doi:10.36849/JDD.7082

BRIEF COMMUNICATION Journal of Drugs in Dermatology

Rethinking the Inflammatory Balance in Psoriasis and Atherosclerosis

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INTRODUCTION

Psoriasis and atherosclerosis have largely been understood as inflammatory diseases. While these two diseases have complex pathophysiologies, they both appear to be mixed Th1/Th17 cell-driven and tied together through the "psoriatic march". Broadly, the psoriatic march establishes a causal link between psoriasis and cardiovascular comorbidity through systemic inflammation and activation of inflammatory pathways that lead to insulin resistance, alterations in angiogenesis, endothelial dysfunction, and subsequent increased risk for atherosclerosis and future myocardial infarction (MI). The inflammatory link between psoriasis and cardiovascular disease may have important clinical implications.

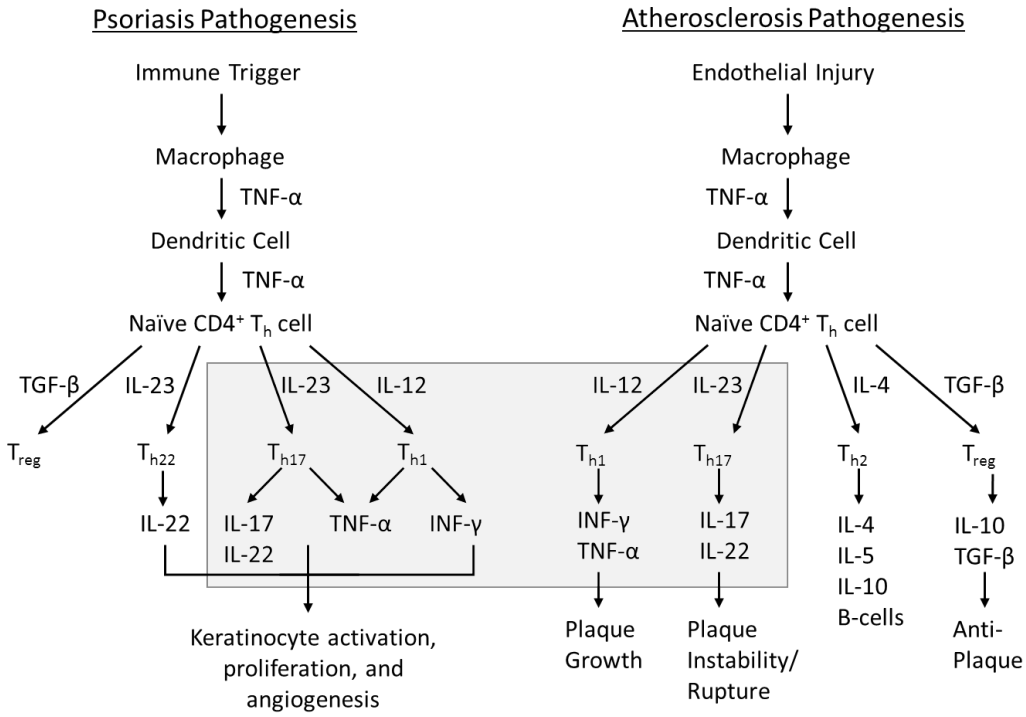
Consistent with the proposed shared pathophysiology, psoriasis is an independent risk factor for atherosclerotic heart disease (Figure 1). In 1978, McDonald and Calabresi linked psoriasis to an increased risk of arterial and venous vascular disease. Almost 30 years later, Gelfand et al. investigated psoriasis as an independent risk factor for MI, and the relative risk of MI was elevated most in young patients with severe forms of psoriasis. In other studies, psoriasis was not found to be an independent risk factor. The association may be confounded by the high rate of metabolic syndrome and obesity associated with psoriasis. Thus, it may be difficult to distinguish psoriasis from metabolic syndrome as an etiology of acute coronary syndrome. In addition, psoriasis drugs such as methotrexate, systemic retinoids, and cyclosporine have atherogenic effects. For example, cyclosporine can induce or worsen arterial hypertension and alter lipid metabolism, while retinoids may increase triglyceride levels.

The effect of psoriasis treatment on cardiovascular morbidity is not clear. In a systematic review investigating the impact of biological agents on cardiovascular disease in patients with psoriasis, there were no significant reductions in biomarkers of cardiovascular disease in patients treated with adalimumab or secukinumab compared to placebo. Adalimumab caused a strong reduction in CRP, TNF-α, IL-6, and GlycA without a decrease in aortic vascular inflammation.[1] In other studies, TNF-α inhibitors had neutral or reductive effects in cardiovascular disease.[2,3] Contradictory results may be explained by opposing signaling events triggered by TNF-α. TNF-α activates both TNFR1 and TNFR2, which lead to both cardiac disease and protection, respectively. TNF-α levels are increased in heart failure and contribute to atherogenesis, inflammatory gene induction, and vascular dysfunction. However, TNFR2 activation may activate the SAFE pathway which signals via JAK/STAT3 and leads to cardioprotective effects through the regulation of oxidative stress.[4] This may be evidenced by worsened heart failure with infliximab treatment.[5]

Cytokines may need to be rebalanced to reduce cardiovascular risk. Based on in vitro and in vivo studies, cytokines such as interleukin (IL)-17, have both pro-atherogenic and anti-atherogenic effects. IL-17 inhibition reduces psoriatic lesions; however, its effects on atherosclerosis is less clear. IL-17a-null mice have reduced atherosclerosis, and IL-17a blockade in ApoE-deficient mice reduces atherosclerosis, suggesting that IL-17 has pro-atherogenic effects.[6,7] Further, IL-17 increases production of pro-atherogenic IL-6, TNF-α and monocyte recruitment. In contrast, IL-17 blockade in human studies appears to have a neutral effect on atherosclerosis burden, implying that IL-17 may also have anti-atherogenic effects. This may be due to IL-17's protective effects on vascular plaque stability via stimulation of collagen type I production by smooth muscle cells. Thus, instead of adopting a global anti-inflammatory approach to reducing cardiovascular risk in psoriasis patients, it may be more useful to envision a fine balance of IL-17 to stabilize existing atherosclerotic plaques while concomitantly reducing the formation of new ones.

Given the opposing effects of many psoriasis-related cytokines in the pathogenesis of atherosclerosis, a non-dichotomous framework for cardiovascular risk reduction in psoriasis may be needed. To date, canakinumab, an IL-1ß inhibitor, is the

FIGURE 1. Psoriasis and aortic inflammation.



Convergence of pathophysiology of psoriasis and atherosclerosis.

only immune-modulating biologic that reduces cardiovascular events independent of lipid reduction. Thus, instead of a general reduction in inflammation, we should strive to identify how inflammation should be modulated to reduce cardiovascular risk. A deeper understanding of the clinical implications of cytokine balance in psoriasis and cardiovascular disease is critical to target and reduce potential morbidity and mortality in these patients.

DISCLOSURES

Steven R. Feldman has received research, speaking, and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. He is the founder and part owner of Causa Research and holds stock in Sensal Health. Authors Guénin, Kazemi, Cline, and Safai have no conflicts of interest to declare.

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