Focus on Managing Patients with Moderate-to-Severe Plaque Psoriasis

EXPERT perspectives

OVERVIEW

Alan Menter, MD, discusses best practices in establishing disease severity in patients with plaque psoriasis, the efficacy and safety of established and newly approved systemic therapies for treating patients with moderate-to-severe disease, and how to optimize treatment for patients with chronic plaque psoriasis.

CONTENT AREAS

- Assessing psoriasis severity
- Comorbidity evaluation
- Tumor necrosis factor-alpha antagonists
- Newly approved IL-17/IL-23 agents
- Emerging oral therapies

FACULTY

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This activity was developed for dermatologists, dermatology fellows, advanced nurse practitioners, physician assistants and other health care professionals who have an interest in moderate-to-severe plaque psoriasis.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Assess psoriasis patients for disease severity
- Discuss safety and efficacy of newly approved and emerging agents for the treatment of plaque psoriasis
- Optimize treatment for patients with chronic psoriasis by tailoring therapy to meet individual health risk factors and comorbidities, prior treatment history, patient quality of life, and patient preferences

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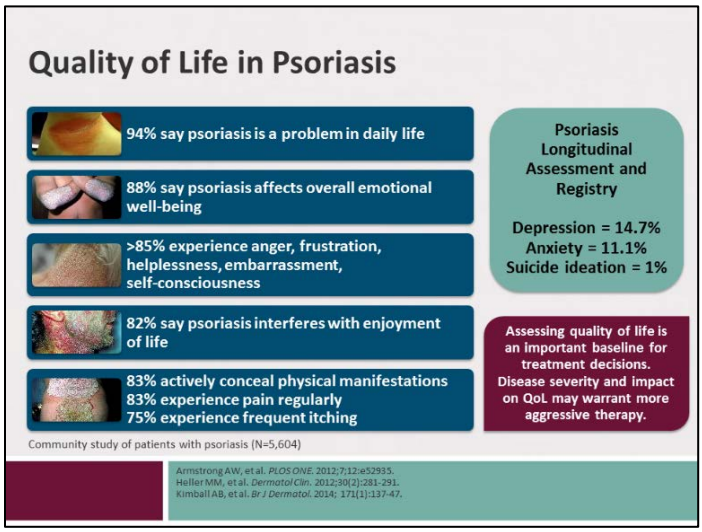
1. What are the most effective strategies for assessing a patient with psoriasis who also has obesity?

Psoriasis is a genetic, chronic, systemic, inflammatory, immune-mediated disease manifesting in the skin and/or joints. Typical symptoms in Caucasian patients include prominent itchy, raised, red areas of skin with scaling and peeling. Clinical presentation in people of color may be more nuanced, including violaceous or hyperpigmented erythema.[1] Severity may range from a few scattered plaques to involvement of almost the entire body surface.[2] Considered the most prevalent autoimmune disease in the United States (US), plaque psoriasis affects 3.5% of adults aged 20-59 years (6.7 million in the US and 120 million worldwide).[3] Primarily diagnosed in people ≤40 years, psoriasis is equally prevalent in both men and women, but has lower prevalence in non-Caucasian populations; 27.3% of people with psoriasis have moderate-to-severe disease.[3-5] Risk factors for psoriasis include family history/genetics, smoking and alcohol use, certain drugs, infections, and obesity (body mass index [BMI] >30 kg/m^2).[6] Higher BMI and weight gain are also risk factors for incident psoriasis in women, and may correlate with the severity of psoriasis.[7-9]

The systemic inflammation associated with psoriasis impacts other organ systems, including the cardiovascular, liver, kidney, respiratory and hematological systems, and may increase the risk for coronary artery disease, type 2 diabetes mellitus, fatty liver disease, stroke, chronic obstructive pulmonary disease, sleep apnea, lymphoma, depression, and neoplasia.[7,10] Patients with psoriasis have higher prevalence of cardiovascular risk factors (obesity, smoking, diabetes, hyperlipidemia, hypertension), and psoriasis itself shares genetic aspects with metabolic syndrome. Psoriasis patients who also have obesity are likely at increased risk for cardiovascular disease.[9] The inflammatory nature of psoriasis with multiple cytologies does bear a close relationship to the inflammatory seen in coronary artery disease.[11]

Physical examination of lesion characteristics (ie, size, shape, boundaries, color, scale, pruritus, and symmetry) is key to initial assessment of all patients with plaque psoriasis, including those with obesity. Clinicians should be sure to include examination of scalp, nails, body folds, and genitalia. Laboratory studies are infrequently required to diagnose and evaluate patients presenting with psoriasis. Clinicians should evaluate the severity of psoriasis, assess patients for the presence of comorbidities, and ask patients about joint symptoms, which could indicate psoriatic arthritis (PSA). Joint pain evaluation is an American Academy of Dermatology competency. Clinicians should consider referral of patients with evidence of psoriatic arthritis to a rheumatologist, as well as patients with cardiovascular comorbidities to a cardiologist. Patients with both moderate-to-severe psoriasis and overweight or obesity should be advised to lose weight as part of cardiovascular risk factor modifications.[12] Studies suggest that weight loss is likely to reduce cardiovascular and metabolic risk and psoriasis severity,[13] and improve response to therapy.[14]

Patient perception of psoriasis is also an important component of assessing disease severity. Psoriasis presents a substantial health care burden on patients and their families, and the psychosocial impact of psoriasis is not always proportional to the severity of skin disease.[5,15] In a National Psoriasis Foundation community-based study on quality of life among patients with psoriasis and psoriatic arthritis (N=5,604), a majority reported these conditions affected their overall emotional wellbeing and interfered with enjoyment of life (88% and 82%, respectively). Most patients reported experiencing anger (89%), frustration (89%), helplessness (87%), embarrassment (87%), and self-consciousness (89%), pain (83%) and pruritus (93%), and also actively concealed physical manifestations of their disease (83%).[14] A registry study also found depression among 14.7% of people with psoriasis, anxiety (11.1%), and suicide ideation (1%).[16]



Therefore, assessing quality of life is an important baseline for treatment decisions, since the impact of disease severity on quality of life may warrant more aggressive therapy. There are several tools for evaluating quality of life and disease burden (Table 1).[17]

Table 1. Validated Quality of Life Evaluation Tools

Dermatology Specific	Psoriasis Specific
Dermatology Life Quality Index	Psoriasis Disability Index
Dermatology Quality of Life Scales	Psoriasis Symptom Inventory
Dermatology Specific Quality of Life	Psoriasis Life Stress Inventory
Skindex-61	Psoriasis Index Quality of Life
Skindex-29	Salford Psoriasis Index
	Koo-Menter Psoriasis Instrument

2. What monitoring strategies should clinicians use when initiating therapy with newly approved systemic agents for patients with moderate-to-severe plaque psoriasis?

A range of approved therapies is available for treating patients with moderate-to-severe psoriasis (ie, 5%-10% of BSA involvement or involvement of the face, palm or sole, or disease), and the American Academy of Dermatology (AAD) has developed algorithms for identifying appropriate therapies for patients (Table 2).[18] The AAD no longer recommends stepwise therapy for patients with moderate-to-severe psoriasis, who are now considered candidates for systemic and/or biologic therapy at diagnosis.[19] Therapeutic decisions should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors, comorbidities, and potential impact on quality of life. Several systemic or biologic medications are also currently under investigation for treating moderate-to-severe psoriasis, including tofacitinib, baricitinib, tildrakizumab, risankizumab, and ponesimod.

First generation biologic agents (ie, infliximab, etanercept, adalimumab) target the proinflammatory cytokine tumor necrosis factor (TNF)-alpha and confer a risk for opportunistic infections, cancer, and reactivation of latent bacterial (eg, tuberculosis [TB], *Legionella*), viral (eg, hepatitis B and herpes zoster), and fungal infections.[20] Infection risk may be greater for patients older than 65 years taking an anti-TNF inhibitor, patients with comorbidities, or patients who are also taking immunosuppressants. An analysis of patients included in the Psoriasis Longitudinal Assessment and Registry (PSOLAR, N=11,466) reported that the cumulative incidence rate of serious infections was 1.45 per 100 patient-years.[21] Treatment with ustekinumab or etanercept was not associated with serious infection, and the most common infections were pneumonia and cellulitis. Second and third-generation biologic agents (ie, ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab), target interleukin (IL)-12/23, IL-17A, and IL-23 and are associated with less immunosuppression, and lower risk for opportunistic infection.

The current standard of care remains to screen patients for TB and hepatitis B and C viruses prior to initiating biologic therapy, in addition to assessing liver function, complete blood count (CBC), liver function tests, and metabolic profile at baseline.[9] Clinicians should ensure that patients are up-to-date with Centers for Disease Control and Prevention recommended immunization vaccines (ie, pneumonia, influenza), which can be downloaded here. Current guidelines also recommend laboratory monitoring every 6 months for patients being treated with biologic agents. With the exception of TB testing, these tests have not been linked to the prevention of adverse outcomes. A recent meta-analysis of studies evaluating biologic therapy monitoring reported the following:[22]

- Strong evidence for TB screening for patients prior to starting therapy with infliximab, etanercept, adalimumab, and ustekinumab with interferon gamma release assay testing
- HBC/HCV screening on the basis of patient history and risk factors (history of liver disease)
- Hepatic function monitoring should be considered for patients with history of HBC/HCV, or patients being treated with infliximab; and
- Insufficient evidence to support monitoring CBC, antinuclear antibodies, C-reactive protein, cholesterol or triglycerides.

The increased risk of renal disease in patients with moderate-to-severe psoriasis means that renal function should be assessed. Likewise, psoriasis patients have a higher risk of increased cholesterol and triglycerides that is not necessarily linked to obesity; therefore, lipid screening is key.

Prescribing information for more recent therapies such as secukinumab, ixekizumab, brodalumab, or guselkumab also recommend screening for TB at baseline and monitoring for the onset or exacerbation of Crohn's disease or ulcerative colitis for ixekizumab. Brodalumab has a black box warning for suicidal ideation and behavior and is available only through a restricted Risk and Mitigation Strategy program, while patients taking apremilast should

be monitored for weight loss as well as for signs of depression.[23]

Table 2. Approved Systemic Therapies for Moderate-to-Severe Psoriasis

Type	Therapy Line
Nonbiologic Systemic Therapies	
Acitretin	First-line in severe disease
Cyclosporine	First-line in severe, recalcitrant disease in patients for whom other systemic therapies are contraindicated; second line in severe, recalcitrant disease in patients who have failed to respond to at least 1 systemic therapy or cannot tolerate other systemic therapies
Methotrexate	First-line in severe, recalcitrant, disabling disease (used short-term, ie, 6 months, as intermittent therapy)
Apremilast	First-line in moderate-to-severe disease
Biologics	
Infliximab	First-line in moderate-to-severe disease
Etanercept	First-line in moderate-to-severe disease
Adalimumab	
Ustekinumab	
Secukinumab	
Ixekizumab	
Brodalumab	
Guselkumab	
Biosimilars	
Infliximab-dyyb	First-line in moderate-to-severe disease
Adalimumab-atto	

3. What are the long-term complications of biologic and other systemic agents in moderate-to-severe plaque psoriasis?

Efficacy for Biologic and Systemic Therapies

Patients with chronic severe plaque psoriasis typically need the continued use of medications during both remission and flare-up periods for long-term psoriasis control.[24] Tumor necrosis factor (TNF)-alpha antagonists have significantly reduced disease activity among patients with psoriasis. A systematic review of randomized trials pointed to the superiority of infliximab for achieving at least 75% PASI improvement following 8 to 16 weeks of treatment, compared with etanercept, adalimumab, ustekinumab, methotrexate, cyclosporine, and alefacept (which is no longer available in the US).[25] However, at week 52 of treated patients, PASI-75 scores for infliximab were reduced to 59%.[26] The same systematic review supported the superior efficacy of infliximab and adalimumab over methotrexate, as well as the superior efficacy of ustekinumab, an IL-12/IL-23p40 subunit inhibitor, over etanercept. Efficacy with apremilast has been reported as lower than success rates reported for cyclosporine, anti-tumor necrosis factor biologic agents, and ustekinumab.[25]

Physician concern about long-term safety and tolerability of currently approved biologic and systemic agents remains a key reason for delays in initiating systemic treatment, switching treatment, discontinuation and restarting, dose escalation and reduction, and combining more than 2 therapies with different mechanisms of action.[27-29] There is no long-term evidence of cumulative toxicities or drug-drug interactions with biologic agents, which generally have a good safety profile besides the small increase in opportunistic infections.[30] Observational studies show treatment persistence rates of 40% to 80% after 1 year of treatment for infliximab, adalimumab, and etanercept and up to 80% at 5 years for ustekinumab and etanercept. Analysis of the length of time that patients stay on biologics, using data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR), showed that drug survival was longest for ustekinumab compared with infliximab, adalimumab, and etanercept across first, second, and third lines of therapy.[31] Although different methodologies are used to report maintenance of response over time, a systematic review of studies on long-term response rates to psoriasis treatment found that the long-term PASI-75 rate was best with ustekinumab (77.7% at 5 years) and worse with etanercept (46% at 24 weeks).[32]

Biologic Failure

However, patient response to treatment with biologic agents can decrease over time as a result of immunogenicity, antidrug antibodies, as well as unknown causes.[28,33] Several studies have reported the formation of antibodies with etanercept, adalimumab, ustekinumab, and, especially, infliximab.[34-37] One review of phase 3 trial data for biologic therapies found that 20% to 32% of patients lost PASI-75 response in 0.8-3.9 years of follow-up, with biologic fatigue most frequent in patients being treated with infliximab.[32] It is difficult to predict which patients will develop antibodies, although biologic therapy interruption may promote antidrug antibody formation.[38]

Clinical trial data demonstrate the efficacy of newer therapies for treating patients with moderate-to-severe plaque psoriasis (ie, secukinumab, ixekizumab, brodalumab, and guselkumab). Data for secukinumab, an IL-17A inhibitor, showed better long-term efficacy for this agent at 52 weeks compared with ustekinumab, with 76% of secukinumab-treated patients achieving PASI-90 vs 61% in the ustekinumab group.[39] Similarly, in patients treated with ixekizumab compared with placebo or etanercept, not only did more patients achieve PASI-75 vs patients treated with placebo or etanercept, but also, 75% of patients treated with ixekizumab every 2 weeks had clear or minimal psoriasis rates at week 60.[40] Long-term treatment with guselkumab is also associated with greater maintenance of response (PASI-90) compared with placebo (89% vs 37%).[41]

Adherence

Patients may not achieve optimal therapeutic response due to a range of other factors such as obesity, their perceptions about disease severity, personal preferences for drug administration, and medication nonadherence.[42] More than 2 out of every 5 psoriasis patients are nonadherent with their prescription medications.[43] Several

strategies can help to optimize adherence, such as explaining the purpose of medication, describing the dosing schedule, addressing patient concerns about the medication, including any anticipated adverse effects, and frequent follow-up during the initiation period.[42] A written treatment plan that includes shorter intervals for follow-up following treatment initiation can improve patient self-efficacy and lead to better treatment outcomes, as can identifying barriers to medication adherence, such as treatment cost.[44]

4. Which proven strategies can clinicians use to help patients with plaque psoriasis become more active in their care?

The overarching goal in treating patients with moderate-to-severe plaque psoriasis is to identify the most appropriate therapy for the level of disease severity while also considering the values, beliefs, preferences, and comorbidities of individual patients. Reaching the best medical decisions depends on understanding what is most important to the individual patient through the process of shared decision-making.[45] While studies find that the majority of patients with psoriasis would like to participate in decision-making, insufficient knowledge about the systemic nature of psoriasis treatment options for psoriasis and their implications represents a barrier to their active involvement.[46]

Actively involving patients in decision-making is a process that includes knowing whether patients understand and can follow through on treatment. Clinicians need to educate their patients about all aspects of psoriasis, especially about the need for long-term management of psoriasis, treatment monitoring, as well as the efficacy, safety, convenience, and insurance coverage of appropriate treatment options.[47] Active solicitation of patient preferences about medication options, including route of administration, can also enhance treatment adherence. In one survey, patients receiving infusions or injectable medications attached greater importance to the probability of benefit, delivery method, treatment location, and treatment duration compared with patients not using infusions or injectables.[48] Revisiting treatment goals at regular intervals, as well as modifying therapy when response is insufficient, can help to achieve and maintain treatment success.[49] Although PASI-75 has long been viewed as a defined treatment target, as suggested in clinical trials of more recently approved biologic agents such as brodalumab, ixekizumab, and apremilast, PASI-90 and PASI-100 may also be considered appropriate outcome measures to evaluate therapeutic response.[50,51]

Studies have shown that patient-physician decision-boards that present treatment options and answer the questions patients most frequently have about those options are useful for educating patients and for facilitating communication and shared decision-making.[45,46] Decision aids have been found to be effective in enhancing patients' knowledge and improving their accuracy of risk perception, leading to decisions that are informed and consistent with their values. The Koo-Menter Psoriasis Instrument (KMPI) is a practical assessment tool that can also aid in clinical decision-making. The KMPI is short and simple enough for the patient and physician to quickly complete, while being comprehensive enough to include a validated Health Related Quality of Life (HRQOL) index, a Psoriasis Quality of Life (PQOL-12) index, and other assessments from both the patient's and the physician's perspective.[28] Decision-making tools represent an effective way for patients and physicians to actively share knowledge with the common goal of ensuring that the patient's psoriasis is treated in the most appropriate way possible.

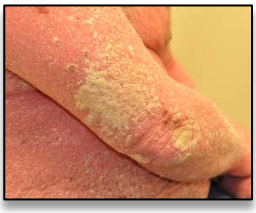
Payer restrictions and prior authorization requirements frequently complicate the use of biologic and systemic therapies. The direct costs of psoriasis are estimated at $12.2 billion annually in the United States.[52] On average, biologics cost an estimated $26,708 per year for maintenance regimens. Ustekinumab can cost as much as $67,148 annually,[53] while maintenance regimens of oral systemic agents can cost an estimated $11,029 per year.[54] Biologic therapies also have different dose regimens across indications, which may not be reflected in payer formularies.[28] Clinicians require an understanding of the various costs of treatment when considering therapy for their patients with psoriasis, in order to work with patients to achieve the desired treatment plan.

Psoriasis Patient Engagement Checklist

- ☑ Initiate treatment during the first consultation
- ☑ Be aware of patients with chronic conditions
- ☑ Review treatment risks/benefits and involve patient in discussion about options
- ☑ Build physician-patient relationship: ***empathy is key***
- ☑ Use EMR for educational materials and an action plan
- ☑ Simplify regimens
- ☑ Use reminder strategies, eg, text messages, weekly pill boxes, multidrug punch cards
- ☑ Support patient self-efficacy, eg, use shorter follow-up intervals and motivational interviewing
- ☑ Consider nonadherence when a given therapy fails
- ☑ Always follow up if in doubt about adherence

Uhlenhake EE, Kurkowski D, Feldman SR. *J Dermatolog Treat.* 2010;21(1):6-12.

5. Case Study



A 60-year-old man presents for an annual wellness check. He has type 2 diabetes mellitus, which he manages with diet and metformin, and has been treated for hypertension for the last 3 years. He has a history of depression, and his body mass index (BMI) is 32 kg/m^2. The patient tells you that he has a "bit of a rash" and his skin has become increasingly itchy. He is currently applying petroleum jelly to his skin after bathing. You suspect the patient may have plaque psoriasis.

◇ Question 1 of 4

Which of the following next steps would you take to evaluate this patient?

A. Recommend a fungal culture
B. Recommend a full skin examination, including all body folds, nails, ears and genitalia
C. Recommend a punch biopsy
D. Switch the patient to a topical corticosteroid

✓ **B is the best answer.**

Full examination of the entire skin surface, including scalp, nails, joints, axial skeleton, and anogenital skin is required to diagnose and classify disease severity in plaque psoriasis.

Discussion

Symptom presentation, combined with the presence of comorbidities (type 2 diabetes and hypertension) and evidence of obesity (BMI ≥30 kg/m^2) should raise suspicion for plaque psoriasis in this patient. Symptoms of psoriasis include rash, itching, joint pain, and nail problems. The diagnosis for plaque psoriasis, which is characterized by symmetric, well-defined erythematous plaques with a silvery scale, is typically based on clinical findings from a full physical examination of the entire skin surface, including scalp, nails, joints, axial skeleton, periumbilical area, and anogenital skin.[30] Examination should assess the distribution, pattern, and morphology of lesions. Skin biopsy is rarely used to diagnose psoriasis and fungal culture is warranted when onychomycosis is suspected.

Disease severity is defined by the extent of body surface area (BSA) involvement as well as involvement of the hands, feet, facial, or genital regions.[18] Even though the involvement of these areas may result in a small BSA, interference with activities of daily life and psychological effects are frequently significant. There are several tools for evaluating disease severity. BSA measures the percentage area of involvement and determines the location of lesions. The patient's palm, measured from the wrist to the tips of their fingers, represents 1% of BSA.[55] BSA <5% is considered mild, ≥5% < 10% moderate, and ≥10% BSA is considered severe. The Psoriasis Areas and Severity Index (PASI) is another measure of overall psoriasis severity and coverage that assesses BSA and erythema, induration, and scaling. A 75% improvement in PASI following 12-16 weeks of treatment is considered a clinically relevant treatment response.[9] The Physician Global Assessment (PGA) assigns a single estimate of a patient's overall severity of disease, typically using a 7-point scale from clear to severe.

Case Continues

Physical examination reveals that the patient has generalized discoid plaques on his elbows, knees and trunk, with coarse, well-defined silvery-scaled plaque on his scalp. You determine that the patient has moderate-to-severe plaque psoriasis (BSA >10%) and initiate a conversation about disease management.

◇ Question 2 of 4

Which of the following steps are required prior to initiating treatment?

A. Examine the patient's joints
B. Order a chest x-ray
C. Assess disease severity from the patient's perspective
D. Assess patient quality of life
E. A, C and D

✓ **E is the best answer.**

Clinicians need to evaluate patients for comorbidities, examine joints and the axial skeleton for psoriatic arthritis, and evaluate the extent to which psoriasis affects patient quality of life.

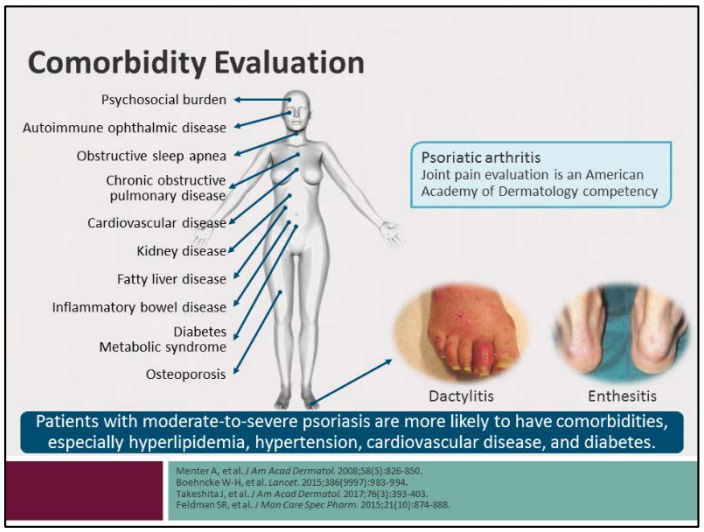
Focus on Managing Patients with Moderate-to-Severe Plaque Psoriasis

Discussion

Psoriasis is a complex, immune-meditated disease associated with genetic predisposition and multiple risk factors, including obesity and higher BMI in adults.[56] Psoriasis can be complicated by arthropathy, erythroderma, the Koebner phenomenon—in which new plaque lesions arise at sites of skin trauma or injury—and psoriatic arthritis, which affects approximately 30% of patients with psoriasis.[57] Obesity, diabetes, lipid abnormalities, and hypertension occur more often in people with psoriasis than in the general population,[6,58] and is associated with an increased risk of cardiovascular disease (CVD).[59,60]

In addition to determining psoriasis severity, clinicians need to examine joints and the axial skeleton for psoriatic arthritis. Common features include dactylitis, in which fingers and toes become swollen, and enthesitis, which involves Achilles swelling and tenderness. Clinicians should also evaluate patients for the presence of other comorbidities, such as inflammatory bowel disease, uveitis, sleep apnea, chronic obstructive pulmonary disease, osteoporosis, and psychiatric/psychological disorders.[59] Patients with psoriasis should also be counselled and educated about the increased risk for CVD and its associated morbidity and mortality risk.

Patient perception of psoriasis is an important component of assessing disease severity. Psoriasis can contribute to significant social and psychological distress and disability via itching, pain, difficulty walking or using one's hands, embarrassment, and anxiety. Therefore, clinicians also need to evaluate the extent to which psoriasis affects patient quality of life.[17] There are several validated instruments for evaluating quality of life in psoriasis, including the Salford Psoriasis Index, the Psoriasis Life Stress Inventory, and the Koo-Menter Psoriasis instrument.[17] These tools can help clinicians to identify patients with reduced quality of life for whom systemic treatment is warranted.[28]



Case Continues

Following a full evaluation, you discuss treatment options with the patient.

◇ Question 3 of 4

Which of the following therapies is most likely to achieve clinical response and improve comorbidities for this patient?

A. Calcipotriene
B. Methotrexate
C. TNF-alpha antagonist
D. Narrow band UVB

✓ **C is the best answer.**

TNF-alpha inhibitors are recommended as first-line therapies for patients with moderate-to-severe disease.

Discussion

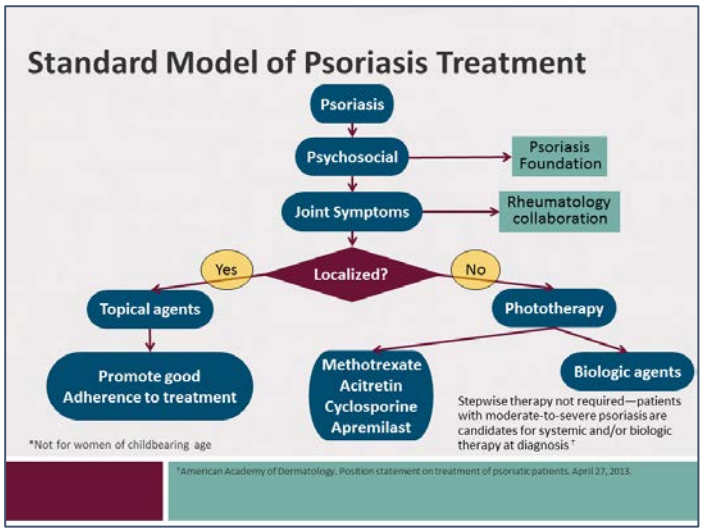
Therapeutic options vary according to the extent of disease.[19] Topical therapies such as steroids and calcipotriene, a vitamin D analogue, are typically reserved for patients with mild-to-moderate disease. Systemic therapies include phototherapy (psoralen plus UVA, broadband UVB, and narrowband UVB), methotrexate, acitretin, cyclosporine, apremilast (an oral phosphodiesterase type-4 inhibitor), and several biologic agents that are administered via subcutaneous injection or intravenous infusion. Treatment of the systemic inflammation of psoriasis may also reduce the burden of psoriasis-related comorbidities, especially for patients with >10% BSA involvement; therefore, American Academy of

Dermatology (AAD) guidelines recommend systemic therapy for patients with severe disease (>10% BSA) and for patients with inadequate response to topical therapies. The old paradigm of "stepwise-therapy", ie, first phototherapy, then oral systemic therapies and finally biologic therapies in ascending order, is no longer an AAD recommendation.[19] As indicated by labelling for approved biologic injectable agents, patients with moderate-to-severe psoriasis are candidates for systemic therapy or phototherapy.

While phototherapy is associated with improvements in psoriatic skin lesions, this modality is time-consuming, mostly beneficial for short-term treatment, and cumulative doses are associated with adverse effects.[30] Low-dose weekly methotrexate (MTX) is demonstrably effective in treating patients moderate-to-severe psoriasis in up to 40% of cases, although this agent is associated with cumulative hepatotoxicity, and has less efficacy for skin clearance than TNF-alpha antagonists.[9] MTX is recommended as second-line therapy in severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. Tumor necrosis factor (TNF)-alpha antagonists include infliximab, adalimumab, and etanercept, as well as newer biologic agents that target interleukin (IL)-12/23, IL-17A, and IL-23, including ustekinumab, brodalumab, ixekizumab, secukinumab, and guselkumab. While there is no single sequence in which biologic therapies should be initiated,[9] a meta-analysis of pivotal phase 3 studies suggested that infliximab might be the most efficacious first-line TNF-alpha antagonist, followed by ustekinumab, adalimumab, and etanercept.[61] Another meta-analysis of 48 trials of approved systemic therapies reported that among biologics, infliximab had the highest efficacy short-term, followed by adalimumab and ustekinumab.[25] However, the early, quick response associated with infliximab is accompanied by significant reduction in efficacy longer-term.

In addition to suppressing psoriasis progression, treatment with tumor necrosis factor alpha blockers is associated with risk reduction for CVD and delays radiographic progression of joint disease.[12]

Psoriasis patients with moderate-to-severe psoriasis are candidates for systemic therapy at diagnosis. In practice, many insurance companies require clinicians to adopt a step-wise approach to treatment, in which failure of response to topical and/or conventional systemic therapies is required before being able to prescribe biologics.[28] Clinicians need to ensure that patients understand the efficacy, safety, convenience, and insurance coverage of appropriate treatment options, so that they can be involved in making decisions about treatment, which can help to maximize adherence.[28]



Case Continues

The patient returns to see you 6 months following treatment. Despite an early, quick response to the first 3 infusions over 6 weeks, he has not achieved BSA ≤3%, and quality of life evaluation reveals that he is becoming despondent. He is embarrassed by his appearance, has considerable pruritus, and has taken several days off work in the last 3 months. The patient is very dissatisfied with treatment thus far.

◇ Question 4 of 4

Which of the following next steps would you recommend?

A. Continue with infliximab for another 3 months
B. Add methotrexate to infliximab
C. Switch to an IL-17 or IL-23 inhibitor
D. Adjust the infliximab dose

✓ **C is the best answer.**

Clinical studies have demonstrated excellent responses to IL-17 and IL-23 agents, which also have good safety profiles; therefore, switching to 1 of 4 newer IL-17 or IL-23 agents will provide a more lasting outcome for this patient.

Discussion

Psoriasis is associated with significant clinical and emotional morbidity, often impacting patient employment and social relationships; therefore, it is important to determine the best treatment possible for patients to achieve skin clearance. Nonetheless, treatment with first-line biologic agents fails for many patients with moderate-to-severe plaque psoriasis. First, patient response to treatment with biologic agents can decrease within the first 12 months of treatment as a result of immunogenicity, antidrug antibodies, or infusion-reactions, especially with infliximab.[28,33] Loss of initial efficacy and inadequate control by current therapy are common reasons that clinicians cite for changing treatment for a patient with moderate to severe psoriasis.[29]

Second, patients may be nonadherent to psoriasis treatment. Nonadherence is associated with having several comorbidities and competing health priorities, being female, being ineligible for low-income subsidies, or being treated with a self-administered biologic agent.[62] It is important to monitor patients for medication adherence at follow-up visits, use reminder strategies to support adherence, and determine how satisfied patients are with their current treatment, as this factor may influence adherence.[49] Studies of patient-reported treatment satisfaction with biologics suggest they consider treatment effectiveness as the most important factor, followed by treatment safety and doctor–patient communication.[63] Indeed, data from the National Psoriasis Foundation show that more than 50% of US patients are dissatisfied with their treatment, although satisfaction was higher for patients treated with phototherapy, biologic monotherapy, or biologics combined with MTX.[27] However, it is important to recognize that this review was published prior to the availability of IL-17 and IL-23 agents.

There are currently no clear sequencing steps or algorithms for treating patients with moderate-to-severe plaque psoriasis following first-line failure of biologic agents, although current US treatment guidelines support using combination therapy with a biologic agent and an immunosuppressant (eg, low-dose methotrexate).[9] These guidelines are being updated and will change significantly to reflect more recent clinical data.

Although meta-analyses have suggested that the magnitude of response for TNF-alpha inhibitors is greatest for infliximab, followed by adalimumab and then etanercept,[25] clinical trial data for more recently approved biologic agents suggest higher efficacy for secukinumab vs ustekinumab at week 16 (79% vs 57.6% PASI-90), with sustained long-term responses.[64,65] Most recently, extended data presented at the European Academy of Dermatology and Venereology 2017 Congress showed that a majority of patients with moderate-to-severe psoriasis who were treated with secukinumab achieved long-lasting skin clearance. PASI-75 and 90 response rates were achieved by 89% and 66% of treated patients and remained consistent over five years of treatment.[66]

Similarly, the sum of clinical data for ixekizumab shows high levels of skin clearance at week 12 (80.9% PASI-75 every 4 weeks, and 89.3% every 2 weeks,[66,40] as well as superiority over both etanercept and ustekinumab at weeks 12 and 24.[66,67] Brodalumab induced an 86% PASI-75 response in the best performing cohort and it was shown to be superior to ustekinumab treatment in the AMAGINE-3 study;[68] however, brodalumab is associated with a short increased risk for suicidal ideation and behavior, and may not be an effective option for patients with a history of depression. Guselkumab is another newly approved option. In a phase 3 trial comparing guselkumab with adalimumab, guselkumab 100 mg was associated with higher Physician Global Assessment [PGA] scores and PASI-90 vs placebo and adalimumab 80 mg (84.1% vs 8.5%/67.7%; 70% vs 2.4%/46.8%, respectively).[16] At week 28, patients who lost response were switched to guselkumab, and 66.1% achieved PASI-90 at week 48. Finally, in clinical trials for newly approved tildrakizumab, a p19 monoclonal antibody, 63% of patients achieved PASI-75 by week 12 after 2 injections, and 77% achieved PASI-75 after 28 weeks and 3 injections of 100 mg tildrakizumab. On average, 57% and 66% of patients had a PGA score of “clear” or “minimal” at weeks 12 and 28, and a higher number of patients achieved PASI-90 and PASI-100 compared to placebo and etanercept.

Several agents targeting different pathways are currently under investigation, such as JAK inhibitors tofacitinib and baricitinib, as well as IL-23 inhibitors risankizumab and tildrakizumab. Early results suggest efficacy and safety for these agents in managing patients with moderate-to-severe psoriasis.[71-73]

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