

Treatment Strategies, Management of Comorbidities, and the Role of IL-23 Inhibitors in Moderate to Severe Psoriasis

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Plaque psoriasis, or psoriasis vulgaris, is a chronic inflammatory disease that affects over 8 million individuals in the United States.^{1,2} It presents as well-demarcated red or pink plaques with silvery scale at the skin's surface.¹⁻³ Patients with moderate to severe psoriasis experience a variety of bothersome cutaneous symptoms that can negatively impact their quality of life (QOL).²⁻⁴ These include itching (pruritus), pain, stinging, burning, skin tightness, skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding.^{5,6} Within a decade of diagnosis, up to one-third (33%) of patients will also develop extracutaneous symptoms in their joints, indicative of inflammatory psoriatic arthritis.^{7,8} Additionally, a high percentage of patients have metabolic and psychological comorbidities, further adding to the substantial disease burden.² In fact, it has been observed that patients who have both plaque psoriasis and psoriatic arthritis have greater risks of concomitant cardiovascular disease, Crohn disease, depression, diabetes mellitus, metabolic syndrome, osteoporosis, uveitis, and/or liver disease.⁹ Therefore, patients with moderate to severe psoriasis often have complex treatment needs requiring long-term therapy.^{2,3,10}

Biologic agents, which function to reestablish immune system homeostasis, have become important treatment options for patients suffering from moderate to severe psoriasis.^{8,11,12} Although earlier biologics targeted broad inflammatory cytokines such as tumor necrosis factor- α (TNF- α), newer classes of biologics target very specific cytokine pathways now known to be central to the pathogenesis of the disease.^{8,11} Interleukin (IL)-23 inhibitors are the newest class of biologics approved for use in plaque psoriasis and may offer several potential benefits to patients, particularly when it comes to the management of patients with certain comorbidities.^{8,13} This article explores those benefits and offers considerations as the treatment spectrum continues to evolve.

The Pathophysiology of Psoriasis

Psoriasis has a complex, immune-mediated pathology.^{1-3,11} It is chiefly driven by inappropriate activation of dendritic cells and T cells.¹³ Activated dendritic cells release a variety of proinflammatory

ABSTRACT

Psoriasis is a complex immune disorder associated with substantial metabolic and psychological comorbidities, posing challenges to treatment. Interleukin (IL)-23 inhibitors, the newest class of biologics for the treatment of moderate to severe psoriasis, are more selective mechanistically than previous biologic classes and may have utility in management of patients with comorbidities, particularly those with metabolic syndrome (MetS). Moreover, recent long-term data suggest that IL-23 inhibitors offer unique advantages in both safety and efficacy. As the relationship between psoriasis and MetS continues to be elucidated, the availability of agents that are safe and effective in patients with and without comorbidities represents an important step in the spectrum of treatment.

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regulatory cytokines, among which are TNF- α , IL-12, and IL-23.¹⁻³ Many agents used in the treatment of plaque psoriasis target these soluble chemical mediators.³

IL-12 is a protein dimer composed of 2 smaller protein subunits, p35 and p40.² IL-12 induces naïve T cells to differentiate and proliferate into T helper (Th)1 cells.² However, it is now understood that the role of Th1 cells as part of the IL-12/Th1 pathway in the pathogenesis of chronic psoriasis is not as central as originally thought.⁸

IL-23 is also a dimer that includes p40, but its other protein subunit is identified as p19.² Like IL-12, IL-23 induces naïve T cells to differentiate and proliferate but instead signals them to become Th17 and Th22 cells. In addition, IL-23 instructs the newly differentiated Th17 and Th22 cells to release several effector cytokines: IL-17, IL-21, IL-22, and TNF- α .² After binding to their respective receptors, these effector cytokines increase transcription of additional proinflammatory cytokines and chemokines, ultimately leading to tissue pathology and scaly plaque formation.¹³ Recent findings identify the IL-23/Th17 axis as a central pathway in psoriasis pathogenesis.^{2,8,11,13}

IL-17 encompasses an entire family of cytokines, including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F.² Psoriatic skin is characterized by high levels of IL-17A and IL-17F, both of which are strong contributors to tissue inflammation.¹⁴ Of note, IL-17C is produced within keratinocytes and upon its release activates Th 17 cells.¹⁴

The Burden of Psoriasis and the Impact of Comorbidities

Patients with psoriasis may experience embarrassment, social isolation, and/or reduced self-esteem from the visual manifestations of their disease, as well as reduced work productivity (absenteeism, presenteeism, lower wages, and/or unemployment).^{7,12,15} All of these can negatively impact overall QOL and contribute to a high indirect cost.^{3,7,15}

Psoriasis has been linked with several psychiatric comorbidities, including depression, anxiety, and suicidal ideation.^{2,4,7,11,16} In an analysis of 50,750 women from the Nurses' Health Study (NHS), a longitudinal data set that has collected information from female registered nurses (N = 121,700) in the United States every 2 years since 1976, those with psoriasis were nearly 30% more likely to develop clinical depression than those without psoriasis, even after adjusting for potential confounders such as age, body mass index (BMI), physical activity, smoking, alcohol intake, and presence of selected comorbidities (cancer, myocardial infarction [MI], diabetes, frequent snoring, hypertension, hypercholesterolemia, hormone replacement therapy, menopausal status, rheumatoid arthritis, sleep duration, and stroke).¹⁶

Patients with psoriatic arthritis often experience enthesitis, dactylitis, periarticular swelling, ankylosis, arthralgia, and paresthesia, which can result in joint deformities and loss of gross and fine motor skills.^{2,7} All of these can significantly affect the ability to

perform activities of daily living, contributing to loss of independence and self-esteem, reduced QOL, and overall disease burden.^{3,7,17}

Similar to other chronic inflammatory disease states, psoriasis has been strongly associated with a variety of cardiometabolic comorbidities and has been linked to vascular inflammation, decreased endothelial function, and formation of high-risk, rupture-prone atherosclerotic plaques.^{2,11,14,18} In a retrospective claims-based analysis of privately insured individuals within the United States, patients with moderate to severe plaque psoriasis (n = 5492) had significantly higher rates of hyperlipidemia, hypertension, diabetes, depression, anxiety, coronary artery disease, obesity, cerebrovascular disease (CVD), peripheral vascular disease, and ulcerative colitis (UC) compared with individuals without psoriasis (n = 5492 matched controls).¹² Patients with psoriasis had significantly higher numbers of prescription medication fills, inpatient admissions, emergency department visits, and outpatient visits per year than their matched controls.⁴ As a result, the annual cost to third-party payers was significantly higher for patients with psoriasis than for patients without psoriasis, even after adjusting for baseline characteristics such as age, sex, geographic region, year, and non-psoriasis-related selected comorbidities (\$23,946 vs \$4986; 2012 USD; $P < .01$).¹²

Psoriasis is an independent risk factor for major cardiovascular adverse events (MACE; including MI, stroke, and mortality from CVD).^{2,7,19} Of note, this risk is more pronounced in patients under the age of 40 compared with those without psoriasis.²⁰

One large, retrospective, observational analysis of medical records in the United Kingdom found that even after adjusting for risk factors known to contribute to CVD risk (age, sex, hyperlipidemia, hypertension, smoking, and diabetes), severe psoriasis independently imparted a 53% higher risk of MACE (HR, 1.53; 95% CI, 1.26-1.85).²¹ More specifically, a meta-analysis found that severe psoriasis was associated with a 39% higher risk of cardiovascular mortality, 70% higher risk of MI, and 56% higher risk of stroke (relative risk [RR], 1.39, 1.70, and 1.56, respectively; 95% CI, 1.11-1.74, 1.32-2.18, and 1.32-1.84, respectively).²² Thus, a growing body of evidence suggests that severe psoriasis is associated with a reduced life expectancy overall and an increased risk of CVD-related mortality specifically.²³ One retrospective cohort-based study conducted in the United Kingdom found that life expectancy among those with psoriasis was reduced by approximately 5 years.²⁴

Increasing attention in recent years has been given to the connection between metabolic syndrome (MetS) and psoriasis.⁷ MetS is a constellation of risk factors that is predictive of diseases such as CVD and type 2 diabetes^{7,25} but may also be associated with higher risk of psoriasis.²⁶ A diagnosis of MetS is generally made based on the presence of several metabolic abnormalities, including impaired glucose metabolism (ie, elevated fasting glucose), indicators of insulin resistance such as abdominal obesity (ie, elevated sex-specific waist circumference), atherogenic dyslipidemia (ie, low

levels of high-density lipoprotein and/or elevated triglycerides), and hypertension.²⁴ Several studies have found that patients with MetS are at greater risk of psoriasis than the general population.²⁶

Obesity has been observed to be an independent risk factor for developing psoriasis and for higher risk of more severe psoriatic disease.²⁷ Over 50% of adults with psoriasis have a BMI that classifies them as overweight or obese.²⁷ In a study designed to evaluate the effect of lifestyle modifications on symptom severity among patients with chronic plaque psoriasis who had elevated BMI (≥ 25 kg/m²), those randomized to undergo a 20-week diet and physical exercise regimen (n = 151) experienced a significant reduction in their symptom severity compared with those that were given only a 15-minute informational session at baseline on the importance of lifestyle modifications for managing their psoriasis symptoms (n = 152; 48.0% vs 25.5% reduction in Psoriasis Area and Severity Index [PASI], respectively; $P = .02$).²⁷

Metabolic disorders (including CVD, obesity, and type 2 diabetes) have all been associated with inflammatory implications.^{14,27} In fact, they share a common pathophysiologic proinflammatory pathway with psoriasis, involving the upregulation of Th1 and Th17 cells and the cytokine IL-17A.¹⁴ Therefore, it is currently unclear whether psoriasis contributes to the onset of MetS or if MetS contributes to the onset of psoriasis.⁴

Finally, patients with plaque psoriasis are at greater risk of inflammatory bowel diseases (IBD) such as Crohn disease and UC.^{2,7,11,28} IBD and psoriasis share similar pathogenic pathways, even though the end-organ effects differ.²⁸ A retrospective chart review of 1669 outpatients from the Netherlands who had a diagnosis of psoriasis found that the prevalence of IBD among these patients was 4 times higher than that observed in the general population (1.6% vs 0.4%, respectively).²⁸ This association may contribute to overall disease burden of psoriasis, as well as higher costs to payers and patients.

Considerations for the Use of Biologic Agents for the Treatment of Moderate to Severe Psoriasis

Several novel, biologic therapies have come to market in recent years for the treatment of plaque psoriasis and can be divided into 4 classes: TNF- α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab), IL-17 inhibitors (brodalumab, ixekizumab, and secukinumab), IL-12/23 inhibitors (ustekinumab), and IL-23 inhibitors (guselkumab, risankizumab, and tildrakizumab).¹¹

For moderate to severe psoriasis, the American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) treatment guidelines recommend use of a biologic, either alone or in combination with topicals or other systemic therapies.³ Although older agents have targeted cytokines such as TNF- α (for which inflammatory effects are more broad), newer biologics have focused on cytokine pathways that are more specific to the pathogenesis of psoriasis (regulatory cytokines IL-23 and IL-12 and effector cytokines IL-17A and IL-17F).

AAD/NPF guidelines emphasize the need to consider a patient's comorbidities when selecting a therapeutic regimen.¹ Obesity and MetS are of particular concern, as they relate to psoriasis severity and treatment efficacy. One study found that patients with psoriasis who had comorbid MetS and took adalimumab had lower response rates than those without comorbid MetS.²⁹ Another study, which was designed to assess the drug survival of 5 biologic agents (adalimumab, efalizumab, etanercept, infliximab, and ustekinumab) in patients with psoriasis, found that those with comorbid MetS were significantly more likely to discontinue their prescribed biologic than those without comorbid MetS.³⁰

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A third study found that patients who received 1 of 4 systemic biologics for their psoriasis (secukinumab, adalimumab, ustekinumab, or etanercept) had numerically higher rates of switching to a different agent at 12 months, 18 months, and 24 months if they had a comorbidity of MetS. Rates of drug discontinuation were also numerically higher at 18 months and 24 months if they had MetS. In addition, those who received the nonbiologic drug apremilast (a phosphodiesterase-4 inhibitor) had numerically higher rates of switching agents at 18 months and 24 months if they had a comorbidity of MetS.³¹

AAD/APF guidelines state that patients who are overweight or obese are less likely to respond to TNF- α inhibitors than patients with lower BMIs.³ Those who are overweight or obese will typically require more frequent dosing and/or higher doses than lower-weight patients to achieve a satisfactory response.³ Both etanercept and adalimumab, for example, have been shown to have lower efficacy in patients who are obese^{32,33}; infliximab is the one exception, as it utilizes weight-based dosing.³ The guidelines specifically state that doses higher than that included on the Food and Drug Administration (FDA)-approved drug labeling may be required to reach efficacy with a TNF- α inhibitor in the setting of obesity and that higher doses are often needed when utilizing ustekinumab with patients who are overweight or obese.³ The IL-17 inhibitor secukinumab has shown efficacy in patients over 90 kg who receive 300 mg every 2 weeks (compared with the standard every 4 weeks), with comparable risk of adverse events.³⁴ Finally, it is worth noting that there are currently no published recommendations for adjusting dosing based on presence of comorbid obesity with IL-17 and IL-23 inhibitors.

Patients with psoriasis and comorbid MetS have higher serum levels of IL-17.¹⁴ Aside from its inflammatory role in the pathogenesis

of psoriasis, there is evidence suggesting that excess IL-17 may contribute to decreased vascular function, interference with insulin signaling, and attenuation of insulin sensitivity, with the latter 2 contributing to insulin resistance.¹⁴

The CARIMA study evaluated vascular endothelial function in patients with psoriasis (N = 151) treated with the IL-17 inhibitor secukinumab.¹⁸ Patients with prior clinical CVD were excluded. Vascular endothelial function was assessed by flow-mediated dilation (FMD).¹⁸ After 52 weeks of treatment with secukinumab, FMD values were significantly higher compared with baseline values (6.3% vs 4.6%; mean absolute change, 2.13%; 95% CI, 0.8–3.3; $P = .0022$).¹⁸ Because a 1% increase in FMD is associated with a 13% decrease in relative CVD risk,¹⁸ this finding could have clinical significance for reducing CVD risk in patients with psoriasis. The authors noted that animal studies have shown that neutralization of IL-17 improves insulin sensitivity and glucose uptake.¹⁴

Safety with established biologics

Biologics approved for use in plaque psoriasis^{35–44} may carry increased risk for hypersensitivity reaction^{25,35–38,40–42,44} and infection,^{35–44} including tuberculosis (TB).^{35–44} Beyond that, some classes of biologics carry stronger warnings and more extensive risks than others as part of their product labeling.

All TNF- α inhibitors currently available on the US market for use in plaque psoriasis (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) carry boxed warnings, the strongest level of caution from the FDA, for increased risk of serious infections (including TB), lymphoma, and other malignancies.^{35–38} Additional warnings and precautions found in the product labeling for this drug class include increased risk for exacerbation or new onset of demyelinating disease,^{35–38} exacerbation or new onset of congestive heart failure,^{35–38} various cytopenias,^{35–38} hepatitis B virus reactivation,^{35–38} and autoimmune reactions (lupuslike syndrome).^{35–38} Warnings and precautions for infliximab also include increased risk of fatal hepatotoxicity,³⁸ cerebrovascular accidents (CVA),³⁸ MI,³⁸ and cardiac arrhythmias.³⁸

Although clinical data initially indicated that use of TNF- α inhibitors in the short term was associated with new or worsening heart failure,⁴⁵ growing evidence (as noted previously) suggests that longer-term use of TNF- α inhibitors may actually be cardioprotective and confer protection against developing atherosclerosis.^{45,46} However, research is ongoing, and definitive conclusions have not yet been reached.⁴⁵

IL-17 inhibitors and the IL-12/23 inhibitor ustekinumab are not associated with the same level of increased risk for TB occurrence or reactivation, lymphoma, or other malignancies as that observed for TNF- α inhibitors, which contain a boxed warning for these adverse effects^{2,8,14,35–38}. Risks unique to IL-17 inhibitors include increased risk of mucocutaneous *Candida* infection^{2,14,39,40,44} and exacerbation of IBD (including Crohn disease and UC).^{14,39,40,44} Use of an IL-17

inhibitor should be avoided in patients with active IBD.^{2,14} Also of note is that brodalumab carries a boxed warning for increased risk for suicidal ideation and behavior³⁹ and is currently available only through a Risk Evaluation and Mitigation Strategy program.³⁹ Additionally, posterior reversible encephalopathy syndrome has been reported with the use of ustekinumab.³⁹

IL-23 Inhibitors

The newest class of biologics for psoriasis, the IL-23 inhibitors,^{8,13} has comparatively short lists of warnings and precautions relative to other biologics used for psoriasis,¹⁰ and these warnings are mainly limited to the risks associated with all the other biologics as a whole.

IL-23 contains the 2 protein subunits p19 and p40; IL-23 inhibitors bind to the p19 subunit of the IL-23 cytokine, preventing its interaction with the IL-23 receptor on naïve T cells. This attenuates the differentiation and proliferation of these T cells and subsequent release of additional cytokines and chemokines (IL-17 and TNF- α), but it also leads to survival and proliferation of Th17 and Tc17 cells. Selective binding to the p19 subunit allows for targeted inhibition of IL-23 only and avoids cross-interaction with IL-12, which contains subunits p35 and p40. This may be beneficial because IL-12 has some protective effects against cancer and infection.^{2,13}

Three novel IL-23 inhibitors are available on the US market: guselkumab, tildrakizumab, and risankizumab. Key phase 3 clinical trials demonstrating favorable safety and efficacy of IL-23 inhibitors versus a TNF- α inhibitor or placebo in the setting of moderate to severe plaque psoriasis included VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT02207244) for guselkumab; reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754) for tildrakizumab; and IMMvent (NCT02694523) for risankizumab.^{47–53} Briefly, these trials demonstrated that receipt of an IL-23 inhibitor was associated with significantly higher proportions of patients who achieved PASI 90 or PASI 75 compared with those who received a TNF- α inhibitor or placebo.^{47–53}

Results from a meta-analysis⁵⁴ of 13 studies examining the pooled data from all IL-23 inhibitors⁵⁴ demonstrated a significant class effect⁵⁴ in efficacy among IL-23 inhibitors compared with both placebo and adalimumab (pooled RR for achieving PASI 75 was 11.5 for IL-23 inhibitors vs placebo⁵⁴ and 1.9 for achieving PASI 100 with IL-23 inhibitors vs adalimumab;⁵⁴ 95% CI were 9.4–13.9⁵⁴ and 1.5–2.2, respectively).⁵⁴ Additionally, results from the long-term follow-up on the phase 3 trials have bolstered the profile of IL-23 agents, with 4-year follow-up data for guselkumab showing that high-efficacy response rates were maintained after continuous treatment, 2-year follow-up for risankizumab showing its superior efficacy to placebo through initial treatment and withdrawal, and 5-year follow-up for tildrakizumab showing that it sustained disease control with a reassuring safety profile.^{26,51,53,55}

Regarding safety, both the original trial findings and the meta-analysis data for IL-23 inhibitors confirmed that risk of adverse events was similar between IL-23 inhibitors and placebo or adalimumab.⁵⁴

Additionally, the long-term findings from all of these agents found no new safety signals in these agents.^{26,53,55}

Of particular note, the reSURFACE studies specifically evaluated patients with and without MetS, with results indicating that tildrakizumab yielded very similar PASI findings between the 2 groups in post hoc analyses.^{26,56} In reSURFACE 1, mean PASI reduction over 148 weeks was 89% among patients with MetS receiving tildrakizumab 100 mg compared with 92% in patients without MetS.²⁶ In reSURFACE 2, the mean PASI reduction over the same period was 93% among patients with MetS receiving tildrakizumab 100 mg compared with 96% in patients without MetS.²⁶

IL-23 inhibitors, which are more selective mechanistically than previous biologic classes, may offer advantages in terms of both efficacy and safety, according to newly available long-term data.

From a safety perspective, findings from the reSURFACE trials by MetS status are also compelling. In the 5-year safety data, among patients receiving tildrakizumab 100 mg, serious infections and infestations occurred in 1% of patients without MetS compared with 0.7% of patients with MetS.²⁶ Malignancies occurred in 1% of patients without MetS and in 1.3% of patients with MetS.²⁶ Confirmed extended MACE occurred in 0.4% of patients without MetS and in 1% of patients with MetS.²⁶ Serious adverse events occurred in 5.9% of patients without MetS and in 8.5% of patients with MetS.²⁶

The half-lives of tildrakizumab and risankizumab are both 20 to 28 days; the half-life of guselkumab is 12 to 19 days.⁵⁷ These may have clinical implications for patients requiring treatment interruption or discontinuation due to surgery or an unexpected medical reason.⁵⁸

As we consider the broader adverse event profile of IL-23 agents, no significant safety issues have emerged for any of the IL-23 inhibitors in these trials. Notably, risks associated with TNF inhibitors for moderate to severe psoriasis, such as MACE, reactivation of TB infection, triggering or worsening of IBD, demyelinating disorders, and suicidal behaviors, have not been observed in the clinical trials for IL-17 or IL-23 agents, making this class an attractive option, from a safety perspective, for use in patients with moderate to severe psoriasis.⁵⁹ IL-17 and IL-23 inhibitors have not been shown to be associated with an increased risk of serious infections.

Considerations and Future Directions

The spectrum of psoriasis research has expanded substantially over the past 2 decades, yielding more refined and efficacious treatment approaches. IL-23 inhibitors, which are more selective mechanistically than previous biologic classes, may offer advantages in terms of both efficacy and safety, according to newly available long-term data.

Another advancement in the spectrum of psoriasis research is the increased knowledge regarding the mechanisms of the disease and its intersections with various comorbid and inflammatory conditions. Continuing efforts to understand the relationship of these comorbid conditions with psoriasis suggest that psoriasis and MetS may be part of the same larger process, and additional research may further elucidate these connections.

Adding to the unique pedigree of IL-23 agents among the broader spectrum treatment options for psoriasis are data showing that tildrakizumab offers benefits in managing patients with comorbid metabolic disorders. It is important to note that tildrakizumab is the only agent in the IL-23 class to be evaluated specifically in patients with MetS. Given the efficacy demonstrated by guselkumab and risankizumab in all patients, it is highly likely that these agents would show the same results of success in any subset of patients with psoriasis, including those with MetS. Additionally, guselkumab and risankizumab have shown benefit in overweight individuals; given the intersections of obesity and MetS, these data may offer insight into the potential of these agents in patients with MetS.

Of note, biologic agents have the potential to improve lipid-rich atherosclerosis, suggesting cardioprotective effects.⁶⁰ Additionally, the positive findings from the reSURFACE trials, the first major trials that included a subset of patients based on a comorbidity, may have significant implications as a precedent for future research and development. It is also possible, preliminary data suggest, that this class is associated with improved drug survival, lower rates of switching, and higher response rates compared with older biologics in this subpopulation of patients. Given the prevalence of MetS (particularly in older populations) and the challenges of delivering reliable treatments to patients with these conditions, the availability of an agent with comparable safety and efficacy data among patients with and without these conditions represents a potentially significant step in the management of moderate to severe psoriasis. ■

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