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Editorial

Does Interleukin-17A Blockade Have a Potential Clinical Role to Reduce Cardiovascular Risk in Psoriasis?

Subodh Verma, MD, PhD,[a] and Deepak L. Bhatt, MD, MPH[b]

[a] *Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, ON, Canada*

[b] *Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, USA*

***See article by Makavos* et al., *pages 100–111 of this issue*.**

Inflammation has emerged as an important pathophysiologic mechanism of atherosclerosis.[1-13] The innate and adaptive immune systems appear to modulate all phases of atherothrombosis, from early endothelial injury and plaque initiation, to more advanced atherosclerosis involving changes in autophagic/mitophagic flux[14,15] and plaque rupture. Additional studies have revealed an important cross-talk between inflammation and vascular repair and regeneration—an effect that appears to be transduced by increased levels of oxidative stress.[16,17] Markers of inflammation (notably high-sensitivity C-reactive protein [hsCRP]) have been shown to identify patients at heightened risk of atherosclerosis, and in whom additional risk-reduction strategies (eg, therapy with statins) may be valuable.[18,19] A causal role of inflammation in atherosclerosis has also been recently demonstrated in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial, in which the interleukin-1β antagonist canakinumab was studied in patients with a history of myocardial infarction.[5,20,21] This approach led to a significant reduction in the primary outcome of major adverse cardiovascular events. Importantly, this effect was observed with no changes in traditional risk factors (such as low-density lipoprotein cholesterol or blood pressure) and was augmented in those with higher baseline levels of hsCRP or with greater hsCRP reductions while on treatment, providing support for the idea that targeting inflammation (in this case via inhibition of the NLRP3 inflammasome) may be an independent pathway of vascular risk reduction.

If inflammation plays a primordial role in the pathogenesis of atherothrombotic cardiovascular disease, are systemic inflammatory conditions associated with increased vascular risk? Several studies have demonstrated a heightened risk of vascular events in patients with inflammatory diseases, such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.[22-25] Regarding psoriasis, numerous studies have confirmed a heightened risk of cardiovascular events in this population.[23-25] Systemic biomarkers of inflammation are increased in patients with psoriasis and correlate with the extent of vascular injury. For example, patients with severe psoriasis were reported to have a 3-fold higher risk compared with healthy individuals. In addition, Lerman et al. recently demonstrated a higher predominance of rupture-prone atherosclerotic plaques in patients with psoriasis.[26]

Interleukin (IL) 17A has been identified as a key cytokine driving psoriasis-induced inflammation. Intriguingly, this cytokine has also been implicated in the pathobiology of vascular disease.[27] IL-17A is produced by Th17 cells, which represent a subpopulation of the $CD4^+$ T-helper cells. It is believed that IL-17A can serve as an upstream stimulus for key atherogenic cytokines such as IL-1β, IL-6, tumour necrosis factor α, and nuclear factor-κB activator 1.[27] In this issue of the *Journal,* Makavos et al. report the results of a study evaluating the impact of IL-17A inhibition (with the use of secukinumab) on measures of cardiovascular function in patients with psoriasis.[28] The authors studied 150 patients with psoriasis who were treated with either secukinumab, cyclosporine, or methotrexate over a 12-month period. Patients were excluded if they had evidence of significant coronary artery disease, diabetes, ejection fraction $< 50\%$, a history of acute coronary syndrome, or ventricular wall motion abnormalities at baseline. Mean age was ~ 53 years, the majority of patients were male, with a psoriasis area and severity index disease-activity score of 13, and a disease duration of ~ 5 years. Secukinumab treatment (compared with cyclosporine or methotrexate) improved the following measures of cardiac function compared with cyclosporine or methotrexate: indices of global longitudinal strain, strain rate, strain rate at early diastole, and left ventricular twist. In addition, secukinumab improved coronary flow reserve (CFR), pulse-wave velocity (PWV), and measures of oxidative stress. In multivariate and mediation analyses, treatment with secukinumab remained independently associated with the benefits noted.

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Corresponding author: Dr Subodh Verma, Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, 8th Floor, Bond Wing, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. Tel.: +1-416-864-5997; fax: +1-416-864-5881.

E-mail: subodh.verma@unityhealth.to

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This study is one of the first to evaluate detailed cardiovascular function, microcirculatory reserve, and oxidative stress with the use of secukinumab in patients with psoriasis. The use of 2 control arms further strengthens the thesis that these effects are likely specific to IL-17A pathway inhibition as opposed to inflammatory pathways that are regulated by cyclosporine or methotrexate. Thus, it is reasonable to suggest that IL-17A blockade may mitigate cardiovascular risk in patients with psoriasis. However, the study methodology, which initially had a randomization to either secukinumab or cyclosporine, with a nonrandomized group of methotrexate patients serving as a standalone control, does limit between-group comparisons to some extent. Furthermore, it would have been desirable to report conventional circulating measures of inflammation (such as hsCRP, IL-6, or IL-1β) in response to treatment. Whether patients with higher baseline levels of inflammation had a greater improvement in cardiac structure, CFR, and PWV also remains an important and unanswered question. The exclusion of patients with diabetes and significant coronary artery disease is a limitation. Finally, a recently completed randomized double-blind study failed to demonstrate an effect of secukinumab on the primary outcome of flow-mediated vasodilation (a surrogate for endothelial function)[29] or biomarkers of inflammation.

In conclusion, we congratulate the authors for presenting an important paper that provides translational insights into the general link between inflammation and cardiovascular risk and specifically the role of IL-17A in the pathophysiology of both diseases. Although the results provide surrogate evidence of cardiovascular benefit, larger studies with hard ischemic events are required to be confident whether these signals translate into reduced rates of vascular disease and heart failure. Antiinflammatory agents with preclinical and surrogate evidence of benefit (such as methotrexate)[30] did not demonstrate efficacy in larger clinical trials,[31] and other agents (such as colchicine) have shown initial success and are being evaluated further for their cardiovascular efficacy in secondary prevention.[32,33]

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Disclosures

See Supplemental Appendix S1 for disclosures.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.11.011.