Diabetes and obesity burden and improvements in cardiometabolic parameters in patients with psoriasis or psoriatic arthritis receiving apremilast in a real-world setting

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Introduction: Patients with psoriasis and psoriatic arthritis have a higher prevalence of cardiometabolic comorbidities compared to the general population. Clinical data suggest apremilast may reduce weight and glycated hemoglobin (HbA1c).

Objective: To describe changes in cardiometabolic parameters among patients with psoriasis and psoriatic arthritis newly treated with apremilast by prediabetes/diabetes or obesity status.

Methods: This was a retrospective cohort study of electronic medical records from patients with psoriasis and/or psoriatic arthritis in the OM1 Real-World Data Cloud who newly initiated apremilast. Changes from baseline in body mass index, weight, HbA1c, and lipids were evaluated at 6 and 12 months using a multivariable linear regression model stratified by prediabetes/diabetes or obesity status.

Results: Of 8487 patients initiating apremilast, 24% had diabetes. Of 8250 patients with body mass index available, 27% were obese and 34% were severely obese. Patients experienced decreases in body mass index and weight at 6 and 12 months regardless of diabetes or obesity status, with the greatest reductions seen in those with diabetes and obesity. Reductions in HbA1c at 6 months were seen in patients without diabetes and patients with severe obesity.

Conclusions: Treatment with apremilast may provide the greatest cardiometabolic benefit to those with the greatest burden of cardiometabolic disease. (JAAD Int 2024;16:244-51.)

Key words: apremilast; body mass index; burden; cardiometabolic; diabetes; effects; HbA1c; lipids; obesity; outcomes; psoriasis; psoriatic arthritis; real-world; weight.

INTRODUCTION

Cardiometabolic comorbidities like diabetes and obesity are more prevalent in patients with psoriasis (PsO) and psoriatic arthritis (PsA) compared to the general population.[1-4] Multiple treatment guidelines for PsA recognize cardiovascular disease, obesity,

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Prior presentation: The results of this study have been presented in 2 posters at the ACR 2022 Annual Meeting in Philadelphia, PA, November 10-14, 2022.

Patient consent: This is an observational research study which used a database of deidentified patient records for medical claims and electronic medical records. No interactions with patients occurred in the conduct of this study.

IRB approval status: Not applicable.

Data sharing: The data sets generated during and/or analyzed during the current study are not publicly available as they are proprietary to OM1, Inc. Aggregate counts or other data records may be provided upon reasonable request.

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and metabolic syndrome as comorbidities that increase patient burden and can complicate PsA treatment.[5-8] Patients with severe PsO also have an increased risk of mortality due to cardiovascular disease.[9] Furthermore, the American College of Cardiology and American Heart Association guidelines on prevention of cardiovascular disease classify inflammatory diseases, such as PsO, as risk factors for cardiovascular disease.[10]

Psoriatic disease and cardiometabolic conditions are connected by immune-mediated mechanisms.[1,11,12] PsO and PsA are primarily driven by T helper 1, T helper 17, and T helper 22 pathways.[13,14] Inflammatory cytokines produced in PsO and PsA, such as tumor necrosis factor-α and interleukin-1, participate in the pathogenesis of cardiometabolic disease due to their effects on insulin signaling, adipogenesis, and lipid metabolism.[1,11,12] Concurrently, conditions such as obesity, diabetes, thrombosis, and atherosclerosis create an inflammatory state that can trigger or worsen PsO.[1,11] Body mass index (BMI) has been shown to correlate with PsO severity.[15] Additionally, risk of diabetes increases with higher BMI,[16] and risks of diabetes and metabolic syndrome have been associated with greater severity of PsO and PsA.[17,18] The relationship between obesity and PsO is obscure; some studies found weight loss may improve PsO disease severity, some found greater BMI negatively impacts response to biologic therapies, particularly among patients with BMI >30 kg/m^2, and others have found no relationship.[15,19] There is a need for safe and effective therapies for psoriatic disease that are neutral or, at best, may improve the metabolic profile.

Phosphodiesterase 4 mediates a broad range of metabolic processes, including glucose metabolism and adipocyte function.[20] Apremilast is a unique immunomodulatory oral inhibitor of phosphodiesterase 4 that causes an increase in cyclic 3′,5′-adenosine monophosphate, which inhibits production of several inflammatory cytokines.[21] Clinical data have shown apremilast may reduce weight and glycated hemoglobin (HbA1c).[22-24] An analysis of the phase 3 efficacy and safety trial evaluating the effects of apremilast in psoriasis (ESTEEM) 1 and 2 trials has suggested weight and BMI do not affect apremilast efficacy.[25] Improvements in cardiometabolic risk factors with apremilast treatment have also been reported in real-world practice, though with limited sample size.[26-28] In addition, apremilast has been shown to be a safe long-term treatment in PsO and PsA clinical trials.[29]

In order to further explore the relationship between apremilast treatment and cardiometabolic risk factors, we conducted a longitudinal study using a large US-based real-world cohort. We describe changes in cardiometabolic parameters over a 12-month period among patients with PsO and PsA newly treated with apremilast stratified by diabetes or obesity status.

CAPSULE SUMMARY

- Patients with psoriasis and psoriatic arthritis have a higher prevalence of cardiometabolic diseases including obesity, dyslipidemia, and diabetes compared to the general population.
- Apremilast, a treatment for psoriasis and psoriatic arthritis, may help reduce cardiometabolic risk factors among those with diabetes and obesity.

METHODS

Study design

This was a retrospective longitudinal cohort study of patients with PsO and/or PsA in the United States in the OM1 Real-World Data Cloud who newly initiated apremilast. The OM1 data cloud includes information derived from deterministically linked, deidentified, individual-level health care claims and electronic medical records. Patients were required to have a baseline period of ≥12 months before the index date (apremilast initiation date) during which demographics, clinical characteristics, treatment history, and baseline values for outcome measures were assessed. The baseline measure was defined as the closest measure to the index date within 3 months prior to the index date. Outcomes were assessed at 6 (4-9 months) and 12 (±3) months postindex date. The study period was from March 2013 (12 months prior to the initial approval of apremilast in the United States) to November 2021. All medications, including antidiabetics, antihypertensives, and lipid-lowering therapies were permitted any time before the index date and at any time during the study.

Eligibility criteria

Patients were ≥18 years old at index date (defined as first observed apremilast prescription or fill between March 2014 and November 2021) who were new initiators of apremilast with a diagnosis of PsO or PsA within the 12 months on or before the index date. Included were patients with BMI, weight, or laboratory measures in the 3 months before and including the index date and at 6 or 12 months after the index date and were persistent on apremilast for ≥6 months (if qualifying for 6-month analysis) or 12 months (if qualifying for 12-month analysis).

Abbreviations used:

BMI: body mass index
HbA1c: glycated hemoglobin
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
PsA: psoriatic arthritis
PsO: psoriasis
T2DM: type 2 diabetes mellitus

Assessments

Assessments included change and percent change from baseline in BMI, weight, HbA1c, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides at 6 and 12 months. Stratified analyses are presented for patients with and without prediabetes/type 2 diabetes mellitus (T2DM) and for patients by BMI status. Prediabetes was identified by either 2 diagnosis codes ≥30 days apart, HbA1c levels between 5.7% and 6.4%, or fasting glucose levels between 100 mg/dL and 125 mg/dL. T2DM was defined as having 2 diagnosis codes ≥30 days apart or evidence of antidiabetic medication during the baseline period. Patients could meet criteria for both prediabetes and T2DM. Obesity status was defined as no obesity (BMI <30 kg/m^2), obesity (BMI ≥30-34.9 kg/m^2), or severe obesity (BMI ≥35 kg/m^2).

Statistical analysis

As this was an observational study, sample size was not determined based on formal statistical considerations with a specified hypothesis. All eligible patients in the OM1 Real-World Data Cloud were included in the analysis. Missing values were not imputed.

Absolute change and percent change from baseline to 6 and/or 12 months in each of the continuous measures were analyzed based on Wilcoxon signed rank test for the overall population and for individual diabetes and obesity subgroups separately. In addition, mixed-effect linear regression was utilized to model changes and percent changes from baseline to 6 and/or 12 months as a function of age, sex, baseline value, and other relevant associated factors, such as concomitant treatments (antihypertensives, antidiabetics, lipid-lowering therapy), separately for each subgroup of the continuous measures. Corresponding 95% CIs were estimated accordingly.

RESULTS

Patient population

There were 8487 patients, including 6436 (76%) with PsO and 5782 (68%) with PsA who met eligibility criteria. Mean age was 55 years; 63% were female.

A total of 2004 (24%) patients had diabetes, of which 25% had prediabetes and 87% had T2DM (patients could be classified as both). The diabetes group was older and had greater proportions of Black and Hispanic patients (Supplementary Table 1, available via Mendeley at https://data.mendeley.com/datasets/zy52nd6c3w/1). Patients with diabetes also had higher prevalence of comorbid PsO, hypertension, and dyslipidemia; lower total cholesterol, LDL-C, and HDL-C; higher triglycerides; and higher use of antihypertensive and lipid-lowering therapies compared to those without diabetes. However, patients without diabetes had higher prevalence of comorbid PsA.

Of the 8250 patients with a baseline BMI measure, 40% were not obese, 27% were obese, and 33% were severely obese. As with the diabetes group, there were significant differences in age, race, and ethnicity among the no obesity, obesity, and severe obesity groups (Supplementary Table 2, available via Mendeley at https://data.mendeley.com/datasets/zy52nd6c3w/1). Additionally, there were differences in the proportions of women among groups. Rates of comorbid PsO, PsA, diabetes, hypertension, and dyslipidemia increased with higher BMI. The no obesity group had higher HDL-C and lower triglycerides than the other 2 groups. Greater proportions of patients in the obesity and severe obesity groups had received antihypertensive, lipid-lowering, and antidiabetic therapies than patients in the no obesity group.

Unadjusted results—overall population

Overall, 7633 (90%) patients were included in the 6-month analysis. In this population, baseline mean BMI was 32.6 kg/m^2, mean weight was 204 lbs, and mean HbA1c was 6.9%. Unadjusted results showed decreases for all parameters at 6 and 12 months, though the changes were small for HbA1c (−0.1% at 6 months and −0.03% at 12 months) (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/zy52nd6c3w/1). Mean LDL-C was 109.1 mg/dL at baseline and mean HDL-C was 49.3 mg/dL. Decreases were seen in LDL-C at 6 (−7.3 mg/dL) and 12 (−6.1 mg/dL) months. HDL-C decreased slightly at 6 months (−0.2 mg/dL) and increased by a mean of 1.5 mg/dL at 12 months.

Subgroup analysis

Patients in the no diabetes group and diabetes group experienced significant percent changes in BMI and weight at 6 months (Fig 1). Results were consistent at 12 months. The number of patients with

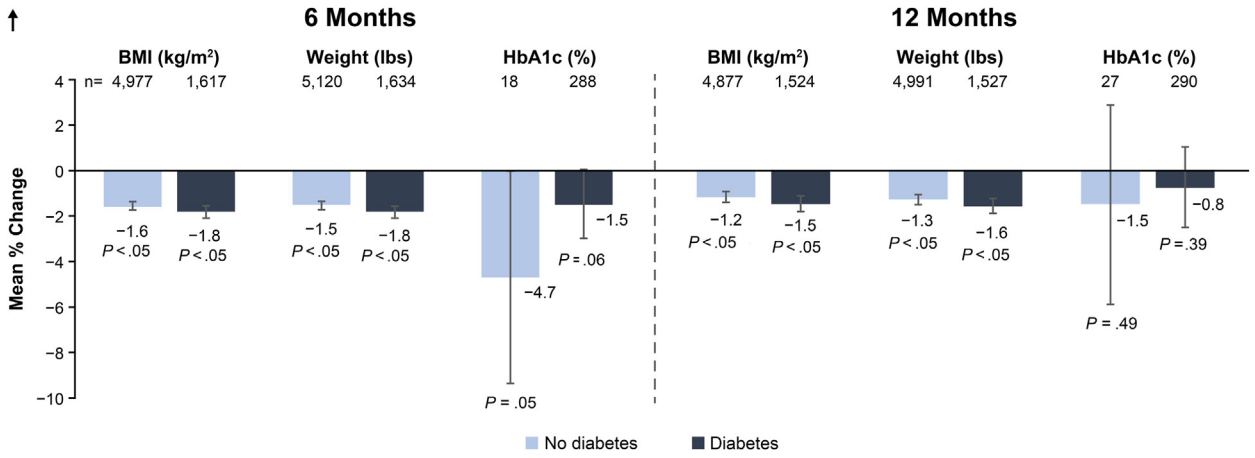

Fig 1. Adjusted mean percent change in cardiometabolic outcomes with apremilast treatment by diabetes status. Error bars represent 95% CI. A mixed-effect linear regression model was utilized separately for each subgroup to model percent changes from baseline to 6 or 12 months as a function of age, sex, the use of antihypertensives, lipid-lowering therapies, steroids, and corresponding baseline outcomes. *P* values were calculated for change from baseline to month 6 or 12. *BMI*, Body mass index; *HbA1c*, glycated hemoglobin.

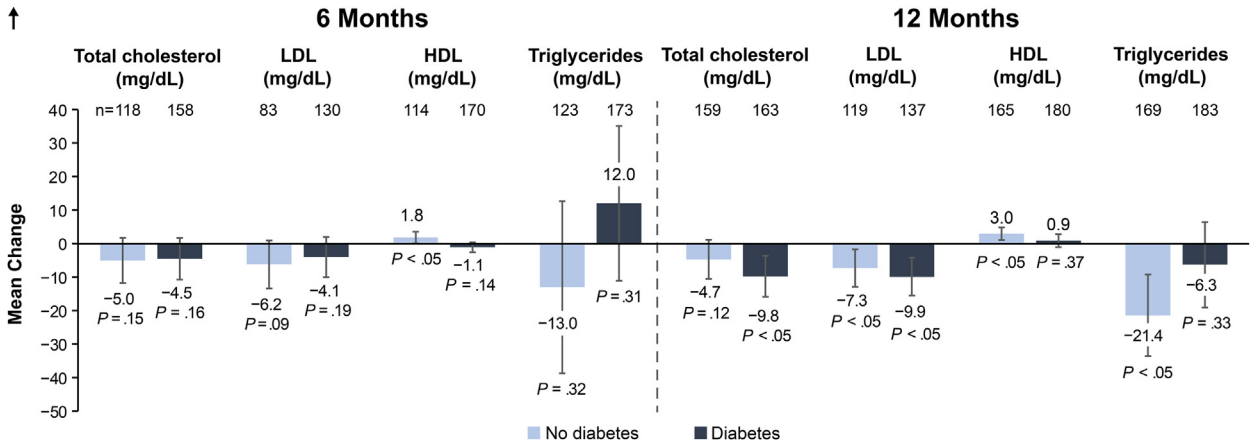

Fig 2. Adjusted mean change in lipid values with apremilast treatment by diabetes status. Error bars represent 95% CI. A mixed-effect linear regression model was utilized separately for each subgroup to model changes from baseline to 6 or 12 months as a function of age, sex, the use of antihypertensives, lipid-lowering therapies, steroids, and corresponding baseline outcomes. *P* values were calculated for change from baseline to month 6 or 12. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein.

HbA1c data were relatively limited. At 6 months, decreases in HbA1c were seen in both patients with and without diabetes, although mean percent changes were larger in patients without diabetes (Fig 1). Smaller reductions in HbA1c were seen in both groups at 12 months, although changes were not significant. At 6 months, the only significant change in lipids was an increase in mean HDL-C in the no diabetes group (Fig 2). At 12 months, total cholesterol decreased significantly in the diabetes group, LDL-C decreased significantly in both groups, and HDL-C increased significantly in the no diabetes group (Fig 2).

Patients experienced significant decreases in weight and BMI regardless of obesity status at 6 and 12 months (Fig 3). A significant reduction in HbA1c was only seen in the severe obesity group at month 6; reductions in HbA1c were not significant in any group at month 12 (Fig 3). There were no significant changes in lipids at 6 months across obesity categories (Fig 4). However, at 12 months, mean total cholesterol and LDL-C decreased, HDL-C

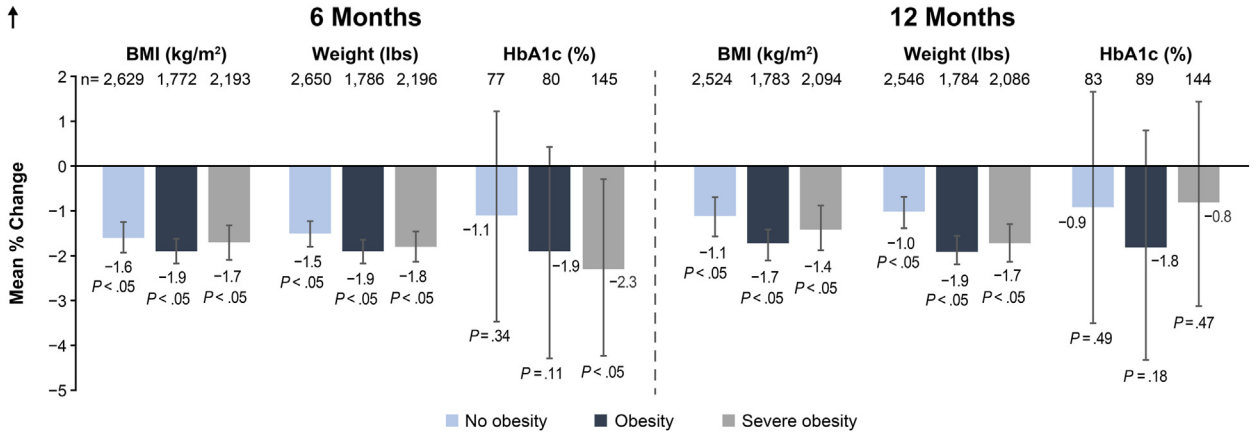

Fig 3. Adjusted mean percent change in cardiometabolic outcomes with apremilast treatment by obesity status. Error bars represent 95% CI. A mixed-effect linear regression model was utilized separately for each subgroup to model percent changes from baseline to 6 or 12 months as a function of age, sex, the use of antihypertensives, lipid-lowering therapies, steroids, antidiabetics, and corresponding baseline outcomes. *P* values were calculated for change from baseline to month 6 or 12. *BMI*, Body mass index; *HbA1c*, glycated hemoglobin.

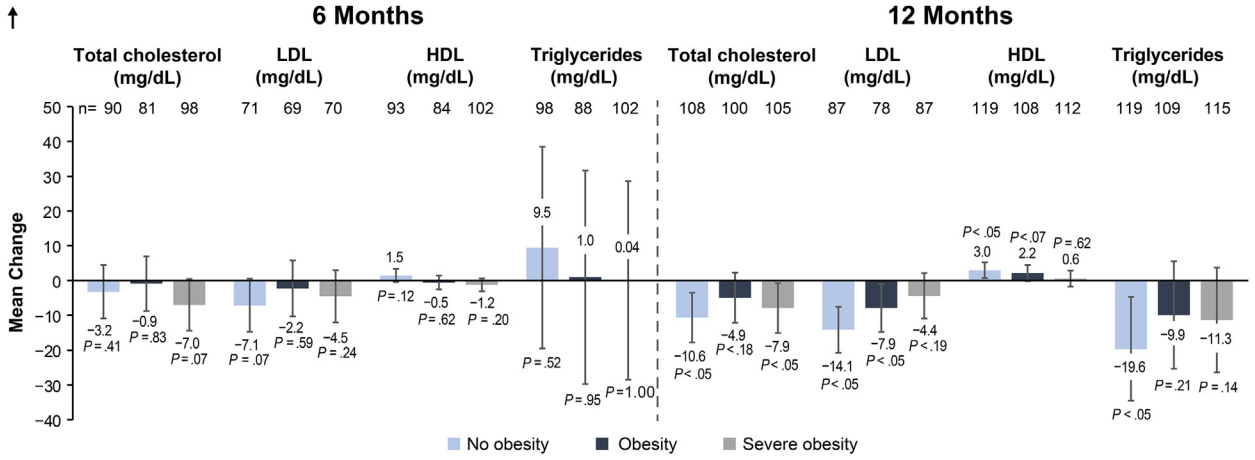

Fig 4. Adjusted mean change in lipid values with apremilast treatment by obesity status. Error bars represent 95% CI. A mixed-effect linear regression model was utilized separately for each subgroup to model changes from baseline to 6 or 12 months as a function of age, sex, the use of antihypertensives, lipid-lowering therapies, steroids, antidiabetics, and corresponding baseline outcomes. *P* values were calculated for change from baseline to month 6 or 12. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein.

increased, and triglycerides increased in the no obesity group; LDL-C decreased in the obesity group; and total cholesterol decreased in the severe obesity group (Fig 4).

More patients experienced decreases in weight than increases over 12 months regardless of diabetes or obesity status (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/zy52nd6c3w/1). Approximately one-half of patients experienced decreases in weight of more than 1% and nearly one-quarter lost ≥5% over 12 months.

DISCUSSION

Diabetes and obesity are common comorbidities of PsO and can have significant impacts on health and quality of life.[2-4,30,31] Because the inflammatory pathways involved in PsO are interconnected with those of cardiometabolic conditions, it is unclear whether diabetes and obesity affect response to treatment for psoriatic disease, and vice versa.[1,11] BMI is a key risk factor for cardiometabolic conditions.[32] Several studies have shown a connection between weight loss and improved PsO.[15] Thus,

whether a therapy for PsO can promote improvements in weight and other cardiometabolic parameters is of interest.

This is one of the first real-world studies presenting data on changes in cardiometabolic outcomes after apremilast initiation in a large cohort of patients with PsO and PsA. There was a high degree of overlap in the presence of PsO and PsA in this population (44% of patients had both). In general, decreases in BMI, weight, and HbA1c were seen after 6 and 12 months of apremilast treatment regardless of diabetes or obesity status after adjusting for relevant variables, with greater reductions in weight and BMI among those with diabetes and obesity and greater reductions in HbA1c in those with obesity.

Mean total cholesterol levels were normal (125-200 mg/dL) at baseline. Triglyceride levels were normal (<150 mg/dL) in the no diabetes and no obesity groups and elevated in the diabetes, obesity, and severe obesity groups at baseline. Mean LDL-C was slightly higher than the recommended range (<100 mg/dL) in all groups at baseline. Although mean changes in LDL-C were not significant at 6 months for any group based on diabetes or obesity status, decreases were observed that brought levels close to the recommended range in all groups. Significant decreases were seen at 12 months in all but the severe obesity group. A significant increase in HDL-C at 6 months was observed only among those without diabetes. However, HDL-C levels were already within normal range (>40-50 mg/dL) at baseline for all groups regardless of diabetes or obesity status. At 12 months, HDL-C further increased significantly only in patients without diabetes and those without obesity.

Our findings are consistent with previous studies of changes in weight and HbA1c with apremilast in clinical trials. In the phase 4 open-label single-arm vascular inflammation in psoriasis-apremilast (VIP-A) trial of patients with moderate-to-severe PsO receiving apremilast, mean decreases of 1.9 kg ($P < .001$) and 1.5 kg ($P = .06$) were seen at 16 and 52 weeks, respectively.[23] In the current study, we observed mean decreases of 3.7 lbs (1.7 kg) at 6 months and 3.2 lbs (1.5 kg) at 12 months. Approximately 25% of patients achieved clinically meaningful weight loss of ≥5% over 12 months. These weight changes are unlikely to be due to gastrointestinal adverse events, as most events such as diarrhea and nausea were reported to resolve within 4 weeks in phase 3 trials.[33] Changes in BMI were also similar between VIP-A and the current study (−0.6 kg/m^2 [16 weeks] and −0.5 kg/m^2 [52 weeks] vs −0.6 kg/m^2 [6 months] and −0.5 kg/m^2 [12 months], respectively). Changes in HDL-C and LDL-C were also observed in VIP-A, although not statistically significant.[23] One study pooled data from 2242 patients from 5 phase 3 trials of apremilast in patients with moderate-to-severe PsO and active PsA.[22] In line with our findings, this analysis also found decreases in weight and HbA1c with apremilast treatment, with greater changes in patients with higher baseline HbA1c. Another study pooled data from 5 phase 3 trials of patients with active PsA receiving apremilast and found decreases in low-density lipoprotein, BMI, and HbA1c after 52 weeks of treatment, with the greatest changes in patients with higher values at baseline.[34]

In previous clinical trials of apremilast, cardiometabolic conditions have been among the most common comorbidities, particularly hypertension (PsO: 30%, PsA: 36%), hypercholesterolemia (9%, 14%), obesity (12%, 12%), hyperlipidemia (12%, 7%), and T2DM (9%, 6%).[29] Despite this high prevalence, rates of major adverse cardiac events and thrombotic events were low with apremilast treatment over long-term exposure, comparable to placebo data.[29] Together with the findings of this study, these results support apremilast as a safe and effective therapy for patients with PsO and PsA with cardiometabolic comorbidities.

Since these data were collected in the course of clinical practice, assessments of HbA1c and lipids are limited due to the small number of patients with data available. All patients were required to remain persistent on treatment through the time point of interest; results are therefore only generalizable to patients who remain persistent on therapy.

CONCLUSION

Obesity, diabetes, and psoriatic disease are connected by shared inflammatory pathways. Nearly one-quarter of patients with PsO and PsA initiating apremilast had prediabetes/diabetes in clinical practice, over one-quarter were obese, and one-third were severely obese. Reductions in BMI, weight, and HbA1c were observed across all categories of diabetes or obesity status. The greatest reductions were seen in those with diabetes and obesity, suggesting treatment with apremilast may benefit those with the largest burden of cardiometabolic diseases. These findings highlight the potential beneficial effects of apremilast on cardiometabolic markers.

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Conflicts of interest

Drs Orroth, Klyachkin, Colgan, and Cordey are employees and stockholders of Amgen, Inc. Author

Cavanaugh, Dr Qian, and Author Kumparatana are employees of OM1.

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