Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Effect of 2 Psoriasis Treatments on Vascular Inflammation and Novel Inflammatory Cardiovascular Biomarkers

A Randomized Placebo-Controlled Trial

See editorial by Daghem and Newby

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BACKGROUND: Psoriasis is a chronic inflammatory disease associated with dyslipidemia, cardiovascular events, and mortality. We aimed to assess and compare the effect of treatment of moderate-to-severe psoriasis with adalimumab or phototherapy on vascular inflammation and cardiovascular biomarkers.

METHODS AND RESULTS: Randomized, double-blind, trial of adalimumab, phototherapy, and placebo (1:1:1) for 12 weeks, with crossover to adalimumab for 52 weeks total. Outcomes included vascular inflammation by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and biomarkers of inflammation, insulin resistance, and lipoproteins. Ninety-seven patients were randomized, 92 completed the randomized controlled trial portion; 81 entered the adalimumab extension with 61 completing 52 weeks of adalimumab. There was no difference in change in vascular inflammation at week 12 in the adalimumab group (change compared with placebo, 0.64%; 95% confidence interval, –5.84% to 7.12%) or the phototherapy group (–1.60%; 95% confidence interval, –6.78% to 3.59%) or after 52-week adalimumab treatment (0.02% compared with initiation; 95% confidence interval, –2.85% to 2.90%). Both adalimumab and phototherapy decreased inflammation by serum CRP, interleukin-6. Only adalimumab reduced tumor necrosis factor and glycoprotein acetylation at 12 and 52 weeks. Neither had an impact on metabolic markers (insulin, adiponectin, and leptin). Only phototherapy increased high-density lipoprotein-p at 12 weeks. At 52-week of adalimumab cholesterol efflux and high-density lipoprotein-p were reduced.

CONCLUSIONS: Adalimumab reduced key markers of inflammation including glycoprotein acetylation compared with phototherapy with no effect on glucose metabolism and vascular inflammation, and potential adverse effects on high-density lipoprotein. Glycoprotein acetylation improvement may partially explain the beneficial effects of adalimumab seen in observational studies. Larger studies with more detailed phenotyping of vascular disease should assess the comparative differences in the effects of adalimumab and phototherapy seen in our study.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT01866592 and NCT01553058.

The full author list is available on page 10.

Key Words: adalimumab ■ biomarkers ■ inflammation ■ psoriasis

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CLINICAL PERSPECTIVE

Inflammation is critical to atherosclerosis. We tested whether anti-inflammatory therapy with anti-tumor necrosis factor agent, adalimumab, reduced vascular inflammation compared with phototherapy and placebo in patients with psoriasis, a chronic inflammatory disease associated with accelerated atherosclerosis. Here, we provide critical data demonstrating significant anti-inflammatory effects of adalimumab in the skin and blood of psoriasis patients without impact on vascular inflammation. Compared with phototherapy and placebo, adalimumab improved skin disease and markers of systemic inflammation. However, it did not change vascular inflammation compared with phototherapy or placebo and was associated with modest impairments in high-density lipoprotein function, providing important information about the impact of targeted inhibition of tumor necrosis factor-α on cardiometabolic biomarkers. This systematic characterization of the effect of anti-tumor necrosis factor therapy on cardiometabolic risk parameters in psoriasis patients provides a reliable framework for future studies to analyze whether targeting other inflammatory pathways to treat psoriasis including anti-interleukin-12/23, anti-interleukin-17 agents, or Phosphodiesterase 4 inhibitors may improve cardiometabolic risk in psoriasis.

Psoriasis is a common chronic Th1/Th17 inflammatory skin disease that affects >125 million people worldwide.[1] Like other diseases of chronic inflammation, it is associated with an increased risk of impairments in lipoprotein metabolism (dyslipidemia and decreased cholesterol efflux capacity), insulin resistance and diabetes mellitus, and major adverse cardiovascular events.[2–5] The risk of cardiometabolic disease increases with increasing psoriasis severity, is independent of traditional risk factors, and culminates in a lifespan reduction of ≈5 years.[5,6]

The aberrant innate and adaptive immune pathways that drive the pathophysiology of psoriasis are known to also promote insulin resistance, atherosclerosis, and thrombosis.[7] Established and novel inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor (TNF) α, interleukin (IL)-6, and glycoprotein acetylation (GlycA) are increased in psoriasis,[8,9] associated with skin disease severity[8,10] and are predictive of future cardiovascular risk in healthy individuals without psoriasis or any other chronic inflammatory condition.[11,12] Consistent with the translational and epidemiological data linking psoriasis to cardiovascular disease, we and others have demonstrated that patients with psoriasis have increased vascular inflammation (VI), as measured by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), that is equivalent to ≈1 decade of aging, and that increasing skin disease severity is associated with increasing VI independent of traditional cardiovascular risk factors.[10,13] ^{18}F-FDG PET/CT is an attractive surrogate marker, as it predicts cardiovascular events[14] and is highly sensitive to change with short-term (ie, weeks-to-months) treatment with interventions known to lower cardiovascular risk, such as statins and therapeutic lifestyle changes.[15] Psoriasis is a reliable disease to study cardiovascular effects of immune-modulating therapy[13] as it can be treated with a variety of targeted modalities.[7]

Adalimumab, a monoclonal antibody that blocks TNF-α, is a standard of care biological therapy used to treat moderate-to-severe psoriasis[16] and is suggested to be associated with a reduction in major cardiovascular events.[17] Narrowband ultraviolet B phototherapy is also highly effective in treating psoriasis but is not associated with clinically significant alterations in systemic immune function.[7] A recently completed randomized trial demonstrated a beneficial effect of a systemic biological anti-inflammatory therapy in reducing rate of myocardial infarction despite minimal change in low-density lipoprotein cholesterol (LDL-C).[18] Phototherapy provides a unique opportunity to compare treatment of psoriasis with a systemic immune-modulating biological therapy (adalimumab) to skin-directed therapy (phototherapy). As such, we conducted a randomized controlled trial, in patients with moderate-to-severe psoriasis, of adalimumab, phototherapy, and placebo to determine the comparative impact of psoriasis treatment with adalimumab and phototherapy on VI measured by ^{18}F-FDG PET/CT and biomarkers of advanced lipoprotein characterization, glucose metabolism, and inflammation.

METHODS

The data will be made available to other researchers for purposes of reproducing the results, however, materials cannot be made available in view of the concerns about the patient privacy. The study was a multicenter randomized controlled trial designed to enroll 96 patients across 8 centers in the United States with 1:1:1 allocation to adalimumab subcutaneous injections or placebo injections every 2 weeks, or narrowband ultraviolet B phototherapy at baseline (NCT01553058). At week 12, eligible patients entered an open-label extension in which they were treated with adalimumab for 52 weeks (if initially assigned to placebo or phototherapy) or an additional 40 weeks if initially assigned to adalimumab, such that all patients received a total of 52 consecutive weeks of adalimumab (NCT01866592; Figure 1). Primary outcome for our study was change in VI, estimated as a target-to-background ratio (TBR) of maximum target aortic activity to blood pool activity by ^{18}F-FDG PET/CT at week 12 compared with baseline in adalimumab and phototherapy groups compared with placebo. We also conducted a series of analyses of biomarkers

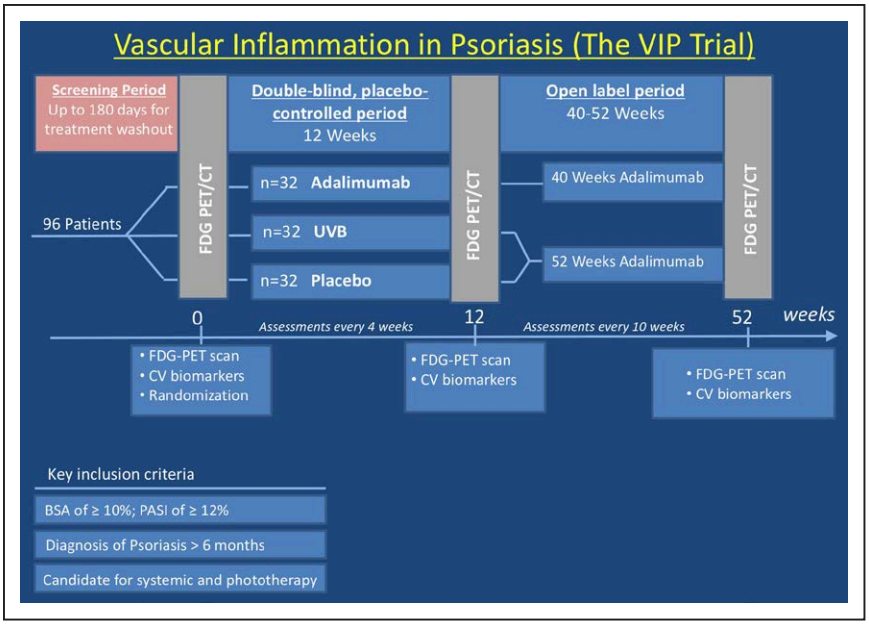

Figure 1. Study protocol for the VIP (Vascular Inflammation in Psoriasis) randomized, controlled trial.
BSA indicates body surface area; CV, cardiovascular; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; PASI, Psoriasis Area and Severity Index; and UVB, ultraviolet B phototherapy.

of cholesterol, glucose metabolism, and inflammation which were selected based on their known association with psoriasis and cardiovascular disease at baseline, week 4, and week 12.

All participants had to be ≥18 years with a diagnosis of psoriasis for at least 6 months and that of moderate-to-severe psoriasis for at least 2 months, defined as body surface area ≥10% and psoriasis area severity index score of ≥12 at baseline. Patients were excluded if they had any of the following treatments: UVB phototherapy within 14 days of baseline, psoralen-UVA phototherapy within 30 days of baseline, oral psoriasis treatments within 30 days of baseline, biologics within 90 days of baseline (or 180 days for ustekinumab); investigational agents within 30 days or 5 half-lives (whichever is longer) of baseline. Adalimumab (or corresponding placebo) therapy was administered in a double-blind manner as a subcutaneous injection with an initial 80 mg dose at week 0, followed by maintenance doses of 40 mg every other week, starting from week 1 and then continued throughout the study. Narrowband ultraviolet B phototherapy dosing was based on estimated minimal erythema dose and Fitzpatrick skin type using a standardized protocol published by Zanolli and Feldman.[19] 18F-FDG PET/CT scans were analyzed to derive TBR values by previously published and validated methods.[10] The extent of ^{18}F-FDG uptake within the aorta was directly measured by using a dedicated image analysis software (OsiriX MD, Pixmeo SARL, Bernex, Switzerland) to measure VI calculated as TBR. The standardized uptake value $(SUV)_{mean}$ from each of the superior vena cava slices were averaged to produce 1 venous value. To account for background blood activity, SUV_{max} values from each aortic slice were divided by the average venous SUV_{mean} value yielding TBR_{max} values, the primary outcome measure. Patients underwent 18F-FDG PET/CT scans using the standard protocol[20,21] after an overnight fast.

Primary analyses were the comparisons of the treatment effects of adalimumab, phototherapy, and placebo, on the outcome measures using intention-to-treat approach. The changes in TBR_{max} and biomarker values were compared across groups using linear regressions, whereas additional multivariate linear regression models were fitted for TBR_{max} to assess sensitivity to a potential imbalance of covariates, adjusting for clinical and demographic covariates using a backward model building approach. Natural log scale was used for all nonparametric variables. The secondary analyses were the changes in outcome measures from baseline to the end of open-label extension period. The mean changes and proportions were calculated along with their respective 95% confidence intervals (CIs) and were reported as such. Sample size calculations were based on changes in SUV. Using a 2-sided α=0.017 (applying a Bonferroni correction), we determined that 32 patients per arm would provide 82% power to detect the clinically significant change in SUV of 0.1 between groups assuming an anticipated SD of the change in SUV of 0.11 and a dropout rate of 15%.

Study approval was obtained from the Institutional Review Board of the University of Pennsylvania or respective local Institutional Review Board when indicated in accordance with the principles of Declaration of Helsinki. All guidelines for good clinical practice and those set forth by the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research) were followed. All study participants provided written informed consent. The randomized placebo-controlled trial was overseen by an independent data monitoring committee. The sponsors (National Heart, Lung, and Blood Institute and Abbvie) had no role in the analysis or reporting of the results. Abbvie reviewed the article for compliance purposes. The detailed methods are elaborated in a separate Methods in the Data Supplement.

RESULTS

We screened 179 patients for eligibility and randomized 97 patients to placebo, adalimumab, or phototherapy treatment (1:1:1), with 92 (95%) patients completing the 12-week controlled portion of the study (Figure 2). Eighty-one patients entered the open-label adalimum-

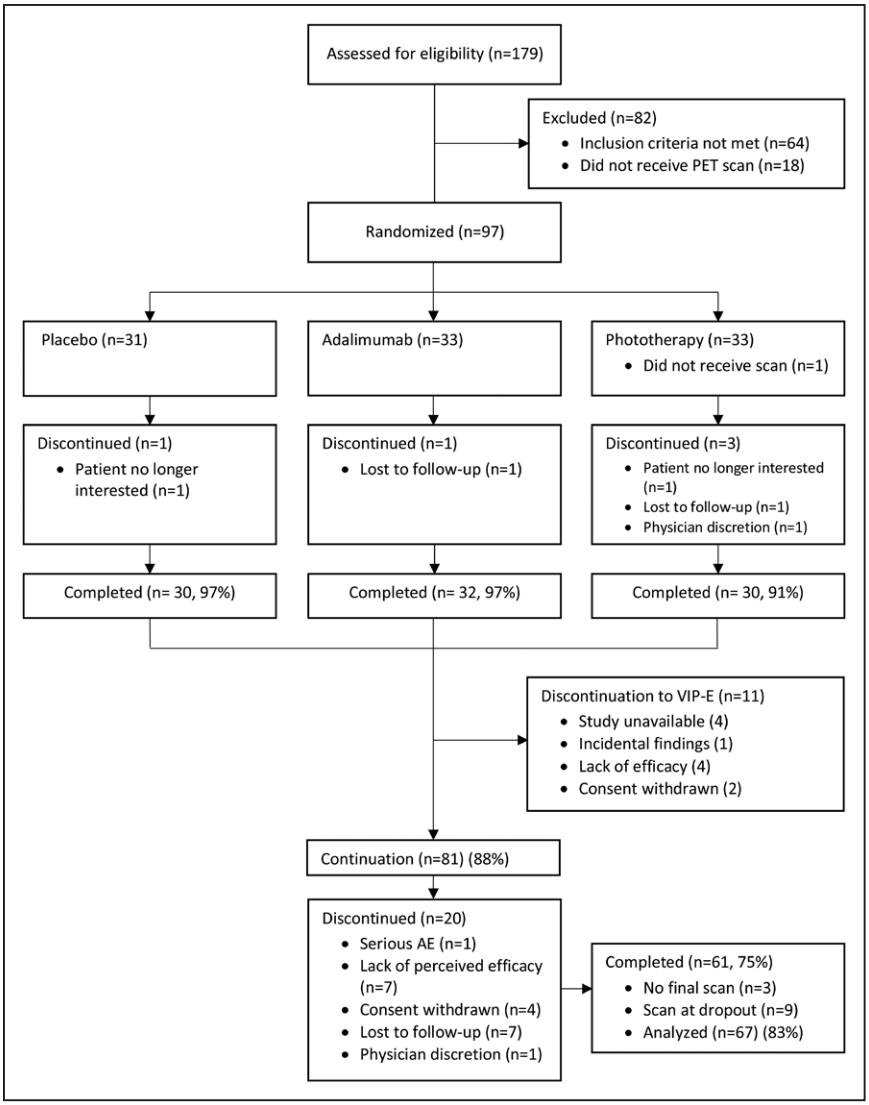

Figure 2. Patient recruitment scheme for the study.
VIP indicates Vascular Inflammation in Psoriasis. AE indicates adverse events.

ab extension portion of the study, of which 58 (72%) completed 52 weeks of adalimumab treatment and had an end of study scan. Nine patients (11%) had an early termination during the extension period and received an early termination scan, thus resulted in 67 (83%) patients being included in the analysis of the open-label extension portion of the study. Study subjects had an average age of 43, were predominantly male (69%), had an average duration of psoriasis of 17 years, and a mean Psoriasis Area and Severity Index of 19. About 10% of patients had a history of psoriatic arthritis, and ≈30% had previously been treated with systemic agents or phototherapy (Table 1). The study groups were well balanced for psoriasis characteristics and cardiovascular risk factors and were similar to populations typically seen in large phase III clinical trials of psoriasis therapeutic agents (Table 1).

Both adalimumab and phototherapy resulted in substantial improvements in psoriasis severity compared with placebo for physician-reported measures (Table I in the Data Supplement). Patients evaluated during the open-label adalimumab extension period achieved a high rate of skin clearance with 53% of patients being clear or almost clear of their skin disease (Table II in the Data Supplement). No statistically significant change was observed in physical activity (as measured using the International Physical Activity Questionnaire metabolic equivalent task minutes) between groups at week 12 or at the end of the extension period. On average, patients reported a reduction in saturated and dietary cholesterol intake at week 12 and end of the open-label period compared with baseline, but there were no group-level differences.

At baseline mean TBR_{max} values were 1.62, 1.61, and 1.64 in the placebo, adalimumab, and phototherapy groups respectively (Table 1). Furthermore, the TBR and SUV values at subsequent visits for all 3 groups are noted under Table III in the Data Supplement. There was no difference in change in VI at week 12 in the adalimumab group (change compared with placebo, 0.64%;

Table 1. Baseline Demographics and Clinical Characteristics

	Placebo	Adalimumab	Phototherapy	Total
N	31	33	33	97
Age				
Mean (SD)	44.32 (14.50)	44.15 (13.97)	41.97 (13.97)	43.46 (14.03)
Sex (%)				
Female	11 (35.48)	9 (27.27)	10 (30.30)	30 (30.93)
Male	20 (64.52)	24 (72.73)	23 (69.70)	67 (69.07)
Pso duration (Y)				
Median (IQR)	20 (7–29)	11 (2–22)	12 (7–17)	13 (6–25)
PsA (%)	2 (6.45)	4 (12.90)	3 (9.68)	9 (9.68)
BMI				
Mean (SD)	31.95 (7.74)	30.93 (7.42)	32.61 (8.66)	31.83 (7.91)
H/o CVD	3 (9.68)	2 (6.06)	2 (6.06)	7 (7.22)
Diabetes mellitus	1 (3.23)	3 (9.09)	0	4 (4.12)
Hypertension	7 (22.58)	6 (18.18)	5 (15.15)	18 (18.56)
Hyperlipidemia	5 (16.13)	5 (15.15)	4 (12.12)	14 (14.43)
Statin use	4 (12.90)	1 (3.03)	3 (9.09)	8 (8.25)
10 y Framingham risk %, median (IQR)	4.9 (2.2–10.1)	6.5 (2.5–12.0)	3.7 (1.4–7.9)	4.8 (1.9–10.7)
BSA %				
Median (IQR)	21 (16–33)	18 (15–25)	19.5 (15–26)	20 (15–29)
PASI				
Median (IQR)	15.0 (13.3–20.6)	17.4 (15.4–22.0)	16.8 (14.5–21.0)	16.7 (13.9–21.6)
H/o Phototherapy (%)	11 (35.48)	5 (16.13)	13 (41.94)	29 (31.18)
H/o oral systemics (%)	10 (32.26)	10 (32.26)	11 (35.48)	31 (33.33)
H/o biologics (%)	11 (35.48)	10 (32.26)	8 (25.81)	29 (31.18)
Baseline target-to-background ratio, mean (SD)	1.620 (0.267)	1.610 (0.334)	1.636 (0.226)	1.622 (0.278)

BMI indicates body mass index; BSA, body surface area; CVD, cardiovascular disease; H/o, history of; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; and Pso, Psoriasis.

95% CI, –5.84% to –7.12%) or the phototherapy group (–1.60%; 95% CI, –6.78% to 3.59%; Table 2; Figure 3). Analysis within groups demonstrated a statistically significant reduction in VI by –4.09% (95% CI, –7.78% to –0.39%) in the phototherapy treatment arm only. At the end of the extension period, there was a –3.80% reduction in VI compared with the absolute study baseline (week 52 or 64 compared with week 0 for all; 95% CI, –6.40% to –1.19%; Table 3). However, there was no change in VI (0.02% difference; 95% CI, –2.85% to 2.90%) during the adalimumab treatment only period comparing end of study assessment to adalimumab baseline (week 52 compared with week 0 for those initially assigned to adalimumab and week 64

Table 2. Changes in TBR_{max} by Treatment Group During Randomized Controlled Trial Period

	Placebo	Adalimumab	Phototherapy
Global change compared with baseline within group			
Mean difference*	–0.052 (0.112)	–0.067 (0.213)	–0.079 (0.020)†
Mean % change (95% CI)*	–2.49% (–6.29% to 1.31%); (0.191)	–1.84% (–7.17% to 3.47%); (0.483)	–4.09% (–7.78% to –0.39%); (0.031)†
Global change compared with placebo			
Difference of differences‡	…	–0.015 (0.795)	–0.027 (0.647)
Difference of % change‡	…	0.64% (–5.84% to 7.12%); (0.844)	–1.60% (–6.78% to 3.59%); (0.540)

CI indicates confidence interval; and TBR, target-to-background ratio.
*One sample test (*P* value).
†Statistically significant findings.
‡Difference of differences (*P* value).

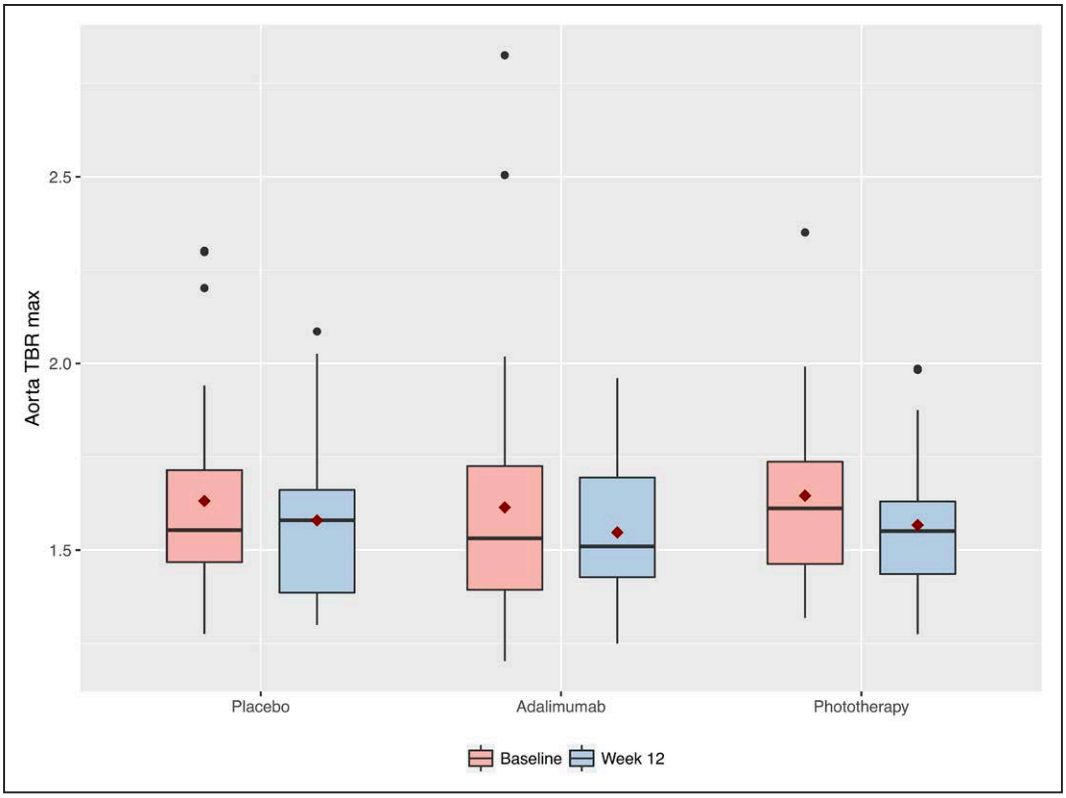

Figure 3. Change in vascular inflammation for the randomized controlled trial period (baseline to week 12) stratified by the treatment group.
TBR indicates target-to-background ratio.

compared with week 12 for those who entered open-label extension but were initially assigned to placebo/phototherapy).

We evaluated biomarkers of advanced lipoprotein characterization, glucose metabolism, and inflammation (Figure 4). During the placebo-controlled period, a reduction in inflammation in the adalimumab group compared with placebo was observed for CRP, TNF-α, IL-6, and GlycA whereas only CRP and IL-6 were reduced in the phototherapy arm (Table 4). There was no change in lipoprotein characterization or glucose metabolism except for HDL-P which increased in the phototherapy group compared with placebo which was only modestly significant. At the end of the extension period, compared with absolute baseline (week 0 for all), there was no change in total cholesterol, LDL-P, or markers of glucose metabolism, but there was a reduction in efflux and HDL-P. Furthermore, we also observed a reduction in markers of inflammation such as CRP, TNF-α, and GlycA, but an increase in the levels of IL-6 (Table 5). A similar pattern of biomarker change was observed during the adalimumab treatment only period comparing end of study assessment to adalimumab baseline (week 0 for those initially assigned to adalimumab or week 12 for those initially assigned to placebo or phototherapy; Table 6).

Table 3. Changes in TBR_{max} Open-Label Extension

	Mean (*P* Value*)
Global change baseline compared with end of open-label extension	
Difference	–0.08 (0.002)†
% change (95% CI)	–3.80% (–6.40% to –1.19%); (0.005)†
Global change start of adalimumab compared with end of open-label extension	
Difference	–0.02 (0.538)
% change	0.02% (–2.85% to 2.90%); (0.987)

CI indicates confidence interval; and TBR, target-to-background ratio.
*One sample *t* test.
†Statistically significant findings.

DISCUSSION

We conducted a randomized, controlled trial to determine the impact of systemic anti-TNF immune targeted (ie, adalimumab) treatment and skin-directed treatment (ie, ultraviolet B phototherapy) on key markers of vascular disease risk compared with placebo in patients with psoriasis, an inflammatory disease well established to be associated with increased VI[10], metabolic dysfunction, and an increased risk of cardiovascular disease and mortality.[3] TNF inhibitors are used in hundreds of thousands of patients with inflammatory bowel, joint, skin, and eye disease. Thus, our findings establish provocative information about their cardio-

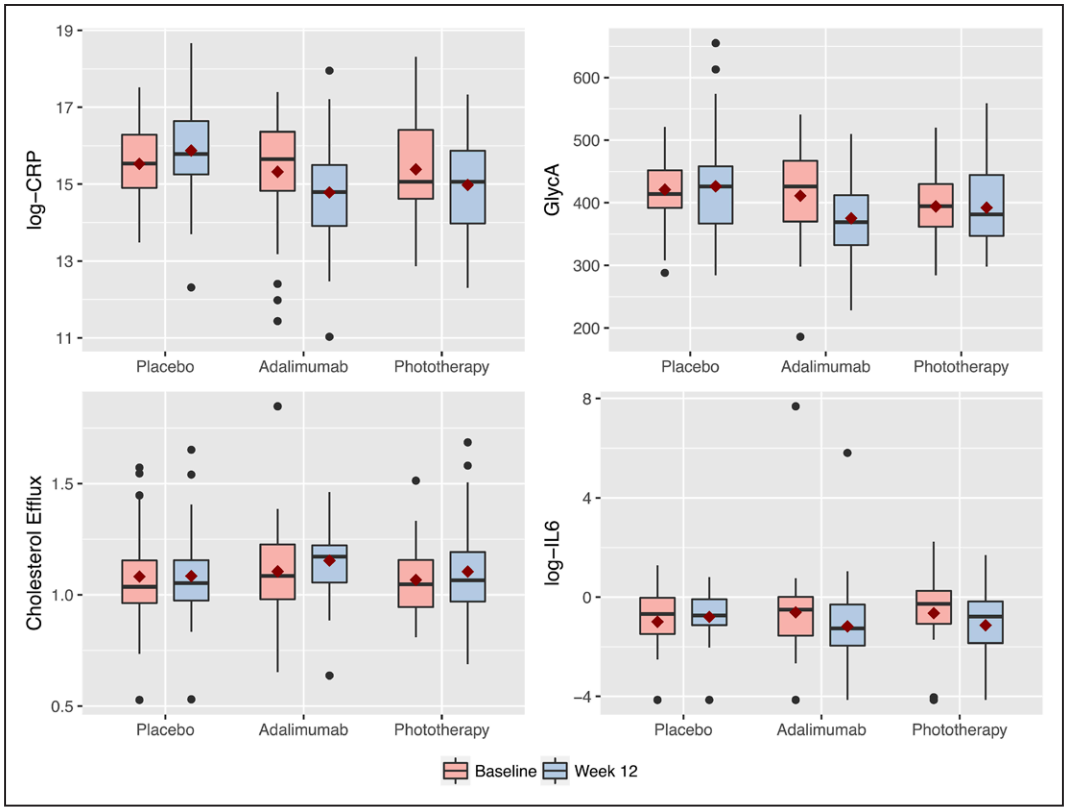

Figure 4. Change in key biomarkers for the randomized controlled trial period (baseline to week 12) stratified by the treatment group.
CRP indicates C-reactive protein; GlycA, glycoprotein acetylation; and IL, interleukin.

metabolic effects under rigorous experimental conditions in humans. Foremost, the study results strongly demonstrate that use of TNF inhibition has no impact, be it adverse, or ameliorative, on VI. Indeed, the 95% CI of our estimate in the open-label extension suggests we had adequate statistical power to exclude clinically significant alterations in VI from adalimumab considering statin effects as reference.[15]

Our results are in line with a study that demonstrated no beneficial effects of TNF inhibition in patients with myocardial infarction,[22] however, they are in strong contrast to a noncontrolled study in rheumatoid arthritis of anti-TNF treatment which observed a reduction in VI by ^{18}F-FDG PET/CT after 8 weeks of therapy.[23] This study was open-label and assessed a reduction in the hottest plaque (most diseased aortic segment). We have also demonstrated improvements in VI in an observational study of psoriasis patients being treated systemically.[8,24] Similarly, we observed a reduction in VI in the overall clinical trial population (comparing baseline to end of study), but this was because of improvements were seen in the period in which patients received placebo or phototherapy. Our patient reported outcomes suggest dietary improvements consistent with lifestyle changes advised by the American Heart Association[25] in the overall study population, which may in part explain the improvements in VI we observed that do not differentiate from placebo. These results emphasize the importance of randomization and placebo control in studies evaluating these highly sensitive outcomes.

We propose several theories for the discrepancy between our experimental results evaluating VI, a surrogate marker of future cardiovascular events, and observational studies of actual cardiovascular events.[17,26] It is possible that TNF associated benefits on cardiovascular events are mediated by pathways beyond VI such as thrombosis.[27] Moreover, large molecules (ie, antibodies) may not be directly active in large vessels such as the aorta because of impaired tissue penetration, which may explain why small molecules such as statins do have a strong anti-inflammatory effect on VI as early as after 4 weeks of treatment.[15] Psoriasis increasingly is recognized to be a Th17 driven disease,[7] and thus more targeted treatments may be necessary to alter VI in this specific patient population. We observed adverse impacts of adalimumab on key mediators of lipid metabolism such as cholesterol efflux capacity, which is a validated surrogate marker for the ability of HDL to perform reverse cholesterol transport, and HDL-P with no evidence of change in LDL-particle number. In contrast, we demonstrated

Table 4. Change in Advanced Lipoprotein Characterization, Glucose Metabolism, and Inflammation Between Baseline and Week 12, by Treatment Group During Randomized Controlled Trial Period

	Adalimumab vs Placebo*	Phototherapy vs Placebo*	F-test *P*†
TC	6.481 (0.386)	8.154 (0.280)	0.514
Efflux	0.046 (0.357)	0.035 (0.496)	0.629
LDL-P	9.193 (0.897)	52.320 (0.467)	0.743
HDL-P	2.558 (0.089)	3.319 (0.030)‡	0.071
Log insulin	0.014 (0.934)	0.071 (0.679)	0.909
Log adiponectin	−0.142 (0.672)	−0.151 (0.655)	0.879
Log leptin	−0.086 (0.504)	0.050 (0.695)	0.568
Log CRP	−0.883 (0.002)‡	−0.752 (0.009)‡	0.004‡
Log TNF-α	−0.411 (<0.001)‡	−0.177 (0.065)	<0.001‡
Log IL-6	−0.764 (0.007)‡	−0.683 (0.019)‡	0.014‡
GlycA	−41.165 (0.006)‡	−7.199 (0.628)	0.015‡

CRP indicates C-reactive protein; GlycA, glycoprotein acetylation; HDL-P, high-density lipoprotein particle; IL, interleukin; LDL-P, low-density lipoprotein particle; TC, total cholesterol; and TNF, tumor necrosis factor.

*Difference of differences.

†Global difference.

‡Statistically significant findings.

strong and consistent improvements in skin inflammation (ie, clearance of psoriasis) and strong reductions in systemic inflammation as measured by serum TNF-α, CRP, and GlycA with short and longer-term adalimumab treatment but an increase in IL-6. It is, therefore, possible that anti-inflammatory benefits of adalimumab may be counteracted by adverse impacts on advanced measures of HDL structure and function resulting in a neutral effect on VI.

Although CRP, IL-6, TNF-α are established markers of cardiovascular disease,[12] GlycA is an emerging novel biomarker of systemic inflammation and cardiovascular disease derived from nuclear magnetic resonance, with value in psoriasis.[8,11] It may be possible that the improvement in inflammatory biomarkers including GlycA seen in our study over a short-term follow-up may partially explain the observational evidence that has demonstrated better cardiovascular outcomes in psoriasis patients treated with anti-TNF therapy.[17] We observed a disconnect between changes in serum inflammatory markers and VI which was reported in a previous study.[28] Indeed, anti-TNF therapy has been associated with a decrease in systemic inflammatory markers[28] and future cardiovascular events in claims database studies.[17] However, in the short term, anti-TNF therapy has been shown to lead to an apolipoprotein B shift whereby LDL and triglycerides increase after initiation of therapy. Furthermore, IL-6 levels increased after anti-TNF treatment. Therefore, it may be possible that potential beneficial effects of anti-TNF therapy on VI were offset by the proatherogenic shift in lipoproteins and IL-6. It may also be possible that this younger group of patients included in our study had changes in biomarkers with less profound impact compared with statin studies which included older adults with more advanced atherosclerosis. Furthermore, other vascular beds including the coronary arteries may have changed coincident to biomarker changes but were not assessed in this study. Additionally, although there is early data for the use of FDG to evaluate treatment change,[15,29] untoward effects of various kinds of treatment on FDG quantification require exploration. Finally, after adalimumab or phototherapy, we did not observe any change in glucose levels or insulin resistance by homeostasis model assessment of insulin resistance nor in adiponectin or leptin. It is entirely possible that homeostasis model assessment of insulin resistance, which detects peripheral skeletal muscle insulin resistance, but not

Table 5. Change in Advanced Lipoprotein Characterization, Glucose Metabolism, and Inflammation Between Baseline and End of Open-Label Extension

	Baseline (SD)	End of Study (SD)	Diff (SE)	*P* Value
TC	171.000 (37.159)	174.164 (34.347)	3.164 (4.216)	0.456
Efflux	1.088 (0.233)	0.871 (0.163)	−0.217 (0.032)*	<0.001*
LDL-P	1256.701 (395.937)	1279.239 (400.703)	22.537 (44.283)	0.613
HDL-P	33.299 (7.543)	30.315 (6.721)	−2.984 (0.786)*	<0.001*
Log insulin	6.284 (0.911)	6.402 (0.795)	0.118 (0.136)	0.388
Log adiponectin	2.240 (0.738)	2.166 (0.571)	−0.074 (0.068)	0.277
Log leptin	9.110 (1.342)	9.158 (1.233)	0.048 (0.195)	0.808
Log CRP	15.412 (1.425)	14.597 (1.383)	−0.815 (0.192)*	<0.001*
Log TNF-α	0.688 (0.554)	0.413 (0.873)	−0.275 (0.131)*	0.040*
Log IL-6	−0.820 (1.809)	0.234 (1.160)	1.054 (0.243)*	<0.001*
GlycA	399.742 (64.876)	370.184 (65.916)	−29.559 (7.749)*	<0.001*

CRP indicates C-reactive protein; GlycA, glycoprotein acetylation; HDL-P, high-density lipoprotein particle; IL, interleukin; LDL-P, low-density lipoprotein particle; and TNF, tumor necrosis factor.

*Statistically significant findings.

Table 6. Change in Advanced Lipoprotein Characterization, Glucose Metabolism, and Inflammation Between Start of Adalimumab and End of Open-Label Extension

	Start of Adalimumab (SD)	End of Study (SD)	Diff (SE)	*P* Value
TC	170.955 (37.236)	174.164 (34.347)	3.209 (4.004)	0.426
Efflux	1.102 (0.235)	0.871 (0.163)	−0.230 (0.032)	<0.001*
LDL-P	1261.358 (364.259)	1279.239 (400.703)	17.881 (40.416)	0.660
HDL-P	32.896 (7.220)	30.315 (6.721)	−2.581 (0.824)	0.003*
Log insulin	6.150 (0.772)	6.402 (0.795)	0.252 (0.128)	0.053
Log adiponectin	2.259 (0.792)	2.174 (0.571)	−0.085 (0.071)	0.235
Log leptin	9.171 (1.334)	9.158 (1.233)	−0.013 (0.197)	0.947
Log CRP	15.522 (1.441)	14.597 (1.383)	−0.925 (0.184)	<0.001*
Log TNF-α	0.725 (0.571)	0.409 (0.867)	−0.315 (0.126)	0.015*
Log IL-6	−0.842 (1.734)	0.233 (1.152)	1.075 (0.235)	<0.001*
GlycA	407.848 (80.882)	370.184 (65.916)	−37.665 (9.022)	<0.001*

*Statistically significant findings.

hepatic insulin resistance did not change because insulin resistance was not affected in the skeletal muscle. Future research should consider the assessment of clamp studies to understand whether hepatic insulin resistance improves.

Our results are similar to a contemporaneous placebo-controlled trial of adalimumab on VI in psoriasis[30] which showed no evidence of change in VI in the aorta assessed by ^{18}F-FDG PET/CT, albeit the specified trial showed an increase in VI in the carotids. Furthermore, our inclusion of a phototherapy arm provides us with a unique opportunity to analyze the effect of biological treatment in relation to an established skin-directed treatment modality on cardiovascular and inflammatory markers, compared with placebo. Additionally, although the previous study only explored the impact of anti-TNF therapy on VI and assessed the baseline association between a few biomarkers and VI as well as psoriasis severity, we provide a more comprehensive assessment of indices of subclinical and clinical atherosclerosis by demonstrating modulation of contemporary inflammatory, cardiometabolic, and lipoprotein biomarkers compared with more standard markers assessed in the prior study.

Despite being randomized and placebo-controlled, our study has important limitations that warrant mention. First, though we had >80% power per our sample size calculations based on the primary outcome, our sample size was still relatively small, and our follow-up duration relatively short for cardiovascular disease study. As such, our results should be interpreted with certain caution, and future trials should consider employment of longer-duration follow-ups with expanded vascular outcomes, such as coronary CT angiography, to further test our findings. Our use of surrogate outcomes instead of hard cardiovascular end points limits our ability to derive definite conclusions. Furthermore, because phototherapy arm cannot be blinded, our comparisons between adalimumab and phototherapy arms in relation to placebo arm are subject to participant bias and as such our results should be interpreted with caution. The subset of 61 patients who participated in the open-label extension period provided critical 1-year data suggesting no significant benefit of anti-TNF in reducing VI >1-year despite changes in biomarkers. However, one-fourth of the patients did not make it to 1-year of adalimumab treatment, and therefore these results should be interpreted with caution. The main reason for dropout was a failure of treatment response in the skin, and therefore, our findings in the extension study may overestimate benefits of adalimumab. Finally, we did not evaluate VI in carotid arteries, which in some studies was suggested to be more sensitive to change,[29] however, a large body of literature has focused on VI in the aorta as a surrogate for atherosclerosis and overall cardiovascular disease risk.[14,31]

In summary, our study demonstrates that anti-TNF therapy has strong and consistent anti-inflammatory effects in the skin and blood of patients with psoriasis in contrast to phototherapy, whereas both anti-TNF therapy and phototherapy had no impact on VI as assessed by ^{18}F-FDG PET/CT compared with placebo. Furthermore, anti-TNF therapy had no impact on glucose metabolism with potentially adverse effects on reverse cholesterol transport (a function of HDL) and HDL-particle size. These findings have important implications for our understanding of the relationship between targeted inhibition of TNF in a rigorous experimental trial of humans and its effect on cardiometabolic biomarkers and biomarkers of systemic and VI. Future experimental study is ongoing to determine the impact of biologics that target IL-12/23 and IL-17 as well as a small molecule (apremilast) that targets Phosphodiesterase 4 on pathways interrogated in the current study. Each of these therapies carries with it a highly specific potential effect on both systemic inflammation and cardio-

metabolic diseases, thereby providing critically needed human data to understand other pathways at play in atherogenesis that result in premature morbidity and mortality in hundreds of millions of people worldwide.

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Disclosures

Dr Mehta is a full-time US Government Employee and receives research grants to the National Heart, Lung, and Blood Institute (NHLBI) from AbbVie, Janssen, Celgene, and Novartis. Dr Gelfand in the past 12 months has served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp, Regeneron, Dr. Reddy's Laboratories, Sanofi and Pfizer Inc, receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer Inc; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. Dr Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr Takeshita receives a research grant from Pfizer Inc (to the Trustees of the University of Pennsylvania) and has received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly. A.B. Troxel is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr Tyring conducts clinical studies sponsored by the following companies: Abbvie/BI; Celgene; Coherus; Dermira; Eli Lilly; Janssen; Leo; Merck; Novartis; Pfizer; Regeneron/Sanofi; and Valeant. He is a speaker for Abbvie, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Regeneron/Sanofi, and Valeant. Dr Armstrong has received research grants and honorarium from AbbVie, Celgene, Janssen, Novartis, Eli Lilly, Regeneron, Sanofi, and Valeant and has participated in continuing medical education work related to psoriasis that was indirectly supported by Eli Lilly and AbbVie. Dr Duffin has received grant/research/clinical trial support from Amgen, Abbvie, Celgene, Eli Lilly, Janssen, Bristol-Myers Squibb, Stiefel, Novartis, and Pfizer over the last 24 months. Additionally, Dr Duffin has served as a consultant/on the advisory boards for Amgen, Abbvie, Celgene, Eli Lilly, Janssen, Bristol-Myers Squibb, Stiefel, Novartis, and Pfizer. Dr Chiesa Fuxench has no conflicts of interest. However, she was being funded, at the time, by a research grant from the National Psoriasis Foundation and a training grant from the National Institutes of Health. Dr Hubbard receives grant funding from the National Institutes of Health and Patient-Centered Outcomes Research Institute. Dr Rader is the co-founder of Vascular Strategies and holds equity in the company. Dr Kalb has received grants/research funding from AbbVie, Amgen, Boehringer Ingelheim, Janssen-Ortho Inc, Merck & Co, Inc, and Novartis Pharmaceuticals Corp over the last 24 months. During this time frame, he has also served as a consultant honoraria for Dermira, Janssen-Ortho Inc, Sun Pharmaceutical Industries Ltd, and a DSMB member honoraria for Eli Lilly and Co. Dr Simpson has served as a consultant for AbbVie, Anacor, Celgene, Dermira, Genentech, Leo, Glaxo Smith Kline, Pfizer, Regeneron, Sanofi-Genzyme, Menlo, and Eli Lilly in the last 24 months. During this time frame, he has also acted as the primary investigator for the following sponsored trials: Anacor, Celgene, Chugai, Dermira, Eli Lilly, Genentech, MedImmune, Merck, Novartis, Regeneron, Roivant, Tioga, and Vanda. Dr Torigian is the co-founder of Quantitative Radiology Solutions LLC. Dr Van Voorhees has served on the advisory board of Celgene, Dermira, Allergan, Merck, Pfizer, Aqua, Astra Zeneca, Jannsen, Amgen, Leo, Allergan, and Lilly. For Novartis and AbbVie, Dr Van Voorhees acts as a consultant as well as serves on the board. Dr Van Voorhees has received a portion of ex-spouse pension from Merck. Dr Menter in the last 24 months has served on the advisory board for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen Biotech, Inc, and LEO Pharma. He has also worked as a consultant for AbbVie, Allergan, Amgen, Eli Lilly, Galderma, Janssen Biotech, Inc, LEO Pharma, Novartis, Pfizer, Vitae, and Xenoport. Additionally, he has acted as an investigator for AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Janssen Biotech, Inc, LEO Pharma, Merck, Neothetics, Novartis, Pfizer, Regeneron, Symbio/Maruho, and Xenoport. He also serves as a speaker for AbbVie, Amgen, Janssen Biotech, Inc, and LEO Pharma. He has received compensation in the form of grants from AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Janssen Biotech, Inc, LEO Pharma, Merck, Neothetics, Novartis, Pfizer, Regeneron, Symbio/Maruho, and Xenoport. He has also received honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen Biotech, Inc, LEO Pharma, Novartis, Pfizer, Vitae, and Xenoport. The other authors report no conflicts.

REFERENCES

1. Goff KL, Karimkhani C, Boyers LN, Weinstock MA, Lott JP, Hay RJ, Coffeng LE, Norton SA, Naldi L, Dunnick C, Armstrong AW, Dellavalle RP. The global burden of psoriatic skin disease. *Br J Dermatol*. 2015;172:1665–1668.
2. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1735–1741.
3. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J*. 2010;31:1000–1006.

4. Mehta NN, Li R, Krishnamoorthy P, Yu Y, Farver W, Rodrigues A, Raper A, Wilcox M, Baer A, DerOhannesian S, Wolfe M, Reilly MP, Rader DJ, VanVoorhees A, Gelfand JM. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. *Atherosclerosis*. 2012;224:218–221. doi: 10.1016/j.atherosclerosis.2012.06.068.
5. Yeung H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A, Margolis DJ, Shin DB, Attor R, Troxel AB, Gelfand JM. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol*. 2013;149:1173–1179. doi: 10.1001/jamadermatol.2013.5015.
6. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol*. 2007;143:1493–1499. doi: 10.1001/archderm.143.12.1493.
7. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY, Gottlieb AB. Psoriasis. *Nat Rev Dis Primers*. 2016;2:16082. doi: 10.1038/nrdp.2016.82.
8. Joshi AA, Lerman JB, Aberra TM, Afshar M, Teague HL, Rodante JA, Krishnamoorthy P, Ng Q, Aridi TZ, Salahuddin T, Natarajan B, Lockshin BN, Ahlman MA, Chen MY, Rader DJ, Reilly MP, Remaley AT, Bluemke DA, Playford MP, Gelfand JM, Mehta NN. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. *Circ Res*. 2016;119:1242–1253. doi: 10.1161/CIRCRESAHA.116.309637.
9. Mehta NN, Li K, Szapary P, Krueger J, Brodmerkel C. Modulation of cardiometabolic pathways in skin and serum from patients with psoriasis. *J Transl Med*. 2013;11:194. doi: 10.1186/1479-5876-11-194.
10. Naik HB, Natarajan B, Stansky E, Ahlman MA, Teague H, Salahuddin T, Ng Q, Joshi AA, Krishnamoorthy P, Dave J, Rose SM, Doveikis J, Playford MP, Prussick RB, Ehrlich A, Kaplan MJ, Lockshin BN, Gelfand JM, Mehta NN. Severity of psoriasis associates with aortic vascular inflammation detected by FDG PET/CT and neutrophil activation in a prospective observational study. *Arterioscler Thromb Vasc Biol*. 2015;35:2667–2676. doi: 10.1161/ATVBAHA.115.306460.
11. Connelly MA, Otvos JD, Shalaurova I, Playford MP, Mehta NN. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J Transl Med*. 2017;15:219. doi: 10.1186/s12967-017-1321-6.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135–1143.
13. Harrington CL, Dey AK, Yunus R, Joshi AA, Mehta NN. Psoriasis as a human model of disease to study inflammatory atherogenesis. *Am J Physiol Heart Circ Physiol*. 2017;312:H867–H873. doi: 10.1152/ajpheart.00774.2016.
14. Figueroa AL, Abdelbaky A, Truong QA, Corsini E, MacNabb MH, Lavender ZR, Lawler MA, Grinspoon SK, Brady TJ, Nasir K, Hoffmann U, Tawakol A. Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. *JACC Cardiovasc Imaging*. 2013;6:1250–1259. doi: 10.1016/j.jcmg.2013.08.006.
15. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, Subramanian SS, Abdelbaky A, Rudd JH, Farkouh ME, Nunes IO, Beals CR, Shankar SS. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol*. 2013;62:909–917. doi: 10.1016/j.jacc.2013.04.066.
16. Gottlieb AB, Kalb RE, Langley RG, Krueger GG, de Jong EM, Guenther L, Goyal K, Fakharzadeh S, Chevrier M, Calabro S, Langholff W, Menter A. Safety observations in 12095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. *J Drugs Dermatol*. 2014;13:1441–1448.
17. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol*. 2012;148:1244–1250. doi: 10.1001/archdermatol.2012.2502.
18. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914.
19. Zanolli MD, Feldman SR. *Phototherapy Treatment Protocols for Psoriasis and Other Phototherapy-Responsive Dermatoses*. New York, NY: Taylor & Francis; 2004.
20. Chen W, Bural GG, Torigian DA, Rader DJ, Alavi A. Emerging role of FDG-PET/CT in assessing atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging*. 2009;36:144–151. doi: 10.1007/s00259-008-0947-2.
21. Bural GG, Torigian DA, Chamroonrat W, Houseni M, Chen W, Basu S, Kumar R, Alavi A. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging*. 2008;35:562–569. doi: 10.1007/s00259-007-0528-9.
22. Padfield GJ, Din JN, Koushiappi E, Mills NL, Robinson SD, Cruden Nle M, Lucking AJ, Chia S, Harding SA, Newby DE. Cardiovascular effects of tumour necrosis factor α antagonism in patients with acute myocardial infarction: a first in human study. *Heart*. 2013;99:1330–1335. doi: 10.1136/heartjnl-2013-303648.
23. Mäki-Petäjä KM, Elkhawad M, Cheriyan J, Joshi FR, Ostör AJ, Hall FC, Rudd JH, Wilkinson IB. Anti-tumor necrosis factor-α therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. *Circulation*. 2012;126:2473–2480. doi: 10.1161/CIRCULATIONAHA.112.120410.
24. Dey AK, Joshi AA, Chaturvedi A, Lerman JB, Aberra TM, Rodante JA, Teague HL, Harrington CL, Rivers JP, Chung JH, Kabbany MT, Natarajan B, Silverman JI, Ng Q, Sanda GE, Sorokin AV, Baumer Y, Gerson E, Prussick RB, Ehrlich A, Green LJ, Lockshin BN, Ahlman MA, Playford MP, Gelfand JM, Mehta NN. Association between skin and aortic vascular inflammation in patients with psoriasis: a case-cohort study using positron emission tomography/computed tomography. *JAMA Cardiol*. 2017;2:1013–1018. doi: 10.1001/jamacardio.2017.1213.
25. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2960–2984. doi: 10.1016/j.jacc.2013.11.003.
26. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, Siu S, Kraft J, Lynde C, Pope J, Gulliver W, Keeling S, Dutz J, Bessette L, Bissonnette R, Haraoui B. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74:480–489. doi: 10.1136/annrheumdis-2014-206624.
27. Pircher J, Merkle M, Wörnle M, Ribeiro A, Czermak T, Stampnik Y, Mannell H, Niemeyer M, Vielhauer V, Krötz F. Prothrombotic effects of tumor necrosis factor alpha in vivo are amplified by the absence of TNF-alpha receptor subtype 1 and require TNF-alpha receptor subtype 2. *Arthritis Res Ther*. 2012;14:R225. doi: 10.1186/ar4064.
28. Duivenvoorden R, Mani V, Woodward M, Kallend D, Suchankova G, Fuster V, Rudd JHF, Tawakol A, Farkouh ME, Fayad ZA. Relationship of serum inflammatory biomarkers with plaque inflammation assessed by FDG PET/CT: the dal-PLAQUE study. *JACC Cardiovasc Imaging*. 2013;6:1087–1094. doi: 10.1016/j.jcmg.2013.03.009.
29. Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, Fuster V, Ballantyne CM, Stein EA, Tardif JC, Rudd JH, Farkouh ME, Tawakol A; dal-PLAQUE Investigators. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet*. 2011;378:1547–1559. doi: 10.1016/S0140-6736(11)61383-4.
30. Bissonnette R, Harel F, Krueger JG, Guertin MC, Chabot-Blanchet M, Gonzalez J, Maari C, Delorme I, Lynde CW, Tardif JC. TNF-α antagonist and vascular inflammation in patients with psoriasis vulgaris: a randomized placebo-controlled study. *J Invest Dermatol*. 2017;137:1638–1645. doi: 10.1016/j.jid.2017.02.977.
31. Bucerius J, Hyafil F, Verberne HJ, Slart RH, Lindner O, Sciagra R, Agostini D, Übleis C, Gimelli A, Hacker M; Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis. *Eur J Nucl Med Mol Imaging*. 2016;43:780–792. doi: 10.1007/s00259-015-3259-3.