

Psoriasis and atherosclerosis: two plaques, one syndrome?

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This editorial refers to ‘Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study’[†], by O. Ahlehoff *et al.*, on page 2054

Psoriasis is a chronic inflammatory disease affecting up to 2% of the global population. While the pathogenesis of psoriasis is not fully understood yet, an increasing body of evidence suggests a genetic predisposition and an environmental component. The most common manifestations are papulosquamous plaques symmetrically located on extensor surfaces of the joints. While most psoriasis patients report that their skin manifestations have a negative impact on their quality of life, psoriasis is not just a skin disease. Indeed, similarly to other systemic inflammatory diseases, inflammation is widespread in psoriasis, and arthritis is found in up to a quarter of patients and precedes the disease in 10% of the patients.¹ Importantly, life expectancy is reduced in psoriasis by up to 4 years, which has been attributed to a higher incidence of cardiovascular diseases.²

Ahlehoff *et al.* now report an association of psoriasis with increased risk of atrial fibrillation and ischaemic stroke.³ The authors analysed 36 765 patients with mild and 2793 patients with severe psoriasis and compared these with > 4 million individuals of a nationwide Danish registry. Indeed, several important pieces of information can be retrieved from this study. First, the study is a further epidemiological milestone in delineating the associated risk of not only severe but also mild psoriasis with vascular disease. Secondly, the study demonstrates a considerably elevated risk not only for cardiovascular disease *per se* but also for atrial fibrillation and ischaemic stroke, in particular. While confounding and misclassification might be a concern in any registry-based study, the authors provide further evidence that psoriasis is not just a skin disease, but indeed a systemic disease. Notwithstanding that patients with psoriasis have a high prevalence of cardiovascular

risk factors, such as smoking, dyslipidaemia, hypertension, obesity, and insulin resistance, systemic inflammation beyond the skin may provide an explanation for the increased cardiovascular risk observed in psoriasis.¹

Psoriasis shares striking similarities with other systemic inflammatory diseases, such as rheumatoid arthritis and atherosclerosis. Intriguingly, the typical histological features of the psoriatic plaque with dermal inflammation and leucocyte infiltration are similar to those of the atherosclerotic plaque (*Figure 1*).⁴ In atherosclerosis, psoriasis, and rheumatoid arthritis, the activation of the innate immune system starts an inflammatory cascade, particularly involving T helper 1, T helper 17, regulatory T cells, and downstream expression of cytokines.⁵ Inflammation induced by psoriasis also impacts on insulin resistance, both of which are important surrogates for early, subclinical atherosclerosis and prognostic markers for cardiovascular disease, and may alter the function of endothelial cells, resulting in a propensity towards endothelial dysfunction and early structural changes of the arterial wall. Indeed, several studies demonstrated impaired endothelial function and increased intima-media thickness in patients with psoriasis.⁶

Does atrial fibrillation fit into the story of psoriasis being a systemic inflammatory disease? Recent studies established chronic inflammation as a risk factor for atrial fibrillation⁷ which is of particular clinical relevance as inflammation might contribute to the prothrombotic state of atrial fibrillation and its clinical sequelae.⁸ Remarkably, Ahlehoff and colleagues also reported an increased rate of venous thrombo-embolism in their cohort of psoriasis patients.⁹

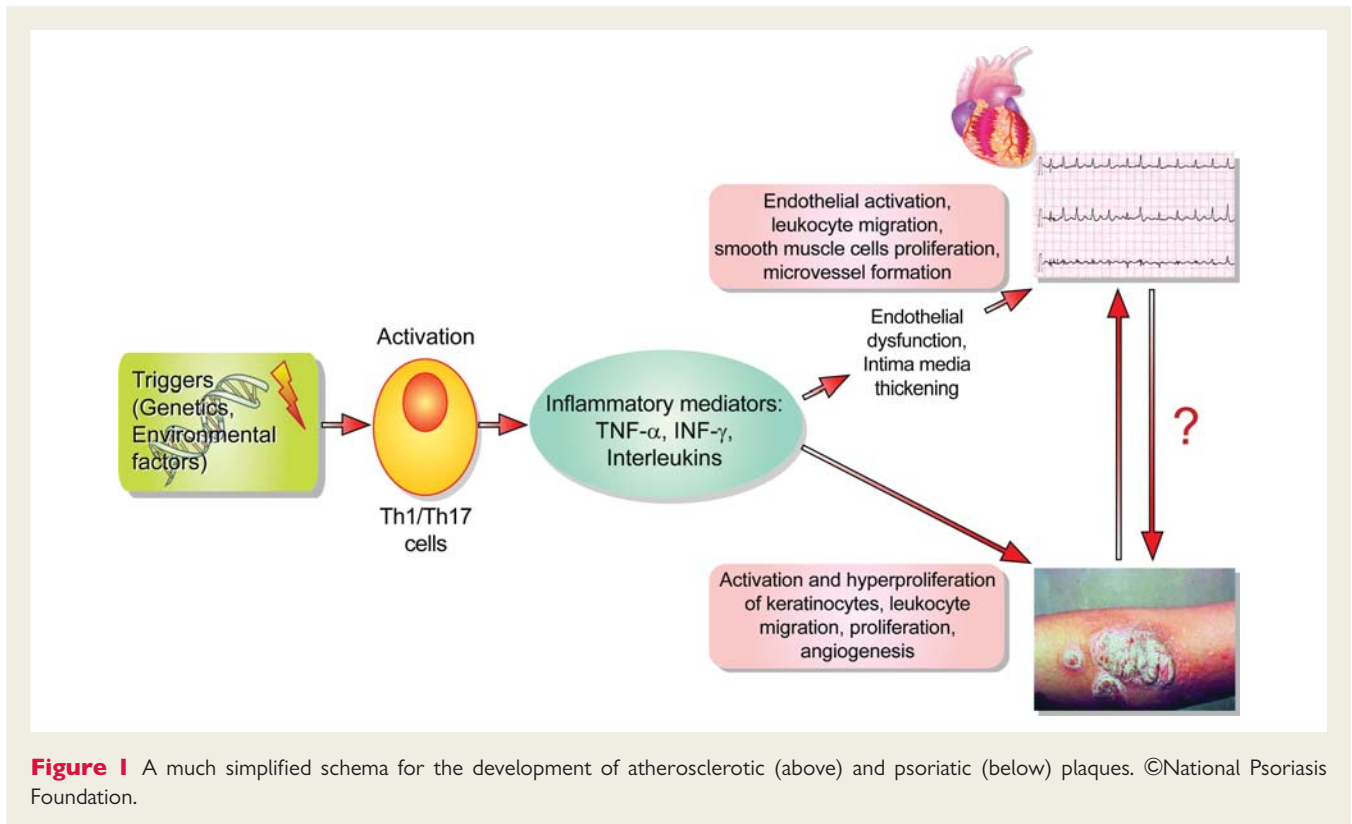
Since the study of Ahlehoff *et al.*³ adds to the increasing evidence of increased cardiovascular risk in patients with chronic inflammatory diseases, patients with psoriasis should be informed by their treating physician that they may have an increased chance of cardiovascular disease. This, however, begs two

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important questions with regard to potential therapeutical implications. First, should we be more aggressive in treating risk factors in these patients, and secondly should we specifically target inflammation? Risk factors should be assessed, and lifestyle interventions and pharmaceuticals prescribed as appropriate.¹⁰ Since LDL levels are elevated and correlate with the severity of psoriasis,¹¹ initiation of statins should be considered, and goals for LDL cholesterol levels should be based on cardiovascular risk assessment. Close monitoring of liver function and creatine kinase are mandatory, especially in patients receiving immunosuppressive drugs, to avoid liver toxicity and rhabdomyolysis. In addition to their well-documented LDL-lowering effects, statins exert additional pleiotropic, anti-inflammatory effects, that may contribute to the improvement of endothelial function demonstrated in patients with atherosclerotic vascular disease as well as in patients with rheumatoid arthritis, especially in those with high levels of systemic inflammation.¹² Intriguingly, cardiovascular treatment aimed at preventing and treating atherosclerosis may also be beneficial in reducing psoriasis disease severity, as statins reduced psoriatic cutaneous plaque activity.¹³ While many patients with psoriasis present with low HDL levels,¹¹ there is currently no indication for niacin and fibrates in patients with psoriasis, especially as both of these drugs are associated with a worrisome higher rate of side effects in patients with systemic inflammatory diseases.

In patients with psoriasis and elevated blood pressure, lifestyle changes should be implemented, and calcium antagonists, thiazide diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) may represent the drugs of first choice. ACEIs also exert anti-inflammatory and antioxidative effects, and are similarly effective

as statins in improving endothelial dysfunction in rheumatoid arthritis.¹⁴ In contrast, beta-blockers should be prescribed with caution since they are reported to be associated with the exacerbation of psoriasis. While patients with systemic inflammatory disease have not been included in previous cardiovascular outcome trials, aggressive management of conventional cardiovascular risk factors seems prudent in patients with systemic inflammatory disease who show an increased cardiovascular risk similar to that of diabetics.

The benefit of any specific anti-inflammatory therapy, however, still remains to be established. In fact, anti-inflammatory drugs might be double-edged, especially non-steroidal anti-inflammatory drugs (NSAIDs) that are commonly used in psoriatic arthritis. Their anti-inflammatory and analgesic effects notwithstanding, NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors increase blood pressure and cardiovascular risk.¹⁵ Their blood pressure-raising effects must not be underestimated—notably an effect is even observed with paracetamol (acetaminophen)¹⁶—as hypertension has well known effects on the incidence of atrial fibrillation and stroke. As such, we are facing a dilemma when trying specifically to target systemic inflammation. While anti-inflammatory drugs have the potential to provide benefit through targeting inflammation, they may exert potent off-target effects. This is even more problematic in severely symptomatic patients receiving immunosuppressive drugs, since corticosteroids and ciclosporin not only increase blood pressure, but also worsen dyslipidaemia, all further enhancing cardio- and cerebrovascular risk. This true equipoise is further documented by observational studies demonstrating beneficial cardiovascular effects of low-dose

methotrexate.¹⁷ This sets the stage for cardiovascular outcome trials with methotrexate currently under way, and will provide the answer as to whether this anti-inflammatory and immunomodulatory drug will improve survival in high-risk cardiovascular patients.

Novel biologics, such as tumour necrosis factor- α (TNF- α) inhibitors have proven to be highly effective in the treatment of psoriasis and other inflammatory diseases. The first evidence of whether potent anti-inflammatory treatment would not only alleviate symptoms but also impact on cardiovascular surrogates came from studies demonstrating that TNF- α suppression improved vascular function in patients with rheumatoid arthritis¹⁸ and may have a beneficial impact on carotid intima-media thickness in psoriasis.¹⁹ Whether TNF- α blockade might beneficially impact on cardiovascular morbidity and mortality in patients at increased risk because of systemic inflammatory disease, however, still remains to be determined.

Novel targeted biological agents for the treatment of psoriasis are on the horizon, among them several monoclonal anti-interleukin antibodies such as briakinumab, ustekinumab, and tocilizumab. Due to the shared immunological mechanisms between psoriasis (and other inflammatory diseases) and atherosclerosis, they may hold the potential for the treatment of both diseases,⁴ but randomized clinical trials addressing efficacy and safety are yet to be performed.

Taken together, the study of Ahlehoff *et al.*³ adds to the increasing body of evidence of an association between psoriasis and cardio- and cerebrovascular diseases. Although inflammation in these patients may not be limited to skin and joints, but indeed be widespread throughout the vascular tree, there is an unmet need for further research and outcome trials in this field. As a consequence for clinicians, psoriasis patients, particularly those with moderate or severe forms, should not only be treated for skin lesions and arthritis but also rigorously screened for vascular risk factors, especially as these patients are often young and could therefore profit most when preventive strategies are implemented early.¹⁰ In the future, large-scale randomized clinical trials are needed to define whether patients with systemic inflammatory diseases such as psoriasis will benefit from aggressive risk factor control and/or anti-inflammatory treatment.

This would be of particular interest for our specialty, as the benefit of a specific anti-inflammatory treatment has yet to be established in the systemic inflammatory disease we care about the most—atherosclerosis.

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