New Horizons in the Treatment and Management of Moderate-to-Severe Psoriasis: Tailoring Treatments to Achieve Improved Patient Outcomes and Quality of Life

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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New Horizons in the Treatment and Management of Moderate-to-Severe Psoriasis: Tailoring Treatments to Achieve Improved Patient Outcomes and Quality of Life

Instructions for CME/CNE: Activity is valid from May 1, 2018 to April 31, 2020.
A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send completed post-test and evaluation to:

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Learning Objectives:

1. Design individualized treatment plans for patients with moderate to severe psoriasis using clinical safety and efficacy data that take into account quality of life and the patient's perspectives on disease severity and measures of treatment success.
2. Examine current and emerging biological therapies with IL-17 and IL-23 pathway inhibitors in patients with moderate-to-severe psoriasis.
3. Explain newer pathways for the development of plaque psoriasis and their implications for determining treatment, based on current evidence.
4. Analyze the most up-to-date diagnostic criteria and standard treatment options for moderate to severe psoriasis patients.
5. Assess practical treatment considerations for patients with psoriasis who have challenging comorbidities.
6. Integrate interventions to coordinate health plan and affiliated provider's efforts that will lead to better outcomes for patients with psoriasis.
7. Address challenges to patient adherence and quality of life and formulate strategies to manage treatment related adverse events.
8. Provide a strategy to identify the appropriate patient populations who will benefit from newer biologic agents.
9. Apply methods to enable optimal cost management of newer biologic therapies to be realized by multiple psoriasis stakeholders including managed care organizations.

Faculty Disclosure:

Dr. Armstrong has disclosed the following relevant financial relationships: serves as a consultant for AbbVie, Amgen, Janssen, Merck, Eli Lilly, Novartis, Pfizer, Celgene, Modernizing Medicine, Regeneron, Sanofi, Science 37, and Ortho Dermatologics; received grants/research support from Amgen, AbbVie, Janssen, and Eli Lilly; and serves on the speaker's bureau for AbbVie, Janssen, and Eli Lilly.
Dr. Kalb has disclosed the following relevant financial relationships: received grant/research funding from AbbVie, Amgen, Janssen, Merck, and Novartis; served as a consultant for Dermira, Janssen, and Sun Pharma; and served on the data safety monitoring board for Lilly USA.
Dr. Owens has disclosed the following relevant financial relationships: serves on an advisory board or panel for Lilly and Novartis and serves as a consultant for Sanofi and Regeneron.

All material has been peer reviewed for bias.

Planning Committee Disclosure

Bill Williams, MD; Jacqueline Cole, RN and Jeremy Williams have no relevant financial relationships to disclose.

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Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit.

This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN re-certification requirements.

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Post-Test Questions

1. Which of the following is NOT an accurate statement about psoriasis?
   a. Psoriasis is a chronic inflammatory systemic disease.
   b. It is a rare autoimmune disease in the U.S.
   c. Plaque psoriasis is the most common type.
   d. Because of the appearance of affected skin and significant itching, psoriasis has a major impact on quality of life.

2. Which of the following has NOT been identified as a trigger for the develop of psoriasis?
   a. Stress b. Skin injury c. Prenatal exposures d. Infection

3. Both localized and systemic inflammation is caused by defects in _____ and upregulation of _____, antigen presenting cells, and cytokines.
   a. Cytokine function, T regulatory cells
   b. T regulatory cells, T helper one (Th1) and Th17 cells
   c. Interleukin regulation, T helper one (Th1) and Th17 cells
   d. Immune cell production, T suppressor cells

4. Up to 30 percent of individuals with psoriasis will develop which of the following comorbidities?
   a. Cancer b. Depression c. Obesity d. psoriatic arthritis

5. The National Psoriasis Foundation treatment target in psoriasis is _____ after treatment initiation and maintained thereafter.
   a. Affected BSA $\leq$ 1 percent at three months
   b. PASI 100 at six months
   c. Affected BSA $\leq$ 3 percent at six months
   d. PASI 75 at three months

6. Which of the following patients will likely need systemic therapy?
   a. 3 percent BSA and minimal impact on quality of life
   b. 2 percent BSA affected
   c. Severe localized psoriasis of the palms
   d. 1 percent facial psoriasis

7. Which of the following classes is associated with increased risk of malignancy, primarily skin cancers with > 12 months use?
   a. TNF inhibitors b. Methotrexate
   c. Anti-IL-23 d. Anti-IL-17

8. Which of the following is an accurate statement about ustekinumamb?
   a. It is the most effective biologic for psoriasis.
   b. Long term efficacy and safety are not known.
   c. There is an increased risk of hematologic malignancies with long-term use.
   d. It blocks the p40 subunit that is found on both IL-12 and IL-23.

9. Which of the following is the major difference of Brodalumab from the other anti IL-17 agents?
   a. It has been shown to be more effective than the other anti IL-17 agents.
   b. It is only available through a REMS program because of suicidal thoughts and behavior.
   c. It inhibits the biological activity of various interleukin isoforms which is a therapeutic advantage.
   d. It causes a much lower rate of adverse effects than the other agents in this class.

10. The anti IL-17A and anti IL-23 agents are the most effective psoriasis therapies currently available?
    a. True b. False

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented, I am better able to:

   Design individualized treatment plans for patients with moderate to severe psoriasis using clinical safety and efficacy data that take into account quality of life and the patient's perspectives on disease severity and measures of treatment success.

   4 3 2 1

   Examine current and emerging biological therapies with IL-17 and IL-23 pathway inhibitors in patients with moderate-to-severe psoriasis.

   4 3 2 1

   Explain newer pathways for the development of plaque psoriasis and their implications for determining treatment, based on current evidence.

   4 3 2 1

   Analyze the most up-to-date diagnostic criteria and standard treatment options for moderate to severe psoriasis patients.

   4 3 2 1

   Assess practical treatment considerations for patients with psoriasis who have challenging comorbidities.

   4 3 2 1

   Integrate interventions to coordinate health plan and affiliated provider's efforts that will lead to better outcomes for patients with psoriasis.

   4 3 2 1

   Address challenges to patient adherence and quality of life and formulate strategies to manage treatment related adverse events.

   4 3 2 1

   Provide a strategy to identify the appropriate patient populations who will benefit from newer biologic agents.

   4 3 2 1

   Apply methods to enable optimal cost management of newer biologic therapies to be realized by multiple psoriasis stakeholders including managed care organizations.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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Introduction

Psoriasis is a chronic inflammatory systemic disease with well characterized pathology occurring in the skin and often the joints. Affecting 7.5 million people, it is the most common autoimmune disease in the United States.[1,2] There are several types of psoriasis – plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis represents about 80 percent of the cases and is the focus of this monograph. Because of the appearance of affected skin and significant itching, psoriasis has a major impact on quality of life. Advances in the understanding of the underlying pathophysiology have led to the development of several biologic agents with significant benefits.

Epidemiology

Psoriasis can present at virtually any age; however, the most common age groups for development are 20 to 30 and 50 to 60 years, with men and women developing psoriasis at similar rates.[1,3] Psoriasis also occurs in all racial groups, but at varying rates. Approximately 1.9 percent of African Americans are affected, compared to 3.6 percent of Caucasians.[1]

Pathophysiology

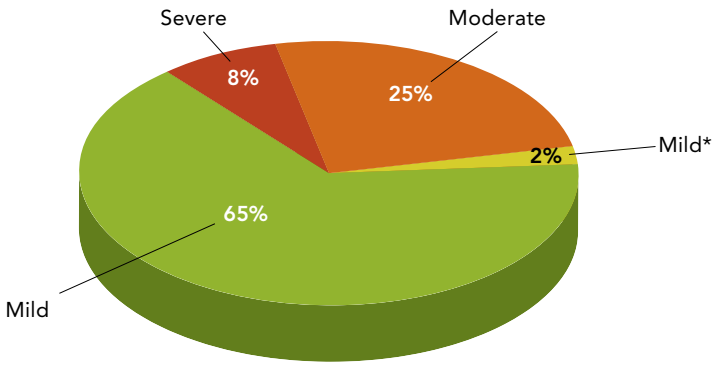
While it is unknown exactly what causes psoriasis, the immune system and genetics play major roles in its development. Twenty-five genetic variants that make a person more likely to develop psoriatic disease have been identified.[1] Approximately 14 percent of those with one parent affected and 41 percent with both parents affected will have the disease. It is postulated that for a person to develop psoriasis, that person must have a combination of the genes that predispose to psoriasis and be exposed to specific external factors (triggers), such as stress, skin injury, certain medications (anti-malarial, indomethacin, lithium, quinidine, propranolol), or infection.[1] Depression, smoking, alcohol, and obesity are other possible triggers.

Psoriasis is driven by inflammation and hyperproliferation of the keratinocytes in the epidermis, with an increase in the epidermal cell turnover rate. The epidermis is infiltrated by a large number of activated T cells, which are capable of inducing keratinocyte proliferation. Both localized and systemic inflammation is caused by defects in T regulatory cells and upregulation of T helper 1 (Th1) and Th17 cells, antigen-presenting cells, and cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukins-12, 17, 22, 23).[1] There is associated elevation of inflammatory markers, such as C reactive protein.

Epidermal hyperproliferation is clinically appreciated as scaling and cracking plaques. There is also angiogenesis which can be seen with the appearance of small bleeding points after successive layers of scale have been removed from the surface of psoriatic plaques. The angiogenesis is associated with increased circulating vascular endothelial growth factor (VEGF).

Psoriasis is not just a skin disease; it is a systemic inflammatory disease. Because of the inflammatory state, psoriasis patients are more likely to have associated comorbidities, including cardiovascular disease, psoriatic arthritis, depression, obesity, diabetes, hypertension, and cancer. Up to 30 percent of individuals with psoriasis will develop psoriatic arthritis (PsA), an inflammatory form of arthritis that can lead to irreversible joint damage if left untreated.[4]

Exhibit 1: Distribution of Psoriasis Severity[7]



* Current phototherapy or systemic medication

Source: National Psoriasis Foundation (random sample of 278 adults with psoriasis)

Someone with psoriasis is 58 percent more likely to have a major cardiac event and 43 percent more likely to have a cerebrovascular accident.[5]

Diagnosis/Classification

Plaque psoriasis can usually be diagnosed by a physical exam of the skin, nails, and scalp.[6] The differential diagnosis includes lichen planus, pityriasis rosea, tinea corporis, and seborrheic dermatitis. Labs and other diagnostics are usually not required except as a prerequisite to biologic or immunosuppressive treatment. Unlike other autoimmune diseases, histopathological examination and blood tests are generally not valuable tools in making the diagnosis of psoriasis. However, on occasion, a skin biopsy may be helpful in confirming the diagnosis of psoriasis. In general, psoriasis is classified as mild [affecting less than 3% of the body surface area (BSA)], moderate [3-10 % BSA] or severe [>10% BSA]. Two-thirds of patients with plaque psoriasis have mild to moderate disease and one-third have a more severe presentation (Exhibit 1).[7]

Unmet Needs

Several unmet needs have been identified in patients with psoriasis, including undertreated symptoms, undertreated disease, general treatment dissatisfaction, and underdiagnosed psoriatic arthritis.[8-11] In a Multinational Assessment of Psoriasis and Psoriatic Arthritis, itching was reported as the most important factor contributing to disease severity by 36 percent of psoriasis patients versus 12 percent of dermatologists.[9] Patients reported lower rates of current treatment than did dermatologists and rheumatologists with conventional oral systemic therapies and biologic therapies only being used by 24.9 and 17.7 percent of patients, respectively.[9] Assuming one-third of patients have moderate-to-severe disease, these figures may be low, but severity was not documented in this survey. Even though the newer biologics can lead to 80 percent or greater skin clearance, many patients still do not achieve the goal of clear or near clear skin. Among patients receiving injectable biologics, treatment dissatisfaction was related to long-term safety/tolerability, injection-related anxiety/fear, and cost.[9] In a patient survey, 46 percent thought that the treatments were worse than the disease, and 85 percent stated there was a need for better therapies.[10]

PsA is underdiagnosed. The percentage of patients who meet the criteria for PsA but are not diagnosed has been reported to be 10 to 50 percent.[11,12] Because of underdiagnosis and undertreatment, the long-term outcomes for patients with PsA tend to be poor, marked by disease progression, poor health-related quality of life (HRQOL), significant disability, comorbidities, and high direct and indirect costs.[11]

Treatment

The goals of treatment are to clear skin symptoms, enhance quality of life by minimizing daily burden of the disease, minimize adverse events through individualization of therapy, minimize comorbid disease burden, and maintain patient involvement. The goal of clearing skin is not well defined. This could be achieving a Psoriasis Area and Severity Index score of 75, 90 or 100 percent clearing (PASI 75, PASI 90

or PASI 100). The long-term benefits of achieving clear (PASI 100) versus almost clear (PASI 75) skin have not been determined. The National Psoriasis Foundation treatment target is a BSA less than or equal to 1 percent at three months after treatment initiation and maintained thereafter.[13] An acceptable response at three months post therapy initiation is either BSA 3 percent or less or BSA improvement 75 percent or more from baseline.[13] During the maintenance period, evaluation every six months is recommended by the National Psoriasis Foundation. Although affected BSA is typically used to evaluate therapy in practice, it does not encompass HRQOL, costs, and risks of side-effects.[13]

One of the challenges in managing psoriasis is that patients present with a broad spectrum of symptoms and severity. A variety of treatment options are available. For mild disease, topical therapy alone is appropriate and this level of disease can typically be managed by primary care providers. Severe disease requires systemic therapy and should be managed by dermatologists or rheumatologists. For moderate disease (>3% but less than 10% BSA), the effect of the disease on the patient's QOL, presence of arthritis, patient preferences, past therapies, and other factors will need to be considered in whether to choose systemic therapy. Most of those with moderate disease will require more than topical therapy to achieve clearing. One caveat is that severe localized psoriasis of the palms, soles, face, or genital area is considered severe disease, even though only 1 percent of BSA is affected, and will likely require systemic therapy.

The traditional treatment approach to psoriasis had been to manage with topical anti-inflammatory corticosteroids, turning to systemic therapy when those failed. Systemic therapy, before the advent of biologics, included nonspecific immune modulators, such as methotrexate and cyclosporine, retinoids (acitretin [Soriatane®]), or phototherapy. Phototherapy is very effective, but it is not widely available in many communities. Additionally, the insurance coverage structure with copays per treatment can make this cost prohibitive for many patients. Apremilast (Otezla®), a phosphodiesterase-4 (PDE4) inhibitor which reduces inflammation, is a relatively new oral systemic agent FDA approved for treatment of moderate-to-severe plaque psoriasis and active psoriasis arthritis. It is modestly effective with 33 percent of patients achieving a PASI 75 with this agent compared with a 5 percent response with placebo.[14]

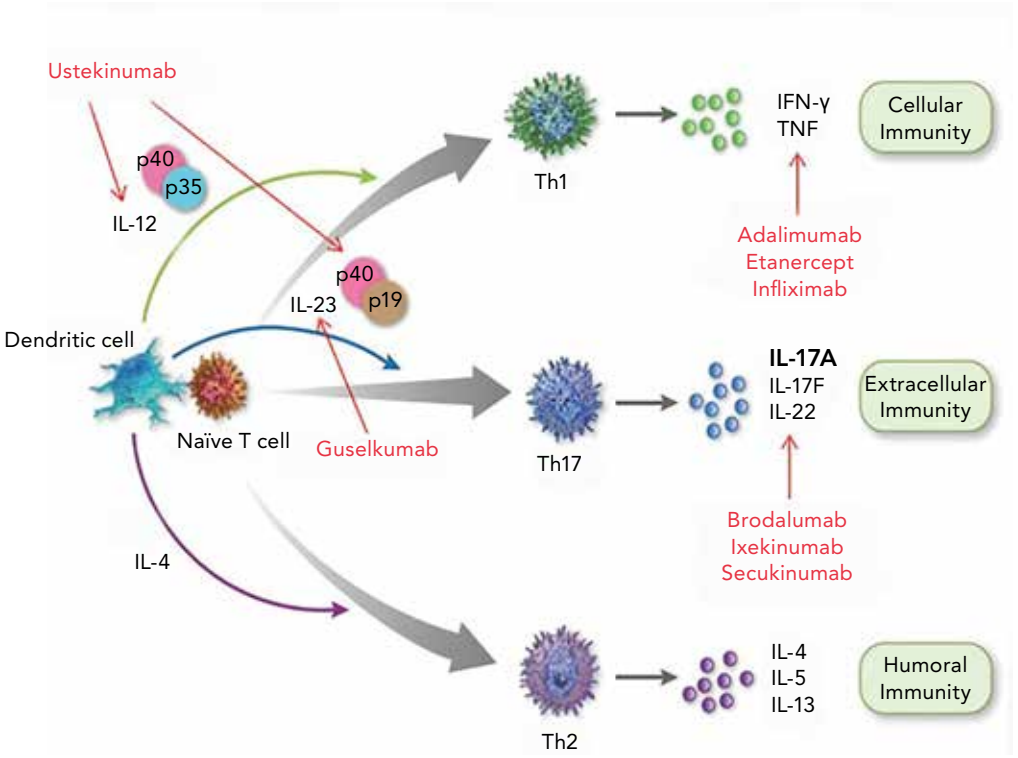
Advances in studies of the immunological basis of psoriasis, combined with progress in genetics, microbiology, and bioengineering, have resulted in a shift in therapeutic focus toward biologic agents that interfere with the psoriasis disease process at the cellular level. The biologic agents have the ability to interrupt the disease pathway through the modulation of T-cell response and cytokine levels and may, therefore, slow or halt disease progression. Biologics are the treatment of choice for moderate-to-severe disease, especially for patients for whom current therapies are no longer effective or cause unacceptable side effects. Biologic therapies have put an end to the graduated approach to psoriasis treatment and have revolutionized the treatment of moderate-to-severe plaque psoriasis. Exhibit 2 illustrates the various immune pathways that are thought to be involved in psoriasis and where the biologics work. The Th17/extracellular immunity pathway is thought to be the most important in psoriasis.

The biologics approved for treating moderate-to-severe psoriasis include etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), ustekinumab (Stelara®), secukinumab (Cosentyx®), ixekizumab (Taltz®), brodalumab (Siliq®), and guselkumab (Tremfya®). All of the biologics significantly improve the PASI 75 score in short-term trials and are better than placebo.[15]

Etanercept, adalimumab, and infliximab are all tumor necrosis factor (TNF) inhibitors and are indicated for moderate-to-severe plaque psoriasis. Etanercept is given as a subcutaneous injection of 50 mg twice weekly for the first three months of therapy, followed by a 50 mg injection once weekly for maintenance therapy. Adalimumab is given as an initial subcutaneous injection of 80 mg and then 40 mg every other week, beginning one week after the initial dose. Standard dosing for infliximab for adults is an intravenous infusion of 5 mg/kg at weeks zero, two, and six, followed by every eight weeks thereafter.

There are some important safety considerations with the anti-TNF biologics for psoriasis. Anti-TNF therapy should not be started or continued in patients with serious active infection and should be used with caution in those at high risk of infection. All patients have to be screened for mycobacteria, human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) infection before starting TNF inhibitors. Prophylactic vaccination for tuberculosis and HBV in high-risk patients should be considered before initiating therapy. In patients with HIV, HBV, or HCV, TNF inhibitors should only be used in those with well-controlled disease. This class also should be avoided in patients with a current or previous history of malignancy, unless there is a high likelihood of cure or the malignancy was diagnosed and treated more than 10

Exhibit 2: Action of Biologics in Psoriasis



years ago. From data in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), long-term (>12 months) TNF inhibitor use is associated with increased risk of malignancy, primarily skin cancers.[16] Thus, patients need regular screening for skin cancers while on therapy. TNF inhibitor therapy must be stopped prior to women getting pregnant and is restarted following the end of lactation or delivery if the mother is not breastfeeding.

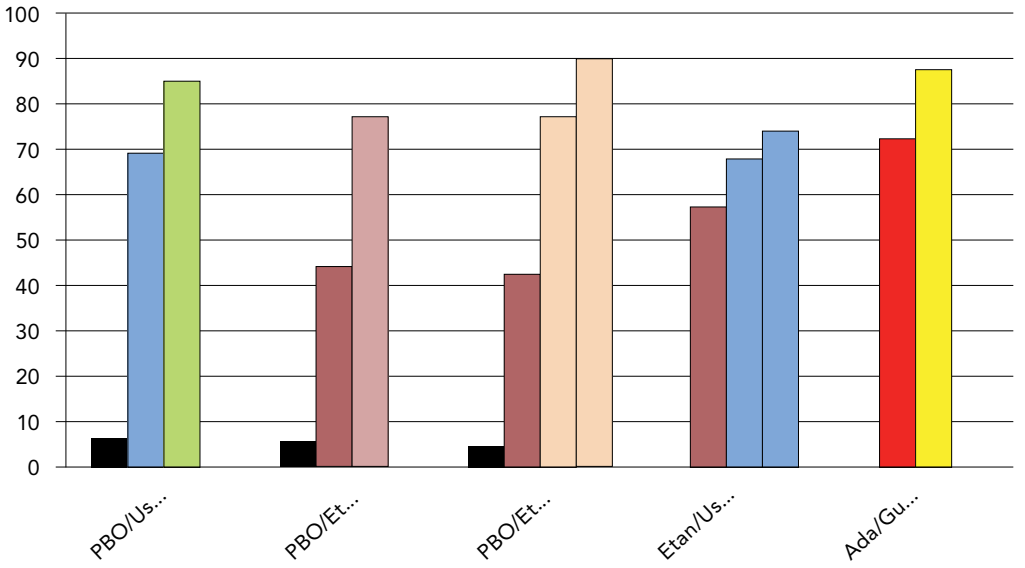
Ustekinumab (Stelara®) is an anti-IL-12 and 23 agent indicated for moderate-to-severe plaque psoriasis. It blocks the p40 subunit that is found on both IL-12 and IL-23 (Exhibit 2). Standard dosing for ustekinumab for adults weighing less than 100 kg is 45 mg given at weeks zero, four, and every 12 weeks thereafter. A 90 mg dose given in the same regimen is recommended for adults who weigh more than 100 kg. It is more effective than placebo (70% vs 3%) and etanercept (68% to 74% vs 57%) in achieving PASI 75.[17-21] Efficacy and safety have been shown out to five years.[17] Based on long-term data, there does not appear to be an increased overall risk of serious infection or malignancy with this agent compared to background rates.[16,17]

Secukinumab (Cosentyx®), an anti- IL-17A agent, was the first in its class of agents targeting IL-17 and is indicated for moderate-to-severe plaque psoriasis. This agent selectively binds with the IL-17A cytokine to inhibit its activity. It is given as an initial 300 mg dose subcutaneously at weeks zero through four and then a 300 mg monthly maintenance dose is started four weeks later. In trials, it has produced superior results to etanercept (PASI 75 77% vs 44%) and ustekinumab (PASI 100 46% vs 36%).[22, 23] Efficacy and safety have been reported out to three years.[24]

A second anti IL-17A agent, ixekizumab (Taltz®), was approved in 2016 and also selectively binds with the IL-17A cytokine to inhibit its activity. It has also been shown superior to etanercept (PASI 75 89.7% vs 48.1%, PASI 100 40% vs 5%).[25] It is given as two 80 mg subcutaneous injections initially, then 80 mg every two weeks for 12 weeks, and then 80 mg every four weeks. Data on use out to 108 weeks with sustained PASI 75 have been published.[26]

Brodalumab (Siliq®), the third anti-IL-17 agent, was approved in 2017. It is different from the other two because it antagonizes the IL-17 pathway by binding with high affinity to the IL-17 receptor. It inhibits the biological activity of IL-17A, IL-17F and other IL-17 isoforms.[27] Whether this difference in mechanism of activity has any efficacy or safety advantage or disadvantage compared with the other anti-IL17 agents is unknown. Given as 210 mg ev-

Exhibit 3: Comparison Trials – PASI 75[19,22,25,28,29]



PBO = placebo
Uste = ustekinumab weight based q2wk
Broda = brodalumab 210 mg q2wks
Secuk = secukinumab 300 mg q month
Ixe q4 = ixekizumab 80 mg q2wks
Ixe q2 = ixekizumab 80 mg q4 wks
Ada = adalimumab 80 mg
Gusel = Guselkumab 100 mg

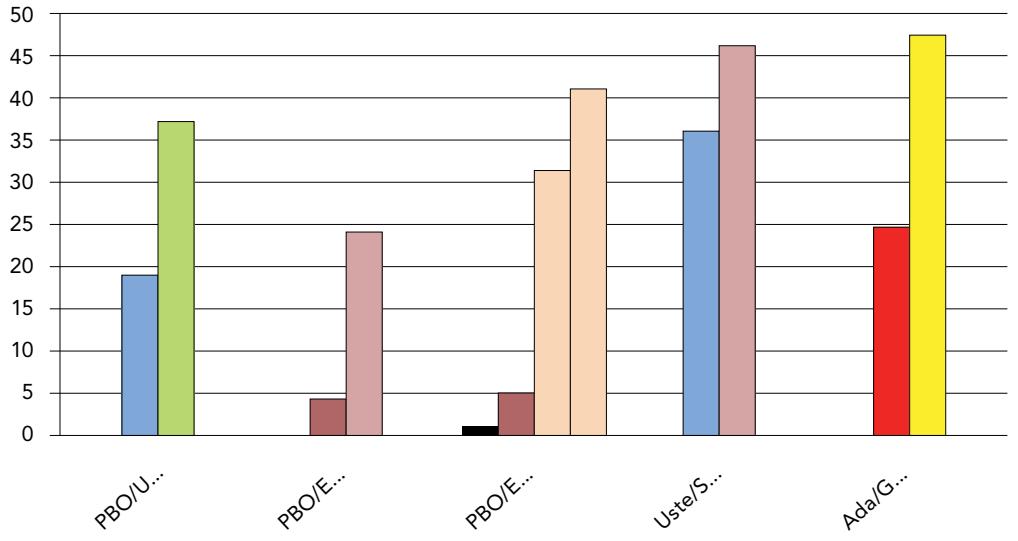
ery two weeks, this agent has shown superior efficacy over ustekinumab (PASI 75 85% vs 69%, PASI 100 46% vs 36%).[28] The major concern with brodalumab, which has not been reported with other psoriasis therapies, is suicidal ideation and behavior. There were four suicides in the clinical trial program before FDA approval. Brodalumab is only available through a REMS program and has a black box warning in the package insert about suicide potential. At this time, it is not known if this agent actually increases the baseline suicide rate in those with psoriasis; however, there is an increased risk of depression in psoriasis patients in general.

The major adverse effects with the anti-IL-17 agents are increased risk of infection (~1 serious infection in 1,000 treated patients or less), cutaneous candida infections (< 1%), injection site reactions (2-17%), and inflammatory bowel (IBD) disease emergence or exacerbation (~1 in 1,000 treated patients). Although the rate of overall infections is higher with the anti-IL-17 agents compared with placebo, the rate of serious infections (requiring hospitalization or intravenous antibiotics) is similar to placebo. IL-17 is important in the mucosal defense against fungal infections, which is why there is an increase in cutaneous candida infections. Injection site reactions occur with all biologics, including anti-IL-17 agents. Rates of injection site reactions appear to be highest for ixekizumab. In terms of the development of IBD, the risk does appear to be slightly increased with anti-IL-17 agents; those with psoriasis have a greater risk of developing Crohn's disease, regardless of the therapy received. Brodalumab is also contraindicated in Crohn's disease in the package labeling. Thus far, there have been no signals for increased risk of malignancy. Overall, the anti-IL-17 agents are well tolerated and very efficacious.

Guselkumab (Tremfya®) is the first in another new class of biologics for psoriasis. It targets the IL-23 subunit alpha (p19 subunit) and was FDA approved for moderate-to-severe disease in 2017. Guselkumab is given as a subcutaneous injection of 100 mg every eight weeks after an induction dose. Its efficacy is similar to anti-IL-17 therapy, with PASI 75 in the 80% range. It was more effective than placebo (PASI 90 2.9% vs 73.3%) or adalimumab (PASI 90 49.7% vs 73.3%) at 16 weeks.[29,30]

With an every eight-week dosing interval, guselkumab can be given in the physician's office, so it can be reimbursed through the medical benefit if

Exhibit 4: Comparison Trials – PASI100[22,23,25,28,29]



PBO = placebo
Uste = ustekinumab weight based q2wk
Broda = brodalumab 210 mg q2wks
Secuk = secukinumab 300 mg q month
Ixe q4 = ixekizumab 80 mg q2wks
Ixe q2 = ixekizumab 80 mg q4 wks
Ada = adalimumab 80 mg
Gusel = Guselkumab 100 mg

the patient does not have pharmacy benefit coverage. The same strategy can be used for ustekinumab. Most clinicians will start this in the office and, if the patient is doing well, may switch to at home administration or alternating home and office injections. Giving the injections in the office improves adherence.

The side effect profile with guselkumab thus far is tolerable, but there is a modest increased risk of infections and injection site reactions. Again there is no known signal for increased risk of malignancies. Tildrakizumab and risankizumab are additional anti-IL-23 biologics which are likely to be approved within the next year.

The anti-IL-17A and anti-IL-23 agents are the most effective psoriasis therapies developed so far (PASI 75 in 80-85% range). They are also safer than conventional systemic therapy such as methotrexate or cyclosporine, and long-term safety appears good. These agents are also effective for palmar and nail psoriasis, which can be difficult to effectively treat.

These agents do have package labeling for infection and malignancy risk. As discussed previously, long-term studies with ustekinumab, which targets IL-12 and IL-23, have not shown an increased malignancy risk, but whether this applies to these newer agents is not yet known.[16,17] Thus, the true risk with the IL-17 or IL-23 targeting therapies is unknown.

Selecting Treatment

Once it is determined that a patient has moderate-to-severe psoriasis and needs systemic therapy, clinicians must make a choice between oral systemic, phototherapy, and biologic therapy. Conventional systemic agents, apremilast, and biologics are significantly more effective than placebo in terms of reaching PASI 90.[31] In terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and TNF inhibitors are significantly more effective than apremilast and the conventional systemic agents.[31]

If a biologic is chosen, then one of the four different classes has to be chosen. The PASI 75 and PASI 100 results from the available head-to-head comparison trials that are shown in Exhibits 3 and 4.[19,22,23,25,28,29] Although no comparison trial has included an agent from each class, based on placebo controlled trials and the available comparison trials, the anti-IL17 and anti-IL23 agents are significantly more effective than the TNF inhibitors, and ustekinumab is superior to etanercept. [19,22,23,

Exhibit 5: Comorbidities and Treatment Selection

Scenario	TNF	IL 12/23	IL-17	IL-23
Psoriatic Arthritis	FDA approved	FDA approved	FDA approved	Promising Phase II data
Crohn's Disease	FDA approved adalimumab infliximab	FDA approved	Warning	To be determined
Decreased MI and Stroke	Some data	To be determined	To be determined	To be determined
CHF	Warning	No warning	No warning	No warning
Multiple Sclerosis		No benefit or harm Phase II	Promising Phase II	To be determined
Depression			Warning brodalumab	
Obese Patient	Infliximab preferred	Weight-based dosing	Flexible dosing	

[25,28,31,33] No clear differences have been shown between infliximab, adalimumab, and etanercept. Overall, a Cochrane review concluded that compared to placebo, ixekizumab, secukinumab, brodalumab, guselkumab, and ustekinumab are the best choices for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of moderate-to-high-certainty evidence.[31]

Beyond just skin clearing, other factors have to be considered in selecting treatment for psoriasis. Clinicians need to consider the benefit-to-risk ratio for each possible agent for the individual patient. In addition to efficacy, the effects on comorbidities, adverse effects, and access (coverage, convenience) need to be considered. The presence of various comorbidities can impacts treatment selection. Exhibit 5 lists some of these.

Psoriatic Arthritis

Since about one-third of patients with psoriasis also have PsA, this is an important factor in choosing therapy. Eighty-five percent of patients with PsA will have skin disease, either prior to or concurrent with joint disease. Half of the patients with PsA seen in dermatology clinics do not know they have it. Regular screening and timely treatment of psoriasis patients with PsA is critical to preventing joint damage. The biologics FDA approved for managing psoriasis and PsA include etanercept, infliximab, adalimumab, ustekinumab, secukinumab, and ixekizumab. Tofacitinib (Xeljanz®), an oral JAK inhibitor, certolizumab (Cimzia®), golimumab (Simponi®, Simponi Aria®), and abatacept (Orencia®) are only indicated for psoriasis arthritis. Like disease-modifying antirheumatic drugs (DMARDs), biologics may slow or stop joint damage and the progression of PsA.

Until the recent newer biologics, etanercept and adalimumab had been the gold standard biologics for treating PsA. Initial studies with ixekizumab and secukinumab show similar efficacy to the TNF inhibitors. The anti-IL-17A agents may not work as quickly as the TNF inhibitors.

Obesity

Obesity is a consideration in selecting agents and choosing doses. Standard dosing for some biologics is not effective for severe or morbidly obese patients. Weight-based dosing is used for ustekinumab and infliximab. All the other currently approved agents for psoriasis use non-weight-based dosing. Etanercept and adalimumab have been shown to be less efficacious when used at approved doses for obese patients, but off-label dose escalation may be helpful.[34,35] For secukinumab, ixekizumab, brodalumab, and guselkumab, the approved dosing is efficacious in patients with obesity.

Cardiovascular Disease

Cardiovascular disease (CVD) is another common comorbidity of psoriasis and the hope would be that treatment reduces the risk of cardiovascular events. Results from one registry study showed that some therapies such as methotrexate and TNF inhibitors statistically reduced events, whereas other biologics

Exhibit 6: Management of Oropharyngeal Candidiasis[39]

Oral	
Severity of Infection	Treatment (strength of recommendation)
Mild	Clotrimazole troches (10 mg, five times daily), nystatin suspension at a concentration of 100,000 U/mL and a dosage of 4 - 6 mL qid, or 1 - 2 nystatin pastilles (200,000 U each) administered qid for 7 - 14 days, is recommended (B)
Moderate-to-severe	Oral fluconazole 100 - 200 mg (3 mg/kg) qd for 7 - 14 days is recommended (A)
Refractory to fluconazole	Itraconazole solution 200 mg qd, or posaconazole suspension at 400 mg bid for 3 days, then 400 mg qd for up to 28 days is recommended (A) Voriconazole 200 mg bid, or a 1 mL oral suspension of AmB-d (100 mg/mL qid), is recommended when treatment with other agents has failed (B) Intravenous echinocandin or AmB-d at a dosage of 0.3 mg/kg qd can be used for treating patients wuth refractory disease (B)
Esophagael	Oral fluconazole 200-400 mg (3-6 mg/kg) qd for 14-21 days is recommended (A)

AmB-d = amphotericin B deoxycholate
bid = twice daily

and systemic treatments do not significantly reduce events.[36] Data from the PSOLAR international registry found no difference in major CVD events with TNF inhibitors and ustekinumab compared with phototherapy treatment.[37] A claims data study found no difference in myocardial infarction rates among patients treated with various system therapies, TNF inhibitors, or phototherapy.[38] Retrospective studies are needed to better clarify the possible CVD benefits of psoriasis and PsA treatment.

Inflammatory Bowel Disease

Emerging data show that the IL-17 inhibitor class may be associated with increased IBD exacerbations or incident IBD, but long-term data are necessary to confirm these findings and to show the rate is higher than the background rate in psoriasis. Clinicians should avoid prescribing IL-17 inhibitors in patients with a history of IBD and exercise caution in patients with first-degree relatives with IBD if choosing IL-17 inhibitors. Adalimumab or infliximab should be considered in patients with IBD and psoriasis. Both agents have proven efficacy in psoriasis, PsA, ulcerative colitis, and Crohn's disease.

Depression

Depression is a common comorbidity of psoriasis for which patients should be screened periodically. The risks of brodalumab should be weighed carefully in those with a history of depression or suicidal behavior and likely should not be used in this type patient. If prescribed, patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional. Clinicians should advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes no matter what treatment is chosen.

Managing Adverse Effects

Injection site reactions (ISRs) occur fairly frequently with biologics and usually occur within the first month of treatment. ISRs include redness, tenderness, warmth, and itching at the location of an injection. They most commonly occur one to two days after an injection, and the duration is usually three to five days. ISRs decrease in frequency with continued treatment in the vast majority of patients, although a persistent or worsening reaction has been described. Additionally, the mechanism by which ISRs occur is unknown.

Most ISRs resolve without treatment, but symptomatic eruptions can be treated with cold compresses, topical corticosteroids, oral antihistamines, or acetaminophen. Discontinuing treatment due to ISRs is rarely necessary.

Patient education is important in preventing and managing ISRs. The proper injection technique should be reviewed and rotation of injection sites should also be encouraged. Recommended sites

Exhibit 7: Shared Decision Making[40]

Choice Talk makes patients aware that reasonable options exist.

- **Offer choices**
- **Justify choice**
  - Emphasize (1) individual responses and preferences and (2) the role of uncertainty
- **Check reaction**
- **Defer closure**

Option Talk provides more detailed information about each option

- **Check knowledge**
- **Describe options**
  - Benefits and harms
    - Express risk in absolute and relative terms
  - Differences between options
  - Give information in chunks – chunking and checking
- **Use patient decision aid tools**
- **Check understanding**

Decision Talk supports consideration of preferences and decides what is best

- **Elicit patient preferences**
- **Moving a decision**
- **Check whether to make or defer a decision**
- **Offer review**

Exhibit 8: Patient Challenges to Shared Decision Making

Cognitive Biases	Lack of Knowledge	Low Health Literacy and Cognitive Impairment
• Availability bias leads to overestimation or underestimation of risks. • Framing bias (a loss is more devastating than the equivalent gain is gratifying.)	• About treatment options, benefits and risks. • About their goals, values and preferences.	• Slowed information processing. • Preferences for choices requiring least effort. • i.e., "choosing the default",and "whatever you recommend doctor".

include the anterior thighs, outer upper arms, and the abdomen two or more inches from the navel. Patients should be instructed to contact their physician if they exhibit severe itching, pain, swelling, or signs of infection. Patients should be instructed to avoid administering the biologic into psoriasis plaques or in the area of prior ISRs. Future injections should be given at least one inch from the periphery of prior ISRs. Patients need to understand that ISRs will resolve and that they are not related to the disease process.

Candidiasis is another possible adverse event which will need to be managed. Absolute rates of candidiasis with the IL-17 inhibitors were increased in trials compared to placebo but generally are low (<1%). Importantly, candida can stimulate the production of cytokines that trigger or exacerbate psoriasis. Therefore, clinicians should regularly screen patients with psoriasis for signs of candida infection, and take steps to effectively treat these infections to prevent worsening of psoriasis symptoms. In general, psoriasis treatments should not be altered or interrupted due to mucocutaneous candidiasis.

Oral candidiasis is the most common event, but vaginal and cutaneous infections can also occur. Patients with oral candidiasis can be asymptomatic or may report pain, burning sensations, sore throat, difficulty swallowing, and/or halitosis. Oral candidiasis can usually be diagnosed through physical examination and clinical history; microscopic examination using potassium hydroxide (KOH) or fungal cultures are both effective and sensitive

methods for detection of oral candida colonization. Standard antifungal treatment regimens are generally safe and well tolerated in psoriasis patients. Exhibit 6 provides recommended regimens for oral and esophageal candidiasis.[39]

Cutaneous candidiasis occurs in the intertriginous areas, such as groin, abdominal skin folds, and inframammary skin; it can also occur in the interdigital spaces. It presents as thin, bright-red plaques that can be erosive, dry, scaly, oozing, or macerated. Diagnosis is based on clinical appearance of the skin, presence of pseudohyphae in KOH wet mounts, or positive fungal culture of scrapings. Cutaneous candidiasis is managed with topical triazoles and polyenes (clotrimazole, miconazole, nystatin).[39]

Vulvovaginal candidiasis (VVC) can also occur. Uncomplicated VVC is treated with topical intravaginal antifungal agents (clotrimazole, butoconazole, tioconazole, miconazole, terconazole) for one to seven days or a single oral fluconazole 150 mg dose.[39] Complicated VVC can be managed with topical intravaginal antifungal agents for seven days or oral fluconazole 150 mg every 72 hours for three doses. Recurrent VVC requires an induction of topical or oral triazole for 10-14 days followed by oral fluconazole 150 mg weekly for six months.

As noted previously, the anti-IL-17 class may lead to the development or worsening of IBD. If this occurs, the anti-IL-17 agent should be discontinued, and the patient switched to an agent with known efficacy in treating both psoriasis and IBD.

Shared Decision Making

Because starting a biologic agent for psoriasis or PsA is a decision not to be taken lightly, clinicians and patients need to work together. In shared decision making, both the provider and the patient actively participate. An invitation is made to share information, and the provider shares facts about treatment, benefits, harms, convenience, and costs. The patient shares values and preferences about treatment attributes. Then, a decision is mutually agreed upon. The essential elements of shared decision making are choice talk (ensure that patients know that reasonable options are available), option talk (more detailed information about options), and decision talk (supports the work of considering preferences and deciding what is best,).[40]

Patients are different in their willingness to participate in shared decision making. Some have a fixed opinion and already know what treatment they want, whereas others think the doctor/health care provider knows best and wants to be told what to do. On the other end of the spectrum is the patient who is open to options. Exhibit 8 lists some patient-related challenges to shared decision making.

Exhibit 9: Drivers of Poor Adherence in the Treatment of Skin Disorders[41]

- Poor doctor–patient relationship
- Inadequate follow-up
- Poor experience of treatment
- Unrealistic expectations from treatment
- Lack of patient knowledge about the disease and/or therapy
- Lack of belief in the treatment
- Side effects, Fear of side effects
- Conflicting/incorrect information on treatment
- Messy, complex treatment regimens
- Forgetfulness
- Life structure
- Social support (family/friends) and psychological support (depression/anxiety)
- Cost

Adherence

Many different issues can lead to medication nonadherence in chronic diseases like psoriasis (Exhibit 9).[41] Motivational interviewing to identify causes of nonadherence, shared decision making, and proactively discussing and managing biologic adverse effects are all strategies for improving adherence. Scheduling one or two visits early after starting a treatment could translate into fewer total visits over the course of the disease by helping patients establish a solid medication-taking habit from the outset. Audio-visual or Internet-based interventions, such as a virtual counselor, patient support programs, and self-management educational training programs, are also options.

Management of Treatment Costs

In general, specialty drug management, which includes the biologics, is posing multiple challenges to managed care. These challenges include a rapidly increasing number of products, increased utilization particularly earlier in disease processes, new indications for already approved agents, a lack of widely accepted evidence-based guidelines which causes variations in clinical practice, lack of data demonstrating best practices in managing the diseases treated with biologics, and lack of comparative effectiveness data.[42] The largest category of specialty spending in commercial markets for several years is the medication for inflammatory conditions, includ-

ing psoriasis.[43] The per-member-per-year (PMPY) spend on treatments for inflammatory conditions was $159 in 2017, up 15.3 percent from 2016.[43]

Management strategies to control psoriasis treatment costs include step therapy through non-biological immune modifiers before biologicals, prior authorization of biological agents, preferred biological agents, limiting prescribing of biologicals to appropriate specialists, guideline-based management, and managing site of service. Other payer strategies include newer benefit designs, multiple tiers of specialty benefit, consideration of the emerging biosimilar marketplace, specialty specific formularies, and alignment of patient incentives.

Managing psoriasis medication spend will get more complicated as more agents are approved. There are numerous additional biologic agents in the pipeline for psoriasis treatment. A few examples include briakinumab, another IL-12/-23 blocker; AMG 827, another IL-17 blocker; tildrakizumab and risankizumab, additional anti-IL-23p19; and BI655066, anti-IL-23.

Conclusion

Biologic agents are shifting the treatment paradigm in psoriasis, offering long-term safety and efficacy to a patient population that has long been underserved – those with moderate-to-severe disease. The IL-17 and IL-23 agents are major advances in the treatment of psoriasis and are generally well tolerated. Clinicians are still learning how to best use these two new classes of agents. Addressing challenges to patient adherence and quality of life will ultimately improve overall patient outcomes. Clinicians should consider a systematic approach to shared decision making in order to fulfill the informational needs of patients regarding their treatment plan.

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