Is It Prime Time for Statin Therapy in Psoriasis?

Nehal N. Mehta1 and Joel M. Gelfand2


It has been over a decade and a half since the first large-scale study of the accelerated risk of myocardial infarction in psoriasis (Gelfand et al., 2006). Since then, a broad range of scientific approaches has determined that psoriasis itself is associated with a higher-risk subclinical vascular disease (Naik et al., 2015), high-risk coronary plaque (Lerman et al., 2017), and major adverse cardiovascular (CV) events (Mehta et al., 2010) and mortality (Noe et al., 2018). Although these studies have established that the risk of CV disease (CVD) is independent of traditional CV risk factors, psoriasis also has complex interactions with metabolic disease. For example, for each 10% increase in body surface area affected by psoriasis, there is a 20% higher risk of developing diabetes, independent of body mass index (Wan et al., 2018). Mechanistic and preclinical studies highlight the role of systemic inflammation (Baumer et al., 2018); immune dysfunction (Teague et al., 2019); and an interplay between adiposity, inflammation, and dyslipidemia (Sajja et al., 2020) in accelerating coronary disease.

Dyslipidemia, defined as either elevated low-density lipoprotein (LDL) and triglycerides or low high-density lipoprotein, is highly prevalent in psoriasis (Neimann et al., 2006; Sorokin et al., 2018); increases with increasing body surface area affected by psoriasis (Langan et al., 2012); and is a driver of multiple systemic comorbid diseases, including stroke, heart attack, and fatty liver disease. Given the accumulation of evidence of accelerated vascular disease in psoriasis, in 2018, the American College of Cardiology/American Heart Association issued landmark guidelines (Grundy et al., 2019) identifying psoriasis as a CV risk enhancer and recommending earlier use of statins (i.e., in patients whose 10-year risk of atherosclerotic disease is ≥5%) in patients with psoriasis. Similarly, the American Academy of Dermatology/National Psoriasis Foundation 2019 guidelines (Elmets et al., 2019) recommended early and more frequent screening for dyslipidemia, especially when skin disease is severe, and recommended earlier use of statins.

Treatment with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor or statin therapy has been the cornerstone of the management of dyslipidemia associated with atherosclerotic CVD. Statins are extremely effective at LDL lowering and provide among the largest benefit in both primary and secondary risk reduction in CVD. Recently, statins were shown to have similar benefits on lipid reduction and reduction of CV events in people with psoriasis as in people without psoriasis (Masson et al., 2020), and in another posthoc analysis, statins were shown to improve LDL levels in those with psoriasis (Ports et al., 2017).

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In this context, the study by Garshick et al. (2022) in the Journal of Investigative Dermatology, “A Randomized Open-Label Clinical Trial of Lipid-Lowering Therapy,” provides a novel context for evaluating the effects of statins in people with psoriasis. Using a randomized open-label trial, 30 young patients with psoriasis were randomly assigned to 2 weeks of statin therapy (40 mg atorvastatin) and were compared with 10 patients with psoriasis who received no additional treatment. Brachial vein endothelial cells were obtained through intravenous scraping. The study’s primary outcome was mean expression values obtained from these endothelial cell transcripts, a surrogate marker of vascular health through the assessment of venous endothelial cell inflammation.

Included patients were young, without CV disease, and with active psoriasis or psoriatic arthritis. Of particular interest, this patient population, owing to normal lipids and low 10-year risk of atherosclerotic CVD, would not have an indication for treatment with statins. Nevertheless, 2 weeks of atorvastatin reduced the median LDL cholesterol (LDL-C) by 40\% (\(P < 0.0001\)) and high-sensitivity C-reactive protein (hs-CRP) by 11\% (\(P = 0.06\)) with no significant changes in those who received no treatment over 2 weeks. The authors did not observe a reduction in plasma inflammatory proteins IL-6, TNF-\(\alpha\), or IL-17A after statin therapy. Individual levels of endothelial cell transcripts showed no associations to weak associations with CV risk factors and biomarkers. After statin therapy, a composite transcript expression score, comprising LTB, CCL3, CX3CL1, CCL2, CXCL1, ICAM1, IL-8, IL-1B, and COX-2 brachial vein endothelial cell transcriptome values, was shown to be decreased in the statin group (log\(_2\) fold change [FC] = -0.10, 95\% confidence interval [CI] = -0.003 to -0.21) compared with the mean expression of endothelial cell (meanEC) change in the no-treatment group (log\(_2\)FC = 0.10, 95\% CI = -0.04 to 0.25). The reduction in meanEC correlated with the degree of LDL-C lowering (\(r = 0.53, P < 0.05\)) but not the reduction in hs-CRP (\(r = 0.09, P = 0.76\)). These findings were significant after adjusting for age, sex, biologic use, psoriasis severity (PASI), and psoriasis duration (\(\beta = -0.49, P = 0.03\)). Interestingly, those participants with more significant reductions in LDL-C or with a follow-up LDL-C <70 mg/dl displayed larger reductions in the composite score of vascular endothelial inflammatory transcript expression from baseline. The authors conclude that statin therapy reduced brachial vein endothelial cell proinflammatory gene expression, which may have beneficial impacts on vascular health.

First, the study showed that a conglomerate score of venous endothelial transcriptome, although not associated with CV biomarkers or risk factors, responded to statin therapy in a favorable direction, beyond adjustment for CV risk factors in a population of patients in which statins would not be ordinarily indicated clinically. These findings support that statin therapy will indeed impart benefit in psoriasis where there is a high degree of vascular inflammation (Naik et al., 2015). Brachial vein sampling may not reflect arterial inflammation and these subjects also lacked vascular imaging. Therefore, future studies including vascular testing and imaging will be informative to better understand the change in endothelial cell inflammation. Finally, the psoriasis population included a portion of patients treated with biologic therapy without substantial inflammatory biomarker elevations with mild-to-moderate skin disease. This selection criteria could potentially underestimate the degree to which statins improve vascular health and especially the systemic inflammatory response in psoriasis and should be repeated in larger samples.

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The paper provides proof of principle of a preclinical benefit of statin therapy on a new vascular surrogate readout in patients with psoriasis, who by age and CV risk-factor criteria would not qualify for statin therapy. Thus, it provokes the following question of whether statins should be used earlier, especially in this disease state known to have diffuse vascular inflammation and dyslipidemia (Figure 1). Recognizing the underdiagnosis and undertreatment of dyslipidemia in psoriasis (Kimball et al., 2012) as well as other major CV risk factors (Takekita et al., 2015), we have conducted a series of qualitative and quantitative studies of dermatologists, rheumatologists, and patients with psoriatic disease to identify the barriers and facilitators to improving the identification and management of traditional CV risk factors in this at-risk population. These studies have shown that both providers and patients are interested in engaging in CV prevention care in the context of management of psoriatic disease but that care coordination is a major barrier to improving outcomes (Barbieri et al., 2021; Gustafson et al., 2021; Ogdie et al., 2021). We plan to test a care coordinator model in the United States to determine whether it can lower CV risk in patients with psoriasis disease as has been shown in other settings (Al Hamarneh et al., 2021). Moreover, there is some evidence that the anti-inflammatory effects of statins may result in improvements in psoriasis (Socha et al., 2019), further prompting the hypothesis that earlier use of statins in patients with psoriasis may result in long-term changes in disease trajectory with amelioration of CV risk and psoriasis severity.

In conclusion, this small pilot study of statins in psoriasis provides evidence for the performance of future studies, which involve vascular imaging and refined mechanistic studies, including cell types of interest beyond venous sampling. Arterial endothelial cells as well as other myeloid cells should be tested for response to statin therapy while simultaneously evaluating multiple vascular beds of interest in CVD. Until then, this study does add to the body of literature supporting statin use in psoriasis and opens the door for deeper investigations.

ORCID
Nehal N. Mehta: http://orcid.org/0000-0003-4939-5130
Joel M. Gelfand: http://orcid.org/0000-0003-3480-2661

CONFLICT OF INTEREST
NNM is a full-time United States government employee and has served as a consultant for Amgen, Eli Lilly, and Leo Pharma, receiving grants/other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Astra Zeneca, Janssen Pharmaceuticals, Novartis, and Abcmena, receiving grants and/or research funding; and as a principal investigator for the National Institutes of Health, receiving grants and/or research funding. He is also a member of the Board of Directors for the American Society of Preventive Cardiology, receiving no honoraria. JMG served as a consultant for Abcmena, AbbVie, BMS, Boehringer Ingelheim, Celldex (DSMB), C2K, Happily, Lilly (DMC), Janssen Biologics, Novartis Corp, UCB (DSMB), Neuroderm (DSMB), Trevi, and Minder Dlx., receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania, Philadelphia, PA) from Boehringer Ingelheim and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by pharmaceutical sponsors. JMG is a copatent holder of resiquimod for the treatment of cutaneous T-cell lymphoma. JMG is a Deputy Editor for the Journal of Investigative Dermatology, receiving honoraria from the Society for Investigative Dermatology; is Chief Medical Editor for Healio Psoriatic Disease (receiving honoraria); and is a member of the Board of Directors for the International Psoriasis Council, receiving no honoraria.

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REFERENCES


