Psoriasis – More Than Just Skin Deep

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Psoriasis is a common inflammatory condition involving the skin, scalp, nails and joints. It significantly increases the risk of cardiovascular events and death in those affected, above Framingham Risk Score (FRS) prediction alone[1]. There is a dose-response element; those with the most severe psoriasis (assessed by the psoriasis area severity index (PASI) score) are at the greatest risk. A UK study estimated the excess risk as being equivalent to having a diagnosis of diabetes[2]. Psoriasis often becomes apparent at a young age, exposing patients to higher risk for several decades. This translates into a lifetime excess of cardiovascular mortality of approximately 2[3].

Psoriasis and atherosclerosis share many pathological pathways. These include T-helper cell activation, an excess of Th-1 cytokines and imbalances in the interleukin 1 pathway favoring inflammation[4]. As well as driving atherothrombosis, there is evidence that psoriasis patients have an excess of both aortic valve stenosis and arterial stiffening, both conditions believed to have inflammatory bases[5,6].

In this edition of ATVB, Naik and colleagues (Naik et al), measured vascular inflammation in a group of 60 subjects with mild to moderate psoriasis and compared their findings to control subjects. They hypothesised that the extent of vascular inflammation, quantified with FDG PET imaging, would be related to the severity of psoriasis, estimated by the PASI score. They also gathered evidence in support of their belief that the well-recognised links between psoriasis and vascular disease might be mediated by inflammation via neutrophils. The recruits were relatively young, although they had suffered psoriasis for a median of 20 years. Many were already receiving systemic psoriasis therapy at the time of PET imaging. Overall, the group was classified as low-risk according to FRS. Their findings were instructive. First, FDG uptake was greater in psoriasis patients than controls, with TBR values suggestive of at least moderate arterial inflammation[7]. Psoriasis severity was significantly positively associated with vascular inflammation, even after adjusting for FRS and CRP levels. Supportive of their second hypothesis, psoriasis patients had significantly higher levels of neutrophil-

associated cytokines than control subjects, and in particular, S100A8/A9 (an endogenous TLR4 activator protein binding complex) was related to both psoriasis severity and arterial inflammation.

FDG PET has been used to measure vascular inflammation in many inflammatory conditions, including rheumatoid disease (where it also demonstrated that systemic therapy lowered vascular inflammation)[8], chronic obstructive pulmonary disease[9] and, most widely atherosclerosis, where it highlighted the beneficial effects of statin therapy on the vessel wall[10] and can predict clinical events[11]. Because FDG accumulation and retention within the vessel wall reflects glucose usage, many cell types located there can influence the final signal. In the hypoxic atherosclerotic plaque micro-environment, macrophages predominate[12], particularly once activated[13]. In psoriasis, the cell type responsible for vascular FDG uptake is unknown.

Does systemic psoriasis therapy influence surrogate markers of cardiovascular risk? In a small study that recruited patients with severe psoriasis and measured carotid and brachial arterial intima-media thickness (IMT), therapy with etanercept, infliximab or adalimumab did result in significant regression of IMT measurements, but this was restricted to those without established atherosclerosis at baseline[14]. Bissonnette and colleagues[15], used vascular FDG PET as a marker of inflammation, but failed to meet their primary endpoint in a larger, randomised study with the potent anti-inflammatory drug adalimumab. Interestingly, a retrospective study by Prodanovich et al. showed that patients with psoriasis treated with methotrexate had decreased rates of vascular disease when compared to controls[16]. It will be instructive to see whether the same holds true in the Cardiovascular Inflammation Reduction Trial that will randomly allocate 7,000 patients with prior myocardial infarction and either type 2 diabetes or the metabolic syndrome to low-dose methotrexate or placebo over an average follow-up period of 3 to 5 years[17].

Summary

This work extends the use of imaging to uncover potentially important links between two, on the face of it, very different conditions. It seems plausible, that, as the authors suggest, smouldering skin lesions produce inflammatory cytokines that can trigger remote inflammation. This has recently been reported[18], albeit in reverse, after myocardial infarction, where global inflammation is up-regulated after an acute coronary syndrome putting patients at high risk of recurrent events[19]. Naik et al's study was cross-sectional, and, as acknowledged by the authors, their hypotheses need to be confirmed or refuted by ongoing longitudinal studies to prove cause and effect.

In terms of psoriasis management, their study elegantly illustrates the paradox of significant vascular inflammation yet low Framingham scores and provides an explanation for it via neutrophil-mediated inflammation. Whether psoriasis patients should undergo testing for subclinical atherosclerosis[20] or receive aggressive statin therapy is not known, but the case is strengthened by this paper. By providing mechanistic insights between psoriasis and atherosclerotic inflammation, this study

suggests new therapeutic targets that could be exploited to lower the excessive cardiovascular disease burden that these patients experience.

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