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Association of Apremilast With Vascular Inflammation and Cardiometabolic Function in Patients With Psoriasis

The VIP-A Phase 4, Open-label, Nonrandomized Clinical Trial

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IMPORTANCE Psoriasis is an inflammatory condition associated with metabolic and cardiovascular disease. Apremilast, a phosphodiesterase 4 inhibitor, is commonly used for psoriasis and can cause weight loss.

OBJECTIVE To determine the association between apremilast and aortic vascular inflammation as assessed by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), cardiometabolic markers (primary outcomes at week 16), and abdominal fat composition.

DESIGN, SETTING, AND PARTICIPANTS A single-arm, open-label, interventional, nonrandomized clinical trial in which the imaging and laboratory outcomes were measured by an investigator who was blinded to time was conducted between April 11, 2017, and August 17, 2021, at 7 dermatology sites in the United States. A total of 101 patients with moderate to severe psoriasis were screened, 70 enrolled, 60 completed week 16, and 39 completed week 52.

INTERVENTION Apremilast, 30 mg, twice daily.

MAIN OUTCOMES AND MEASURES Aortic vascular inflammation (measured by FDG-PET/CT), 68 cardiometabolic biomarkers, and abdominal fat composition (measured by CT) at week 16 and week 52 compared with baseline.

RESULTS The mean (SD) age of the 70 patients was 47.5 (14.6) years, 54 were male (77.1%), 4 were Black (5.7%), and 58 were White (82.9%). There was no change in aortic vascular inflammation at week 16 (target to background ratio, −0.02; 95% CI, −0.08 to 0.05; P = .61) or week 52 (target to background ratio, −0.07; 95% CI, −0.15 to 0.01; P = .09) compared with baseline. At week 16, potentially beneficial decreases in interleukin 1b, valine, leucine, isoleucine, fetuin A, and branched-chain amino acids were observed. At week 52 compared with baseline, potentially beneficial decreases in ferritin, β-hydroxybutyrate, acetone, and ketone bodies, with an increase in apolipoprotein A-1, were observed, but there was a reduction in cholesterol efflux. There was an approximately 5% to 6% reduction in subcutaneous and visceral adiposity at week 16 that was maintained at week 52.

CONCLUSIONS AND RELEVANCE The findings of this nonrandomized clinical trial suggest that apremilast has a neutral association with aortic vascular inflammation, variable but generally beneficial associations with a subset of cardiometabolic biomarkers, and associations with reductions in visceral and subcutaneous fat, indicating that the drug may have an overall benefit for patients with cardiometabolic disease and psoriasis.

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Supplemental content

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Psoriasis is a common, chronic, inflammatory disorder associated with an increased risk of cardiometabolic disease and premature mortality, largely attributable to major cardiovascular events.[1-4] Severity of psoriasis, as measured by body surface area affected, is closely associated with the risk of cardiometabolic disease and mortality. For example, for every 10% increase in body surface area affected, there is a 20% increased risk of developing diabetes, independent of traditional risk factors.[5] Similarly, the prevalences of obesity, metabolic syndrome, dyslipidemia, and aortic vascular inflammation are all positively correlated with the body surface area affected by psoriasis.[6,7]

Psoriasis can be effectively treated with oral apremilast, a small molecule, which inhibits phosphodiesterase 4 in immune and nonimmune cells. Phosphodiesterase 4 inhibition leads to increases in cyclic adenosine monophosphate, an intracellular messenger that controls a network of inflammatory mediators, including decreases in the expression of inducible nitric oxide synthase, tumor necrosis factor α, and interleukin 23 (IL-23) and increases in IL-10.[8] Apremilast is associated with a reduction in inflammatory activity of monocytes, dendritic cells, and macrophages, key cellular mediators of both psoriasis and atherosclerosis.[9-11] Furthermore, apremilast is associated with decreased body weight by 5% to 10% in 12% of patients with psoriasis, an association not related to gastrointestinal symptoms.[12] The mechanism of apremilast-induced weight loss and the association between apremilast and body composition (ie, adiposity) is not well established in patients with psoriasis.

We have previously conducted a series of placebo-controlled trials to determine the effect of phototherapy and biologics targeting tumor necrosis factor α, IL-17, and IL-12/23 on aortic vascular inflammation as measured by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) and cardiometabolic biomarkers in patients with moderate to severe psoriasis.[13-15] Here, we extended this approach by conducting an open-label, nonrandomized clinical trial to determine the associations of apremilast with aortic vascular inflammation, adiposity, and blood-based biomarkers of inflammation and lipid and glucose metabolism in patients with moderate to severe psoriasis.

Key Points

Question What is the association of apremilast with aortic vascular inflammation cardiometabolic biomarkers and adiposity?

Findings In this open-label, nonrandomized clinical trial of 70 adults with moderate to severe psoriasis, apremilast had a neutral association with aortic vascular inflammation and a variable but generally beneficial association with several cardiometabolic biomarkers. It was also associated with a 5% to 6% reduction in subcutaneous and visceral adiposity, which occurred at 16 weeks of treatment and persisted through 52 weeks.

Meaning Apremilast may have a beneficial association with cardiometabolic disease in patients with psoriasis, but these findings should be confirmed by placebo-controlled trials.

Methods

Study Design

This nonrandomized clinical trial was an open-label, self-controlled, multicenter trial including adult patients with moderate to severe chronic plaque psoriasis. Seven investigative sites in the United States participated between April 11, 2017, and August 17, 2021. The trial consisted of a screening period (≤4 weeks) and an open-label treatment period (52 weeks) (trial protocol in Supplement 1).

Participants

Adult patients (≥18 years) who had a diagnosis of moderate to severe chronic plaque psoriasis (≥6 months before randomization), had at least 10% body surface area involvement, had a Psoriasis Area and Severity Index (PASI) score greater than or equal to 12 at baseline, had stable disease for more than 2 months before screening and baseline, and who were judged by the principal investigator to be candidates for systemic therapy and in good general health according to the results of screening medical history, laboratory profile, and physical examination were included in the study. Patients underwent clinical examinations (including FDG-PET/CT), and their results were required to not alter the risk-benefit profile of apremilast in the investigator's opinion.

Patients could not have received biologics within 90 days of baseline (or 180 days for ustekinumab), oral psoriasis therapies or investigational agents within 30 days or 5 half-lives (whichever was longer) of baseline, or UV-B phototherapy/laser therapy or topical prescription psoriasis treatment (with the exception of hydrocortisone, 2.5%, for the face and intertriginous areas) within 14 days of baseline. Women of childbearing potential were eligible if they had a negative pregnancy test result at screening and baseline, agreed to undergo pregnancy testing during the study, and agreed to use at least 1 form of contraception. Men, including those who had had a vasectomy and who engaged in activity in which conception was possible, were eligible if they used an effective barrier contraception while receiving apremilast and for at least 28 days after the last dose of the drug.

Patients were excluded if they used prohibited psoriasis treatments, including apremilast; used cholesterol-lowering medications (unless the use of cholesterol-lowering medications involved a dose that was stable ≥90 days before randomization and remained stable during the study) or medication that interferes with the metabolism of apremilast; used oral or injectable corticosteroids, with the exception of inhaled corticosteroids; weighed 135 kg or more or had notable current cardiovascular or cerebrovascular disease; had significant medical or psychiatric problems; had a prior diagnosis of erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or exacerbated psoriasis, or new-onset guttate psoriasis, other active skin diseases, or skin infections that may interfere with evaluation of psoriasis; had an active infection or risk factors for severe infections; received a live vaccination within 30 days before screening or

required live vaccination during study participation; had a history of hematologic or solid malignant neoplasms other than successfully treated basal cell carcinoma, nonmetastatic cutaneous squamous cell carcinoma or cervical intraepithelial neoplasia, or carcinoma in situ of the cervix with no evidence of recurrence within 5 years; had a recent history of substance abuse; or had clinically significant hematologic, glucose, or liver or kidney function test abnormalities. See the trial protocol in Supplement 1 for detailed inclusion criteria.

Interventions and Follow-up

Apremilast was given (per US Food and Drug Administration–approved dosing regimen) with an initial dosage titration for the first 5 days (day 1, 10 mg; day 2, 10 mg twice daily; day 3, 10 mg in the morning and 20 mg in the evening; day 4, 20 mg twice daily; and day 5, 20 mg in the morning and 30 mg in the evening) and then 30 mg twice daily thereafter. Patients were evaluated at baseline and at weeks 4, 8, 12, 16, 28, 40, and 52.

Outcomes

The primary outcomes were change in total aortic vascular inflammation and 68 cardiometabolic biomarkers at week 16 compared with baseline. Secondary outcomes included changes in body composition as measured by FDG-PET/CT between week 52 and earlier time points (baseline and week 16); changes in physician-reported outcomes (PASI and the Physician Global Assessment) between week 52 and earlier time points (baseline and week 16); changes in patient-reported outcomes (Dermatology Life Quality Index score and pruritus by visual analog scale score) between week 52 and earlier time points (baseline and week 16); change in total aortic vascular inflammation and cardiometabolic biomarkers between week 52 and earlier time points (baseline and week 16); and adverse events.

The target to background ratio (TBR) was used to evaluate aortic vascular inflammation. Patients underwent FDG-PET/CT scans using the standard protocol[16,17] after overnight fasting; the prescan glucose level was less than 150 mg/dL before FDG administration. Bed positions of 3 minutes each, scanning from the neck to the iliac crests 120 minutes after administration of FDG, were used. After qualitative review of PET and CT images, the extent of FDG uptake within the aorta was directly measured using OsiriXTM version 12 (OsiriX) to calculate the TBR. Each aortic region of interest produced 2 measures of metabolic activity: a mean standardized uptake value and a maximal standardized uptake value. Moreover, regions of interest were also placed on 6 contiguous slices over the superior vena cava to obtain the background activity of the FDG tracer. The mean standardized uptake values from each of the superior vena cava slices were averaged to produce 1 venous value. To account for background blood activity, the maximal standardized uptake value from each aortic slice was divided by the average venous mean standardized uptake value, yielding the TBR.[6,18,19]

We also evaluated changes in inflammatory, lipid, and metabolic biomarker levels between baseline and weeks 16 and 52. Inflammatory biomarkers C-reactive protein, tumor necrosis factor α, IL-6, IL-17α, vascular cell adhesion molecule 1, intracellular adhesion molecule 1, serum amyloid A, IL-8, IL-10, interferon γ, IL-1β, IL-9, and monocyte chemotactic protein 1 were measured using multiplex (Uplex and Vplex) technology (Mesoscale). Lipid particle size and number, glycine A, the indicated amino acids, apolipoprotein A-1 and apolipoprotein B, and other metabolites were assessed using nuclear magnetic resonance spectroscopy and calculated using the LP4 algorithm (Labcorp). High-density lipoprotein cholesterol efflux capacity was calculated as previously described.[14,20] Metabolic markers, including insulin, leptin, and adiponectin, were assayed using Vplex technology (Mesoscale). Plasma concentrations of fetuin A (R&D Systems), ferritin, and IL-2RA (Thermo Fisher Scientific) were measured by enzyme-linked immunosorbent assay.

Body composition consisted of measuring adipose tissue volumes at L2 to L3 using automated in-house software.[21] The algorithm consisted of body masking, noise reduction, adipose tissue labeling, visceral adipose tissue and subcutaneous adipose tissue separation, and quantitation. The adipose tissue volume inside the internal contour is associated with the visceral adipose tissue, and the adipose tissue volume between the external and internal contour is associated with subcutaneous adipose tissue, as described previously.[22]

The clinical safety and tolerability of apremilast were evaluated by monitoring vital signs, clinical laboratory variables, and adverse events. Safety assessments consisted of recording all adverse events and serious adverse events, with their severity and association with study drug and pregnancies. The safety assessments also included regular monitoring of hematologic, blood chemistry, and regular assessments of vital signs, physical condition, and body weight.

Sample Size

The sample size was based on primary and secondary outcomes of changes in the TBR of the standardized uptake values of the tracer measured by FDG-PET/CT. Using a 2-sided test with $\alpha = .05$ and a prior SD estimate of the change in the TBR (SD = 0.263), we estimated that 35 patients would provide 90% power to detect a clinically significant change in the TBR of 0.15 between pretreatment and posttreatment measurements. The 35 patients would also provide 90% power to detect clinically relevant differences in cardiometabolic biomarkers before and after treatment of approximately 0.57 SD, well below the general threshold for significance of 1 SD. To accommodate potential dropout of up to 50% at 52 weeks, we accrued 70 patients. However, at 16 weeks, we assumed our dropout rate would be only 20%. Assuming 56 patients would undergo an FDG-PET/CT at 16 weeks, we estimated that we would have 98.7% power to detect the change in the TBR of 0.15, as already discussed. Aortic vascular inflammation, cardiometabolic biomarkers, and body composition were measured and analyzed by an investigator blinded to time point in the study. The study protocol and all amendments were approved by the independent ethics committee or institutional review board at the University of Pennsylvania. The study was conducted according to the Declaration of Helsinki, in accordance with good clinical practice, and written informed consent was obtained from each participant.

Table 1. Baseline Characteristics

Variable	No. (%) (N = 70)
Age, mean (SD), y	47.5 (14.6)
Sex	
Female	16 (22.9)
Male	54 (77.1)
Race	
American Indian or Alaska Native	1 (1.4)
Asian	3 (4.3)
Black or African American	4 (5.7)
White	58 (82.9)
Other[a]	4 (5.7)
Ethnicity	
Hispanic or Latino	24 (34.3)
Not Hispanic or Latino	46 (65.7)
Alcohol consumption	
Yes	39 (55.7)
No	31 (44.3)
Smoking status	
Current	17 (24.3)
Former	23 (32.9)
Never	30 (42.9)
BMI, mean (SD)	30.2 (5.0)
Weight, mean (SD), kg	90.4 (17.4)
Medical history	
Diabetes	6 (8.6)
Hyperlipidemia	16 (22.9)
Hypertension	19 (27.1)
Statin use	12 (17.1)
Age at psoriasis diagnosis, median (IQR), y	29 (17-42)
History of psoriatic arthritis	
Yes	8 (11.4)
No	62 (88.6)
Psoriasis treatment history	
Phototherapy	21 (30.0)
Oral systemics	24 (34.3)
Biologics	30 (42.9)
Investigational agents	7 (10.0)
Baseline PASI score	
Mean (SD)	18.6 (6.0)
Median (IQR)	17.1 (14.8-20.6)
Baseline BSA, m^2	
Mean (SD)	22.3 (13.8)
Median (IQR)	18 (12-28)
Baseline PGA rating	
Mean (SD)	3.2 (0.5)
Median (IQR)	3 (3.0-3.7)
Baseline DLQI score	
Mean (SD)	11.6 (6.7)
Median (IQR)	11 (6-15)
Baseline pruritus VAS score	
Mean (SD)	57.2 (30.0)
Median (IQR)	69.5 (30.0-80.0)
Range	1.4-99.0
Baseline maximum TBR, aorta	1.61
Mean (SD)	1.61 (0.37)
Median (IQR)	1.53 (1.37-1.72)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; TBR, target to background ratio; VAS, visual analog scale.

[a] Patients could select "other" if they did not believe their race fit into the categories provided.

Statistical Analysis

The primary effectiveness variables (changes from baseline) were analyzed with a paired *t* test in Stata version 17 (StataCorp). Because observed analyses were performed for week 16 and week 52 outcomes using all available data from patients who reached and had the outcomes measured at week 16 and week 52, respectively, missing data were not imputed. Binary outcomes (PASI score of 75/90 and Physician Global Assessment rating of clear/almost clear) at week 16 and week 52 were summarized using proportions and exact 95% CIs. Sensitivity analyses were performed in subgroups defined by clinical treatment response (PASI score of 75), baseline aortic inflammation (baseline TBR ≥1.6), and adherence with apremilast (defined as taking 90% or more of expected doses). Sensitivity to missing data was assessed with multiple imputation using chained equations. No adjustments were made for multiple hypothesis testing.

Results

The mean (SD) age of the 70 patients was 47.5 (14.6) years, 54 were male (77.1%), 1 was American Indian or Alaska Native (1.4%), 3 were Asian (4.3%), 4 were Black or African American (5.7%), 24 were Hispanic or Latino (34.3%), 58 were White (82.9%), and 4 were of other race (5.7%) (patients could select "other" if they did not believe their race fit into the categories provided). A total of 8 patients (11%) had a history of psoriatic arthritis, and 21 (30%) to 27 (39%) patients reported prior use of phototherapy or oral or biologic treatment. The mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 30.2 (5.0), the mean (SD) body surface area was 22% (13.8%), the mean (SD) PASI score was 18.6 (6.0), and the mean (SD) Dermatology Life Quality Index score was 11.6 (6.7), consistent with moderate to severe psoriasis (**Table 1**).

One hundred one patients were screened, 70 were enrolled (eFigure in Supplement 2), and 60 completed to week 16 (10 [14.3%] discontinued before week 16 [4 for other reasons, 3 for loss to follow-up, 2 for early terminations by the physician, and 1 for lack of effectiveness]; 57 patients completed a week 16 scan). A total of 39 patients completed to week 52 (21 [30%] discontinued before week 52 [8 for lack of effectiveness, 8 for other reasons, 4 for loss to follow-up, and 1 for withdrawal of consent]; 38 completed the week 52 scan).

As anticipated, apremilast was effective in treating psoriasis and was associated with weight loss (**Table 2** and **Table 3**). The drug had a neutral association with aortic vascular inflammation and was associated with a 5% to 6% reduction of subcutaneous and visceral fat at 16 weeks of treatment, which was maintained through 52 weeks of treatment. At week 16, the response proportions were 0.35 (95% CI, 0.23-0.48) for a PASI score of 75, 0.12 (95% CI, 0.05-0.23) for a PASI score of 90, 0.25 (95% CI, 0.15-0.38) for a Physician Global Assessment rating of clear or almost clear, and 0.65 (95% CI, 0.52- 0.77) for a Dermatology Life Quality Index score of less than or equal to 5. At week 52, the response proportions were 0.31 (95% CI, 0.17-0.48) for a

Table 2. Physician- and Patient-Reported Psoriasis Outcomes

Instrument	Baseline (n = 70), mean (SD)	Week 16 (n = 60)			Week 52 (n = 39)		
		Mean (SD)	Difference or proportion (95% CI)	*P* value	Mean (SD)	Difference or proportion (95% CI)	*P* value
PASI score	18.6 (6.0)	7.7 (6.7)	−10.8	<.001[a]	8.9 (8.0)	−9.9	<.001[a]
PASI score of 75, No. (%)	NA	21 (35.0)	35.0 (23.1 to 48.4)[b]	NA	12 (30.8)	30.8 (17.0 to 47.6)[b]	NA
PASI score of 90, No. (%)	NA	7 (11.7)	11.7 (4.8 to 22.6)[b]	NA	5 (12.8)	12.8 (4.3 to 27.4)[b]	NA
PGA	3.2 (0.5)	2.0 (0.8)	−1.2	<.001[a]	2.1 (0.9)	−1.1	<.001[a]
PGA rating of clear or almost clear	0 (0)	15.0 (25.0)	25.0 (14.7 to 37.9)[b]	NA	9 (23.1)	23.1 (11.1 to 39.3)[b]	NA
DLQI score	11.6 (6.7)	4.9 (5.2)	−6.1	<.001[a]	5.9 (6.3)	−5.7	<.001[a]
DLQI score ≤5	14.0 (20.0)	39.0 (65.0)	65.0 (51.6 to 76.9)[b]	NA	26.0 (66.7)	66.7 (49.8 to 80.9)[b]	NA
Pruritus VAS score	57.2 (30.0)	30.6 (26.3)	−27.5	<.001[a]	37.7 (27.2)	−19.1	.004[a]

Abbreviations: DLQI, Dermatology Life Quality Index; NA, not applicable; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; VAS, visual analog scale.

[a] From paired *t* test.

[b] The 95% CI is for a single proportion (Clopper-Pearson interval expressed as a percentage).

Table 3. Changes in Aortic Vascular Inflammation and Adiposity

Variable	Week 16 vs baseline		Week 52 vs baseline		Week 52 vs week 16	
	Mean change (95% CI)[a]	*P* value[b]	Mean change (95% CI)[a]	*P* value[b]	Mean change (95% CI)[a]	*P* value[b]
No.	57[c]	NA	38[c]	NA	38[c]	NA
TBR (aorta)	−0.02 (−0.08 to 0.05)	.61	−0.07 (−0.15 to 0.01)	.09	−0.02 (−0.09 to 0.06)	.68
Visceral fat	−10.68 (−16.80 to −4.57)	.001	−12.52 (−22.44 to −2.60)	.02	2.19 (−4.94 to 9.31)	.54
Subcutaneous fat	−19.86 (−30.68 to −9.03)	.001	−19.59 (−34.11 to −5.06)	.01	0.64 (−11.79 to 13.06)	.92
Weight, kg	−1.90 (−2.73 to −1.07)	<.001	−1.47 (−3.03 to 0.09)	.06	0.58 (−0.52 to 1.67)	.30
BMI	−0.63 (−0.90 to −0.35)	<.001	−0.51 (−1.05 to 0.04)	.07	0.19 (−0.21 to 0.58)	.35

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; TBR, target to background ratio.

[a] The 95% CI is for the difference between the later time vs the earlier time (paired *t* test).

[b] From paired *t* test.

[c] Number of patients with positron emission tomographic/computed tomographic data; weight and BMI data were available for 60 and 39 patients at weeks 16 and 52, respectively.

PASI score of 75, 0.13 (95% CI, 0.04-0.27) for a PASI score of 90, 0.23 (95% CI, 0.11-0.39) for a Physician Global Assessment rating of clear or almost clear, and 0.67 (95% CI, 0.50-0.81) for a Dermatology Life Quality Index score of less than or equal to 5. Patients also experienced a statistically significant reduction in pruritus at weeks 16 and 52.

No significant changes in aortic vascular inflammation were observed in the overall study population. Patients had a −0.02 reduction (95% CI, −0.08 to 0.05; *P* = .61) in TBR at week 16 compared with baseline, a −0.07 reduction (95% CI, −0.15 to 0.01; *P* = .09) at week 52 compared with baseline, and a −0.02 reduction (95% CI, −0.09 to 0.06; *P* = .68) at week 52 compared with week 16 (Table 3).

Changes in blood biomarkers of advanced lipoprotein characterization, inflammation, and glucose metabolism are shown in **Table 4**. At week 16, there were reductions in levels of IL-1b, fetuin A, valine, leucine, and isoleucine (Table 4). At week 52, compared with baseline, there were reductions in levels of ferritin, cholesterol efflux capacity, β-hydroxybutyrate, acetone, and ketone bodies, and an increase in levels of apolipoprotein A-1 (Table 4).

Changes in body composition are shown in Table 3. There was a 5.32% reduction in visceral adipose tissue and a 5.53% reduction in subcutaneous adipose tissue at week 16 compared with baseline, which was maintained at week 52. No significant change in visceral adipose tissue or subcutaneous adipose tissue was observed between weeks 16 and 52.

Safety data are presented in the eTable in Supplement 2. A total of 96 adverse events in 46 patients were reported, the most common of which were nausea, diarrhea, headache, and upper respiratory tract infection. Seven serious adverse events occurred in 6 patients, 2 of which occurred before the administration of apremilast (a stroke and a fall that resulted in a fracture); the other serious adverse events were hospitalization due to a fall (n = 2), hospitalization due to acute kidney injury (n = 1), and new mildly FDG-avid amorphous soft tissue mass in the left breast (n = 1).

Sensitivity analyses are shown in **Table 5**. No differences in aortic vascular inflammation were observed for patients who achieved a PASI score of at least 75 or who were at least 90% adherent with all doses of apremilast, but a reduction in aortic vascular inflammation was observed in patients with a TBR of at least 1.6 at week 52 compared with baseline. There was no difference in the results when missing data were assessed with multiple imputation using chained equations.

Table 4. Changes in Blood-Based Biomarkers of Inflammation, Lipoprotein Characterization, and Glucose Metabolism

	Week 16 vs baseline (n = 57-59)		Week 52 vs baseline (n = 37-38)	
Biomarker	Change (SE)	*P* value[a]	Change (SE)	*P* value[a]
Markers of inflammation				
Ferritin, ng/mL	−13.4 (7.6)	.08	−22.6 (9.3)	.02
CRP, mg/dL	−41.4 (82.3)	.62	3.6 (104.4)	.97
ICAM-1, µg/mL	−169.9 (265.0)	.52	41.1 (667.6)	.95
SAA, µg/mL	46.1 (1324.3)	.97	1586.1 (3114.5)	.61
VCAM-1, µg/mL	−11.2 (11.1)	.32	10.3 (10.2)	.32
IFN-γ, pg/mL	−1.9 (2.5)	.44	0.3 (5.5)	.96
IL-1b, pg/mL	−0.5 (0.2)	.03	0.3 (0.4)	.50
IL-10, pg/mL	−0.1 (0.1)	.39	0.6 (0.6)	.26
IL-17A, pg/mL	−0.9 (0.6)	.12	−1.4 (0.9)	.14
IL-6, pg/mL	2.7 (2.8)	.33	22.7 (21.7)	.30
IL-8, pg/mL	24.0 (19.6)	.23	369.4 (349.1)	.30
IL-9, pg/mL	−0.1 (0.1)	.14	−0.0 (0.1)	.81
MCP-1, pg/mL	3.1 (20.6)	.88	101.7 (93.4)	.28
TNF-α, pg/mL	17.9 (18.1)	.33	100.6 (71.9)	.17
IL-2RA, ng/mL	−3.3 (1.9)	.09	−1.6 (2.4)	.53
GlycA, µmol/L	10.7 (6.1)	.09	4.3 (7.8)	.58
Lipid function and metabolism				
Cholesterol efflux capacity	−0.01 (0.03)	.77	−0.16 (0.05)	.005
Triglyceride, mg/dL	−3.5 (5.1)	.49	4.7 (7.4)	.53
Total cholesterol, mg/dL	0.3 (2.7)	.92	4.3 (4.4)	.34
HDL-C, mg/dL	0.1 (0.8)	.87	1.8 (1.1)	.10
HDL-P, µmol/L	0.1 (0.6)	.92	1.0 (0.8)	.23
HDL-Z, nm	−0.1 (0.1)	.19	0.1 (0.1)	.38
S-HDL-P, µmol/L	0.5 (0.7)	.45	0.4 (0.9)	.64
M-HDL-P, µmol/L	−0.2 (0.6)	.71	0.2 (0.8)	.80
LM-HDL-P, µmol/L	−0.4 (0.6)	.43	0.6 (0.8)	.44
L-HDL-P, µmol/L	−0.2 (0.2)	.33	0.3 (0.3)	.28
LDL-C, mg/dL	0.1 (2.5)	.96	1.2 (4.4)	.80
LDL-P, nmol/L	−21.7 (25.6)	.40	5.6 (36.8)	.88
LDL-Z, nm	0.1 (0.1)	.22	0.0 (0.1)	.75
S-LDL-P, nmol/L	−31.8 (26.8)	.24	−9.2 (38.8)	.81
L-LDL-P, µmol/L	21.8 (23.0)	.35	25.1 (36.4)	.49
VL-LDL-P, nmol/L	−18.7 (23.2)	.42	9.6 (33.7)	.78
VLDL-P, nmol/L	1.23 (2.8)	.67	4.9 (4.1)	.24
VLDL-Z, nm	−1.6 (1.1)	.14	−0.0 (1.3)	.98
VLDL-TG, mg/dL	−4.4 (4.5)	.33	3.6 (6.6)	.59
S-VLDL-P, nmol/L	1.4 (2.2)	.54	2.9 (2.5)	.26
M-VLDL-P, nmol/L	0.6 (2.4)	.79	1.8 (2.9)	.55
LM-VLDL-P, nmol/L	−0.2 (2.2)	.93	1.7 (2.7)	.54
L-VLDL-P, nmol/L	−0.9 (0.6)	.16	0.1 (0.9)	.92
IDL-P, nmol/L	−11.8 (19.4)	.55	−12.3 (18.5)	.51
ApoA1, mg/dL	0.9 (2.2)	.67	5.8 (2.8)	.046
ApoB, mg/dL	0.3 (1.5)	.84	2.2 (2.6)	.39
TRLTG, mg/dL	−5.1 (5.7)	.37	420 (8.2)	.58
TRLC, mg/dL	−0.4 (1.2)	.77	1.5 (1.9)	.42
TRLP, nmol/L	0.3 (6.9)	.97	5.5 (10.8)	.61
VS-TRLP, nmol/L	0.4 (7.6)	.95	0.6 (11.3)	.96
S-TRLP, nmol/L	0.5 (4.8)	.91	2.7 (6.9)	.70
M-TRLP, nmol/L	0.1 (1.6)	.94	2.0 (2.1)	.36

(continued)

Table 4. Changes in Blood-Based Biomarkers of Inflammation, Lipoprotein Characterization, and Glucose Metabolism (continued)

	Week 16 vs baseline (n = 57-59)		Week 52 vs baseline (n = 37-38)	
Biomarker	Change (SE)	*P* value[a]	Change (SE)	*P* value[a]
L-TRLP, nmol/L	−0.8 (0.7)	.23	0.2 (1.0)	.81
VL-TRLP, nmol/L	−0.000 (0.009)	.99	−0.003 (0.011)	.75
Glucose metabolism				
Insulin, μIU/mL	4.6 (3.5)	.19	12.1 (10.4)	.25
HOMA-IR	0.6 (0.8)	.49	1.8 (1.4)	.22
Glucose, mg/dL	2.6 (4.1)	.52	8.0 (7.8)	.31
DRI score	−3.0 (1.6)	.06	−2.8 (1.9)	.14
LP-IR	−0.8 (2.7)	.78	−1.2 (3.2)	.72
Markers of adipose dysfunction and general metabolism				
Leptin, ng/mL	−84.2 (1232.4)	.95	−498.8 (1993.6)	.80
Adiponectin, μg/mL	−1.4 (1.5)	.35	−2.1 (2.0)	.29
Fetuin A, μg/mL	−50.7 (24.2)	.04	−53.5 (31.8)	.10
Citrate, mg/dL	0.01 (0.06)	.88	−0.11 (0.07)	.14
Valine, mg/dL	−0.17 (0.07)	.02	−0.15 (0.09)	.12
Leucine, mg/dL	−0.12 (0.06)	.046	−0.11 (0.07)	.12
Isoleucine, mg/dL	−0.08 (0.03)	.02	−0.05 (0.05)	.32
Alanine, mg/dL	−0.18 (0.16)	.28	0.21 (0.22)	.35
BCAA, μmol/L	−29.5 (11.1)	.01	−24.4 (14.1)	.09
Ketone bodies, μmol/L	−30.3 (33.6)	.37	−79.3 (33.8)	.02
β-Hydroxybutyrate, μmol/L	−13.9 (23.3)	.56	−48.5 (22.9)	.04
Acetoacetic acid, μmol/L	0.7 (1.1)	.53	1.6 (2.1)	.45
Acetone, mg/dL	−0.010 (0.066)	.14	−0.189 (0.73)	.01

Abbreviations: ApoA1, apolipoprotein A-1; BCAA, branched-chain amino acids; CRP, C-reactive protein; DRI, Diabetes Risk Index; GlycA, glycine A; HDL, high-density lipoprotein; HDL-C, -P, and -Z, HDL cholesterol, particle concentration, and average particle size; HOMA-IR, homeostatic model assessment of insulin resistance; ICAM-1, intracellular adhesion molecule 1; IDL-P, intermediate-density lipoprotein particle concentration; IFN-γ, interferon γ; IL, interleukin; L, large; LDL, low-density lipoprotein; LM, large and medium; LP-IR, Lipoprotein Insulin Resistance Index; M, medium; MCP-1, monocyte chemotactic protein 1; S, small; SAA, serum amyloid A; TNF-α, tumor necrosis factor α; TRLC, TRLP cholesterol; TRLP, triglyceride-rich lipoprotein; TRLTG, TRLP triglyceride; VCAM-1, vascular cell adhesion molecule 1; VL, very large; VLDL, very LDL; VLDL-TG, VLDL triglyceride; VS-TRLP, very small TRLP.

SI conversion factors: To convert CRP to mg/L, multiply by 10; triglyceride to mmol/L, multiply by 0.0113; total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; ApoA1 to g/L, multiply by 0.01; insulin to pmol/L, multiply by 6.945; glucose to mmol/L, multiply by 0.0555; citrate to μmol/L, multiply by 52.05; valine to μmol/L, multiply by 85.361; leucine to μmol/L, multiply by 76.237; isoleucine to μmol/L, multiply by 76.236; alanine to μmol/L, multiply by 112.2; and acetone to mmol/L, multiply by 0.172.

[a] From paired *t* test.

Table 5. Sensitivity Analyses

	Week 16 vs baseline			Week 52 vs baseline		
Analysis	No.	Mean (95% CI)[a]	*P* value[b]	No.	Mean (95% CI)[a]	*P* value[b]
Primary analysis	57	−0.02 (−0.08 to 0.05)	.61	38	−0.07 (−0.15 to 0.01)	.09
Baseline TBR >1.6	25	−0.12 (−0.24 to 0.01)	.07	16	−0.21 (−0.35 to −0.08)	.005
PASI score 75	20	−0.09 (−0.24 to 0.05)	.18	12	−0.14 (−0.30 to 0.02)	.07
Treatment adherent[c]	23	−0.07 (−0.17 to 0.02)	.14	16	−0.07 (−0.17 to 0.03)	.14

Abbreviations: PASI, Psoriasis Area and Severity Index; TBR, target to background ratio.

[a] The 95% CI is for the difference between the later time vs the earlier time (paired *t* test).

[b] From paired *t* test.

[c] Defined as at least 90% adherent with all doses of apremilast.

Discussion

In a population of patients with moderate to severe psoriasis, apremilast had a neutral association with aortic vascular inflammation and was associated with a 5% to 6% reduction of both subcutaneous and visceral fat, which occurred at 16 weeks of treatment and was maintained through 52 weeks of treatment. Visceral fat is metabolically active and promotes metabolic and atherosclerotic disease, and therefore its reduction may portend meaningful health benefits.[22,23] The associations with blood-based biomarkers were generally favorable. At week 16, there was a reduction in IL-1b, a proinflammatory cytokine causally linked to cardiovascular disease.[24,25] Additionally, compared with baseline, there was a decrease in fetuin A (associated with diabetes risk) and branched-chain

amino acid levels (valine, leucine, and isoleucine) associated with incident cardiovascular disease.[26] At week 52 compared with baseline, there was a reduction in ferritin, an acute-phase reactant and marker of inflammation and cellular damage, as well as in β-hydroxybutyrate, acetone, and ketone bodies, all implicated in cardiovascular disease, including heart failure,[27] and an increase in apolipoprotein A-1 (which is considered atheroprotective), but there was a reduction in cholesterol efflux capacity (which could be negatively associated with the atheroprotective effects of high-density lipoprotein cholesterol).[28]

Clinically, the safety and effectiveness of apremilast for treatment of psoriasis were as expected according to phase 3 trials.[29] Analyses limiting the population to patients with a TBR greater than 1.6 at baseline demonstrated a reduction in aortic vascular inflammation at week 52. This finding is post hoc and thus needs further confirmation, but it is in contrast to the results of a study of adalimumab, a tumor necrosis factor inhibitor in patients with psoriasis and a TBR greater than 1.6 at baseline, which observed no change in aortic vascular inflammation at week 52.[30]

These results add substantially to our knowledge of the association between apremilast and cardiometabolic disease. Recently, apremilast was demonstrated to have anti-inflammatory effects in human umbilical vein endothelial cells in vitro.[31] An open-label study of 60 patients with psoriatic arthritis (n = 56) or psoriasis (n = 4) treated with apremilast found a reduction in subcutaneous fat but not visceral fat as measured by magnetic resonance imaging (n = 29).[32] There was no change in adipocyte diameter; levels of hemoglobin A_{1c}, lipids, or glucagon-like peptide 1; or vascular function (as determined indirectly through biomarkers).[32] A small study of 14 patients with psoriatic arthritis observed that apremilast downregulated almost all cardiovascular disease–related molecules that were altered in patients with psoriatic arthritis.[33] In a study of electronic medical data, apremilast treatment of psoriatic arthritis did not signal potential acute cardiovascular harm and was not associated with a material increase in the risk of serious cardiac events.[34] A French nationwide study of patients with psoriatic arthritis observed no statistical difference in the risk of major adverse cardiovascular events for patients receiving apremilast compared with tumor necrosis factor inhibitors (hazard ratio, 1.3; 95% CI, 0.8-2.2).[35]

Strengths and Limitations

The strengths of this study include the robust and comprehensive imaging and blood-based biomarker evaluation of the cardiometabolic associations of apremilast. Moreover, the sample size was adequate to detect meaningful differences in the highly sensitive outcomes we studied.[36] Important limitations include the lack of placebo control, and although our comprehensive assessment of biomarkers is a strength, it also may result in α error, given the large number of pathways interrogated, and thus the cardiometabolic biomarkers may be considered exploratory. Finally, we evaluated only surrogate markers and not actual clinical events.

Conclusions

In this nonrandomized clinical trial, apremilast had a neutral association with aortic vascular inflammation and variable but generally beneficial associations with cardiometabolic biomarkers, and reductions in visceral and subcutaneous fat suggest that apremilast has an overall potential benefit regarding cardiometabolic disease in patients with psoriasis. Larger placebo-controlled trials, particularly those that focus on cardiovascular events, are necessary to confirm these findings.

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