



REVIEW

# Clinical Efficacy and Safety of Psoriasis Treatments in Patients with Concomitant Metabolic Syndrome: A Narrative Review

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## ABSTRACT

Metabolic syndrome (MetS) is well recognized as a frequent comorbidity of psoriasis with important implications for efficacy and safety of psoriasis treatment. The presence of concomitant MetS is associated with decreased efficacy response to biologic treatment for psoriasis in observational studies. In post hoc analyses of clinical trial data, the anti-IL-23p19 antibody tildrakizumab appears to maintain efficacy in patients compared to those without MetS; no

published subgroup analyses by MetS status are yet available for other biologics. However, there is some evidence that obese patients have decreased psoriasis treatment efficacy with biologics with certain mechanisms of action relative to overweight patients. This confounds interpretation of the effect of MetS due to the association between MetS and body weight. Because of the association between MetS and cardiovascular risk, treatment of psoriasis in patients with concomitant MetS requires special consideration for cardiovascular safety and attention to potential for exacerbation of MetS and related conditions, including nonalcoholic fatty liver disease. Additional studies are needed to clarify the risks for treatment failure and cardiovascular safety concerns in patients with psoriasis and concomitant MetS.

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### Key Summary Points

Metabolic syndrome is a common comorbidity of psoriasis with implications for both the safety and efficacy of psoriasis treatments

Metabolic syndrome is associated with decreased effectiveness of some psoriasis treatments, but it is unclear whether this effect is independent of body weight

The exacerbation of metabolic syndrome may affect patients' body weight, cholesterol, hyperglycemia/insulin resistance, and liver function

Treatment selection in patients with psoriasis and concomitant metabolic syndrome requires special consideration of both potential treatment failure and cardiovascular concerns

Biologic therapeutics appear to be safe for patients with both psoriasis and metabolic syndrome and may be preferable to methotrexate and other conventional systemic therapies

## INTRODUCTION

Metabolic syndrome (MetS) is a frequent comorbidity of psoriasis, affecting 34% of patients in a 2012 population-based study in the UK [1]. MetS is a combination of risk factors, including hypertension, dyslipidemia, elevated blood glucose, and central obesity—possibly linked by insulin resistance [2]—that confers significant risk for developing cardiovascular disease (CVD) or diabetes [3]. The number of MetS risk factors increases the risk of disease progression [2]. The National Cholesterol Education Program Adult Treatment Panel III

defines MetS as present when patients meet  $\geq 3$  of the following 5 criteria: abdominal obesity (waist circumference  $> 102$  cm in men and  $> 88$  cm in women), triglycerides  $\geq 150$  mg/dl ( $\geq 1.8$  mmol/l), high-density lipoprotein (HDL) cholesterol  $< 40$  mg/dl in men and  $< 50$  mg/dl in women, blood pressure  $\geq 130/85$  mmHg, and fasting glucose  $\geq 110$  mg/dl [4]. MetS is associated with twofold increased risk for CVD, a fivefold increased risk for diabetes, and increased risk of stroke and fatty liver disease relative to individuals without MetS [2, 5, 6].

Psoriasis is associated with cardiovascular comorbidities of MetS in a “dose response” manner; prevalence of cardiovascular conditions is increased in patients with severe psoriasis relative to those with less-severe disease [1, 3, 7, 8]. Additionally, patients diagnosed with psoriasis have increased risk of developing insulin resistance or diabetes mellitus [9]. There is evidence for a shared genetic basis for psoriasis and MetS, with psoriasis-associated genes also implicated in the development of MetS, type II diabetes, and cardiovascular disease (recently reviewed in detail [10]). The American Heart Association (AHA) and the American College of Cardiology (ACC) now classify psoriasis (among other inflammatory diseases) as a risk factor for CVD [11] because of accumulating evidence that adults diagnosed with chronic inflammatory disorders have increased rates of multiple cardiovascular conditions [11, 12]. Current psoriasis treatment guidelines recommend screening patients for MetS to enable early intervention and appropriate treatment escalation but offer little guidance on psoriasis treatment selection in these patients [3, 12]. This review summarizes the clinical evidence for efficacy and cardiovascular safety of biologic psoriasis therapies for patients with concomitant MetS. It is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## EFFICACY OF AVAILABLE BIOLOGIC AGENTS FOR TREATMENT OF PSORIASIS IN PATIENTS WITH METABOLIC SYNDROME

### Clinical Efficacy of Biologic Treatment of Psoriasis in Patients With vs Without Metabolic Syndrome

MetS and its components, especially obesity, may decrease efficacy of biologic treatment for psoriasis. In the retrospective noninterventional Outcome of Psoriatic Patients Switched to Adalimumab (OPPSA) study, absence of MetS was associated with greater probability of achieving Psoriasis Area and Severity Index (PASI) responses after 3, 6, and 12 months of psoriasis treatment with adalimumab relative to patients with MetS in a multivariate analysis; neither body weight nor body mass index (BMI) was included as a dependent variable [13]. In the prospective, multicenter, non-interventional CorEvitas Psoriasis Registry, including 2924 patients diagnosed with psoriasis who initiated biologic therapy, more frequent treatment failure was observed in obese relative to nonobese patients and patients with vs without

diabetes mellitus [14]. Additionally, in a real-world study to assess the impact of secukinumab treatment on MetS parameters in patients diagnosed with psoriasis, PASI ≥ 90 responders more frequently had lower BMI when compared to PASI ≤ 90 responders [15]. Tildrakizumab demonstrated comparable efficacy based on PASI response rates and median PASI scores, with no apparent difference in discontinuation rates, in patients with or without MetS through up to 5 years of treatment in post hoc analyses of clinical trial data [16–18]. However, the subgroup of patients with MetS was not large enough to examine the effect of body weight. In a post hoc analysis of pooled data from phase 3 trials of secukinumab for treatment of moderate-to-severe plaque psoriasis, prevalence of MetS was higher among patients with lower responses after 16 weeks of treatment with secukinumab relative to those with better responses (63.2% in patients who did not achieve PASI 50 vs 26.6% in those who achieved PASI 100); similar but less consistent trends were apparent among patients in the ustekinumab and etanercept active-controlled arms [16, 19]. Effects of MetS on the efficacy of biologics for psoriasis treatment are summarized in Table 1.

**Table 1** Evidence for efficacy of biologic treatment for psoriasis based on MetS

Study	Agent/s	Result
Talamonti et al., 2018 [13]	Adalimumab	Absence of MetS, dyslipidemia, hypertension, lower PASI, and lower baseline age were associated with PASI 50, 75, 90, and 100 at 3, 6, and 12 months
Jacobi et al., 2016 [20]	Adalimumab Efalizumab Etanercept Infliximab Ustekinumab	Patients with MetS displayed loss of adherence to all biologics
Pinter et al., 2019 [19]	Secukinumab	MetS, hypertension, and diabetes were associated with lower PASI responses
Lebwohl et al., 2020 [17]	Tildrakizumab	No difference in efficacy between patients with vs without MetS

MetS metabolic syndrome, PASI 50/75/90/100 50%/75%/90%/100% improvement from baseline Psoriasis Area and Severity Index score

Treatment persistence or drug survival is often used as a proxy for effectiveness for psoriasis treatment. Among a group of patients treated with adalimumab, efalizumab, etanercept, infliximab, and/or ustekinumab, components of MetS including arterial hypertension, diabetes mellitus, dyslipidemia, and/or obesity were present in 55.2% of patients and were associated with significantly shorter drug survival time relative to patients without these comorbidities ( $P = 0.033$ ) [20]. Similarly, in an analysis of real-world patterns of biologic and apremilast treatment for psoriasis, patients with metabolic conditions (diabetes, hyperlipidemia, hypertension, metabolic syndrome, or obesity) had significantly higher rates of discontinuation and switching on adalimumab and ustekinumab and numerically higher rates on secukinumab and etanercept relative to patients without these conditions [21]. However, in a retrospective study of 907 patients with psoriasis treated in Israel between 2002 and 2015, metabolic syndrome was a significant positive predictor for biologic drug survival [22]. The effect of metabolic syndrome on persistence of biologics in treatment of psoriasis was explored in a 2019 meta-analysis, but the authors concluded there were insufficient data for pooled analysis [23].

### Body Weight as a Confounder in Randomized Controlled Trials and Observational Studies

Although the above results suggest MetS may decrease efficacy of some biologics for psoriasis treatment, the question cannot be properly addressed without controlling for the effects of obesity. Obesity is a component of the cluster of risk factors in MetS; increased body weight is also a potential confounder for the efficacious treatment of psoriasis; studies on the effects of body weight and obesity on the efficacy of biologics for psoriasis treatment are summarized in Table 2. The IL-12/IL-23p40 inhibitor ustekinumab is dose-adjusted by weight because of decreased efficacy for treatment of psoriasis in patients weighing  $> 100$  kg vs patients weighing  $\leq 100$  kg within the clinical trial population

[24, 25], and increased ustekinumab concentrations had a direct effect on the clinical efficacy in overweight patients [26]. A retrospective subgroup analysis of the etanercept clinical development program showed a tendency toward greater efficacy in patients with body weight less than the population mean (89 kg) relative to obese (BMI  $\geq 30$ ) patients; however, the effect of body weight was not consistently apparent in observational studies [27, 28]. Additionally, higher body weight and BMI are associated with decreased rates of  $\geq 75\%$  improvement from baseline PASI score (PASI 75 response) in patients with psoriasis treated with adalimumab [29]. A 2018 meta-analysis found that obese patients had 60% higher odds for treatment failure with tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors for immune-mediated diseases such as psoriasis [30]. Furthermore, a recent retrospective analysis found that both short- and long-term efficacy is negatively affected by higher BMI, particularly for anti-interleukin (IL) therapeutics such as ixekizumab, secukinumab, and ustekinumab [31].

Data for the effect of body weight on efficacy of anti-IL-17 and anti-IL-23p19 agents for the treatment of psoriasis are limited to subgroup analyses of clinical trial populations. Patients with psoriasis who failed to respond to treatment with secukinumab were more frequently obese (BMI  $\geq 30$ ) relative to responders (mean weight, 103.9 kg for nonresponders [ $<$  PASI 50] vs 81.2 kg for PASI 100 responders); a clinical trial evaluating higher doses of secukinumab in obese patients has been completed with results forthcoming [19, 32]. Response rates following treatment were modestly lower in guselkumab-treated patients weighing  $\geq 100$  kg vs  $< 100$  kg at week 24 and tildrakizumab-treated patients weighing  $> 90$  kg vs  $\leq 90$  kg at week 12 [33, 34]. In a follow-up analysis of the tildrakizumab results, the difference in PASI score improvement from baseline between patients in the lowest weight decile vs patients in the highest weight decile narrowed by week 28, and efficacy in all weight deciles was maintained at week 52, suggesting the effect of body weight on efficacy may be transient [35]. Subgroup analysis of the risankizumab clinical trials showed comparable efficacy across weight

**Table 2** Evidence for efficacy of biologic treatment for psoriasis based on body weight or obesity

Study	Agent	Result
Randomized controlled trials		
Gordon et al., 2006 [104]	Etanercept	PASI 75 response rate 41% in patients weighing < 89.36 kg vs 25% in those weighing > 89.36 kg
Menter et al., 2010 [29]	Adalimumab	“Modestly reduced” PASI 75 response rates in patients weighing 90–140 kg vs < 90 kg and in obese vs nonobese patients
Gordon et al., 2018 [33]	Adalimumab; guselkumab	Lower IGA response rates in patients weighing > 90 kg vs ≤ 90 kg after 16 weeks; lower IGA response rates in patients weighing > 90 kg vs ≤ 90 kg after 16 weeks, although “more consistent” compared with adalimumab
Pinter et al., 2019 [19]	Secukinumab	Nonresponders at week 16 are obese relative to responders
Hsu et al., 2020 [105]	Brodalumab	Comparable efficacy in obese and nonobese patients
Reich et al., 2017 [106]	Ixekizumab	Comparable efficacy across body weight categories < 80 kg, 80– < 100 kg, and ≥ 100 kg
Poulin et al., 2020 [34]	Tildrakizumab	Higher PASI 75 response rates in patients weighing ≤ 90 kg vs > 90 kg after 12 weeks
Leonardi et al., 2019 [35]	Tidrakizumab	Patients in the heavier weight deciles had slightly higher PASI scores than those in the lighter weight deciles; difference between highest and lowest weight deciles diminished by week 28
Strober et al., 2020 [36]	Risankizumab	Comparable efficacy in healthy, overweight, and obese patients
Real-world evidence		
de Groot et al., 2006 [107]	Etanercept	No effect of BMI
Esposito et al., 2009 [28]	Etanercept	No effect of BMI
Giunta et al., 2016 [27]	Etanercept	Significantly higher PASI score in obese patients vs healthy-weight or overweight patients after 48 weeks
Vilarrasa et al., 2016 [108]	Adalimumab, etanercept, infliximab, or ustekinumab	Cumulative probability of drug survival significantly lower in obese vs nonobese patients (23.0 [95% CI 17.4–28.6] months vs 37.3 [95% CI 29.4–45.1] months)
Menter et al., 2016 [109]	Ustekinumab, infliximab, adalimumab, etanercept	No significant effect of obesity on drug survival
Meta-analyses		
Singh et al., 2018 [30]	TNF- $\alpha$ inhibitors	Clinical trial and real-world data; odds ratio for treatment failure in obese vs healthy patients 1.57 (95% CI 1.30–1.89)

**Table 2** continued

Study	Agent	Result
Mourad et al., 2019 [23]	Adalimumab, etanercept, infliximab, ustekinumab	Obesity predicted treatment discontinuation for all biologics combined and for etanercept and ustekinumab

*BMI* body mass index, *CI* confidence interval, *IGA* Investigator Global Assessment, *PASI 75* 75% improvement from baseline Psoriasis Area and Severity Index score, *TNF* tumor necrosis factor

categories of  $\leq 100$  kg and  $> 100$  kg, weight quartiles, and BMI categories of  $< 25$ ,  $25- < 30$ , and  $\geq 30$  kg/m<sup>2</sup> [36]. As the studies on the effect of MetS on psoriasis treatment efficacy were not controlled for the effects of weight and obesity, comparison between patients with MetS and “healthy obese” patients is needed to determine whether MetS is truly an independent risk factor for treatment failure.

## SAFETY CONCERNS FOR PSORIASIS TREATMENT WITH RESPECT TO METABOLIC SYNDROME

Because MetS is associated with increased risk for CVD, nonalcoholic fatty liver disease (NAFLD), and other adverse outcomes, psoriasis treatment safety is of particular concern in patients with concomitant MetS [2, 3, 6]. Despite the prevalence of MetS in patients with psoriasis, relatively few studies have prospectively evaluated the effect of MetS on biologic treatment safety. In the study to explore the effect of secukinumab compared to placebo on fat tissue and skin (ObePsO-S)(NCT03055494), secukinumab treatment reduced systemic inflammation markers relative to patients receiving the placebo, which is suggestive of safety in obese patients and those with MetS [37]. In the tildrakizumab subgroup analyses, adverse events—including those of special concern in patients with MetS, such as major adverse cardiovascular events (MACE), infections, malignancies, and new-onset or worsening diabetes mellitus—were similar among patients with and without MetS through up to 3 years of treatment [16, 17], but clinical trial data stratified by MetS status are lacking for other agents.

In the absence of data specifically in patients with MetS, safety of biologics in patients with psoriasis and MetS may be inferred from the effects of treatment on safety issues related to MetS including cardiovascular safety, potential for exacerbation of MetS, and complications such as NAFLD, infections in patients with diabetes, and polypharmacy due to treatment for multiple comorbidities. Available data in these areas suggest that biologics may have safety advantages over conventional systemic treatment for psoriasis in patients with MetS, as discussed in detail below.

### Cardiovascular Events

Because CVD is the chief risk of MetS, cardiovascular safety of psoriasis treatment is particularly important in patients with concomitant MetS. Systemic treatment with biologic agents is largely neutral with respect to cardiovascular safety, with the possible exception of the anti-IL-12/23p40 antibodies [38]. A 2011 meta-analysis of 22 placebo-controlled clinical trials revealed no significant difference in the frequency of MACE with TNF- $\alpha$  inhibitors and anti-IL-12/23p40 antibodies compared to placebo; MACE occurred in 10/3179 patients treated with ustekinumab or briakinumab vs 0/1474 placebo-treated patients (Mantel-Haenszel risk difference, 0.012 events/person-year; 95% CI – 0.001 to 0.026;  $P = 0.12$ ) and in 1/3858 patients treated with TNF- $\alpha$  inhibitors vs 1/1812 placebo-treated patients (Mantel-Haenszel risk difference, – 0.0005 events/person-year; 95% CI – 0.010 to 0.009;  $P = 0.94$ ) [39]. A 2013 meta-analysis revealed a statistically significant increase in MACE risk in patients with psoriasis treated with ustekinumab or briakinumab vs placebo (OR = 4.23; 95% CI 1.07–16.75;



$P = 0.04$ ), but not when ustekinumab-treated patients were analyzed separately (OR = 3.96; 95% CI 0.51–30.41;  $P = 0.19$ ) [40]. Briakinumab was ultimately withdrawn from development for psoriasis treatment [41]. Integrated safety data from the ustekinumab development program suggested no effect of ustekinumab treatment on serious cardiovascular events, and MACE risk was similar in patients treated with ustekinumab relative to those receiving TNF- $\alpha$  inhibitors in a 2019 cohort study (adjusted hazard ratio [HR], 1.10; 95% CI 0.80–1.52) [42, 43]. Further, in the Vascular Inflammation in Psoriasis—Ustekinumab (VIP-U) trial, patients treated with ustekinumab had reduced aortic vascular inflammation at week 12 compared to baseline ( $-6.58\%$ ; 95% CI  $-13.64$  to  $0.47\%$ ) compared with placebo-treated patients ( $12.07\%$ ; 95% CI  $3.26$ – $20.88\%$ ) [44].

Other biologics used in psoriasis treatment have no specific cardiovascular safety concerns. A 2017 meta-analysis of randomized controlled trials of TNF- $\alpha$  inhibitors (adalimumab, etanercept, and infliximab), anti-IL-17A agents (secukinumab and ixekizumab), and ustekinumab detected no association of MACE with treatment using any of these biologic agents during the clinical trial periods [45]. There was no overall differential risk in serious cardiovascular events or MACE in a large observational cohort study including 60,028 patients with psoriasis or psoriatic arthritis treated with ustekinumab or TNF- $\alpha$  inhibitors [42]. Clinical trial data for several anti-IL-17 and anti-IL-23p19 antibodies suggested no cardiovascular safety signals [46–50]. In a post hoc analysis of pooled phase 3 and 4 data in patients with psoriasis, secukinumab treatment reduced the inflammatory biomarkers' high-sensitivity C-reactive protein and neutrophil-lymphocyte ratio with no effect on traditional cardiovascular risk parameters compared with placebo [51]. Postmarketing data for the IL-17A antibody secukinumab also contained no cardiovascular safety signals; the exposure-adjusted incidence rate of MACE per 100 patient-years over the entire treatment period remained low for each indication (psoriasis, psoriatic arthritis, and ankylosing spondylitis) [52]. In analyses of the US Truven Health Analytics MarketScan Database, patients

with psoriasis treated with TNF- $\alpha$  inhibitors had significantly lower risk for MACE compared with patients treated with methotrexate (adjusted HR, 0.55; 95% CI 0.45–0.67;  $P < 0.0001$ ) or phototherapy (adjusted HR, 0.77; 95% CI 0.60–0.99;  $P = 0.046$ ) [53, 54].

Conventional psoriasis therapeutics like methotrexate and cyclosporine, although older and more established treatment options, may pose increased cardiovascular risks compared with biologics [38, 53, 55]. Patients using methotrexate had higher frequency of cardiovascular events in the US Truven Health Analytics MarketScan Database (Kaplan-Meier rates, 1.5% for the TNF inhibitors cohort vs 4.1% for the methotrexate cohort,  $P < 0.001$ ) [53]. In a recent randomized, placebo-controlled, double-blind clinical trial, low-dose methotrexate treatment did not reduce inflammatory cytokine levels or decrease the risk for cardiovascular events in patients with atherosclerosis but also did not exacerbate or increase the number of cardiovascular events compared with placebo [56]. Similarly, in a nationwide Danish cohort study in patients with severe psoriasis, the incidence of cardiovascular events per 1000 patient-years was 6.28, 6.08, 18.95, and 14.63 among patients receiving methotrexate, cyclosporine, retinoid, and other therapies (including topical medications, phototherapy, and climate therapy), respectively, compared with 4.16 in patients treated with biologics [38].

## Exacerbation of MetS

### Body Weight

Another area of concern is the potential for psoriasis treatment to worsen components of MetS, which would be expected to indirectly increase risk for related conditions. Association between treatment with TNF- $\alpha$  inhibitors and weight gain was apparent in several observational studies [28, 57–60], and a 2020 meta-analysis confirmed that psoriasis patients treated with TNF- $\alpha$  inhibitors had a significant increase in body weight compared with patients receiving conventional systemic therapies (mean difference, 1.4 kg; 95% CI 0.88–1.93 kg) [61]. The same meta-analysis detected no

significant increase in weight or BMI in psoriasis patients treated with anti-IL-12/23p40 or anti-IL-17 antibodies [61]. Conversely, in the PSOLAR registry, treatment with TNF- $\alpha$  inhibitors, ustekinumab, or methotrexate was associated with weight loss after 6 and 12 months of use; however, the study was not designed to test weight, and > 50% of patients were excluded from the analysis because weight was not measured within prespecified windows [62]. Another single, small study documented that a subset of patients treated with ustekinumab had an increase in mean weight [57]. Clinical trial data analyses for both secukinumab and tildrakizumab presented no clinically significant change from baseline body weight [17, 63]. Overall, no evidence yet suggests that change in body weight or body composition during biologic treatment significantly affects cardiometabolic risk in patients with psoriasis.

### **Cholesterol**

The Janus-associated kinase (JAK) inhibitors tofacitinib, upadacitinib, baricitinib, and filgotinib are associated with increases in both HDL and low-density lipoprotein cholesterol levels. Because all of the fractions of cholesterol are affected, in general the “atherogenic index” does not change, and the alterations are therefore not generally considered clinically significant [64–68]. In 2021, the US Food and Drug Administration required an update of the package insert for tofacitinib and other JAK inhibitors to carry a warning of risk for serious heart-related events, blood clots, cancer, and death based on data from a clinical safety trial in high-risk patients treated with tofacitinib compared with TNF blockers [69]. The conventional systemic psoriasis therapies methotrexate, cyclosporine, and acitretin are also associated with an increased risk of hypertriglyceridemia or increased lipid levels; however, the implications of these changes are not known [55, 70, 71]. In contrast, biologics used in psoriasis treatment have minimal effects on serum lipid profile. In one retrospective study, treatment with adalimumab, etanercept, and ustekinumab was associated with a 9% increase in serum triglyceride levels in 139 patients diagnosed with psoriasis [72]. Safety analyses of

the secukinumab and ixekizumab clinical trials revealed no clinically relevant effects on lipid profiles [73, 74], and analysis of serum lipid profiles in patients with or without MetS treated with tildrakizumab showed very limited changes from baseline [75].

### **Hyperglycemia/Insulin Resistance**

Insulin resistance may be the underlying source of MetS [2]. The majority of studies show no changes in glucose metabolism or insulin sensitivity during biologic treatment of psoriasis. A 2015 meta-analysis of seven studies of patients with rheumatoid arthritis and other smaller studies in patients with psoriasis or MetS suggested that biologic treatment with TNF- $\alpha$  inhibitors may decrease fasting glucose and/or improve insulin resistance [76–78]. However, there were no significant changes in fasting glucose levels or insulin sensitivity following 12 weeks of treatment with adalimumab and infliximab [79]. In the VIP studies, there was no change in baseline markers for glucose metabolism following treatment with adalimumab, ustekinumab, or secukinumab [44, 80, 81]. Clinical trial data assessing cardiometabolic laboratory parameters following secukinumab and ixekizumab treatment showed no significant changes from baseline fasting glucose levels or insulin sensitivity [63, 73, 74]. Tildrakizumab use was not associated with consistent changes from baseline glucose levels, and favorable trends were observed in some patients [75]. Comparable data are not yet available for risankizumab and guselkumab. In contrast, patients with psoriasis treated with cyclosporine for 16 weeks had an increased risk of developing diabetes compared with all other treatment regimens (acitretin, efalizumab, and etanercept) in a large observational study [82]. Any effects of biologic treatment of psoriasis on glucose levels or insulin sensitivity seem unlikely to affect cardiovascular risk.

### **Liver Function**

NAFLD is often found in patients with MetS and is significantly more prevalent in patients with vs without psoriasis, occurring in 65.6% of patients with psoriasis vs 35.0% of controls



matched for age, sex, and BMI ( $P < 0.01$ ) in one study and in 21.2% of patients with psoriasis vs 7.8% of controls ( $P < 0.04$ ) in another [55, 83, 84]. Additionally, in a two-stage, cross-sectional study, patients diagnosed with psoriasis had higher prevalence of NAFLD and patients diagnosed with both NAFLD and psoriasis had increased prevalence of subclinical atherosclerosis compared with controls [85]. Biologic therapies for psoriasis appear to be relatively safe with respect to liver disease. In 89 patients with moderate to severe plaque psoriasis, MetS, and NAFLD, treatment with etanercept (but not psoralen/ultraviolet light A therapy) was associated with reduction from baseline in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio—a marker for hepatic damage—at week 24 [86]. In an observational study of 44 patients with psoriasis treated with ustekinumab in Spain, 6 patients developed Grade 1 elevated hepatic transaminases during 52 weeks of treatment, of whom 5 had liver toxicity associated with other psoriasis treatments; no signs or symptoms of liver disease or severe adverse liver effects were detected [87]. Pooled analysis of phase 3 secukinumab data found no increase in AST and ALT levels during 52 weeks of treatment, although increases were noted in the patients in the etanercept active-control arm after week 16 [63]. Lastly, tildrakizumab treatment was not associated with liver-related adverse events or elevations in transaminase levels relative to treatment with placebo through week 12 or etanercept through week 28 or with liver-related safety signals through 1 year of exposure [88].

In contrast, many conventional systemic agents can be harmful to liver function in patients with psoriasis [55]. Patients with NAFLD or chronic liver disease are at increased risk of hepatotoxicity and hepatic fibrosis with methotrexate use [89]. In a 2007 study of patients with psoriasis treated with methotrexate, patients who were overweight or had type 2 diabetes mellitus were at a higher risk of developing severe liver fibrosis during methotrexate treatment (even at lower doses) compared with patients without such risk factors [90]. Incidence of liver disease was higher in patients with psoriasis compared with the general

population and even higher among patients receiving systemic therapy—most frequently, methotrexate (adjusted HR for patients treated with systemic therapy = 1.97; 95% CI 1.63–2.38)—compared with those not treated with systemic agents (adjusted HR = 1.37; 95% CI 1.29–1.45) [83]. Biologics may thus be preferable to conventional systemic agents in patients with MetS due to the elevated risk for liver damage in these patients.

#### **Other Safety Concerns for Patients with MetS**

A number of biologic treatments for psoriasis are associated with increased risk for infections. This may be of particular concern in patients with concomitant MetS, as diabetes mellitus is a significant risk factor for serious infections among hospitalized patients with psoriasis (OR, 1.14; 95% CI 1.13–1.15) [91]. The TNF- $\alpha$  inhibitors all carry “black box” warnings in the US for risk of serious infections; the labeling for ustekinumab and the anti-IL-17 antibodies note that “serious infections have occurred” [24, 25, 74, 92–96]. Prescribing information for the anti-IL-23p19 antibodies states only that these “may increase the risk of infection,” which may make them preferable in patients with diabetes mellitus [97–99].

Finally, patients with multiple comorbidities associated with MetS typically need to use multiple medications [100]. Conventional treatments for psoriasis need to be used carefully when polypharmacy is a concern because of potential for drug interactions and organ impairment; however, polypharmacy is less of a concern for biologic use [101].

## CONCLUSIONS

Many factors, including medical history and comorbidities, must be considered when selecting the optimal therapy for patients with psoriasis [102, 103]. Although MetS is a frequent comorbidity that may reduce treatment efficacy, few specific data are available on psoriasis treatment in patients with concomitant MetS. There is a need for larger studies controlled for obesity and body weight to determine the effect of MetS on treatment efficacy. The majority of

biologic treatments appear relatively safe for patients with psoriasis and MetS, with no harmful effects on cardiovascular health or other safety concerns.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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