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Effect of Two Psoriasis Treatments on Vascular Inflammation and Novel Inflammatory Cardiovascular Biomarkers: A Randomized Placebo-Controlled Trial

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Abstract

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

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Clinical Trial Registration Information

URL: https://clinicaltrials.gov/ct2/show/NCT01866592?term=vascular+inflammation+in+psoriasis&rank=1

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moderate-to-severe psoriasis with adalimumab or phototherapy on vascular inflammation (VI) and cardiovascular biomarkers.

Methods and Results—Randomized, double-blind, trial of adalimumab, phototherapy, and placebo (1:1:1) for 12 weeks, with cross-over to adalimumab for 52 weeks total. Outcomes included VI by ^{18}F-FDG-PET/CT and biomarkers of inflammation, insulin resistance and lipoproteins. 97 patients were randomized, 92 completed the RCT portion; 81 entered the adalimumab extension with 61 completing 52 weeks of adalimumab.

There was no difference in change in VI at week-12 in the adalimumab group [change compared to placebo 0.64%, 95% CI −5.84% to 7.12%)] or the phototherapy group [−1.60%, (−6.78%, 3.59%)] or after 52-week adalimumab treatment (0.02% compared to initiation, 95% CI −2.85%, 2.90%). Both adalimumab and phototherapy decreased inflammation by serum CRP, IL-6. Only adalimumab reduced TNF and GlycA at 12 and 52 weeks. Neither had impact on metabolic markers (insulin, adiponectin, leptin). Only phototherapy increased HDL-p at 12 weeks. At 52-week of adalimumab cholesterol-efflux and HDL-p were reduced.

Conclusions—Adalimumab reduced key markers of inflammation including GlycA compared to phototherapy with no effect on glucose metabolism and VI, and potential adverse effects on HDL. GlycA 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.

SUBJECT TERMS

Nuclear Cardiology and PET; Vascular disease; Biomarkers

Keywords

Vascular inflammation; psoriasis; 18F-FDG PET/CT; cardiovascular disease; biomarkers; adalimumab; phototherapy

INTRODUCTION

Psoriasis is a common chronic Th1/Th17 inflammatory skin disease that affects over 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, 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 approximately 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-alpha (TNF-alpha), interleukin-6 (IL-6) and glycoprotein acetylation (GlycA) are increased in psoriasis[8, 9], associate 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-FDG-PET/CT, that is equivalent to approximately one 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 (i.e., 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-alpha, is a standard of care biologic therapy used to treat moderate to severe psoriasis[16] and is suggested to be associated with a reduction in major cardiovascular events[17]. Narrow band ultraviolet B phototherapy (NB-UVB) 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 biologic anti-inflammatory therapy in reducing rate of myocardial infarction despite minimal change in LDL cholesterol[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 regarding the patient privacy. The study was a multi-center 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 NB-UVB 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 to baseline in adalimumab and phototherapy groups compared to placebo. We also conducted a series of analyses of biomarkers of cholesterol, glucose metabolism, and inflammation which were selected based on their known association with psoriasis and/or 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 ≥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 subcutaneous injection with an initial 80mg dose at week 0, followed by maintenance doses of 40mg every other week, starting from week 1 and then continued throughout the study. NB-UVB phototherapy dosing was based on estimated minimal erythema dose (MED) and Fitzpatrick skin type using a standardized protocol published by Zanolli and Feldman[19]. ^{18}F-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 SUV_{mean} from each of the superior vena cava slices were averaged to produce one 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 ^{18}F-FDG PET/CT scans using the standard protocol[20, 21] following overnight fast. Using a two-sided test with α=0.017 (with Bonferroni correction), we needed 32 patients in each arm to have 82% power in our study to detect a change in SUV of 0.1 with a presumed drop-out rate of 15%.

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 potential imbalance of covariates, adjusting for clinical and demographic covariates using a backward model building approach. Natural log scale was used for all non-parametric 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 two-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 standard deviation (SD) of the change in SUV of 0.11 and a drop-out rate of 15%.

Study approval was obtained from the Institutional Review Board (IRB) of the University of Pennsylvania or respective local IRB 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 (NHLBI and Abbvie) had no role in the analysis or

reporting of the results. Abbvie reviewed the manuscript for compliance purposes. The detailed methods are elaborated in a separate Online only 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). 81 patients entered the open-label adalimumab extension portion of the study, of which 58 (72%) completed 52 weeks of adalimumab treatment and had an end of study scan. 9 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 PASI (a measure of psoriasis area and severity index) of 19. About 10% of patients had a history of psoriatic arthritis, and about 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 to placebo for physician reported measures (Supplemental Table 1). 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 (Supplemental Table 2). No statistically significant change was observed in physical activity (as measured using the IPAQ metabolic equivalent task (MET) minutes) between groups at week 12 or at end of extension period. On average, patients reported reduction in saturated and dietary cholesterol intake at week 12 and end of open label period compared to 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 three groups are noted under Supplementary Table 3. There was no difference in change in VI at week 12 in the adalimumab group (change compared to placebo 0.64%, 95% CI −5.84% – 7.12%) or the phototherapy group (−1.60%, 95% CI −6.78% – 3.59%) (Table 2 & Figure 3). Analysis within groups demonstrated a statistically significant reduction in VI by −4.09% (95% CI −7.78%, −0.39%) in the phototherapy treatment arm only. At the end of the extension period there was a −3.80% reduction in VI compared to the absolute study baseline (week 52 or 64 compared to week 0 for all) (95% −6.40%, −1.19%) (Table 3). However, there was no change in VI (0.02% difference, 95% CI −2.85%, 2.90%) during the adalimumab treatment only period comparing end of study assessment to adalimumab baseline (week 52 compared to week 0 for those initially assigned to adalimumab, and week 64 compared to 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 to placebo was observed for CRP, TNF-alpha, 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 to placebo which was only modestly significant. At the end of the extension period, compared to 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-alpha, 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).

DISCUSSION

We conducted a randomized, controlled trial to determine the impact of systemic anti-TNF immune targeted (i.e., adalimumab) treatment and skin directed treatment (i.e., ultraviolet B phototherapy) on key markers of vascular disease risk compared to 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 cardiometabolic 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% confidence interval 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 non-controlled study in rheumatoid arthritis of anti-TNF treatment which observed a reduction in VI by ^{18}F-FDG-PET/CT following 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 due to improvements 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 (i.e., antibodies) may not be directly active in large vessels such as the aorta due to 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 strong and consistent improvements in skin inflammation (i.e., clearance of psoriasis) and strong reductions in systemic inflammation as measured by serum TNF-alpha, 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 lipoprotein structure and function resulting in a neutral effect on VI.

While CRP, IL-6, TNF-alpha 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 CV 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 following initiation of therapy. Furthermore, IL-6 levels increased following anti-TNF treatment. Therefore, it may be possible that potential beneficial effects of anti-TNF therapy on VI were offset by the pro-atherogenic 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 to 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, while 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, following adalimumab or phototherapy, we did not observe change in glucose levels or insulin resistance by HOMA-IR nor in adiponectin or leptin. It is entirely possible that HOMA-IR, which detects peripheral skeletal muscle insulin resistance, but not hepatic insulin resistance did not change because insulin resistance was not affected in the skeletal muscle. Future research should consider 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 a biological treatment in relation to an established skin directed treatment modality on cardiovascular and inflammatory markers, compared to placebo. Additionally, while 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 to more standard markers assessed in the prior study.

Despite being a randomized and placebo-controlled, our study has important limitations that warrant mention. First, though we had more than 80% power per our sample size calculations based on 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 endpoints limits our ability to derive definite conclusions. Furthermore, since 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 one-year data suggesting no significant benefit of anti-TNF in reducing VI over one-year despite changes in biomarkers. However, one-fourth of the patients did not make it to one-year of ADA treatment, and therefore these results should be interpreted with caution. The main reason for drop out was failure of treatment response in the skin and therefore, our findings in the extension study may over estimate 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, while both anti-TNF therapy and phototherapy had no impact on VI as assessed by ^{18}F-FDG-PET/CT compared to 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 work is ongoing to determine the impact of biologics that target IL12/23 and IL-17 as well as a small molecule (apremilast) that targets PDE-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

cardiometabolic 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLOSURES

Dr. Mehta is a full-time US Government Employee and receives research grants to the 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 labs, 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.

Dr. 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/or 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 with 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.

All other authors have no conflict of interest.

ABBREVIATIONS

18F-FDG PET/CT	18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography
PASI	Psoriasis Area and Severity Index
HOMA-IR	Homeostasis model assessment of insulin resistance

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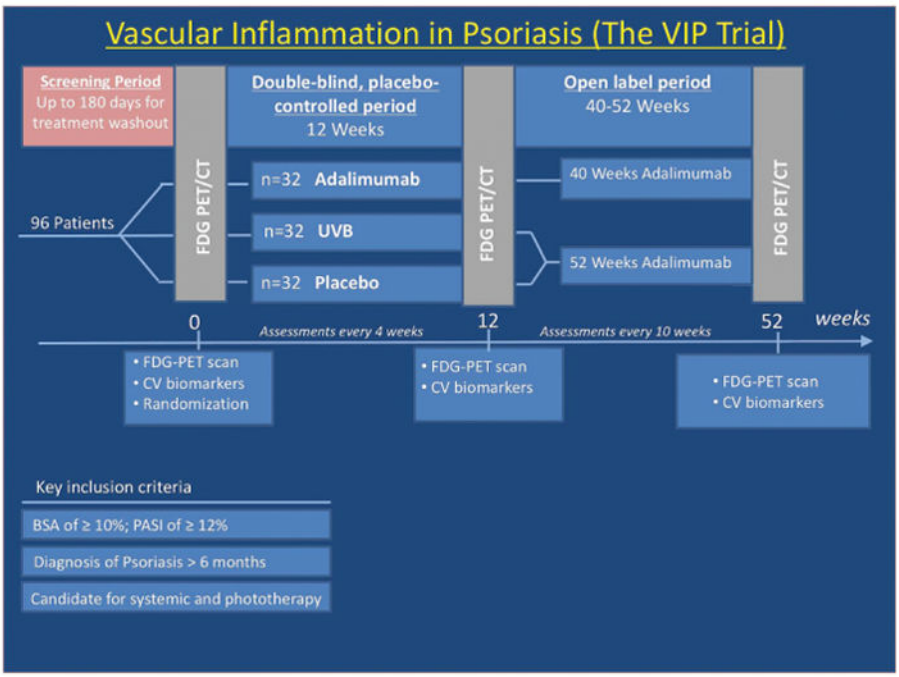

Figure 1.
Study protocol for the Vascular Inflammation in Psoriasis (VIP) randomized, controlled trial

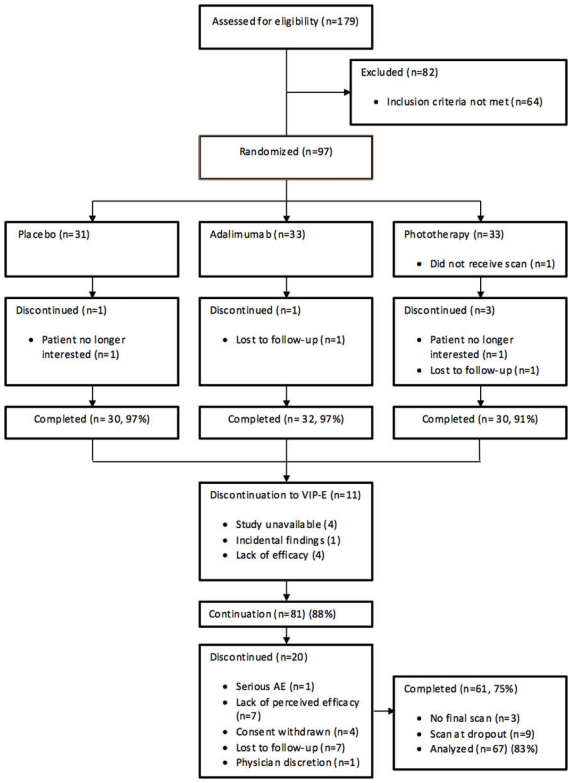

Figure 2.
Patient recruitment scheme for the study.

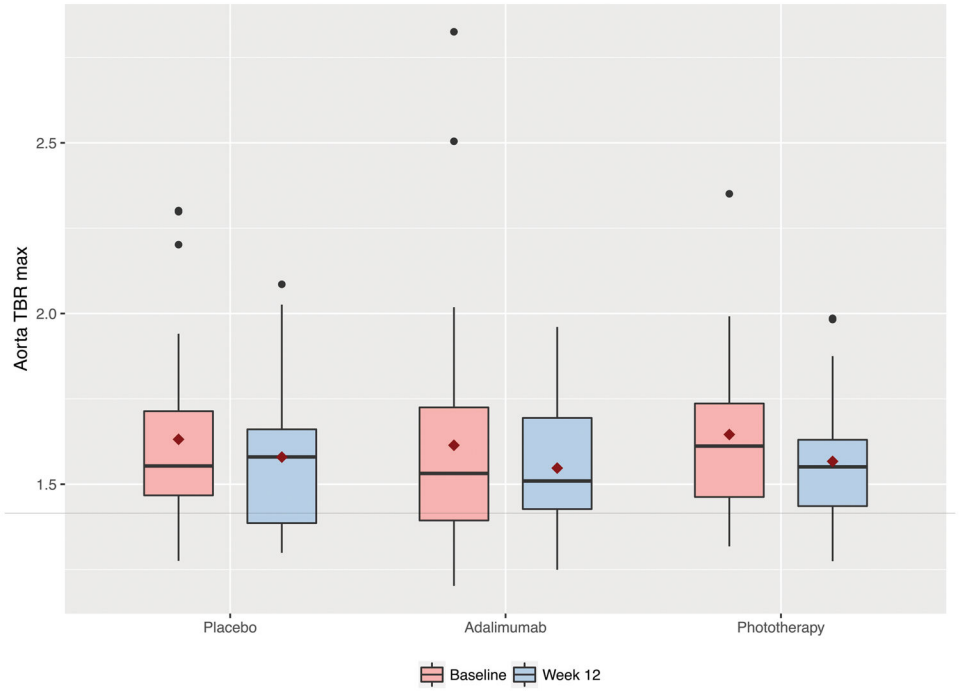

Figure 3.
Change in vascular inflammation for the randomized controlled trial period (baseline to week-12) stratified by the treatment group.

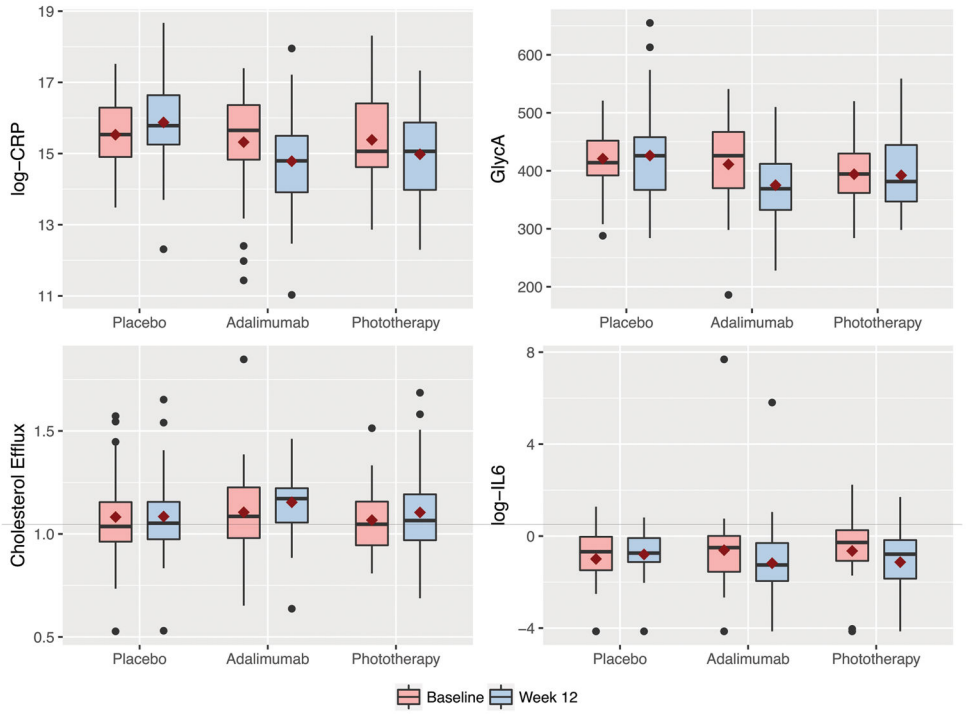

Figure 4.
Change in key biomarkers for the randomized controlled trial period (baseline to week-12) stratified by the treatment group.

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 Male	11 (35.48) 20 (64.52)	9 (27.27) 24 (72.73)	10 (30.30) 23 (69.70)	30 (30.93) 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) H/o CVD	31.95 (7.74) 3 (9.68)	30.93 (7.42) 2 (6.06)	32.61 (8.66) 2 (6.06)	31.83 (7.91) 7 (7.22)
Diabetes	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 year 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)

Table 2

Changes in TBR_{max} by treatment group during RCT period

	Placebo	Adalimumab	Phototherapy
Global Change compared to baseline within group			
Mean difference[1]	−0.052 (0.112)	−0.067 (0.213)	**−0.079 (0.020)**
Mean % change (95% CI) [1]	−2.49% (−6.29%, 1.31%) (0.191)	−1.84% (−7.17%, 3.47%) (0.483)	**−4.09% (−7.78%, −0.39%) (0.031)**
Global Change compared to placebo			
Difference of differences[2]	NA	−0.015 (0.795)	−0.027 (0.647)
Difference of % change[2]	NA	0.64% (−5.84%, 7.12%) (0.844)	−1.60% (−6.78%, 3.59%) (0.540)

[1] One sample test (p-value)

[2] Difference of differences (p-value)

(statistically significant findings bolded)

Table 3

Changes in TBR_{max} open label extension

	Mean (p-value[1])
Global change baseline compared to end of open label extension	
Difference	**−0.08 (0.002)**
% change (95% CI)	**−3.80% (−6.40%, −1.19%) (0.005)**
Global change start of adalimumab compared to end of open label extension	
Difference	−0.02 (0.538)
% change	0.02% (−2.85%, 2.90%) (0.987)

[1]One sample t-test

(statistically significant findings bolded)

Table 4

Change in advanced lipoprotein characterization, glucose metabolism, and inflammation between baseline and Week 12, by treatment group during RCT period

	Adalimumab vs Placebo[1]	Phototherapy vs Placebo[1]	F-test p[2]
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-alpha	**−0.411 (<0.001)**	−0.177 (0.065)	**<0.001**
Log IL6	**−0.764 (0.007)**	**−0.683 (0.019)**	**0.014**
GlycA	**−41.165 (0.006)**	−7.199 (0.628)	**0.015**

[1] Difference of differences (statistically significant findings bolded)

[2] Global difference (statistically significant findings bolded)

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-alpha	0.688 (0.554)	0.413 (0.873)	**−0.275 (0.131)**	**0.040**
Log IL6	−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**

(statistically significant findings bolded)

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-alpha	0.725 (0.571)	0.409 (0.867)	−0.315 (0.126)	**0.015**
Log IL6	−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 bolded)