjusted hazard ratio for death of 0.65 [95% confidence interval 0.46-0.93]).

Although there are no comparative studies demonstrating the effect of body weight on the effectiveness of the TNF-alfa antagonists, extensive clinical experience demonstrates the importance of accounting for patient weight when choosing a TNF-alfa inhibitor. Etanercept is given as a fixed dose (the FDA-approved dose is 50 mg twice weekly for the first 3 months of therapy followed by 50 mg once weekly thereafter). Of interest, when etanercept was given on a weight basis in a pediatric trial of patients with psoriasis, higher PASI-75 responses were noted as compared with the adult studies where a fixed dose was used, and a significant drop off in efficacy was seen as patients’ weight increased. Adalimumab is also given as a fixed dose (the FDA-approved dose is 80 mg the first week, 40 mg the next week, and then 40 mg every other week) and is less effective in patients with significant obesity. Infliximab is given intravenously on a weight basis (the FDA-approved dosage is 5 mg/kg every 8 weeks...
after an initial 3 doses at weeks 0, 2, and 6) making this a potential positive choice for the obese patient with psoriasis.

All of the TNF-alfa antagonists carry warnings about infections, particularly granulomatous infections, such as tuberculosis, histoplasmosis, and coccidiomycosis; therefore, patients should be appropriately screened for these infections before starting and during therapy with TNF-alfa antagonists.

Although all of the TNF-alfa antagonists approved for treating psoriasis are FDA pregnancy category B, infliximab and etanercept have been rarely associated with the VACTERL syndrome (vertebral, anal, cardiovascular, tracheoesophageal, renal, and limb abnormalities) when used during pregnancy.128 Although congenital anomalies were not reported in babies born to women taking adalimumab during pregnancy, the database where these data are derived ended in 2005, which was relatively soon after adalimumab received FDA approval.128 Careful consideration of the risks and benefits of TNF-alfa antagonists is warranted before they are used to treat psoriasis in pregnant women.

Adalimumab was started and after 12 weeks of therapy, the patient’s involved BSA had decreased to 4%, which was maintained for the first year of therapy. However, in the subsequent 4 months, her psoriasis flared significantly, resulting in 15% BSA involvement. Loss of efficacy over time may occur with all of the TNF-alfa antagonists. At this point, the choices for controlling this patient’s psoriasis include increasing the dosage of adalimumab to weekly, which is seldom approved by third-party payers because of cost considerations; combination therapy, eg, MTX, retinoids, or phototherapy; or switching to another agent. Unfortunately there are no well-controlled studies demonstrating the safety and/or efficacy of biologic agents in combination with traditional systemic agents in patients with psoriasis as there are in rheumatoid arthritis and Crohn’s disease. In the current case, the patient was switched to ustekinumab, the most recently approved biologic agent, which blocks the p40 subunit of both IL-12 and IL-23.14 Because of her weight, she was treated with the higher dose of 90 mg of ustekinumab at baseline, 4 weeks later, and then every 12 weeks. Four weeks after the third dose of ustekinumab, the patient showed dramatic improvement in her skin involvement, with a reduction in her BSA to 2%. Because of differences in efficacy based on weight, ustekinumab is dosed at 45 mg for patients weighing less than 100 kg and 90 mg for patients who weigh more than 100 kg. Patients being treated with ustekinumab are screened in a similar fashion to the other biologic agents. In the clinical trials, ustekinumab was well tolerated with no evidence of significant laboratory abnormalities.

**Erythrodermic psoriasis.** Case 6. A 29-year-old man with a family history of psoriasis presented for evaluation of a severe flare of his pre-existing psoriasis. The patient developed plaque type psoriasis at 12 years of age, and was initially treated with low-potency topical corticosteroids. His disease became progressively worse over the subsequent 6 years with the development of extensive plaques involving his scalp, trunk, and extremities. He was treated initially with 15 mg per week of oral MTX that unfortunately led to significant elevations in his LFT findings after 9 months of therapy, requiring discontinuation of MTX. Subsequently, he failed to respond to a 12-week course of intramuscular alefacept, but thereafter obtained significant improvement with etanercept treatment. Nine months before his presentation, he left the United States to join his family in Mexico and failed to renew his etanercept. Approximately 7 months after his last dose of etanercept, he noticed an increased number of new psoriatic plaques. Thereafter, an upper respiratory infection led to a rapid worsening of his psoriasis, and eventual involvement of most of his BSA with sparing only of the palms and soles. His psoriasis was painful, and he developed frequent chills, leg swelling, and generalized arthralgias. The patient did not smoke or drink alcohol and denied exposure to toxic chemicals.

On physical examination, the patient was afebrile with other vital signs within normal limits. He had generalized erythematous, inflammatory patches and plaques covering 95% of his BSA (Fig 9). Superficial exfoliation of the face, palms, and soles were noted, along with pitting edema of the lower extremities. Joint examination revealed swelling of the toes without any specific individual joint tenderness.

![Fig 9. Patient with erythrodermic psoriasis. Generalized inflammatory patches and plaques cover 95% of the BSA.](image-url)
Discussion

Severe flares of psoriasis can be induced by multiple factors including stress, systemic infections, and medications. The most severe form of psoriasis, erythrodermic psoriasis, may closely resemble other forms of erythroderma including atopic dermatitis, contact dermatitis, seborrheic dermatitis, cutaneous T-cell lymphoma, and pityriasis rubra pilaris, both clinically and histologically. Often, the diagnosis is made by the patient’s history and subtle clues in the clinical presentation with skin biopsy specimens aiding in the diagnosis in selected cases.

In this patient, the personal and family history of psoriasis strongly favors the diagnosis of erythrodermic psoriasis. In addition, he had areas of indurated plaques and associated silvery scale on his trunk that would be much more consistent with psoriasis than atopic dermatitis. Although no histologic studies were performed in this patient, the presence of atypical lymphocytes on biopsy specimen would be the primary clue for a diagnosis of cutaneous T-cell lymphoma. Screening for HIV, which may present as an erythroderma, can be useful. In addition, obtaining blood for flow cytometry and Sézary cell count (to assess the potential involvement of blood involvement cutaneous T-cell lymphoma or Sézary syndrome, the leukemic form of cutaneous T-cell lymphoma) and possibly for T-cell receptor gene rearrangement clonality, can also be useful. The most difficult differential diagnosis is often pityriasis rubra pilaris, which not uncommonly presents as a diffuse erythroderma with psoriatic-like scale in a young person. However, the deeply erythematous color of his skin eruption, the lack of “skip” areas, along with a lack of significant keratoderma of his palms and soles make psoriasis the more likely clinical diagnosis in our patient.

Although the patient has diffuse arthralgias, he had no definitive history of PsA. The swelling present in his toes is likely related to his lower leg edema, a common presentation in patients with erythrodermic psoriasis. He has no individual tender “sausage type” joints (known as dactylitis) noted in his toes, making a diagnosis of associated PsA unlikely.

The treatment of erythrodermic psoriasis requires a distinct approach from other forms of the disease. These patients often have systemic symptoms including chills and night sweats, and may have generalized arthralgias along with pedal edema. Because patients may have systemic illness associated with the activity of the skin disease, treatment decisions should favor those options that act quickly and have more predictable responses. Therefore, although topical treatments, including mid-potency topical corticosteroids and emollients, particularly when applied under occlusion, may be helpful for patient comfort as well in the restoration of the normal barrier function of the skin, systemic treatments are inevitably necessary for the majority of patients presenting with erythrodermic psoriasis. Likewise it is imperative to rule out sepsis with blood cultures, which frequently may be a trigger factor for erythrodermic psoriasis.

The specific systemic therapy for a patient with erythrodermic psoriasis should be based on short-term efficacy rather than on the basis of long-term results or potential side effects. After the patient’s acute illness has improved, it will be possible to introduce therapies more appropriate for long-term therapy. Although there are no controlled studies evaluating the treatment of erythrodermic psoriasis, oral cyclosporine in a dose of 3 to 5 mg/kg/d is a logical choice in a systemically ill young, erythrodermic patient because of its rapid and impressive onset of action.

In addition, erythrodermic psoriasis also occurs in patients with no evidence of a systemic illness and for which cyclosporine therapy would be considered an appropriate therapeutic option. Although care should be taken in patients who are at higher risk for cyclosporine toxicity including the elderly, those with renal disease or hypertension, or those on medications that influence cyclosporine levels, generally only a short 3- to 4-month “interventional” course of cyclosporine treatment is indicated. With careful monitoring, the majority of patients will tolerate this course well and respond appropriately. Other systemic choices for erythrodermic psoriasis include acitretin, MTX, and the TNF-alfa inhibitors. Acitretin has been used in erythrodermic psoriasis but given its slow onset of action in patients with plaque psoriasis, it may not be sufficiently predictable to improve disease in a rapid enough time frame in the subset of patients with erythrodermic psoriasis who are systemically ill. In addition, acitretin cannot be used in women of childbearing potential because of its teratogenicity. MTX given subcutaneously, thus bypassing the liver, may be a reasonable choice, as well, but the possible need to upwardly titrate the initial dose of this medication may limit its usefulness in patients requiring rapid response. Care should also be taken in patients with hepatic and renal diseases when using MTX (Guidelines, Section 4). As MTX may have effects on spermatogenesis, conception should be avoided in male patients until 3 months after discontinuation of MTX. Patients are frequently placed on antibiotics for concerns of secondary infection. Thus, it is imperative to avoid the use of
sulfa-based antibiotics simultaneously with MTX as this combination can lead to severe bone-marrow suppression.

Biologic therapies may be useful in erythrodermic psoriasis. Although there are no direct comparative studies, preference could possibly be given to infliximab, which has the greatest short-term efficacy and most rapid effects.\textsuperscript{129} Etanercept, adalimumab, and ustekinumab could also be given due consideration.\textsuperscript{126,133,134} Sepsis was ruled out by negative blood cultures in this patient and oral cyclosporine was initiated at 4 mg/kg/d with dramatic improvement during a period of 2 to 3 weeks. The cyclosporine was tapered and discontinued over the ensuing 2 months while etanercept was reintroduced with maintenance of clinical response over the ensuing 1 year. Fig 10 is an algorithm to approach the treatment of patients with erythrodermic psoriasis.

**Conclusions—approach to patients with moderate to severe psoriasis without PsA**

**Phototherapy.** UV therapy remains an important therapeutic option for patients with moderate to severe disease. It is effective in the majority of patients, is cost-effective, and lacks the systemic toxicities and immunosuppressive properties of systemic and biologic treatments. Moreover, NB-UVB is particularly useful for the treatment of psoriasis in pregnancy, and should be considered first line for the treatment of pregnant women with moderate to severe disease (Guidelines, Section 5).\textsuperscript{54} Treatment with phototherapy, which is typically given two to three times a week, requires a significant time commitment, which can lead to work-related difficulties and impinge on quality of life. This needs to be taken into consideration when deciding on the optimal treatment plan for an individual patient. Detailed guidelines for administration of BB-UVB, NB-UVB, topical and systemic PUVA, and their adverse effects have been described (Guidelines, Section 5).\textsuperscript{54}

PUVA has been shown to cause a dose-dependent increase in the risk of nonmelanoma skin cancer with a reversal in the usually observed ratio of basal cell carcinoma to SCC.\textsuperscript{94} The most recent results from an ongoing study aimed at defining the long-term carcinogenic risk of NB-UVB in human beings have shown no significant association between NB-UVB treatment and skin cancer.\textsuperscript{135} Because the median total number of NB-UVB treatments was only 29 with a median follow-up time of 5.5 years in this study, further follow-up data are required before the true potential carcinogenic effect of NB-UVB can be conclusively determined.

**ERYTHRODERMIC PSORIASIS IN MALES OR FEMALES NOT OF CHILDBEARING POTENTIAL**

*Initially For All Patients*
- Appropriate wet dressings with mid-potency topical steroids
- Attention to fluid balance with control of ankle edema
- Rule out sepsis
- Rule out other causes of erythroderma, including pityriasis rubra pilaris, and Sezary syndrome, drug eruption, and atopic eczema

*Systemic therapy*

**First Line in alphabetical order**
- Acitretin
- Biologic agents (Infliximab, Adalimumab, Ustekinumab)
- Cyclosporine approximately 3-4 month course
- Methotrexate

**Second Line in alphabetical order**
- Acitretin and CsA
- Acitretin and TNF Blocker
- CsA and MTX
- Etanercept
- MTX and TNF Blocker

Fig 10. Algorithm for treatment of patients with erythrodermic psoriasis. CsA, Cyclosporine; MTX, methotrexate; TNF, tumor necrosis factor.

Although there are conflicting reports regarding the benefit of combining topical corticosteroids or vitamin D analogs with UVB, the combination of MTX with BB-UVB, NB-UVB, or PUVA produces a synergistic effect, allowing enhanced efficacy, reduced treatment duration, and lower cumulative UV doses.\textsuperscript{136-138} Numerous studies have also shown acitretin to be effective in combination with NB-UVB or PUVA, increasing response rates, decreasing the total number of treatments, and thus the cumulative dose of UV exposure (Guidelines, Section 5).\textsuperscript{54} In addition, oral retinoids suppress the development of cutaneous SCC in patients treated with PUVA, making this an attractive combination therapy.\textsuperscript{159}
Few studies have examined the combination of phototherapy with biologic agents. In a 12-week, single-arm, open-label study combining etanercept 50 mg twice weekly and NB-UVB thrice weekly in 86 patients, 85% of patients achieved a PASI-75 response.\textsuperscript{140} Although there was not an etanercept monotherapy arm in this study, the response rate was significantly higher than the expected response rate seen in etanercept monotherapy studies. Similarly, two studies comparing patients treated with alefacept alone with patients treated with a combination of alefacept and NB-UVB or BB-UVB also showed a higher response rate and a more rapid response in those treated with the combination.\textsuperscript{141,142}

**Traditional systemic agents—sequence and duration of use.** Recommendations for use, baseline screening and monitoring guidelines, absolute and relative contraindications, adverse events, and drug interactions of traditional systemic agents are comprehensively summarized in Section 4 of the Guidelines.\textsuperscript{53} MTX remains the most widely used systemic agent for the treatment of psoriasis since its introduction 40 years ago and is a logical first choice of systemic agent, because it is the most cost-effective systemic psoriasis agent with the longest safety follow-up data.\textsuperscript{143}

In studies of oral MTX given at doses of 15 to 20 mg weekly for patients with moderate to severe plaque psoriasis, approximately 50% to 60% of patients achieved a PASI-75 response whereas up to 30% experienced adverse effects, including gastrointestinal side effects, hepatotoxicity, bone-marrow suppression, acute pneumonitis, and pulmonary fibrosis that necessitated discontinuation of therapy.\textsuperscript{144} The coadministration of folic acid is important to help ameliorate the hematologic and hepatic side effects of MTX.

The National Psoriasis Foundation has recently published comprehensive guidelines for the use of MTX in the treatment of psoriasis.\textsuperscript{145} Based on more recent data, this consensus group re-evaluated the need for liver biopsies in patients with psoriasis on long-term MTX treatment, which were previously recommended after 1.0 to 1.5 g of cumulative MTX.\textsuperscript{146,147} In patients without any risk factors for hepatic toxicity (which include, among others: obesity, diabetes, hyperlipidemia, and history of or current alcohol consumption) who reach a cumulative dose of 3.5 to 4.0 g of oral MTX in the presence of normal liver chemistry test results, 3 options are suggested: performing a liver biopsy, continuing to monitor without a liver biopsy, or switching to an alternative therapy if possible. Likewise, our AAD guidelines recommend liver biopsy at this same cumulative 3.5- to 4-g level of oral MTX therapy (Guidelines, Section 4)\textsuperscript{53} but there are no dosage guidelines for liver biopsy after subcutaneously administered MTX. In patients with one or more risk factors for hepatic toxicity, more stringent monitoring is necessary if another systemic agent is contraindicated. This entails a liver biopsy soon after onset of therapy, preferably after 2 to 6 months to avoid unnecessary biopsies in those who do not tolerate the drug or show a lack of response, with repeated biopsies after every 1.0 to 1.5 g of oral MTX. The monitoring of serum levels of the aminoterminal peptide fragment of type III procollagen may also prevent the need for a liver biopsy in patients on long-term MTX therapy.\textsuperscript{148} Although this screening test is routinely used in many centers in Europe, it is not available in the United States. New noninvasive sonographic techniques for evaluating liver fibrosis will soon become available, which could further reduce the need for liver biopsies. It is also always an option to refer patients being treated with MTX to a hepatologist to make recommendations regarding the need for a liver biopsy.

Because of its rapid onset of action and marked efficacy, cyclosporine is particularly useful in the treatment of significant flares of psoriasis unresponsive to other therapies, and as a bridging agent during the induction of other maintenance agents.\textsuperscript{149,150} The efficacy of cyclosporine is dose dependent, with a shorter time to remission at higher doses.\textsuperscript{151,152} Benefit in efficacy gained by using oral doses higher than 5 mg/kg/d is, however, offset by an increase in toxicity. Current consensus guidelines recommend starting at a low oral dose of 2.5 mg/kg/d, unless a rapid improvement is considered necessary, when an oral dose of up to 5 mg/kg/d may be used (Guidelines, Section 4).\textsuperscript{54}

Patients who fail to obtain an adequate response after 4 weeks of low-dose oral cyclosporine can have their dose increased gradually by 0.5 to 1.0 mg/kg/d at 2- to 4-week intervals, up to a maximum of 5 mg/kg/d. If an adequate response has not been achieved after 3 months of treatment at an oral dose of 5 mg/kg/d, cyclosporine should be withdrawn. Once a good response to cyclosporine has been obtained, the dose can be reduced in increments of 0.5 to 1.0 mg/kg/d at 2-week intervals to the lowest possible dose that maintains control of disease. Intermittent short-term therapy with oral cyclosporine (12-16 weeks) is the most frequently recommended regimen, with treatment being withdrawn once significant improvement is achieved. When relapse occurs, cyclosporine therapy is re instituted at the previously established effective dose. Alternatively, patients can be treated with maintenance therapy for up to 1 year (Guidelines, Section 4).
The aim of maintenance therapy is not necessarily to achieve complete clearance, but to attain a significant clinical improvement with the lowest effective dose. The maintenance oral dose typically used is 3.0 to 3.5 mg/kg/d.

A short course of cyclosporine can be used in severe flares of disease as rescue or bridging therapy because of its rapid onset of action, until an alternative maintenance treatment is instituted. This is particularly useful in the treatment of erythrodermic, suberythrodermic, or generalized pustular psoriasis. Overlapping cyclosporine with alternative treatments, such as MTX or biologic therapies, can avoid further deterioration of disease at the early stages of treatment while the introduction of the new drug is taking effect. Cyclosporine can then be withdrawn without the danger of flaring and with minimal risk of side effects for the short period the two medications are used simultaneously.

Acitretin, although normally less effective than other traditional systemic agents when used as a monotherapy, can play an important role in patients with generalized pustular psoriasis and palmoplantar disease. Because of the lack of associated immunosuppression, it can be of particular value in patients with known infection, active malignancy, or HIV. Acitretin also has the advantage of displaying relatively little cumulative toxicity even after use for extended periods of time. As mentioned previously, its use is contraindicated in women of childbearing potential and more specifically, should not be used in women who may become pregnant within 3 years of discontinuing the drug.

Chronic elevation of triglycerides may increase the risk of atherosclerosis, therefore monitoring and treatment of acitretin-induced hypertriglyceridemia (often with fibrates) is necessary. Diffuse idiopathic hyperostosis has been rarely reported in patients treated with long-term retinoids. Although fumaric acid esters are used as a first-line treatment for moderate to severe psoriasis in several European countries, particularly Germany, this treatment is not approved in the United States. Several well-designed placebo-controlled studies have shown fumaric acid esters to be safe and efficacious. Detailed guidelines for their use have been summarized (Guidelines, Section 4).

Other less commonly used second-tier systemic agents are occasionally used in treatment-resistant disease or if the previous systemic agents are not tolerated. They include oral leflunomide, sulfasalazine, and tacrolimus. Although there are reports of oral azathioprine, hydroxyurea, mycophenolate mofetil, and 6-thioguanine showing efficacy in the treatment of psoriasis, the evidence supporting their use is lacking (Guidelines, Section 4).

Biologic agents

Biologic agents are now routinely used when one or more traditional systemic agents fail to produce an adequate response, are not tolerated because of adverse effects, or are unsuitable because of the presence of comorbidities. Recommendations for use, baseline screening, vaccination and monitoring guidelines, absolute and relative contraindications, and adverse events associated with biologic agents have been comprehensively summarized (Guidelines, Section 1). The currently approved biologic agents for the treatment of either psoriasis or PsA include alefacept, infliximab, etanercept, adalimumab, golimumab, and ustekinumab, with alefacept and ustekinumab FDA approved for psoriasis only and golimumab FDA approved for PsA only. Another anti-IL-12/23 antibody, briakinumab, is in the late stages of phase III clinical trials, whereas phase II and phase III clinical trials are ongoing for numerous other agents including anti-IL-17 antibodies, IL-17 receptor blockers, p-selectin inhibitors, and JAK inhibitors.

Although, overall, alefacept shows inferior efficacy compared with other biologic agents, a small subset of patients demonstrate a prolonged response to a 12-week course of alefacept, maintaining a 50% or greater improvement from baseline in PASI score for a median of 10 months. The identification of pharmacogenetic markers of treatment response to alefacept may be very valuable in the future and allow targeting of alefacept to this subset of patients.

There is no specific sequence in which the currently available TNF-alfa antagonists should be used. In the absence of studies directly comparing the efficacy of these agents, pivotal phase III studies would suggest the initial response rate of cutaneous disease to infliximab is superior to that of adalimumab, which is superior to that of etanercept (Table I, Guidelines, Section 1). However, over the course of a year, a loss of response may be noted with these agents, necessitating the addition of phototherapy or MTX when appropriate or switching from one biologic to another. Interestingly, one retrospective study demonstrated that patients who develop positive antinuclear and antidualle-stranded DNA antibodies to the two monoclonal antibody TNF-alfa inhibitors (adalimumab and infliximab) as compared with the fusion protein TNF-alfa inhibitor etanercept, were more likely to lose response to treatment than those who did not develop these antibodies. The efficacy of golimumab for treating cutaneous psoriasis was assessed in the golimumab PsA studies as a secondary end point. In these studies, where...
Table I. Ustekinumab recommendations

<table>
<thead>
<tr>
<th>Indications: moderate-severe psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing: 45 mg of ustekinumab at baseline, 4 wk, and every 12 wk in those &lt; 100 kg, and 90 mg of ustekinumab at same intervals for those &gt; 100 kg</td>
</tr>
<tr>
<td>Short-term efficacy: PASI-75 in 67% at 12 wk</td>
</tr>
<tr>
<td>Long-term efficacy: PASI-75 maintained in 87% of patients at 52 wk who attained PASI-75 at wk 12</td>
</tr>
<tr>
<td>Toxicities:</td>
</tr>
<tr>
<td>Occasional injection-site reactions</td>
</tr>
<tr>
<td>Rare reports of serious infections and malignancies including skin cancers</td>
</tr>
<tr>
<td>Rare reports of major adverse cardiovascular events</td>
</tr>
<tr>
<td>Single report of reversible posterior leukoencephalopathy</td>
</tr>
<tr>
<td>Baseline monitoring: (similar to other biologic agents)</td>
</tr>
<tr>
<td>PPD is required</td>
</tr>
<tr>
<td>LFT, CBC, and hepatitis profile</td>
</tr>
<tr>
<td>Ongoing monitoring:</td>
</tr>
<tr>
<td>Periodic history and physical examination recommended while on treatment</td>
</tr>
<tr>
<td>Yearly PPD, and consider periodic CBC and LFT</td>
</tr>
<tr>
<td>Pregnancy category B</td>
</tr>
</tbody>
</table>

CBC, Complete blood cell count; LFT, liver function test; PASI-75, 75% improvement from baseline in Psoriasis Area and Severity Index score; PPD, purified protein derivative.

Table II. Strength of recommendations for use of ustekinumab and golimumab

<table>
<thead>
<tr>
<th>Agent</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab*</td>
<td>A</td>
<td>I</td>
<td>38, 39, 164, 171</td>
</tr>
<tr>
<td>Golimumab$y$</td>
<td>A</td>
<td>I</td>
<td>4</td>
</tr>
</tbody>
</table>

For strength of recommendations in treatment of psoriasis with tumor necrosis factor inhibitors, see Table V, Section 1 of Guideline.

For strength of recommendations in treatment of psoriatic arthritis, see Table VIII, Section 2 of Guideline.

*Data from phase III psoriasis trials.

$y$Data from phase III psoriatic arthritis trials.

concomitant MTX and/or low-dose corticosteroids were also allowed, the efficacy of golimumab on the skin appeared to be lower as compared with the 3 other TNF-alfa inhibitors.

The incidence of infections including the reactivation of tuberculosis and rare opportunistic infections appears to be lower for etanercept than for the monoclonal antibodies infliximab and adalimumab.\textsuperscript{160} A risk-benefit assessment of the TNF-alfa inhibitors in the treatment of psoriasis demonstrated that during the first year of treatment, the likelihood of success with TNF-alfa inhibitors for psoriasis (calculated as the number of patients needed to be treated) was approximately two orders of magnitude higher than the likelihood of toxicity (calculated as the number of patients needed to harm).\textsuperscript{161}

Since publication of Section 1 of the Guidelines, ustekinumab, an anti-IL-12/23 antibody, has received regulatory approval for the treatment of moderate to severe psoriasis. Two large-scale phase III, multicenter, randomized, double-blind, placebo-controlled, parallel studies showed that between 66% and 76% of patients achieved a PASI-75 response after 12 weeks.\textsuperscript{42,43} As increased body weight was associated with a decrease in efficacy, the current FDA-approved dosage regimen is 45 mg of ustekinumab at baseline, 4 weeks, and every 12 weeks in those weighing less than 100 kg, and 90 mg of ustekinumab at the same intervals for those who weigh more than 100 kg. Adverse events in the ustekinumab clinical trials have been, for the most part, mild and similar to that in placebo-treated patients. Recommendations for ustekinumab are listed in Table I. The strength of recommendations for the treatment of psoriasis using ustekinumab is shown in Table II. Compared with the TNF-alfa inhibitors, which have now been available for more than 10 years and have been used in approximately 2 million patients across several indications, the most comprehensive ustekinumab safety data to date come from a pooled analysis of phase II and phase III clinical trials involving slightly more than 3000 patients with just over 3 years of continuous therapy.\textsuperscript{162} Therefore, the use of registries to monitor the long-term safety of ustekinumab and other new agents currently under development, and to monitor the long-term safety of all of the systemic agents available, is an essential step in defining the long-term adverse effects of ustekinumab and other new agents. A critical first step in the development of a national registry occurred in December 2009, when Congress allocated $1.5 million to start a psoriasis
patient registry at the Centers for Disease Control and Prevention. In addition, a $1.0 million challenge grant was awarded by the National Institutes of Health in 2010 to create the Dermatology Clinical Effectiveness Research Network, which focuses on psoriasis treatment outcomes (www.niams.nih.gov/Recovery/Chronicles/chronicle_psoriasis_network.asp). Another important method for obtaining valuable information about the long-term safety of newer medications is postmarketing surveillance, a point that has become emphasized in recent years by the FDA.

Studies of both traditional systemic and biologic agents in children are lacking despite being the group most likely to experience the psychological and stigmatizing effects of psoriasis. Only one clinical study has evaluated the use of a biologic agent (etanercept) in children with psoriasis. In this study, 57% of children aged 4 to 17 years treated with a once weekly dose of 0.8 mg/kg of etanercept achieved a PASI-75 response compared with 11% of placebo-treated children along with a good safety profile.165 Although etanercept is approved in Europe for children aged 8 to 17 years with psoriasis, it has not been approved, and is unlikely to be approved, for use in patients younger than 18 years with psoriasis in the United States. Fig 11 is an algorithm to approach the treatment of pediatric patients with psoriasis with more than 5% BSA.

**Combination therapy of systemic and biologic agents**

The goal of combination therapy is to maintain or improve efficacy while decreasing the toxicity of each agent by allowing lower individual doses to be used. Given for short periods of time, the combination of orally administered MTX and cyclosporine has been shown to be effective for the treatment of recalcitrant psoriasis resulting in a lower cumulative dose of each agent, thus potentially diminishing the associated hepatotoxicity and nephrotoxicity, respectively.163,164 MTX can also be combined with phototherapy, as described previously, or less frequently with low-dose acitretin.165 MTX has been safely combined with all the biologic therapies currently approved for psoriasis in studies of PsA and rheumatoid arthritis, but to date, no randomized controlled study has compared the benefit of combining MTX with any biologic agent in the treatment of cutaneous disease.166,167 The addition of low-dose MTX to biologic treatments may also serve to reduce the immunogenicity associated with these treatments especially with the monoclonal antibody TNF-alfa inhibitors.168,169 Although there is one anecdotal report of combining two biologic agents (efalizumab and etanercept) to treat patients with psoriasis and PsA,170 increased toxicity without increased efficacy has been observed in two controlled studies of rheumatoid arthritis when two biologics were combined, even when the dosages were decreased.171

Cyclosporine has been successfully combined with topical corticosteroids, anthralin, and topical vitamin D analogs with improved responses.172-174 Other systemic treatments such as fumaric acid esters and mycophenolate mofetil have also been used in combination with cyclosporine, allowing for dose reduction of cyclosporine.164,175,176

**Rotational therapy**

Rotational therapy of the aforementioned systemic agents and/or phototherapy can also be used to minimize duration of treatment with individual drugs and thus reduce cumulative toxicities.177,178 Rotational therapy is particularly useful for cyclosporine and MTX, where adverse effects are generally related to duration of treatment with interruption of treatment allowing for recovery of reversible side effects. The use of rotational therapy has diminished significantly since the advent of the biologic agents.

**Comparison studies of systemic and biologic agents**

There are few studies evaluating the comparative effectiveness of the various different systemic agents to treat psoriasis. There is one published study that compares a traditional systemic agent, MTX, with a biologic agent, adalimumab. In this multicenter, randomized, placebo-controlled trial, 271 patients were given either oral MTX, initiated at only 7.5 mg per week and slowly increased, or adalimumab dosed in the standard fashion, ie, 80 mg initially, 40 mg 1 week later, and 40 mg every other week thereafter. The primary end point was measured at 16 weeks and a placebo arm was also included.179 In all, 74% of patients treated with adalimumab achieved PASI-75 response compared with 36% of patients treated with MTX. At 16 weeks, patients being treated with oral MTX were still continuing to improve, suggesting that a higher PASI-75 response would likely have been obtained by the patients treated with MTX if the study had been extended, or if MTX had been given at a higher dosage from the beginning. Another critical issue with this study was an extremely high placebo response rate of 19% in untreated patients whereas no other phase II or III biologic psoriasis study has shown a placebo response above 11%. For these two important reasons, the results of this study must be interpreted with caution.
There is one published comparator study of two different biologic agents. In this multicenter, comparator trial, 903 patients were randomized to receive either 45 or 90 mg of ustekinumab at weeks 0 and 4 or etanercept at 50 mg twice weekly for 12 weeks in a ratio of 3:5:5. No placebo arm was included. After 12 weeks, 68% and 74% of those in the ustekinumab 45 mg group and 90 mg group, respectively, achieved PASI-75 response compared with 57% of patients in the etanercept group ($P = .01$ and $P < .001$, respectively). Overall adverse events and serious adverse events were similar in patients given either etanercept or ustekinumab.

Two studies have compared MTX and cyclosporine in patients with psoriasis, but unfortunately both of these studies have limitations that diminish the reliability of their results. In a randomized controlled trial comparing 88 patients treated for 16 weeks with either oral cyclosporine or oral MTX, the PASI-75 response was 71% for cyclosporine and 60% for MTX. This study had no placebo arm and the patients were not given supplemental folic acid. Although patients were excluded from this study if they had a high risk of liver function abnormalities (not defined in the study), 12 of the 44 patients treated with oral MTX dropped out because of abnormal LFT results. In another randomized controlled trial of 84 patients with moderate to severe plaque psoriasis, after 12 weeks, the mean PASI score change was 72% in the oral cyclosporine group and 58% in the oral MTX group. This study also lacked a placebo arm and there was a high drop-out rate as a result of laboratory abnormalities and withdrawal of consent in both arms. In a clinical trial that compared 210 patients treated with low-dose oral cyclosporine (2.5 mg/kg/d) or oral etretinate (0.5 mg/kg/d), the mean PASI score improvement was 71% in the cyclosporine group compared with 47% in the etretinate group.

Fig 11 is an algorithm to approach the treatment of healthy male patients without PsA with greater than 5% BSA. Fig 12 is an algorithm to approach the treatment of women of childbearing potential using appropriate contraception without PsA with greater than 5% BSA. Fig 13 is an algorithm to approach the treatment of healthy women trying to conceive without PsA and with greater than 5% BSA.

**TREATMENT OF PATIENTS WITH PSA**

PsA, an inflammatory arthropathy, may be associated with psoriasis in up to 42% of patients. Most common estimates, however, suggest that approximately 25% to 30% of patients with psoriasis will develop PsA usually 5 to 12 years after the onset of their skin disease. Left untreated, a proportion (up to 50%) of patients with PsA may develop persistent inflammation with progressive joint damage that can
lead to severe physical limitations and disability. For this reason, early diagnosis of PsA is critical. Dermatologists are in an excellent position to make the early diagnosis of and treat PsA appropriately, and thus should actively elicit signs and symptoms of PsA at every patient visit. If PsA is diagnosed, treatment should be initiated to alleviate the signs and symptoms of PsA, inhibit structural damage, and maximize quality of life. Dermatologists uncomfortable or untrained in evaluating or treating patients with PsA should refer to rheumatologists. Preferably, close cooperation between dermatologists and rheumatologists will offer optimal benefit to patients with both psoriasis and PsA.

**Case 7**

An obese, 55-year-old Caucasian man with psoriasis for 12 years presented with an 8-month history of painful and swollen joints in the hands, feet, and knees; bilateral heel pain; and morning stiffness of approximately 2-hour duration, unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs). On physical examination, he had psoriatic plaques on the knees, elbows, genitals, and scalp. The majority of his fingernails showed pitting and onycholysis. Joint evaluation demonstrated multiple tender and swollen joints including the second and third metacarpal-phalangeal joints of both hands; the second, third, and fourth
WOMEN OF CHILDBEARING POTENTIAL USING APPROPRIATE CONTRACEPTION WITH CHRONIC PLAQUE PSORIASIS (>5% BSA), W/O PSORIATIC ARTHRITIS

Fig 13. Algorithm for treatment of women of childbearing potential with psoriasis involving greater than 5% body surface area. BB, Broadband; CsA, cyclosporine; MTX, methotrexate; NB, narrowband; PUVA, psoralen plus ultraviolet A; UV, ultraviolet.

distal interphalangeal joints bilaterally; and both knees. Dactylitis (“sausage digit”) was present on multiple digits in both the hands and the right fourth toe along with a tender and swollen right Achilles tendon (Fig 15). Rheumatoid factor was negative and C-reactive protein was elevated. MTX at 25 mg given orally once weekly along with daily 1 mg of folic acid for 12 weeks failed to adequately control either the joint or skin disease. A TNF-alfa inhibitor was introduced with eventual tapering of MTX to 10 mg once weekly. The patient’s arthritis and skin disease dramatically improved after 4 months of this combination regimen (Fig 16, A and B), which was maintained, allowing for significant improvement in his quality of life.

Discussion

PsA is common in patients with psoriasis. PsA can be disabling with radiographic damage noted in 7% to 47% of patients at a median interval of 2 years despite clinical improvement with standard disease-modifying antirheumatic therapy. Because the vast majority of patients with PsA have cutaneous manifestations for up to 12 years before the onset of PsA, dermatologists are uniquely positioned to detect the early signs and symptoms of PsA. Patients may also have severe PsA with little to no evident skin disease. Treatment with TNF-alfa-blocking agents can relieve signs and symptoms, inhibit structural damage, and improve quality-of-life parameters in a significant proportion of patients with PsA. Thus dermatologists, in consultation with
MEN TRYING TO CONCEIVE WITH CHRONIC PLAQUE PSORIASIS (>5% BSA), W/O PSORIATIC ARTHRITIS

Topical therapy

UVB available

First Line
- Topical Calcipotriene+/Calcitriol+
- Topical Corticosteroids*
- UVB Phototherapy (NB or BB)

UVB Not available

First Line in alphabetical order
- Adalimumab*
- Alefacept*
- Cyclosporine+
- Etanercept*
- Infliximab*
- PUVA +
- Ustekinumab*

Fig 14. Algorithm for treatment of women trying to become pregnant with psoriasis involving greater than 5% body surface area. BB, Broadband; FDA, Food and Drug Administration; NB, narrowband; PUVA, psoralen plus ultraviolet A; UV, ultraviolet. *These medications are FDA pregnancy category B. +These medications (including psoralen) are FDA pregnancy category C.

rheumatologists when necessary, can certainly prevent disability from PsA by initiating the appropriate treatment early on.

The exact proportion of patients with psoriasis who will develop PsA is an area of significant controversy with studies demonstrating a range from 6% to 10% in broadly representative population-based studies to as high as 42% of patients with psoriasis in clinic-based populations (Guidelines, Section 2). Of special interest to dermatologists, the prevalence of PsA increases in patients with more extensive skin disease. The prevalence of PsA in the general population of the United States has been estimated to be 0.1% to 0.25%. PsA can develop at any time from childhood on, but for the majority of patients it presents between the ages of 30 and 50 years. PsA affects men and women equally. PsA is characterized by stiffness, pain, swelling, and tenderness of the joints and the surrounding ligaments and tendons. Recurrent early morning stiffness lasting longer than 30 minutes is a valuable question to ask of all patients with psoriasis at each visit when considering the diagnosis of PsA. The enthesis is the anatomic location where tendon, ligament, or joint capsule fibers insert into the bone. Enthesitis may occur at any such site, with common locations including the insertion sites of the plantar fascia, the Achilles tendons, and ligamentous attachments to the ribs, spine, and pelvis. Dactylitis, or “sausage digit,” as seen in our patient, is a combination of enthesitis of the tendons and ligaments along with synovitis involving a whole digit.

Symptoms of PsA can range from mild to very severe. The severity of the skin and joint disease usually do not correlate with each other. Nail disease is commonly found in patients with PsA especially those with distal interphalangeal joint involvement. PsA may start slowly with mild symptoms, and, on occasion, may be preceded by a joint injury. The course is variable and unpredictable ranging from mild and nondestructive to a severe, debilitating, erosive arthropathy. Although data from rheumatology referral centers indicate that erosive and deforming arthritis occurs in 40% to 60% of patients with PsA and may be progressive within the first year of diagnosis, studies from the general population suggest that PsA may have a milder course and that it is not associated with excess mortality. Data on the clinical course of PsA in the dermatology setting are not currently available. Flares and remissions usually characterize the course of PsA. Left untreated, patients with PsA can have persistent inflammation,
progressive joint damage, severe physical limitations, and disability.

When caring for a patient with possible PsA, the dermatologist will need to address the important question of when to consult a rheumatologist. For example, if a patient with a 12-year history of psoriasis develops classic signs and symptoms of PsA including swollen and tender joints along with 2 hours of early morning stiffness and is unresponsive to NSAIDs as in our patient, the diagnosis is generally clear. If, however, the treating dermatologist is unsure of the diagnosis, a rheumatology consult is

necessary. The rheumatologist will perform a full assessment of all the joints, small and large, with assessments such as the American College of Rheumatology 20 and an actual count of the number of tender and swollen joints being performed. In addition, x-rays are frequently requested and blood drawn to measure signs of systemic inflammation, e.g., erythrocyte sedimentation rate or the C-reactive protein level. At this time no specific serologic or genetic test is available in the United States to definitely diagnose PsA, although a genetic test has recently been licensed in Europe.

Conclusions—approach to patients with PsA

Mild PsA is most often managed with NSAIDs alone. If the PsA is unresponsive after 2 to 3 months of therapy with NSAIDs, treatment with MTX should be considered (Guidelines, Section 4). For patients with moderate to severe PsA, MTX, TNF-alfa blockade, or the combination of these therapies is considered first-line treatment (Table III, Guidelines, Section 2). The data supporting the use of monotherapy with MTX in PsA are based on only two small randomized placebo-controlled studies (Guidelines, Section 2). However, MTX is often used as a first-line therapy before TNF-alfa blockade treatment, largely because of its significantly lower cost. The combination of orally administered MTX and cyclosporine can also be effective in the treatment of PsA. In a 12-month, randomized, multicenter, double-blind, placebo-controlled trial combining oral cyclosporine with oral MTX in patients with PsA who had a prior incomplete response to MTX monotherapy, there was a significant improvement in the swollen joint count and C-reactive protein levels in the combination MTX-cyclosporine arm when compared with baseline, but not in the MTX-placebo group when compared with baseline.

The comparative efficacy of the 4 currently approved TNF-alfa blocking agents and ustekinumab for both the skin and joints in pivotal trials (not head-to-head) is shown in Table III. At the primary end point and at the marketed dosages, all 4 TNF-alfa inhibitors show similar efficacy for the signs and symptoms of PsA (Table III). There are, however, observed differences in the efficacy of these agents for the treatment of cutaneous psoriasis (Table III). Infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept. It is important to note that in all of the TNF-alfa inhibitor studies of patients with PsA, between 40% and 50% of patients were taking concomitant MTX along with the TNF-alfa inhibitor under evaluation. Golimumab, the most recently approved TNF-alfa inhibitor, has not been tested as monotherapy in patients with moderate to severe psoriasis who do not have PsA. Evaluations of PASI scores in PsA studies have shown that on average the initial PASI score at the beginning of these studies is below 10, making evaluation of PASI-75 response through the course of the study difficult to interpret statistically. Recommendations for golimumab are listed in Table IV. The strength of recommendations for the treatment of PsA using golimumab is shown in Table II. Ustekinumab has shown efficacy against the signs and symptoms of PsA in a recently published small phase II clinical trial. In this study, 42% of the 76 ustekinumab-treated patients achieved an American College of Rheumatology 20 response at week 12 compared with 14% of the 70 placebo-treated patients. This is somewhat inferior to what has previously been seen
in pivotal studies of all 4 TNF-alfa inhibitors for the treatment of PsA (Guidelines, Section 2). Until the results of the phase III trials of ustekinumab for PsA become available, the TNF-alfa inhibitors should be considered the biologic class of choice for these patients.

Although MTX is far less expensive than the TNF-alfa inhibitors, only recently have there been prospective, randomized, adequately powered clinical trials comparing MTX with the TNF-alfa inhibitors in PsA. In one trial, treatment with 15 mg a week of oral MTX did not prevent radiologic progression of PsA, whereas in another trial, increasing the weekly MTX dosage to 25 mg did appear to reduce radiologic progression of PsA. All of the TNF-alfa inhibitors appear to diminish the likelihood of radiographic progression of PsA compared with MTX, but these findings are derived from comparing several different studies rather than one large comparator study. Well-controlled clinical studies are therefore needed to directly compare these agents.

Adding low-dose MTX to one of the TNF-alfa inhibitors leads to further improvement in PsA joint responses. Because of the lack of sufficient data, however, it is difficult for the clinician to make definitive recommendations regarding the proper sequence or duration of therapies that should be used to treat patients with moderate to severe PsA.

### Table III. Comparative efficacy of biologics for psoriasis and psoriatic arthritis—results of pivotal trials

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Golimumab</th>
<th>Infliximab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point for PsA trials, wk</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>12 (^\dagger)</td>
</tr>
<tr>
<td>Percent of patients achieving ACR 20*</td>
<td>58</td>
<td>59</td>
<td>51</td>
<td>58</td>
<td>42 (^\dagger)</td>
</tr>
<tr>
<td>Percent of patients in PsA trials on concurrent MTX</td>
<td>50</td>
<td>46</td>
<td>46</td>
<td>49</td>
<td>20 (^\dagger)</td>
</tr>
<tr>
<td>Mean MTX dose in PsA trials, mg/wk</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Primary end point for psoriasis trials, wk</td>
<td>16</td>
<td>12</td>
<td>14</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Percent of patients achieving PASI-75*</td>
<td>75</td>
<td>49</td>
<td>40 (^\dagger)</td>
<td>80</td>
<td>67</td>
</tr>
</tbody>
</table>

ACR, American College of Rheumatology; MTX, methotrexate; PASI-75, 75% improvement from baseline in Psoriasis Area and Severity Index score; PsA, psoriatic arthritis.

For psoriasis trials, no patients were on concurrent MTX.

*At primary end point.

\(^\dagger\)Data are for patients receiving 50 mg every 4 wk.

\(^\ddagger\)Data derived from phase II PsA trial.

### Table IV. Golimumab recommendations

- **Indications:** moderate to severe psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis. Note, golimumab does not have indication for psoriasis.
- **Dosing:** 50 mg every 4 wk subcutaneously.
- **Efficacy for psoriatic arthritis:** ACR 20 in 51% at wk 14.
- **Efficacy for psoriasis:** PASI-75 in 40% at wk 14.
- **Toxicities:**
  - Occasional injection-site reactions
  - Rare reports of serious infections and nonmelanoma along with systemic malignancies
  - Although there are rare reports of drug-induced reversible side effects including lupus without central nervous system or renal complications, cytopenias, multiple sclerosis, and exacerbation along with new-onset congestive heart failure with other 3 TNF inhibitors, there have been no reports of these reactions with golimumab to date. However, golimumab is TNF inhibitor and it should be used cautiously.

- **Baseline monitoring:**
  - PPD is required
  - LFT and CBC

- **Ongoing monitoring:**
  - Yearly PPD and consider periodic CBC and LFT treatment
  - Consider yearly PPD, and periodic CBC and LFT treatment

- **Pregnancy category B**

ACR, American College of Rheumatology; CBC, complete blood cell count; LFT, liver function test; PASI-75, 75% improvement from baseline in Psoriasis Area and Severity Index score; PPD, purified protein derivative; TNF, tumor necrosis factor.

*Based on psoriatic arthritis study.
Table V. Selected gaps in knowledge for psoriasis and psoriatic arthritis

<table>
<thead>
<tr>
<th>Area of knowledge gap</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Natural history of disease          | 1. There is a need for large prospective longitudinal broadly representative cohort studies of psoriasis.  
2. Environmental risk factors remain poorly defined.  
3. For identified risk factors (eg, smoking, alcohol, and obesity) data are necessary to determine if modification of these risk factors will prevent psoriasis or modify its severity.  
4. Prognosis of psoriasis is poorly understood. Rate at which psoriasis will get worse over time vs spontaneously clear and determinants of alterations in psoriasis activity need to be further elucidated. |
| Subpopulations                      | 1. Natural history and morbidity in subpopulations including children, pregnant and lactating women, the elderly, and minorities requires more study.  
2. Little is known about disparities in treatment, health-related quality of life, and other factors in subpopulations. |
| Comorbidities                       | 1. PsA  
   a. Natural history of PsA is poorly defined in dermatology setting. It is necessary to determine severity of PsA and prognosis of PsA of patients who are identified in dermatology setting.  
   b. Data are necessary to determine if better control of psoriasis through more aggressive therapy will lead to lower incidence of PsA.  
2. CV disease  
   a. Impact of objective psoriasis severity on CV risk is unknown.  
   b. Studies are needed to determine how to optimize prevention of CV events in patients with psoriasis.  
   c. A central question is whether aggressive systemic therapy of psoriasis leads to lower CV risk.  
3. Obesity and metabolic disease  
   a. Data are necessary to determine if achieving ideal BMI will lower risk of developing psoriasis and if, among those with psoriasis, achieving normal BMI will improve skin and joint disease.  
   b. Degree to which obesity explains higher risk of diabetes and metabolic syndrome observed in some studies requires additional study.  
4. Many comorbidities have been relatively understudied including psychiatric (anxiety, depression, suicide), osteoporosis, infection, and chronic obstructive pulmonary disease.  
5. Mortality: studies indicate that patients with severe psoriasis have excess mortality. Causes of death and degree to which these are altered by psoriasis itself, its treatments, or comorbid behaviors requires further study. |
| Treatment                           | 1. Comparative effectiveness of psoriasis treatments for plaque psoriasis is understudied. Few studies that exist are short term. Current data make it difficult to determine which drugs are most safe and effective long term for psoriasis and therefore should be considered preferred treatment for most patients. As a result, most recommendations are broad and list options in alphabetical order.  
2. Comparative effectiveness of psoriasis treatments for clinical variants including guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, inverse psoriasis, and palmoplantar psoriasis is area with almost no data.  
3. Most safety data for psoriasis therapies come from other diseases particularly rheumatoid arthritis. It is unclear if such data acutely reflect safety of TNF inhibitors, methotrexate, and other therapies in psoriasis population.  
4. Risks of clinically significant liver toxicity when using existing liver biopsy guidelines to treat psoriasis with methotrexate requires further study.  
5. Safety and effectiveness of home- or office-based NB-UVB in comparison with other treatments in US population requires additional study.  
   Studies indicate that majority of patients with objectively severe psoriasis are treated only topically or not all. More data are necessary to determine patient, physician, treatment, and economic factors that result in most patients with severe disease not achieving long-term control of their psoriasis. |
| Genetics and pathomechanisms        | 1. Studies evaluating correlation between psoriasis genotype and phenotype should be undertaken.  
2. Vasculature has been understudied. Animal model that overexpresses angiopoietin receptor in keratinocytes leads to mice bearing numerous criteria of psoriasis. |

BMI, Body mass index; CV, cardiovascular; NB, narrowband; PsA, psoriatic arthritis; TNF, tumor necrosis factor; UV, ultraviolet.
We would suggest however that, in general, it is appropriate to initiate MTX treatment for patients with moderate to severe PsA who have no contraindications to MTX therapy. If after 12 to 16 weeks of MTX therapy with appropriate dose escalation there is minimal improvement in the signs and symptoms of PsA, it is very appropriate to either add or switch to a TNF-alfa inhibitor, with all of the TNF-alfa inhibitors being equally reasonable choices. Fig 17 is an algorithm to approach the treatment of adults with psoriasis involving greater than 5% BSA with concomitant moderate to severe PsA.

PATIENT EDUCATION

Patient education is essential to optimizing psoriasis treatment for all categories of disease severity. A good physician-patient relationship fosters confidence and trust, likely improving adherence to treatment. Patients should be fully informed of the benefits and risks of their treatments and believe that they have a significant input into their treatment plan. Psoriasis nurse specialists play an important role by spending time counseling and educating patients and are a valuable asset. Patient pamphlets, psoriasis clinical guidelines, and peer support are easily accessible via the Internet at the AAD World Wide Web site (www.aad.org). Patient advocacy groups such as the National Psoriasis Foundation (www.psoriasis.org) and the International Federation of Psoriasis Associations (www.IPFA-pso.org) are also important resources for patients with psoriasis, providing published materials on psoriasis treatments.

As psoriasis is predominantly a disease of younger patients, a dermatologist may be the sole physician a patient with psoriasis sees on a regular basis. In recent years, patients with moderate to severe psoriasis have been shown to have an increased incidence of obesity, cardiovascular disease, diabetes mellitus, hypertension, metabolic syndrome, and depression.14-26 Dermatologists are thus in a unique position to identify comorbidities associated with psoriasis, to counsel patients with regard to lifestyle modifications, and to appropriately liaise with other relevant medical specialties and primary care physicians to ensure a comprehensive approach to disease management. In this regard, all patients with moderate to severe psoriasis should be strongly encouraged to develop an ongoing relationship with a primary care provider so that potential comorbidities can be prevented or diagnosed and treated early to minimize end organ damage.

GAPS IN RESEARCH/KNOWLEDGE

We have described above the significant progress that has been made in understanding the pathogenesis and treatment of psoriasis. Unfortunately, as with many other immune-mediated inflammatory disorders, there are still large gaps in our knowledge base. In Table V, we address some of the most important gaps in research and care that currently exist and make suggestions for studies to address these gaps.

We thank the AAD Board of Directors, the Council on Science and Research: Chair, Henry W. Lim, MD, Robert Swerlick, MD, Michael D. Tharp, MD, Elise A. Olsen, MD, Diane R. Baker, MD, Kevin D. Cooper, MD, Steven R. Feldman, MD, PhD, Abby S. Van Voorhees, MD, Karl R. Beutner, MD, PhD, Mark R. Pittelkow, MD, Brian Kim, MD, and the Clinical Research Committee: Chair, Karl A. Beutner, MD, PhD, Stephen Burtis Webster, MD, Jeremy S. Bordeaux, MD, MPH, Pearnon G. Lang Jr, MD, Abrar A. Qureshi, MD, MPH, Lorraine C. Young, MD, Heidi T. Jacob, MD, Melody J. Eide, MD, and Daniel M. Miller, MD, for reviewing the manuscripts and providing excellent suggestions. We thank Cristina Martinez, MA, Kathleen M. Muldowney, MS, and Terri Zylo for technical help in preparing the manuscript.

Disclosure: Alan Menter, MD, Chair Psoriasis Work Group: Dr Menter served on the Advisory Board and was a consultant, investigator, and speaker for Abbott Labs, Amgen, and Centocor receiving grants and honoraria; was a consultant, investigator, and speaker for Wyeth receiving honoraria; served on the Advisory Board and was an investigator and consultant for UCB receiving grants and honoraria; was a consultant, investigator, and speaker for
Warner Chilcott and Wyeth receiving honoraria; served on the Advisory Board and was an investigator for Galderma and Genentech receiving grants and honoraria; was a consultant and investigator for Eli Lilly receiving grants and Astellas receiving grants and honoraria; was an investigator for Celgene, Ausbio, and Syntrix Biosystems receiving grants and Novo Nordisk receiving no compensation, and an investigator and speaker for Pfizer receiving grants and honoraria.

Neil J. Korman, MD, PhD: Dr Korman has served on the Advisory Board and was investigator and speaker for Genentech and Astellas receiving grants and honoraria; served on the Advisory Board and was investigator for Centocor receiving grants and residency/fellowship program funding; was investigator and speaker for Amgen receiving grants and honoraria; and served on the Advisory Board, was consultant, investigator, and speaker for Abbott Labs receiving grants and honoraria.

Craig A. Elmets, MD: Dr Elmets has served as an investigator for Abbott and Genentech receiving grants; was consultant for Astellas receiving honoraria; and was a consultant for ISDIN receiving other financial benefit.

Steven R. Feldman, MD, PhD: Dr Feldman served on the Advisory Board and was investigator and speaker for Galderma, Stiefel, Warner Chilcott, Abbott Labs, and Astellas receiving grants and honoraria; served on the Advisory Board for Photomedex receiving stock options; received grants from National Psoriasis Foundation and Dermatology Foundation, Coria, ADS, Aventis Pharma Ortho Pharma, Pharmaderm, and Roche Dermatology; was an investigator and speaker for Amgen, Centocor, Connetics, and Genentech receiving grants and honoraria; was a speaker and consultant for Bristol-Myers Squibb Derm receiving grants; a speaker for Novartis and 3M receiving grants; and a consultant and speaker for Bristol-Myers Squibb Derm and Biogenidec receiving grants. He received separate department funding from Acuderm, Advanced Tissue Sciences, Allergan, Aventis, Bristol-Myers Squibb, Combe, Curatek, Ferndale, Fujisawa, Hermal, Hoffman LaRoche, Galderma, Genderm, Glaxo Wellcome, Hill, Janssen, Mayrand, Neostrata, Neutrogena, Novartis, Oclassen, Ortho, Person & Covey, Proctor & Gamble, RJR Nabisco, Schering-Plough, Shelton, SmithKline, Stiefel, 3M, United Catalyst, Upjohn and Wolff Systems.

Joel M. Gelfand, MD: Dr Gelfand served as consultant and investigator with Amgen, Centocor, Abbott, Pfizer, Novartis, and Genentech receiving grants and honoraria; was consultant with Wyeth, Shire Pharmaceuticals, Galderma, Celgene, UBC, and Merck receiving honoraria; and investigator with Shionogi and NIH receiving grants.

Kenneth B. Gordon, MD: Dr Gordon served on the Advisory Board and was consultant, investigator, and speaker for Abbott Labs and Amgen receiving grants and honoraria; was investigator for Celgene receiving grants and was on the Advisory Board, a consultant, and investigator for Centocor receiving grants and honoraria; and on the Advisory Board for Lilly, Pfizer receiving honoraria and on the Advisory Board and investigator for Merck receiving grants and honoraria.

Alice Gottlieb, MD, PhD: Dr Gottlieb served as a consultant, investigator, and on the Advisory Board for Amgen Inc, receiving grants and honoraria; a consultant and served on Advisory Board for Celgene receiving honoraria, served on Advisory Board for Actelion, Cytokine Pharmasciences, Pfizer, and UCB receiving honoraria, consultant for BIND Biosciences, Inc, Magen Biosciences, Schering, Canfite, Incyte, Merck, Ono, and Puretech receiving honoraria; investigator and Advisory board for NovoNordisk and Abbott and Centocor receiving grants and honoraria, and an investigator for Immune control receiving grants.

John Y. M. Koo, MD: Dr Koo served on the Advisory Board, was speaker, consultant and investigator for Amgen, Abbott Labs, Astellas, Warner Chilcott, and Galderma, receiving grants and honoraria; was investigator for Genentech receiving grants; and was on the Advisory Board, consultant and investigator for Photomedix and Teikoku, receiving no compensation.

Mark Lebwohl, MD: Dr Lebwohl served as consultant receiving honoraria for Abbott Laboratories, Allostera, Amgen/Pfizer, Astellas, Cambridge Pharma, Can-Fite Biopharma, Celgene, Centocor/Janssen/J&J, DermaGenoma, DermiPosor, GlaxoSmith Kline- Stiefel, Novartis, and Ranbaxy. Members of Dr Lebwohl’s department own patents on short-contact tazarotene, topi- genistein, and use of the excimer laser for vitiligo. Members of Dr Lebwohl’s department serve as investigators for numerous companies including: Abbott, Actavis, Amgen, aRigen, Astellas, Basilea, Bioform, Celgene, Centocor, Dusa, Galderma, Genentech, Graceway, Lumenis, Longpon, Medicis, Novartis, NovoNordisk, Peplin, Pharmaderm, Profectus, Ranbaxy, Roche, Stiefel, and Wyeth. Dr Lebwohl is a course director for the annual Fall and Winter Clinical Dermatology Conferences and the annual Mount Sinai Winter Symposium which receive support from numerous dermatology companies.

Craig L. Leonardi, MD: Dr Leonardi served as investigator, speaker, and on the advisory Board for Abbott, Amgen, Centocor receiving honoraria and other financial benefit; investigator for Celgene, Eli Lilly, Galderma, Genentech, Glaxo Smith Kline, Novartis, Novo Nordisk, Sirtris, Stiefel, Vascular Biogenics, and Wyeth, receiving other financial benefit, served as investigator and on the Advisory Board for Pfizer receiving honoraria and other financial benefit, and as speaker and Advisory board for Centocor receiving honoraria.

Henry W. Lim, MD: Dr Lim is consultant receiving honoraria for LaRoche-Posay and Orfagen.

Abby S. Van Voorhees, MD: Dr Van Voorhees served on the Advisory Board, was an investigator and speaker and consultant for Amgen receiving grants and honoraria; advisory board member and speaker for Abbott, Connetics, Centocor receiving honoraria; Advisory board, speaker, and investigator for Genentech receiving honoraria and grants; consultant for Incyte, VGX, Leo, and Xtrac receiving honoraria, advisory board and investigator for Warner Chilcott, Bristol Myers Squibb receiving grants and honoraria; Investigator for Roche, Astellas, IDEC receiving
grants; and served another role for Synta receiving honoraria. Dr Van Voorhees' husband is an employee of Merck, receiving salary, stock, and stock options.

Karl R. Beutner, MD, PhD, Chair Clinical Research Committee: Dr Beutner was consultant for Anacor receiving honoraria, stock and stock options.

Caitleona Ryan, MD: Dr Ryan was a speaker for Jansen-Cilag receiving honoraria, served on the advisory board for Galderma receiving honoraria, and had another role with Abbott receiving grants.

Reva Bhushan, PhD: Dr Bhushan had no relevant conflicts of interest to disclose.

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