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A Randomized Open-Label Clinical Trial of Lipid-Lowering Therapy in Psoriasis to Reduce Vascular Endothelial Inflammation

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AUTHOR CONTRIBUTIONS

Conceptualization: MSG, JSB; Data Curation: MSG, KD; Formal Analysis: MSG, FS, KD, TJB; Funding Acquisition: MSG, JSB; Investigation: MSG, TJB, ALN, JUS; Methodology: MSG, SJ, ALN, JUS, JK, JSB; Resources: EAF, JK, JSB, SK; Supervision: EAF, JK, JSB; Writing - Original Draft Preparation: MSG, JSB; Writing - Review and Editing; JUS, TJB, EAF, SK, JK, ALN, SK

ETHICS STATEMENT

The study protocol was approved by the New York University School of Medicine Institutional Review Board (i17-00692). All subjects provided written informed consent before participation, in line with the Declaration of Helsinki protocols, which were followed.

CONFLICT OF INTEREST

MSG has received personal fees from Abbvie. JUS has served as a consultant for Janssen, Abbvie, Novartis, Sanofi, UCB, and BMS. JK has received grants from Novartis, Pfizer, Amgen, Lilly, Boehringer, Innovaderm, BMS, Janssen, Abbvie, Paraxel, Leo Pharma, Vitae, Akros, Regeneron, Allergan, Novan, Biogen MA, Sienna, UCB, Celgene, Botanix, Incyte, Avillion, and Exicure. He has received personal fees from Novartis, Pfizer, Amgen, Lilly, Boehringer, BiogenIdec, Abbvie, Leo Pharma, Escalier, Valeant, Aurigne, Allergan, Asana, UCB, Sienna, Celgene, Nimbus, Menlo, Aristea, Sanofi, Sun Pharma, Almirall, Arena, and BMS. JSB has grants from the National Institutes of Health/National Heart, Lung, and Blood Institute related to the topic and has served on the advisory board for Amgen and Jannsen.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2021.07.190.

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TO THE EDITOR

In psoriasis, immune systemic activation and cardiometabolic abnormalities, including dyslipidemia, play a role in promoting impaired endothelial health and increased cardiovascular (CV) risk (Greb et al., 2016). Patients with psoriasis have elevated brachial vein endothelial proinflammatory transcript expression (impaired vascular endothelial health), with the degree of impairment directly correlated with skin activity and circulating biomarkers of systemic inflammation (Garshick et al., 2019). In psoriasis, TNF and IL-17A synergism promote inflammasome (IL-1β) signaling and downstream IL-6 production (driver of CRP) (Verma et al., 2021), which associates with vascular endothelial inflammatory transcript expression, suggesting a pathogenic (immune-mediated) mechanism of atherosclerosis development (Garshick et al., 2019).

In general (nonpsoriasis) populations, β-hydroxy β-methylglutaryl-CoA reductase inhibitors (e.g., statins) reduce cholesterol and CV risk, improve endothelial function, and have pleiotropic and anti-inflammatory effects (Adhyaru and Jacobson, 2018; Garshick and Underberg, 2017; Ridker et al., 2008). In psoriasis, although observational data suggest a benefit (Wu et al., 2012), randomized controlled trial data showing the efficacy of statins whether through lipid-mediated or antiinflammatory properties are yet to be established. We therefore conducted a randomized open-label controlled trial to investigate the effect of high-intensity atorvastatin on vascular endothelial health in the psoriatic population.

Patients with active psoriasis (≥1% body surface area of psoriasis or psoriatic arthritis ≥1 swollen/tender joint; consort diagram in Supplementary Figure S1) without clinical CV disease were recruited as part of ongoing studies (NCT03228017) to investigate vascular endothelial health in psoriasis at NYU Langone Health (New York City, NY) (Institutional Review Board approval i17–00692) (Garshick et al., 2019). To directly assess the endothelium and vascular endothelial cell proinflammatory activation, subjects underwent brachial vein endothelial harvesting and serum lipid and inflammatory biomarker assessment (Jelic et al., 2010). Participants with psoriasis were then randomized to 40 mg atorvastatin per day or to no treatment (Supplementary Figure S1), and a repeat assessment occurred at week 2. The primary study endpoint and outcome measure was a change in the composite brachial vein endothelial cell inflammatory transcriptomeedefined as the mean expression values from endothelial cell proinflammatory transcripts (i.e., mean expression of proinflammatory vascular endothelial transcript [meanEC]) (composite transcript expression of *LTB*, *CCL3*, *CX3CL1, CCL2, CXCL1*, *ICAM1, IL-8*, *IL-1B*, COX-2) (Garshick et al., 2020). Subjects provided written informed consent before participation, in line with the Declaration of Helsinki protocols (Supplementary Materials and Methods).

For sample size determination in this pilot study, 10 subjects (control) and 20 subjects (treatment) per group provided a margin of error (95% confidence interval half width) of 0.13 for the $\log_2$ fold change in vascular endothelial inflammation between treatment groups (Garshick et al., 2020; Kianifard and Islam, 2011; nQuery, 2017, Statistical Solutions, Cork,

Ireland). For the primary outcome, log transformation with paired sample *t*-test or Wilcoxon test for changes between baseline and follow-up data points were also performed with multivariable modeling as appropriate. Statistical significance was determined using a two-tailed $\alpha < 0.05$, with full study details in the Supplementary Materials and Methods. The datasets, including circulating and vascular endothelial inflammatory and lipid biomarkers, which support the findings of this study, are available from the corresponding author (MSG) on reasonable request.

Recruited patients with psoriasis were young and of low CV risk with moderate psoriasis disease severity, many (40%) of whom were on biologic therapy (Table 1 and Supplementary Table S1). At baseline, meanEC (mean expression of proinflammatory brachial vein endothelial cell transcripts) correlated with both PASI ($r = 0.41$, $P = 0.02$) and high-sensitivity CRP (hs-CRP) ($r = 0.61$, $P < 0.01$; Supplementary Figure S2a and b) but not with psoriasis disease duration ($r = -0.09$, $P = 0.64$), CV risk score ($r = 0.01$, $P = 0.95$), low-density lipoprotein cholesterol (LDL-C) ($r = 0.18$, $P = 0.36$), or total cholesterol ($r = 0.15$, $P = 0.45$). After 2 weeks of high-intensity statin therapy, the median reduction from baseline LDL-C was 44% ($P < 0.001$), and that of hs-CRP was 41% ($P = 0.06$), with no significant changes noted in the no-treatment group (Supplementary Table S2). Other measures, including IL-6, TNF-α, and IL-17A, were not significantly decreased in both groups (Supplementary Figure S3a–f and Supplementary Table S2).

For the primary outcome, after 2 weeks of high-intensity statin therapy, meanEC was reduced ($\log_2$fold change = −0.10, 95% confidence interval = −0.003 to −0.21) in the atorvastatin group compared with the meanEC change in the no-treatment group ($\log_2$fold change = 0.10, 95% confidence interval = −0.04 to 0.25; $P = 0.01$; Figure 1a). This difference between no-treatment and statin randomized participants remained after adjusting for potential confounders, including age, sex, biologic use, psoriasis severity (PASI), and psoriasis duration ($\beta = -0.49$, $P = 0.03$), showing that atorvastatin reduced vascular endothelial inflammation. The reduction in meanEC correlated with the degree of LDL-C lowering (Figure 1b) but not with a reduction in hs-CRP or IL-6 (Supplementary Figure S4a and b). In line with these observations, participants with a more significant reduction in LDL-C (Figure 1c and d) or in a follow-up LDL-C <70 mg/dl (Supplementary Figure S4c) displayed the largest reductions in vascular endothelial inflammatory transcript expression from baseline.

Patients with psoriasis have a heightened prevalence of dyslipidemia and an elevated risk of CV disease compared with those without psoriasis (Greb et al., 2016). A posthoc analysis of two secondary prevention lipid-lowering trials identified ~500 (of ~19,000) patients with psoriasis (Ports et al., 2017). Patients with psoriasis on high-intensity statins displayed a similar reduction in lipids and CV events to those in patients without psoriasis. Our findings support and expand on these analyses, whereby after atorvastatin therapy, the lower the LDL-C (<70 mg/dl) achieved, the greater the improvement in vascular health. Although specific LDL-C goals are no longer firmly recommended in the primary prevention of CV disease (Arnett et al., 2019), our findings are similar to those of other high CV risk groups, whereby aggressive lowering of LDL-C (<70 mg/dl) correlates with reduced CV risk.

To explore the mechanisms of CV risk in psoriasis, we employed a surrogate of vascular health, brachial vein endothelial analysis, and cannot definitively state that statins improve CV outcomes in psoriasis. However, analysis of directly obtained venous endothelium is an innovative technique, and in other studies, reductions in brachial vein endothelial inflammation correlate with improvement in endothelial flow–mediated dilation, which itself is predictive of CV events (Jelic et al., 2010; Michelson et al., 2000). Other limitations include a high proportion of participants on biologic therapy and some randomization imbalance between psoriasis groups, but these were adjusted for in multivariable analyses. Finally, we did not observe a reduction in inflammatory biomarkers (IL-6, TNF-α, or IL-17A) after statin therapy nor a significant correlation between changes in hs-CRP and vascular endothelial transcriptome expression. Whether this was due to the short, pilot nature of our study with limited sample size or other factors intrinsic to psoriasis itself requires larger, longer-duration investigations.

In summary, in a pilot randomized clinical trial of patients with psoriasis without clinical CV disease, 40 mg of atorvastatin reduced vascular endothelial proinflammatory transcript expression, a surrogate of CV risk. The degree of improvement correlated with the degree of LDL-C reduction and not with hs-CRP, with those observing the most benefit achieving an LDL-C below 70 mg/dl. Our findings highlight the need for larger clinical trials to investigate the clinical benefit of statin therapy in psoriasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CV	cardiovascular
hs-CRP	high-sensitivity CRP
LDL-C	low-density lipoprotein cholesterol
meanEC	mean expression of proinflammatory vascular endothelial transcript

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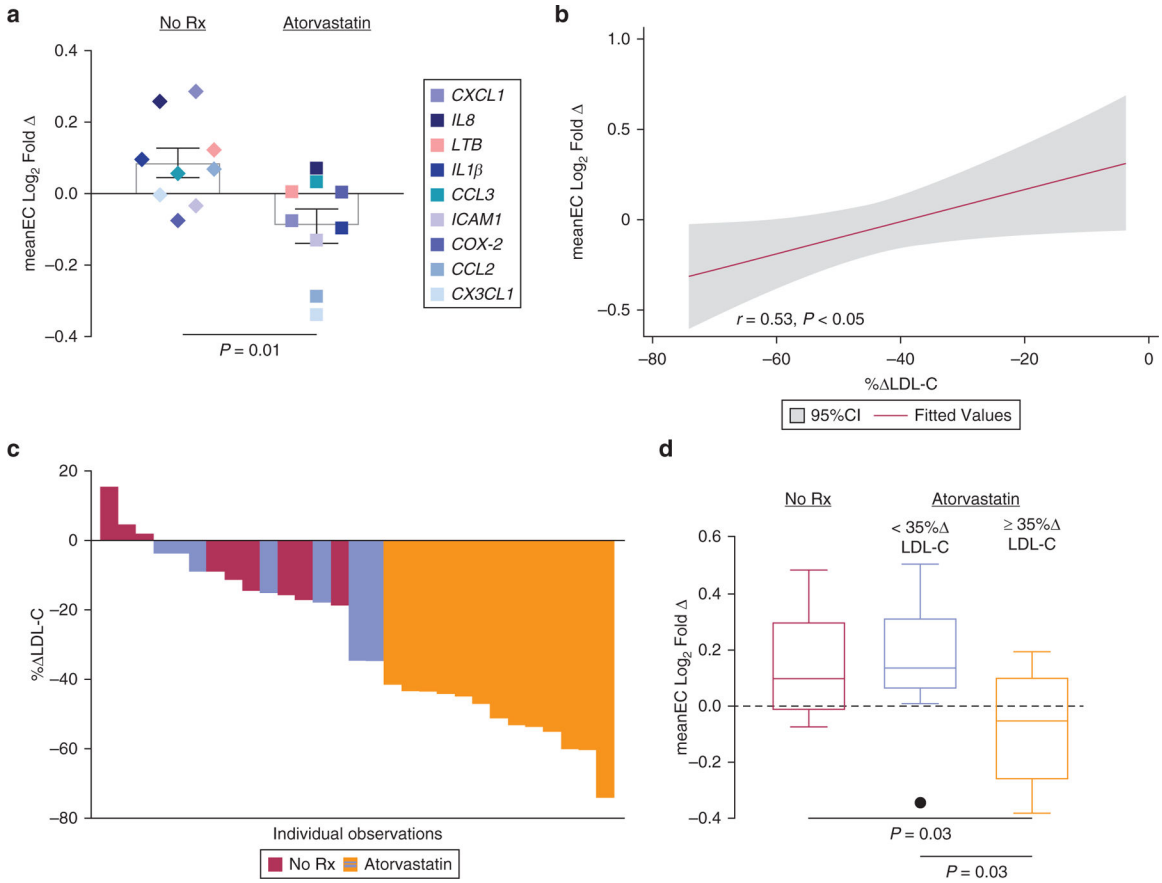

Figure 1. A 2-week lipid-lowering therapy with atorvastatin reduces vascular endothelial inflammation.

(a) Composite $\log_2$ fold change in brachial vein endothelial inflammatory transcript expression in those randomized to atorvastatin (n = 18[1]) or no treatment (n = 10) for 2 weeks. (b) Correlation between atorvastatin-treated patients and composite $\log_2$ fold change in brachial vein endothelial inflammatory transcript expression. (c) Percentage change in LDL-C over 2 weeks[1]; colors correspond to <35% or ≥35% reduction in LDL-C. (d) Composite $\log_2$ fold change in brachial vein endothelial inflammatory transcript expression stratified by no treatment (n = 10), <35% reduction in LDL-C (n = 6), and ≥35% reduction in LDL-C (n = 12[1]) after atorvastatin treatment.

[1]One patient in the No Rx group did not have a follow-up LDL-C, whereas two atorvastatin-treated patients with psoriasis did not have adequate follow-up brachial vein endothelial collection. meanEC of *LTB, CCL3, CX3CL1, CCL2, CXCL1, ICAM1, iNOS, IL-8, IL-1B, COX*-2 is shown. CI, confidence interval; meanEC, mean expression of proinflammatory vascular endothelial transcript; LDL-C, low-density lipoprotein cholesterol; No Rx, no treatment.

Table 1.

Baseline Characteristics

Characteristics	No Treatment (n = 10)	Atorvastatin (n = 20)	*P*-Value
Age, y, median (IQR)	35 (28–37)	44 (32–52)	0.16
Male sex, n (%)	5 (50)	9 (45)	0.80
Body mass index, kg/m^2	28 ± 6	28 ± 7	0.97
Caucasian, n (%)	6 (60)	15 (75)	0.40
Systolic blood pressure (mm Hg)	121 ± 10	127 ± 17	0.40
Diastolic blood pressure (mm Hg)	75	76 ± 12	0.87
ACC/AHA ASCVD Risk Score, %	2.7 ± 3.5	3.3 ± 5.4	0.77
Psoriasis			
PASI score, median (IQR)	5.6 (3.2–19)	4.0 (3.6–6.9)	0.69
Psoriasis duration, y, median (IQR)	8 (3–10)	20 (12–29)	0.01
Psoriatic arthritis, n (%)	3 (15)	4 (40)	0.13
Biologic therapy, n (%)	6 (60)	6 (30)	0.11
Laboratory studies			
WBC, ×10^3 cells/mm^3, median (IQR)	7.9 (6.1–9.9)	6.2 (5.3–7.1)	0.11
hs-CRP, mg/l, median (IQR)	2.1 (1.0–4.2)	1.7 (0.8–2.0)	0.45
IL-17A, NPX, median (IQR)	3.5 (1.8–6.1)	2.4 (1.8–3.6)	0.43
IL-6, NPX, median (IQR)	3.8 (3.4–4.6)	3.3 (3.1–4.2)	0.20
TNF-α, NPX, median (IQR)	3.9 (3.7–4.7)	3.6 (3.3–3.9)	0.22
Lipids			
Total cholesterol, mg/dl, median (IQR)	179 (178–186)	182 (162–216)	0.79
Triglycerides, mg/dl, median (IQR)	83 (58–150)	85 (61–104)	0.98
LDL-C, mg/dl, median (IQR)	111 (110–121)	108 (83–131)	0.20
HDL-C, mg/dl, median (IQR)	45 (43–52)	56 (46–63)	0.07
meanEC, median (IQR)	5.9 (2.8–13)	4.7 (3.2–7.4)	0.96

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity CRP; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; meanEC, mean expression of proinflammatory vascular endothelial transcript; NPX, normalized eXpression unit; WBC, white blood cell.

Data are presented as mean ± SD or n (%) unless otherwise stated. meanEC indicates mean vascular endothelial transcript inflammation (arbitrary units standardized to the housekeeping gene *hARP*).