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Psoriasis Is a Systemic Disease



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Obesity in the US is a significant public health concern. According to the CDC, 22 states have an adult obesity prevalence of 35 percent or higher.¹ Obesity is a proinflammatory state and is associated with increased risk for cardiovascular disease, diabetes mellitus, certain malignancies, musculoskeletal diseases, and liver disease, as well as psychiatric effects and decreased life expectancy.²

The risks of obesity are not unlike those of psoriatic disease. Psoriasis and psoriatic arthritis are associated with increased risk for cardiovascular disease, hypertension, metabolic disease, and liver disease.³ The risk for systemic comorbidities appears to increase with more severe psoriatic disease.⁴ Psoriasis and obesity are proinflammatory diseases that frequently co-exist and may have cross-directional influence.⁵ Therefore, their concomitant presentation can complicate treatment of psoriatic disease.

In the dermatology clinic, treatment of moderate-to-severe psoriasis with systemic anti-inflammatory agents is believed to modulate the systemic inflammatory effects of psoriasis.⁶ In short, providing effective treatment of skin and joint disease may reduce overall inflammation in the body and improve the patient's health status.

As discussed in the pages ahead, obesity presents a complication to psoriasis management, since it appears that some targeted psoriasis treatments are less effective in patients with higher Body Mass Index (BMI).⁷ However, the IL-17R antagonist brodalumab has both clinical trial and real-world data that show consistent efficacy across BMI categories.⁸

In addition to systemic treatment, lifestyle modification is an important aspect of management of psoriasis in the obese patient. Interestingly, data show that caloric restriction, irrespective of weight loss, may have beneficial effects on psoriasis.⁹ The emergence of GLP-1 receptor agonists for weight reduction may also offer an option for reducing BMI in overweight psoriasis patients. Controlled research is needed, but case reports suggest these agents may have a direct effect on psoriasis.¹⁰

The management of each individual patient with psoriasis requires the thoughtful assessment of a variety of considerations, including lifestyle factors, among others. For obese patients with psoriasis, it is increasingly important to consider the impact of excess weight on treatment efficacy. Treatments that are provided in a weight-based dose may warrant consideration. However, the potential benefit of brodalumab, which has been shown effective across a range of BMIs, should not be overlooked.

We should always remember "Psoriasis is a complex systemic disease "!

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DISCLOSURE

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Psoriasis and Obesity: Optimizing Pharmacologic Treatment and Lifestyle Interventions

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ABSTRACT

Obesity is a metabolic disease that is marked by excessive fat accumulation and is objectively defined as a body mass index (BMI) ≥ 30 kg/m². Obesity is associated with several other comorbidities, including psoriasis, which is a chronic autoimmune skin disease. Adipocytes produce pro-inflammatory signaling molecules, namely adipokines and classic cytokines, that drive increased inflammation and may contribute to the pro-inflammatory pathways driving psoriasis disease pathogenesis. Optimizing dermatologic management of obese patients with psoriasis may be challenging due to the effect of comorbid obesity on the pharmacokinetics of systemic therapies. Biologic therapy is a mainstay of psoriasis treatment in these patients. The IL-17 and IL-23 inhibitor classes, including those targeting the IL-17 receptor (brodalumab), IL-17 cytokine antagonists (secukinumab, ixekizumab, bimekizumab), and IL-23 cytokine antagonists (guselkumab, risankizumab, tildrakizumab). In general, the most efficacious biologics that work well for generalized plaque psoriasis also tend to work well for most obese psoriasis patients. For example, brodalumab, an IL-17 receptor inhibitor, demonstrated comparable efficacy across BMI categories in both clinical trial and real-world practice data. In addition to psoriasis-specific therapy, interventions targeted at weight loss may help treat obesity and decrease psoriasis disease severity. These interventions include glucagon-like peptide-1 receptor agonist therapy, caloric restriction, and different forms of bariatric surgery. Clinical trials and real-world data evaluating the efficacy of different biologic treatments and weight-loss interventions in the treatment of obese psoriasis patients should be used to support clinical decision-making for treatment options.

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INTRODUCTION

Defining Obesity

Obesity is a multifactorial disease with a rapidly increasing global prevalence.¹ Its etiology is driven by a chronic imbalance between energy intake and energy expenditure.¹ Excess energy is stored in adipocytes, which undergo hyperplasia and hypertrophy over time. The resulting excess fat stores contribute to a myriad of pathologies in different organ systems.

Obesity is defined by the World Health Organization (WHO) as “abnormal or excessive fat accumulation [that] presents a health risk” and measured by body mass index (BMI).² BMI is calculated by dividing a person’s weight in kilograms by their height in square meters. Increased BMI can indicate

an increased degree of body fatness.³ For adults, the WHO defines normal weight as a BMI of 18.5 to 24.9 kg/m², overweight as BMI ≥ 25 kg/m², and obese as BMI ≥ 30 kg/m². Definitions of obesity can further be subdivided based on central vs peripheral distributions of adipose tissue. Obese individuals with abdominal circumferences ≥ 40 inches (102 cm) in men and ≥ 35 inches (88 cm) in women are classified as having central obesity.⁴ However, in the setting of healthcare and clinical trial research, BMI is the most commonly used metric to define obesity.⁵

Obesity Increases Risk of Comorbid Conditions

Obesity is a proinflammatory state that increases a patient’s risk for cardiovascular disease, diabetes mellitus, certain malignancies, musculoskeletal diseases, liver disease, and psychiatric comorbidities and decreases a patient’s

life expectancy.⁶ In addition, obesity has been linked to psoriasis, a similarly inflammatory dermatologic disease. Prior literature has demonstrated that obesity and psoriasis have a bidirectional relationship: Patients with obesity are at an increased risk of developing psoriasis, and patients with psoriasis are more likely to have obesity compared to the general population.^{7,8} Furthermore, as BMI increases, psoriasis risk exponentially increases and psoriasis severity worsens.^{9,10} In addition to obese BMI, prior literature has demonstrated that other measures of increased body adiposity, such as weight gain, waist circumference, and waist-to-hip ratio, are similarly associated with an increased risk of psoriasis.⁹

Obesity and Psoriasis

The relationship between obesity and psoriasis may be explained by increased inflammatory signaling by adipocytes. Adipocytes make up adipose tissue and store excess energy as triglycerides. In addition to its energy storage role, adipose tissue functions as an endocrine organ that regulates lipid and glucose metabolism, inflammation, coagulation, and insulin-mediated processes.¹¹ These diverse endocrine functions are mediated by adipocytes, which produce bioactive signaling molecules known as adipokines in addition to classical cytokines such as MCP-1, IL-6, and TNF- α .¹¹⁻¹³ In obesity, expansion of adipose tissue and increased adipose tissue infiltration by leukocytes, particularly macrophages, lead to dysregulation of adipocytes, increased adipokine secretion, and baseline inflammation.^{11,12,14} The proinflammatory adipokines and resultant chronic inflammation present in obesity may contribute to the inflammatory pathways that drive psoriasis pathogenesis, thus linking the 2 diseases.

Challenges in Treating Psoriasis Patients With Obesity

Patients with psoriasis who have obesity may be more challenging to treat than psoriasis patients without obesity for a variety of reasons. In terms of clinical outcomes, patients with psoriasis and obesity are less likely to achieve adequate treatment response to systemic therapies.¹⁵ High body weight may have a negative effect on the efficacy of systemic psoriasis treatments due to changes in drug pharmacokinetics and resulting accelerated clearance of systemic therapies.^{16,17} This problem is further exacerbated by the fact that a limited number of systemic psoriasis medications offer weight-based dosing regimens.¹⁸ In addition to issues with treatment response, patients with psoriasis and obesity are more likely to experience certain adverse events while on systemic therapies for psoriasis.¹⁵

However, with the recent advent of currently available psoriasis biologic therapies, the treatment of patients with psoriasis and comorbid obesity may be optimized. In this review, we will examine clinical trials and real-world data to better understand the efficacy of biologic therapies in patients with psoriasis and obesity. Specifically, we will discuss the efficacy of biologic therapies targeting the interleukin-17 (IL-17) and interleukin-23 (IL-23) pathways in patients with comorbid psoriasis and obesity.

Biologic Therapies in Psoriasis Patients With Obesity: Clinical Trial Data

IL-17 Receptor Antagonist

Mechanism of action. Brodalumab is a fully human monoclonal antibody that binds the IL-17 receptor subunit A. Binding IL-17RA results in inhibition of signaling via multiple downstream IL-17 family cytokines, including IL-17A, IL-17F, and IL-17C.¹⁹ This distinguishes brodalumab from other biologics that target specific members of the IL-17 cytokine family, such as secukinumab and ixekizumab, which only target the IL-17A cytokine, and bimekizumab, which only targets the IL-17A and IL-17F cytokines.²⁰⁻²² While most research has focused on IL-17A as the predominant cytokine in psoriasis pathogenesis, many patients may lack or lose response to treatments that target only one cytokine molecule, potentially because of the overexpression of multiple IL-17 family members and functional redundancy among IL-17 cytokines.²³

Brodalumab clinical trials. In the phase 3 AMAGINE-2 and AMAGINE-3 trials, brodalumab treatment demonstrated good efficacy, safety, and tolerability in comparison to placebo and the active comparator ustekinumab for moderate-to-severe plaque psoriasis.²⁴

The two phase 3 trials shared the same design. Patients were randomized to receive subcutaneous brodalumab 210 mg, brodalumab 140 mg, or placebo at weeks 0, 1, 2, and every 2 weeks thereafter (Q2W); or ustekinumab (45 mg for patients weighing ≤ 100 kg or 90 mg for patients weighing ≥ 100 kg) at weeks 0, 4, and every 12 weeks thereafter (Q12W). At week 12, patients receiving brodalumab therapy were randomized again to receive a maintenance dose of brodalumab 210 mg Q2W; or brodalumab 140 mg Q2W, every 4 weeks (Q4W) or every 8 weeks (Q8W) through week 52. Patients receiving ustekinumab therapy continued receiving ustekinumab Q12W through week 52 unless needing rescue due to inadequate response. Inadequate response was defined as patients with sPGA ≥ 3 or persistent sPGA ≥ 2 over a >4 -week period after at least 16 weeks of treatment with ustekinumab.

At week 16, patients who were not responding to treatment with ustekinumab were switched to brodalumab 210 mg treatment. Patients receiving placebo therapy received brodalumab 210 mg Q2W through week 52.

Efficacy of brodalumab in patients with psoriasis with and without obesity. Hsu et al performed a *post-hoc* analysis of pooled data from the AMAGINE-2/3 trials to determine how obesity affected the efficacy, safety, and tolerability of brodalumab 210 mg Q2W compared to ustekinumab.²⁴ This analysis included all patients receiving continuous brodalumab 210 mg, patients receiving continuous ustekinumab treatment, and ustekinumab non-responders.

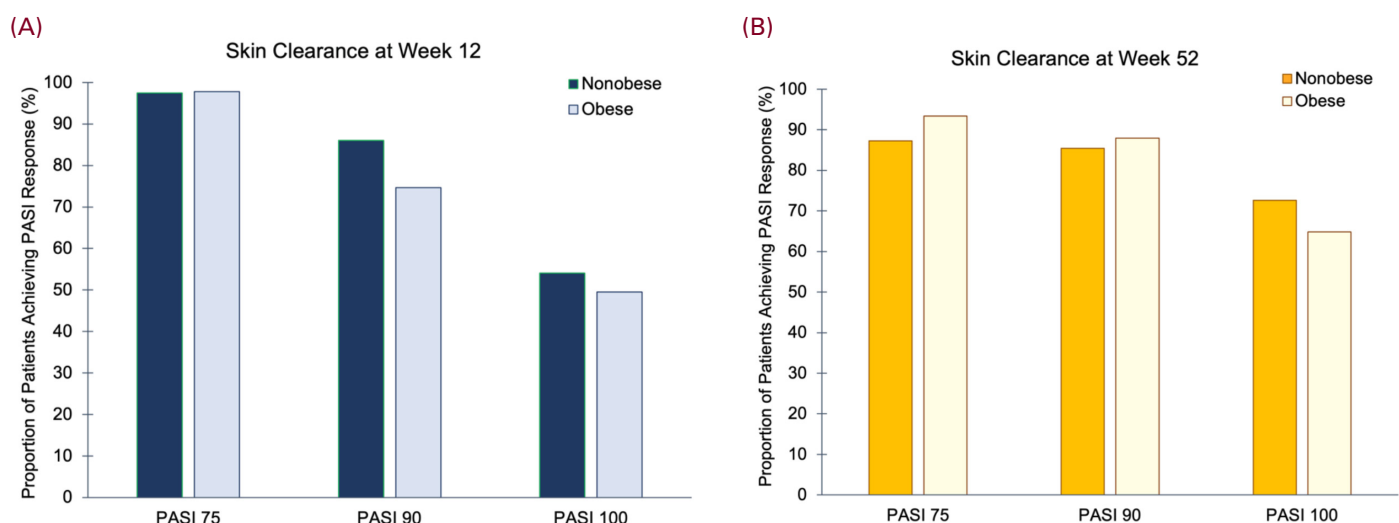
Kokolakis et al performed a similar *post-hoc* analysis of data from the AMAGINE-2/3 trials to determine how lifestyle risk factors – defined as obesity, smoking, or alcohol use – affected the efficacy of brodalumab 210 mg Q2W compared to ustekinumab.²⁵ This analysis included all patients receiving continuous brodalumab 210 mg and patients receiving continuous ustekinumab treatment. Ustekinumab non-responders were not included.

Among the 2 studies, patients with obesity were defined as those with a BMI ≥ 30 kg/m², and patients without obesity were those with a BMI <30 kg/m². Efficacy endpoints included the proportion of patients who achieved PASI score reductions of $\geq 75\%$ (PASI75), $\geq 90\%$ (PASI90), or 100% (PASI100) compared to baseline; the proportion of patients with an sPGA score ≤ 1 ; and the proportion of patients with a Psoriasis Symptom Inventory (PSI) total score ≤ 8 and no

single item score >1 , which defined PSI response. Safety and tolerability were assessed through monitoring of treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events of special interest.

Skin clearance. Overall, both Hsu et al and Kokolakis et al found that brodalumab demonstrated unchanged, strong efficacy in achieving skin clearance in patients with psoriasis who have obesity regardless of BMI status. To begin with, on *post-hoc* analysis, Hsu et al found that 40.9% of patients (n=281/687) had obesity. PASI response rates were similar between the 2 BMI sub-groups in the brodalumab treatment arm.²⁴ At week 12, PASI75 response rates in patients without obesity and those with obesity were 97.5% and 97.8%, respectively, and PASI100 response rates were 54.1% and 49.5%, respectively (Figure 1). At week 52, PASI75 response rates in patients without obesity and those with obesity were 87.3% and 93.4%, respectively; PASI90 response rates were 85.4% and 87.9%, respectively; and PASI100 response rates were 72.6% and 64.8%, respectively (Figure 1). Skin clearance, as quantified by sPGA ≤ 1 , was also comparable between patients without obesity and those with obesity receiving brodalumab. At week 52, 86.6% of patients without obesity achieved sPGA ≤ 1 , and 92.3% of patients with obesity achieved sPGA ≤ 1 . After 12 weeks of treatment with ustekinumab, more patients without obesity achieved PASI90 (77.8%) compared to those with obesity (61.1%), an almost 17% difference. Similarly, there was a 13% difference in ustekinumab patients achieving complete clearance (37.3% of obese; 24.4% of nonobese) by week 12. In addition, at week 52, both patients without obesity and

FIGURE 1. Brodalumab treatment response by BMI category. Proportion of nonobese and obese patients on brodalumab achieving PASI75, PASI90, and PASI100 response at (A) week 12 and (B) week 52.



those with obesity receiving brodalumab achieved greater skin clearance compared to those receiving ustekinumab. Among patients with obesity at week 52, 65% in the brodalumab group achieved PASI100 compared to 51.9% of patients with obesity in the ustekinumab group ($P=0.02$).²⁴ For their *post-hoc* analysis, Kokolakis et al stratified patients by number of reported risk factors. In their study population, 45.0% of patients ($n=418/929$) had obesity, 56.9% of normal-weight patients with no risk factors in the brodalumab group achieved PASI100 compared to 34.2% in the ustekinumab group ($P=0.0186$), 55.0% of patients with one risk factor in the brodalumab group achieved PASI100 compared to 22.2% in the ustekinumab group ($P<0.0001$), and 45.9% of patients with 2 risk factors in the brodalumab group vs 32.2% in the ustekinumab group achieved PASI100 ($P=0.0045$).²⁵ When taken together, the *post-hoc* analysis findings from Hsu et al and Kokolakis et al demonstrate that brodalumab remains highly efficacious in patients with psoriasis who have obesity, and its clinical efficacy is unchanged by obese BMI status.

Patient-reported outcomes in patients with vs without obesity. Hsu et al found that both patients with normal weight and obesity receiving brodalumab reported similar rates of PSI response. At week 12, 78.3% of patients without obesity and 71% of patients with obesity reported PSI scores that classified them as PSI responders.²⁴

Similarly, Kokolakis et al found that PSI response was achieved in 72.5% of patients without obesity with no risk factors, 63.6% of patients with one risk factor, 62.3% of patients with 2 risk factors, and 76.9% of patients with 3 risk factors. In addition, regardless of patient risk factors, more patients in the brodalumab group were PSI responders compared to patients in the ustekinumab group.²⁵

Safety and tolerability in patients with vs without obesity.

Overall, the findings from both sub-analysis studies demonstrated that brodalumab consistently showed strong, comparable efficacy with regard to both clinical disease measures and patient-reported outcomes for patients with psoriasis and with vs without obesity. Even in patients with psoriasis and obesity, brodalumab continued to show superior efficacy over the active comparator, ustekinumab. Additionally, both sub-analyses found that brodalumab had a favorable safety profile that was comparable in both patients with psoriasis and obesity and those without obesity. Specifically, Hsu et al found that patients without obesity and those with obesity had similar overall safety and tolerability of brodalumab.²⁴ Patients with obesity had a slightly lower exposure-adjusted rate of TEAEs than patients without obesity (366.3 vs 404.4 per 100 patient-

years, respectively). The most common TEAEs reported across all patients were arthralgias and headache. Among patients receiving brodalumab, patients without obesity and those with obesity reported similar rates of arthralgias. In contrast, patients with obesity who received brodalumab reported fewer headaches than patients without obesity who received brodalumab. Occurrence rates of grade ≥ 2 TEAEs, grade ≥ 3 TEAEs, and serious adverse events were comparable in patients with and without obesity who received brodalumab.

IL-17 Cytokine Antagonists

Efficacy of IL-17 Antagonists Stratified by Patient Weight

Secukinumab. Secukinumab is a fully human, immunoglobulin G1 κ (IgG1 κ) monoclonal antibody that selectively binds and inhibits IL-17A.²⁶ A post-hoc analysis of pooled data from the ERASE, FIXTURE, FEATURE,²⁷ and JUNCTURE²⁸ phase 3 trials was performed to evaluate the effect of medical comorbidities, including obesity, on secukinumab efficacy and safety.²⁹ Of the 2401 total patients included, 37.2% ($n=892$) had obesity at baseline. Comorbidities evaluated included angina pectoris, arthritis, cardiac failure, coronary artery disease, depression, diabetes, gout, hyperlipidemia, hypertension, osteoarthritis, rheumatoid arthritis, obese BMI, and psoriatic arthritis. Secukinumab patients with no baseline comorbidities and secukinumab patients with at least one baseline comorbidity were both significantly more likely to achieve PASI75 response and IGA mod 2011 ≤ 1 response at week 12 compared to placebo or etanercept patients. When the effects of individual comorbidities on treatment response were evaluated, only bodyweight had a significant effect. Increased bodyweight (≥ 90 kg) was found to significantly decrease the likelihood of achieving PASI75, PASI90, PASI100, IGA mod 2011 score of 0/1, and IGA mod 2011 score of 1 ($P<0.05$ for each comparison).²⁹

To determine how to optimally manage high bodyweight patients with secukinumab, a multicenter, randomized, double-blind, parallel-group phase 3 trial was conducted.³⁰ Overall, 331 patients with moderate-to-severe plaque psoriasis weighing ≥ 90 kg ($n=331$) were randomized to receive secukinumab 300 mg Q2W ($n=165$) or secukinumab 300 mg Q4W ($n=166$). Patients receiving Q2W dosing achieved a significantly greater proportion of PASI90 responses compared to the Q4W cohort at week 16 (73.2% vs 55.5%, $P=0.0003$). Non-responders at week 16 in the Q4W group were evaluated with regard to PASI90 response rates at week 32, the time-point 16 weeks after re-randomization. Non-responders who were up-titrated to Q2W dosing achieved significantly higher rates of PASI90 response compared to those who remained on Q4W dosing (38.7%

vs 16.5%, $P=0.0439$). Secukinumab safety in this study was consistent with its known, previously published safety profile, and safety remained similar across treatment arms.³⁰ Taken all together, these findings suggest that secukinumab treatment response is worse with increased bodyweight. High bodyweight patients may benefit from more frequent dosing of secukinumab.

Ixekizumab. Ixekizumab is a fully human, IgG4- κ monoclonal antibody that also selectively binds and inhibits IL-17A.³¹ In a sub-analysis of pooled data from the UNCOVER-1/2/3 trials,³¹ the effect of bodyweight on treatment response to ixekizumab 80 mg Q2W or Q4W was evaluated through week 12.³² Patients were divided into 3 bodyweight cohorts: <80 kg, 80 to <100 kg, and ≥ 100 kg. Across bodyweight cohorts in the ixekizumab Q2W group, rates of PASI75 and sPGA ≤ 1 at week 12 were similar. The ixekizumab Q4W group exhibited a numerical trend of decreasing PASI75 response rates with increasing bodyweight (Table 1). Overall, however, both ixekizumab Q2W and ixekizumab Q4W treatment resulted in significantly better treatment response across all bodyweight cohorts compared to both placebo and etanercept. In terms of safety, the rate of TEAEs was similar across bodyweight cohorts, including commonly reported TEAEs such as nasopharyngitis and upper respiratory infections.³² This sub-analysis suggests that bodyweight does not have a meaningful impact on ixekizumab treatment response.

Bimekizumab. Bimekizumab is a humanized IgG1 monoclonal antibody that selectively binds and inhibits both IL-17A and IL-17F.³³ A sub-analysis studied the efficacy of bimekizumab across subgroups of patient baseline characteristics, including bodyweight ≤ 100 kg vs >100 kg.³⁴ Pooled data was used from the BE SURE, BE VIVID, and BE READY trials and the first 96 weeks of data from their open-label extension (OLE) trials, BE BRIGHT and BE RADIANT. Regardless of dosing regimen, patients ≤ 100 kg were more likely to achieve PASI90 and PASI100 at week 156 compared to patients >100 kg (Table 2).²² Altogether, the results of these pooled analyses suggest that bimekizumab efficacy decreases with increased bodyweight, and patients with a high bodyweight may benefit from more frequent dosing. Bimekizumab is the only IL-17 cytokine antagonist with a weight-based dosing regimen.⁵⁰

IL-23 Antagonists

Efficacy of IL-23 Antagonists Stratified by Weight, Obesity, or Metabolic Syndrome Status

Guselkumab. Guselkumab is a fully human, IgG1 λ monoclonal antibody that selectively binds the p19 subunit of IL-23 to inhibit downstream IL-23 signaling.^{35,36} An analysis of pooled data from the phase 3 VOYAGE 1/2 trials evaluated the efficacy of guselkumab across patient subpopulations stratified by baseline characteristics, including weight and BMI.³⁷ Bodyweight was sub-categorized in 2 ways: ≤ 90

TABLE 1.

Ixekizumab Treatment Response Across Weight Categories. Proportion of patients achieving PASI75, PASI90, and PASI100 response by weight category in the ixekizumab Q2W arm and the ixekizumab Q4W arm.

Weight (kg)	Ixekizumab Q2W			Ixekizumab Q4W		
	PASI75 Response Rate (%)	PASI90 Response Rate (%)	PASI100 Response Rate (%)	PASI75 Response Rate (%)	PASI90 Response Rate (%)	PASI100 Response Rate (%)
<80	90.9	77.9	46.7	85.6	72.6	43.8
80 to <100	89.4	70.6	39.1	85.6	65.4	34.3
≥ 100	85.7	60.2	25.8	74.2	52.7	22

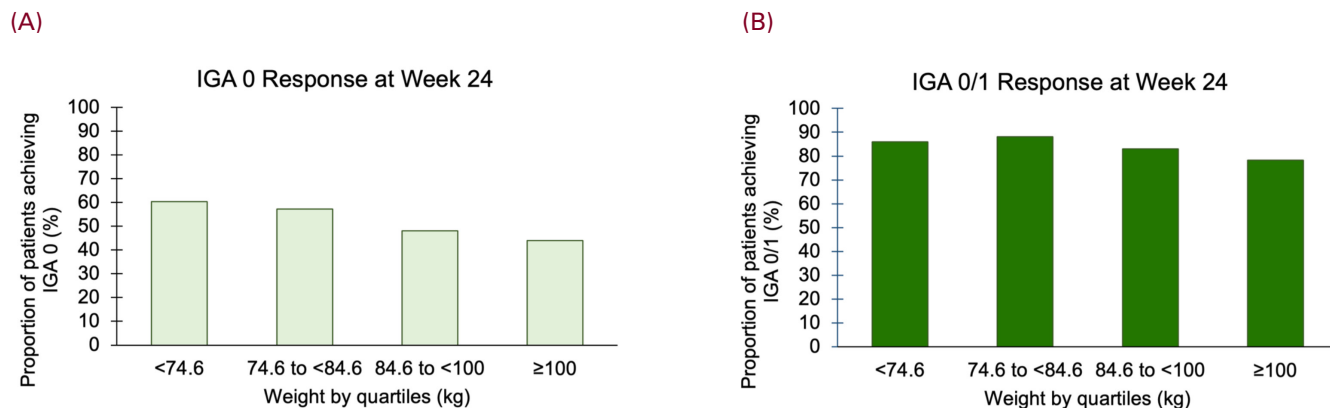
TABLE 2.

Bimekizumab Treatment Response by Weight Category. Proportion of patients achieving PASI90 and PASI100 response by weight category across all bimekizumab treatment arms and in the bimekizumab Q4W/Q8W/Q8W treatment arm.

Weight (kg)	All Dosing Regimens ¹		Q4W/Q8W/Q8W Dosing Regimen ²	
	PASI90 Response Rate (%)	PASI100 Response Rate (%)	PASI90 Response Rate (%)	PASI100 Response Rate (%)
≤ 100	92.6	72.9	95.4	78.9
>100	88.6	64.1	93.2	61.4

¹Dosing regimens included bimekizumab Q4W (initial treatment)/Q4W (maintenance treatment)/Q4W (OLE), Q4W/Q4W/Q8W, Q4W/Q8W/Q4W, and Q4W/Q8W/Q8W.

²Sub-analysis was performed for patients receiving the bimekizumab Q4W/Q8W/Q8W dosing regimen.

FIGURE 2. Guselkumab treatment response by weight quartile. Proportion of patients on guselkumab achieving (A) IGA 0/1 response and (B) IGA 0 response by weight quartile.

kg and >90 kg, or in weight quartiles (<74.6 kg, 74.6 kg to <86.4 kg, 84.6 kg to <100 kg, and ≥100 kg). Obese BMI was defined as BMI ≥30 kg/m². Of the 1829 patients included, 41.9% (n=765) weighed >90 kg, 26% (n=530) weighed ≥100 kg, and 40.2% (n=735) had an obese BMI. Across all weight categories, patients receiving guselkumab had similar IGA ≤1 response rates (range: 78.3%-88.1%). Regardless of weight, patients receiving guselkumab had significantly higher rates of IGA ≤1 compared to patients on both placebo and adalimumab at week 24. The superiority of guselkumab over adalimumab was particularly pronounced in the ≥100kg weight quartile, with 78.3% of guselkumab patients ≥100kg achieving IGA ≤1 vs 45.2% of adalimumab patients ≥100 kg. Similarly, 79.0% of guselkumab patients with obesity achieved IGA ≤1 compared to 46.7% of adalimumab patients with obesity.³⁷ Overall, this suggests that high bodyweight does not impact guselkumab efficacy. Additionally, patients with high bodyweight and/or obese BMI may have a more pronounced treatment response to guselkumab compared to adalimumab (Figure 2).

Risankizumab. Risankizumab is a humanized, IgG1 monoclonal antibody that similarly inhibits IL-23 by targeting the p19 subunit.³⁸ The UltIMMa-1/2 phase 3 trials evaluated the efficacy and safety of subcutaneous risankizumab compared to placebo or the active comparator ustekinumab for moderate-to-severe plaque psoriasis.³⁹ Patients could continue in the open-label extension study, LIMMitless, to take risankizumab 150 mg Q12W at week 52 through week 256.⁴⁰

A sub-analysis of the LIMMitless trial studied the effects of baseline characteristics, including BMI, on risankizumab treatment response. BMI was sub-categorized as <25 kg/m², 25 to <30 kg/m², and ≥30 kg/m².⁴¹ The authors quantified treatment efficacy using PASI90 or PASI100 response rates.

Of the 525 total patients enrolled, 48.6% (n=255/525) had BMI ≥30 kg/m². At week 256, patients across BMI categories had similar PASI90 response rates (89.7% for BMI <25, 87.6% for BMI 25 to <30, and 82.7% for BMI ≥30) and PASI100 response rates (61.5%, 56.9%, and 57.3%, respectively).⁴¹ Overall, the sub-analysis results did not suggest any differences in risankizumab treatment response based on BMI.

Tildrakizumab. Tildrakizumab is a humanized, IgG1κ monoclonal antibody that also targets IL-23 via the p19 subunit.⁴² A post-hoc analysis of the reSURFACE 1/2 and extension studies evaluated the effect of metabolic syndrome on tildrakizumab 100 mg or 200 mg treatment response.⁴³ Of 640 total patients included, 20.1% (n=134) had metabolic syndrome at baseline. At week 244, PASI75, PASI90, and PASI100 response rates were comparable between patients with and without metabolic syndrome in both tildrakizumab treatment groups. The median decrease from baseline PASI score between weeks 28 and 244 were also similar between patients in the tildrakizumab 100 mg treatment group (>83% vs >89% for patients with vs without metabolic syndrome) and in the tildrakizumab 200 mg treatment group (>85% vs 90%, respectively). In terms of safety, the safety profile of tildrakizumab was similar when comparing TEAEs, serious adverse events, and adverse events of special interest in patients with vs without metabolic syndrome.⁴³ Taken together, these results suggest that tildrakizumab maintained similar efficacy and safety in patients with and without metabolic syndrome.

Biologic Therapies in Psoriasis Patients with Obesity: Real-World Data

In addition to clinical trial data, real-world clinical experiences add additional perspectives that complement evaluations of obesity and psoriasis treatment response.

With regard to IL-17R antagonists, real-world practice data supports the effectiveness of brodalumab regardless of BMI. A retrospective study of patients seen at 14 Italian dermatology clinics studied the effectiveness of brodalumab over 3 years.⁴⁴ Patients were categorized as normal-weight (BMI <25 kg/m²), overweight (25 to <30 kg/m²), and obese (≥30 kg/m²). Overweight patients were significantly more likely to achieve PASI100 response than patients with obesity at weeks 24 and 52 only, but no significant differences were found at any other time points. In addition, there were no significant differences in treatment response between patients with obesity and normal-weight patients at any time points. Similar to clinical trial findings,^{24,25} brodalumab continued to show strong efficacy against moderate-to-severe psoriasis regardless of BMI. Interestingly, although there was a slight signal with overweight patients on brodalumab achieving higher PASI100 response rates at weeks 24 and 52 compared to patients with obesity, this difference normalized at all other time points, which suggests that from a long-term perspective, any slight changes in efficacy may be simply temporary. Additionally, there were no differences in clinical response to brodalumab between normal-weight patients and those with obesity at any time point. This further supports the clinical trial data, which showed that brodalumab remained similarly and highly efficacious in patients with psoriasis with and without obesity. Overall, BMI did not appear to affect brodalumab effectiveness in real-world clinical practice.

In terms of treatment response to IL-17 antagonists, real-world findings are less clear for patients with obesity. For example, a recent single-center, retrospective study evaluated treatment response in the first 35 patients treated with ixekizumab following drug approval by the European Medicines Agency.^{45,46} These patients were compared to the first 28 patients treated with ustekinumab following EMA drug approval.⁴⁷ Patients were grouped by BMI into 2 categories: normal weight (BMI <27) and “slight overweight” (BMI >27). The study found that “slight overweight” patients on ixekizumab had increased PASI90 response rates at week 52 compared to those on ustekinumab. However, “slight overweight” patients on both treatments had numerically decreased PASI100 response rates compared to PASI90 response rates, although no statistical differences were found.⁴⁶ In contrast, a multicenter retrospective study from Italy looked at treatment response and drug survival in psoriasis patients initiating biologic therapies that included adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab.⁴⁸ BMI categories were defined as <30 kg/m² and ≥30 kg/m². On multivariate analysis, patients with BMI ≥30 kg/m² were less likely to respond clinically to secukinumab and ixekizumab, and they were more likely to

discontinue secukinumab and ustekinumab treatment at 24 months. However, BMI had no effect on clinical response for adalimumab, etanercept, and ustekinumab. The long-term drug survival of adalimumab, etanercept, and ixekizumab was also unaffected by BMI.⁴⁸ Taken together, the real-world data on the effectiveness of IL-17 antagonists across BMI groups has yielded mixed results in comparison to clinical trial data.

Lastly, in terms of IL-23 antagonists, a recent study using the CorEvitas Psoriasis registry aligned with clinical trial findings for guselkumab treatment response in patients with psoriasis who have obesity.⁴⁹ Real-world data from American and Canadian clinical sites was used to determine whether guselkumab effectiveness varied across different BMI categories. Disease activity, clinical treatment response, and patient-reported outcomes were collected at baseline visits and follow-up visits after 9-12 months of persistent guselkumab treatment; both clinical and patient-reported outcomes were used to determine effectiveness of guselkumab therapy. Patients were grouped into the following categories based on BMI: underweight/normal weight (<25 kg/m²), overweight (25 to <30 kg/m²), and obese (≥30 kg/m²). The study found no significant difference in clinical and patient-reported outcomes across BMI groups following guselkumab treatment,⁴⁹ further demonstrating that BMI does not negatively impact guselkumab effectiveness in a real-world setting (Table 3).

Taken together, real-world data suggests that obese BMI may have a variable effect on clinical treatment response and drug survival depending on the biologic therapy regimen. Brodalumab and guselkumab demonstrated comparable efficacy across BMI categories, while the data on IL-17 receptor antagonists is somewhat inconclusive. Clinical trial data and real-world findings should be integrated to better inform biologic choices.

Optimizing Management of Psoriasis Patients With Obesity *Considerations for Pharmacologic Management of Psoriasis Patients With Obesity*

When determining the appropriate treatment regimen for psoriasis patients, integrating their comorbid conditions into the medical decision-making process is key to optimizing management. This is particularly true for patients with psoriasis and comorbid obesity, who represent such a large proportion of the overall psoriasis patient population.¹⁵ Therefore, when treating patients with psoriasis and obesity, clinicians should consider biologic therapies that have demonstrated comparable efficacy in both patients with and without obesity. The IL-17R antagonist brodalumab

TABLE 3.

Real-World Guselkumab Treatment Response Across BMI Categories. Proportion of patients achieving IGA 0/1, IGA 0, and PASI90 response by BMI category following 9-12 months of guselkumab treatment.

BMI Category	Proportion of Patients Achieving IGA 0/1 (%)	Proportion of Patients Achieving IGA 0 (%)	Proportion of Patients Achieving PASI90 (%)
Underweight/Normal	72	48	56
Overweight	58	35	46
Obese	57	33	46

has strong clinical trial and real-world data showing its consistent efficacy across BMI categories.^{24,25,44} The IL-23 antagonist guselkumab has shown similar efficacy in treating both patients with and without obesity.³⁷ The IL-17 antagonist ixekizumab has some comparable efficacy in treating both patients with and without obesity in clinical trial analyses, although further real-world data may help to clarify trends in ixekizumab treatment response across BMIs.^{32,46,48}

In addition, some biologic therapies offer weight-based dosing regimens, such as bimekizumab, ustekinumab, and infliximab. Bimekizumab is a humanized IgG1 monoclonal antibody that selectively targets IL-17A and IL-17F.³³ After patients are loaded with 320 mg subcutaneous injections Q4W through week 16, the dosing regimen is stratified by bodyweight: patients weighing <120 kg receive 320 mg Q8W, while patients weighing ≥120 kg receive 320 mg Q4W.⁵⁰ Ustekinumab is a fully human, high-affinity monoclonal antibody that binds the p40 subunit of IL-12 and IL-23 to block signaling through both cytokines.³⁸ Patients weighing ≤100 kg receive 45 mg subcutaneously at week 0, week 4, and Q12W thereafter, and patients weighing >100 kg receive 90 mg at week 0, week 4, and Q12W thereafter.⁵¹ Lastly, infliximab is a mouse-human chimeric IgG1 monoclonal antibody that selectively binds and neutralizes human TNF-α.⁵² For treatment of psoriasis and psoriatic arthritis, patients receive 5 mg/kg via intravenous infusion at week 0, 2, 6, and Q8W thereafter.⁵³ However, because infliximab must be administered via intravenous infusion for at least 2 hours, this biologic therapy is not widely used in dermatologic practice. In addition, prior literature has identified an association between anti-TNF-α therapy (ie, infliximab, etanercept) and weight gain, which may have the unwanted effect of potentially exacerbating comorbid obesity.⁵⁴⁻⁵⁶

Lifestyle Modifications for Psoriasis Patients With Obesity

Psoriasis patients with obesity should also be encouraged to make lifestyle changes to complement pharmacologic management of their disease. Weight loss interventions may have the dual benefit of addressing obesity and improving

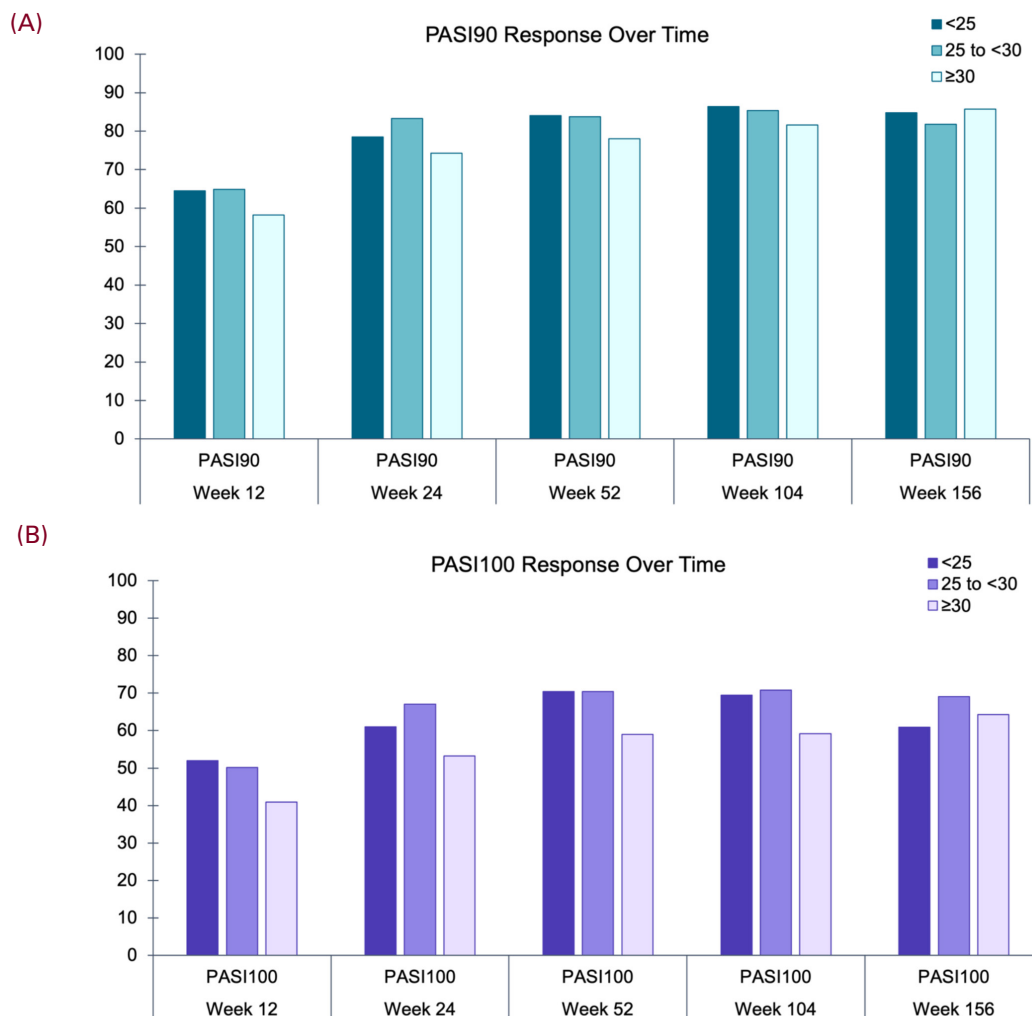
From a nutritional standpoint, prospective studies of calorie restriction in patients with psoriasis have suggested that calorie restriction – with or without weight loss – may improve psoriasis.^{57,58} In one randomized controlled trial, 60 patients with plaque psoriasis and BMI >27 were randomized to consume a low-energy diet (LED, 800-1000 kcal/day) for 8 weeks followed by 8 weeks of normal food intake (up to 1200kcal/day) vs an ordinary healthy diet.⁵⁷ Patients continued on anti-psoriatic therapies while in the study if therapy had not been changed <3 months prior to study entry. The primary endpoint was PASI at week 16, and the secondary endpoint was DLQI at week 16. Patients in the LED group experienced significantly more weight loss ($P<0.001$), greater reductions in PASI score ($P=0.06$), and greater improvements in DLQI scores ($P=0.02$).⁵⁷

Additionally, a prospective study from Croatia studied the effects of calorie restriction and topical steroid treatment compared to topical steroid treatment alone.⁵⁸ Of patients hospitalized with moderate psoriasis, 42 received topical steroids twice daily with calorie restriction, while 40 patients only received topical steroids. Although there were no significant differences in weight change between the calorie restriction and control group, the calorie restriction group did experience a significant reduction in psoriasis disease severity and serum lipid levels compared to the control group.⁵⁸ Taken together, patients with comorbid psoriasis and obesity may be recommended a calorie-restricted diet to promote reduction of weight, markers of metabolic disease such as serum lipids, and psoriasis disease severity.

Pharmacologic Weight Loss Interventions for Psoriasis Patients With Obesity

In addition to lifestyle changes, pharmacologic interventions such as glucagon-like peptide (GLP)-1 receptor agonists (GLP-1rA) may help patients reduce weight and enhance glycemic control in patients with obesity and type 2 diabetes mellitus (T2DM).⁵⁹ A prospective case series followed 7 patients with T2DM and psoriasis who received GLP-1rA treatment with either liraglutide or exenatide for 16 to 20 weeks. Participants' mean BMI was 32. Following treatment, patients experienced a significant decrease in PASI (mean

FIGURE 3. Real-world brodalumab treatment response by BMI category. Proportion of normal weight, overweight, and obese patients on brodalumab achieving (A) PASI90 and (B) PASI100 response at weeks 12, 24, 52, 104, and 156.



12 to 9.2, $P=0.04$), HbA1c (mean 7.5 to 6.5, $P=0.014$), and BMI (mean 32.0 to 30.6, $P=0.05$).⁵⁹ Therefore, GLP-1rA treatment may be useful in psoriasis patients with both obesity and T2DM to improve blood sugar, psoriasis disease severity, and enhance weight loss.

Surgical Weight Loss Interventions for Psoriasis Patients With Obesity

In addition to calorie restriction, gastric bypass surgery may also improve psoriasis disease. In one retrospective study, 34 psoriasis patients with morbid obesity undergoing gastric bypass surgery trended towards decreased psoriasis severity following surgery.⁶⁰ Sixty-two percent of patients reported improvement in their psoriasis following surgery,

4 patients tolerated a decrease from systemic treatment to topicals, and 7 patients tolerated a decrease from topical therapies to no treatment. A retrospective cohort study of Danish patients further supported the benefits of gastric bypass surgery in the setting of psoriasis. Egeberg et al evaluated Danish patients who underwent gastric bypass surgery ($n=12364$) or gastric banding ($n=1071$).⁶¹ Compared to patients who underwent gastric banding, patients in the gastric bypass cohort were significantly less likely to develop new psoriasis, and those with pre-existing psoriasis were significantly less likely to progress from mild to severe psoriasis. Therefore, gastric bypass may be considered for surgical weight reduction in patients with morbid obesity and psoriasis.

CONCLUSION

Obesity and psoriasis are both pro-inflammatory states with a bidirectional association. When managing patients with comorbid psoriasis and obesity, clinicians should take care to select effective systemic therapies that have been proven to achieve good treatment responses across a range of BMIs in both clinical trials and real-world data. Current psoriasis biologics include options across classes – including IL-17R antagonists, IL-17 antagonists, and IL-23 antagonists – that have demonstrated similar efficacy and safety in patients with and without obesity. In particular, clinicians may consider brodalumab as a strong treatment option in patients with psoriasis and comorbid obesity. Some therapies also offer weight-based dosing regimens, which may further aid in optimizing the pharmacologic management of patients with psoriasis and obesity. From a lifestyle standpoint, patients with psoriasis and obesity should be encouraged to pursue weight loss via calorie restriction. In terms of medical weight loss interventions, GLP-1rA therapy or gastric bypass surgery may help to improve both psoriasis and obesity. Future work can be done to characterize the effect of obese BMI more definitively on a wider array of biologics in real-world settings.

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