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The Effect of Tildrakizumab on Cardiometabolic Risk Factors in Psoriasis by Metabolic Syndrome Status: Post Hoc Analysis of Two Phase 3 Trials (ReSURFACE 1 and ReSURFACE 2)

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ABSTRACT

Background: Metabolic syndrome (MetS) is the most prevalent comorbidity in psoriasis and increases the risk of cardiovascular disease, diabetes, and mortality. Assessment of impacts of biologic therapies on cardiometabolic risk factors are relatively limited. This study evaluated the effect of tildrakizumab on cardiometabolic risk factors in patients with moderate to severe plaque psoriasis and stratified by MetS status.

Methods: In this post hoc analysis of reSURFACE 1/2, tildrakizumab 100 and 200 mg were continuously administered to patients with moderate to severe plaque psoriasis at weeks 0 and 4, and every 12 weeks thereafter. Mean and mean percent changes from baseline were assessed for fasting serum glucose, low/high-density lipoprotein-cholesterol, total cholesterol, triglyceride levels, body weight, and blood pressure at week 64/52 for reSURFACE 1 and 2, respectively, in patients with and without MetS.

Results: A total of 369 patients in reSURFACE 1 and 2 received continuous tildrakizumab 100 mg and 330 received tildrakizumab 200 mg; 21.4% and 20.3% in reSURFACE 1 and 2, respectively, had MetS. At week 64/52, mean changes in cardiometabolic risk factors from baseline did not significantly differ regardless of MetS status. Numerically larger mean decreases in fasting glucose, triglycerides, and systolic blood pressure following tildrakizumab 100 mg and in systolic and diastolic blood pressure following tildrakizumab 200 mg were observed in patients with MetS relative to those without MetS.

Conclusions: Changes in cardiometabolic disease risk factors following tildrakizumab treatment were limited. Risk factors were not increased in patients with MetS vs without MetS.

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INTRODUCTION

Metabolic syndrome (MetS) is a combination of factors including dysglycemia, raised blood pressure (BP), dyslipidemia (raised triglycerides [TG] and lowered high-density lipoprotein cholesterol [HDL-C]), raised fasting glucose (FG), and central obesity[1] that increase the risk of cardiovascular (CV) disease,[1] diabetes,[1] and mortality.[2] In patients with moderate-to-severe plaque psoriasis, MetS is the most prevalent comorbidity.[3-5] Relative to the general population, patients with psoriasis have a higher prevalence of MetS with a reported pooled odds ratio (95% confidence interval [CI]) of 2.14 (1.84, 2.48) from 35 studies.[6]

The presence of MetS risk factors may influence future treatment decisions, as they reduce the efficacy of some medications in psoriasis, including anti-tumor necrosis factor alpha (TNF-α) and anti–interleukin (IL)-17 based biologic therapies,[7-9] or have neutral effects with other treatments.[10,11] Both ustekinumab and TNF-α antagonists have been associated with weight gain during treatment.[12-15] Adalimumab, etanercept, and ustekinumab were associated with a 9% increase in serum triglyceride levels in patients with psoriasis.[16] Biologic therapies for psoriasis may increase body weight and total cholesterol, triglycerides, and low density lipoprotein in patients not taking statins.[12,17] Higher rates of risk for complications of preexisting obesity, hypertension, and/or hypertriglyceridemia, as well as higher rates of cardiovascular disease and new or worsening diabetes mellitus are anticipated in patients with psoriasis and concomitant MetS relative to patients without MetS while receiving biologic therapy.[1] There are no published data evaluating biologic therapy-induced changes in cardiometabolic risk factors based on concomitant MetS status in psoriasis.

Tildrakizumab is a high-affinity, humanized, immunoglobulin G1κ, anti–IL-23p19 monoclonal antibody approved for treatment of moderate to severe plaque psoriasis. Tildrakizumab specifically blocks IL-23 function without affecting the IL-12 heterodimer.[18] Recently, Lebwohl et al showed for the first time that tildrakizumab efficacy and safety in patients with moderate to severe psoriasis did not differ based on concomitant MetS status through 52 weeks.[19] Elevated IL-23 levels in patients with CV disease—which has been linked to increased morbidity and mortality—suggests inhibition of IL-23 via tildrakizumab may have the potential to directly or indirectly impact CV risk factors.[20] Here, we evaluate changes in 6 cardiometabolic risk factors for MetS after tildrakizumab treatment based on MetS status at baseline—FG, low-density lipoprotein-cholesterol (LDL-C)/HDL-C, total cholesterol (TC), TG, body weight, and BP.

METHODS

Methods for this pooled, post hoc analysis of 2 phase 3, 3-part, double-blind, randomized, placebo-controlled studies (reSURFACE 1 [NCT01722331] and reSURFACE 2 [NCT01729754]) were previously reported.[19,21] Briefly, patients were ≥18 years of age with moderate to severe plaque psoriasis (body surface area involvement ≥10%, Physician's Global Assessment score ≥3, and Psoriasis Area and Severity Index score ≥12). All protocols were reviewed and approved by local institutional review boards or ethics panels and conducted according to the Declaration of Helsinki. A placebo treatment arm was included for the first 12 weeks of these studies.

Only patients who continuously received tildrakizumab 100 or 200 mg at weeks 0 and 4 and then every 12 weeks throughout the base study periods for a total of 64 weeks for reSURFACE 1 and 52 weeks for reSURFACE 2 were included; patients receiving placebo during the first 12 weeks of the base study period prior to reassignment to tildrakizumab were not included. A retrospective clinical evaluation of baseline MetS status was conducted[19] as defined by National Cholesterol Education Program Adult Treatment Panel III criteria.[22] Body mass index, calculated from body weight, was used as a proxy for waist circumference data, as this parameter was not collected. Cardiometabolic factors FG, LDL-C/HDL-C, TC, TG, body weight, and systolic/diastolic BP (SBP/DBP) were measured in all patients who received tildrakizumab 100 or 200 mg. The last body weight measurement was at week 28.

Results for week 64 (reSURFACE 1) and week 52 (reSURFACE 2) were combined by tildrakizumab dose. Mean (95% CI) values of cardiometabolic factors stratified by MetS status within each treatment cohort, mean/median absolute and percent change (95% CI) from baseline to weeks 64/52 were calculated.

RESULTS

Of 1862 patients entering reSURFACE 1 (n = 772) and reSURFACE 2 (n = 1090), 369 received tildrakizumab 100 mg and 330 received tildrakizumab 200 mg continuously throughout the base study, with no placebo exposure or dose modifications. In total, 79 (21.4%) and 67 (20.3%) patients receiving tildrakizumab 100 and 200 mg, respectively, met MetS criteria. Baseline demographics and disease characteristics were similar between treatments.[19] As expected, patients with MetS had lower baseline HDL-C; higher baseline body weight, body mass index, TG, FG, and SBP/DBP (Table 1); and prevalence of CV disease and diabetes mellitus[19] compared with patients without MetS. Six (4.1%) patients with MetS (n = 5 tildrakizumab 100 mg; n = 1 tildrakizumab 200 mg) and 25 (4.5%) patients without MetS (n = 12 tildrakizumab 100 mg; n = 13 tildrakizumab 200 mg) did not complete week 64/52.

TABLE 1.

Mean Values of Cardiometabolic Risk Factors at Baseline

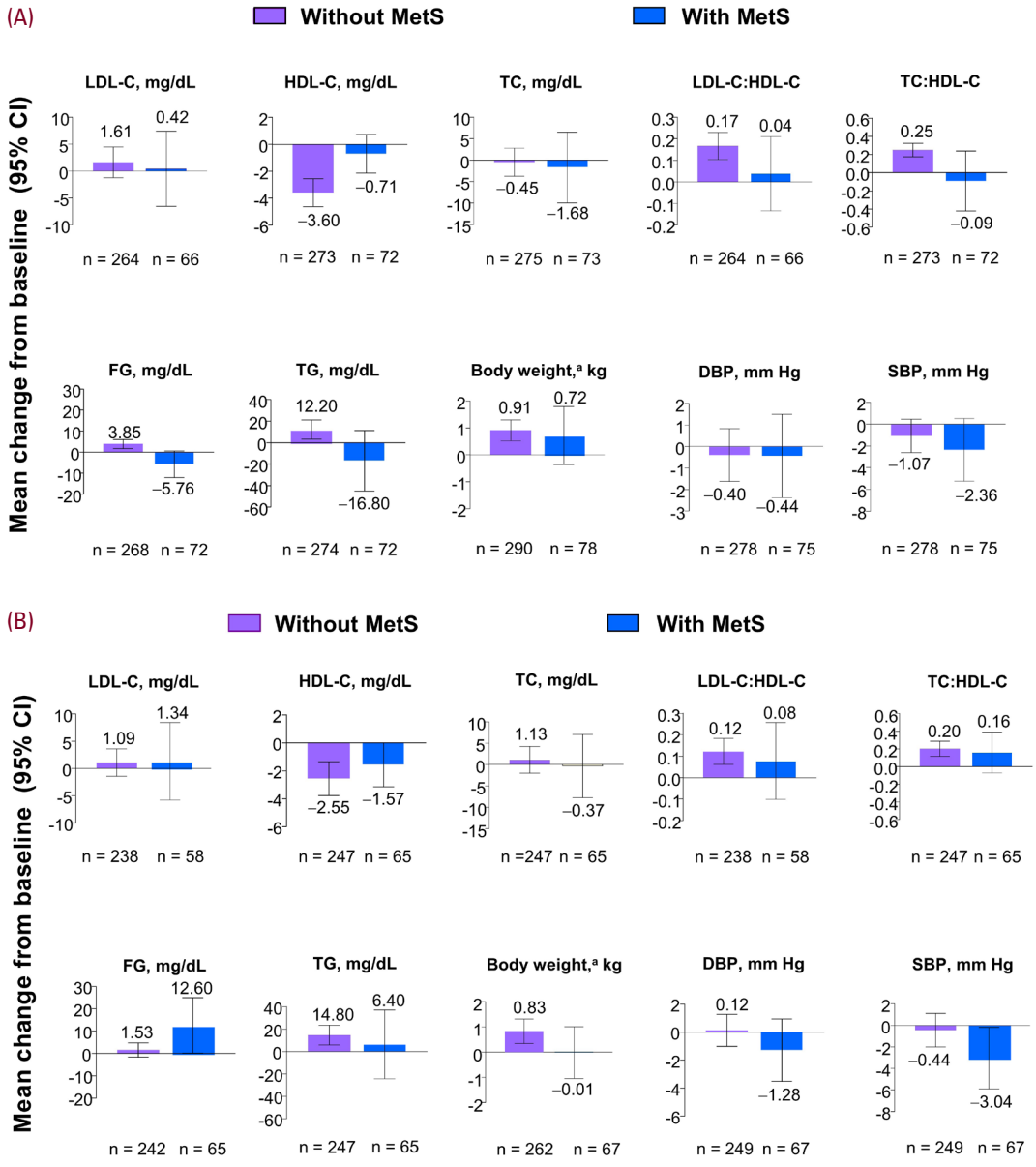
Parameter	TIL 100 mg		TIL 200 mg	
	Without MetS (n = 290)	With MetS (n = 79)	Without MetS (n = 263)	With MetS (n = 67)
LDL-C, mg/dL	112.9 ± 34.2	107.6 ± 29.2	113.5 ± 33.4	110.2 ± 32.4
HDL-C, mg/dL	58.0 ± 16.8	42.9 ± 10.0	57.4 ± 16.6	43.7 ± 10.2
TC, mg/dL	197.9 ± 39.2	195.4 ± 40.3	197.0 ± 39.5	198.8 ± 40.5
LDL-C:HDL-C	2.1 ± 0.8	2.6 ± 0.8	2.1 ± 0.8	2.6 ± 0.8
TC:HDL	3.6 ± 1.0	4.8 ± 2.0	3.6 ± 1.0	4.7 ± 1.0
FG, mg/dL	93.1 ± 15.1[a]	117.8 ± 42.3	97.2 ± 25.1[b]	112.7 ± 31.7
TG, mg/dL	134.0 ± 70.6[c]	237.3 ± 190.7	128.1 ± 65.8	229.0 ± 87.4
SBP, mm Hg	126.0 ± 13.4[d]	137.4 ± 10.1	126.9 ± 14.2[e]	133.4 ± 13.3
DBP, mm Hg	78.3 ± 10.0[f]	85.0 ± 8.9	78.3 ± 8.7[g]	82.6 ± 9.9
Body weight, kg	82.9 ± 18.5	106.9 ± 25.3	82.8 ± 18.1	109.6 ± 25.8
BMI, kg/m²	27.9 ± 5.9[h]	35.7 ± 7.3	28.0 ± 5.5	38.0 ± 8.8

Data presented as mean ± standard deviation.
[a]n = 283; [b]n = 260; [c]n = 286; [d]n = 289, [e]n = 262; [f]n = 289; [g]n = 262; [h]n = 289.
BMI, body mass index; DBP, diastolic blood pressure; FG, fasting serum glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TIL, tildrakizumab.

Mean changes in cardiometabolic risk factors LDL-C, TC, body weight, and DBP were similar in patients with and without MetS receiving tildrakizumab 100 mg (Figure 1A). Both FG and TG were numerically decreased relative to baseline in patients with MetS but not in patients without MetS; patients with MetS had numerically larger decreases in SBP from baseline relative to patients without MetS at week 64/52 (Figure 1A). Mean percent changes from baseline (95% CI) at week 64/52 for patients with MetS relative to patients without MetS were –1.4 (–6.0, 3.2) vs 4.7 (2.6, 6.8) for FG, 4.4 (–5.0, 13.8) vs 16.6 (10.6, 22.6) for TG, and –1.5 (–3.6, 0.6) vs –0.3 (–1.5, 0.9), for SBP.

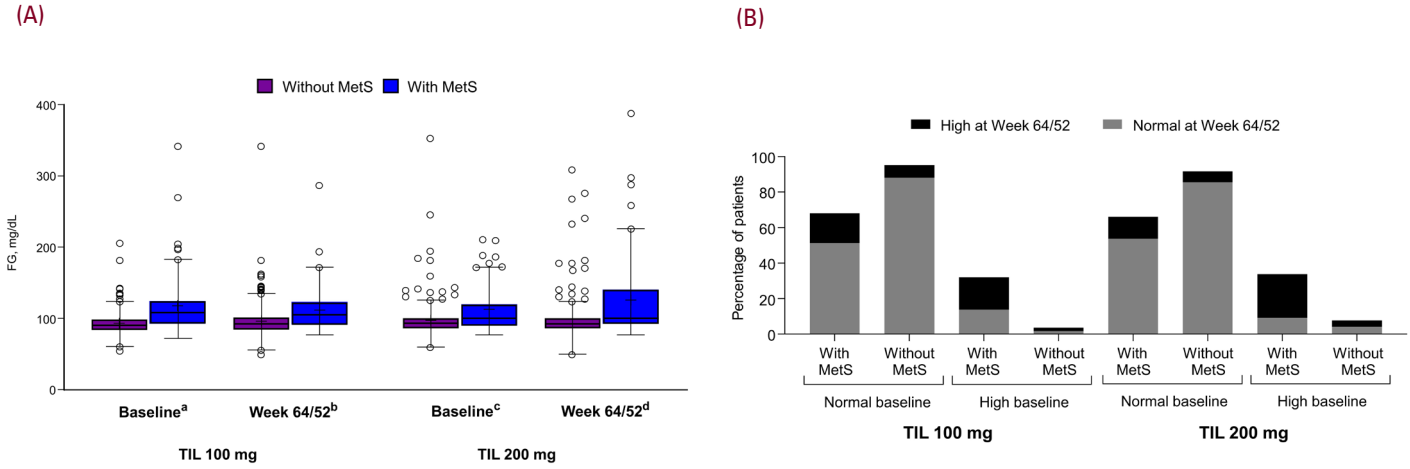
Patients with MetS receiving 200 mg tildrakizumab had similar mean changes from baseline in LDL-C, HDL-C, TC, TG, and body weight relative to patients without MetS (Figure 1B). Patients with MetS had numerically larger mean decreases in SBP and DBP and a numerically larger mean increase in FG from baseline relative to patients without MetS at week 64/52 (Figure 1B).

FIGURE 1. Mean change from baseline to week 64/52 by MetS status following (A) continuous tildrakizumab 100 mg and (B) continuous tildrakizumab 200 mg.



Error bars represent 95% CIs.
[a]Last measurement at week 28.
CI, confidence interval; DBP, diastolic blood pressure; FG, fasting serum glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

FIGURE 2. (A) Distribution of FG values by week and MetS status and (B) percentage of patients with shift in glucose values at week 64/52 vs baseline following continuous tildrakizumab 100 and 200 mg.



Upper and lower ends of boxplots indicate Q1 and Q3, respectively.
Horizontal line indicates median.
Plus symbol indicates mean. Upper and lower whiskers identify upper and lower boundaries for determining outliers.
[a]n = 283 without MetS; n = 79 with MetS.
[b]n = 274 without MetS; n = 72 with MetS.
[c]n = 260 without MetS; n = 67 with MetS.
[d]n = 244 without MetS; n = 65 with MetS.
FG, fasting glucose; MetS, metabolic syndrome; Q1, quartile 1; Q3, quartile 3; TIL tildrakizumab.

Mean percent changes from baseline (95% CI) at week 64/52 for patients with MetS relative to patients without MetS were –1.9 (–4.0, 0.2) vs 0.2 (–1.0, 1.4) for SBP, –0.8 (–3.6, 2.0) vs 0.9 (–0.5, 2.3) for DBP, and 12.6 (0.8, 24.4) vs 2.9 (–0.3, 6.1) for FG. The increased mean change in FG was due to 3 outlier values; median percent change in FG was 0.7% vs 1.0% in patients with vs without MetS, respectively.

Median FG values at baseline and week 64/52 for patients receiving tildrakizumab 100 mg with (109.0 and 103.0 mg/dL) and without MetS (91.0 and 93.0 mg/dL) were comparable; values for tildrakizumab 200 mg with (both 101.0 mg/dL) and without MetS (94.0 and 93.0 mg/dL) were also similar (Figure 2A). Percentages of patients with glucose values shifts from baseline are shown in Figure 2B.

DISCUSSION

This is the first study to examine the impact of IL-23 inhibition alone on cardiometabolic risk factors in patients with moderate to severe psoriasis with and without MetS. In this exploratory analysis, changes in cardiometabolic disease risk factors following treatment with tildrakizumab were limited and generally similar regardless of tildrakizumab dose or MetS status. In patients with MetS receiving tildrakizumab 100 mg, mean changes in FG, TG, and SBP were numerically decreased relative to patients without MetS; patients with MetS receiving tildrakizumab 200 mg had numerical decreases in mean changes in SBP and DBP relative to patients without MetS. Patients without MetS did not show increases in risk factors for MetS during the study. Targeted, prospective studies may provide further understanding of these findings.

The limited changes in cardiometabolic risk factors in patients with psoriasis following tildrakizumab treatment are consistent with a recent post hoc clinical study reporting no increased short-term risk of increased CV events or worsening diabetic complications by MetS status.[19] These results support the safety of tildrakizumab on cardiometabolic risk factors for psoriasis patients regardless of MetS status. Since the odds of having cardiometabolic risk factors of MetS increase with the severity of psoriasis,[23] further analyses on patient subgroups by disease severity are needed to evaluate differential impact of tildrakizumab on these factors. In addition, there were no dose-related effects of tildrakizumab treatment. Importantly, unlike with other biologics,[12,17] patients without MetS did not develop new MetS risk factors following tildrakizumab treatment.

While recent studies demonstrate an association between MetS and psoriasis, and recently published guidelines address management of comorbidities—including MetS—in psoriasis patients, there are limited data on the effect of biologic treatments on CV risk factors of MetS.[19,24] In a recent study in patients with psoriatic arthritis, etanercept and adalimumab significantly improved the MetS components of waist circumference, TG, HDL-C, and glucose compared with methotrexate.[25] Treatment of psoriasis with secukinumab did not alter adipocytokine lev-

els, which are implicated in glucose metabolism.[11] In a pooled analysis of 3 phase 3 studies, ixekizumab had no impact on CV-related parameters of TC, HDL-C, LDL-C, LDL-C:HDL-C, and TG.[10] The effect of TNF-α antagonists on cardiometabolic risk factors remains controversial; anti-TNF-α treatment with some antagonists is associated with weight gain and differing effects on insulin resistance and CV biomarkers.[17,26,27] Here, mean change in FG in MetS patients receiving tildrakizumab 200 mg at week 64/52 was numerically higher relative to baseline, although the median value (101.0) was identical at both time points. A previously reported positive correlation between IL-23 and FG in patients with plaque psoriasis suggests a potential role of IL-23 in metabolic processes, including glucose homeostasis.[28]

In conclusion, changes in cardiometabolic disease risk factors following tildrakizumab treatment were limited. Risk factors were not increased in patients with MetS vs without MetS. Study limitations include that the analyses were not powered to assess statistical differences between groups based on MetS status and the physiological variability of CV risk factors were not considered in reporting numerical changes. Additionally, the clinical meaningfulness of numerical differences is unclear. Further prospective analyses with larger sample size are needed to support these findings.

DISCLOSURES

M.A.M. has received grants and/or honoraria as a consultant, investigator, and/or speaker for AbbVie, Abbott Labs, Amgen, Anacor, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Biotech, LEO Pharma, Merck & Co., Novartis, Sienna, and UCB; and has been on an advisory board for AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen Biotech, LEO Pharma, and Sienna.

N.N.M. is a full-time employee of the US government and has received support in the form of grants to the NIH from AbbVie, Celgene, Janssen, and Novartis.

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A.M.M., and **S.J.R.** are employees of Sun Pharmaceutical Industries, Inc.

C.L. has served as a consultant for and/or has been an investigator for and/or is on the speaker bureaus for AbbVie, Actavis, Amgen, Boehringer Ingelheim, Celgene, Coherus, Corrona, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB, Vitae, and Wyeth.

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