From the Medical Board of the National Psoriasis Foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies

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Background: Many studies have identified cardiovascular risk factors in patients with psoriasis. Some psoriasis therapies may increase cardiovascular disease (CVD) and others may decrease CVD.

Objective: We reviewed the literature to define the impact of common psoriasis therapies on cardiovascular measures and outcomes.

Results: Phototherapy has no major cardiovascular impact and may reduce levels of proinflammatory cytokines. Acitretin increases serum lipids and triglycerides, but has not been shown to increase cardiovascular risk. Cyclosporine A increases blood pressure, serum triglycerides, and total cholesterol. Methotrexate is associated with a decreased risk of CVD morbidity and mortality. Among the biologics, data for tumor necrosis factor inhibitors suggest an overall reduction in cardiovascular events. Most data on short-term ustekinumab use suggest no effect on major adverse cardiovascular events, however some authorities remain concerned. Nevertheless, ustekinumab use over a 4-year period shows a decrease in major adverse cardiovascular events when compared both with the general US population and with psoriatics in Great Britain.

Limitations: Most studies lack the power and randomization of large clinical trials and long-term follow-up periods. In addition, the increased risk of CVD associated with psoriasis itself is a confounding factor.

Conclusion: Some therapies for moderate to severe psoriasis, including methotrexate and tumor necrosis factor inhibitors, may reduce cardiovascular events in psoriatic patients. Ustekinumab appears to be neutral but there may be a long-term benefit. Appropriate patient counseling and selection and
Psoriasis is a chronic disorder in which elevated levels of inflammatory biomarkers have been demonstrated. Psoriasis and psoriatic arthritis (PsA) are both immune-mediated inflammatory disorders, similar to rheumatoid arthritis (RA). It has been proposed that this chronic inflammatory state may cause increased risk for cardiovascular disease (CVD) such as atherosclerosis, myocardial infarction (MI), and stroke, and CVD risk factors may be underdiagnosed and undertreated. The concept of the “psoriatic march” reflects that this systemic condition triggers a cascade of inflammatory events that leads to these disease states.

Studies have evaluated the effect of psoriatic therapies on cardiovascular risk factors and outcomes in these patients. This article comprehensively reviews the current literature regarding the impact of systemic treatments on CVD.

ASSOCIATION OF THE PSORIATIC DISEASE STATE AND CVD

In 1995, the association of psoriasis with diabetes mellitus (DM), obesity, heart failure, and hypertension (HTN) was first observed. Since then, cardiovascular risk factors have been demonstrated in numerous studies. In fact, some reports suggest psoriasis is an independent risk factor for cardiovascular morbidity. Patients with psoriasis may have a predisposition to DM and HTN, and several studies have shown higher rates of DM, HTN, hyperlipidemia, smoking, obesity, and metabolic syndrome. It has been suggested that chronic inflammation from psoriasis may cause insulin resistance, and thus systemic treatment may help in preventing a prediabetic state.

Although cardiovascular risk in patients with mild psoriasis may be relatively small, it increases with severity of disease. Disease severity has been linked to a higher prevalence of these risk factors with higher rates noted in approximately 25% of patients who require systemic therapies. A study of patients with severe psoriasis requiring inpatient admission found that their drug-treated HTN was higher than in matched cohorts.

There is, however, conflicting evidence as to whether psoriasis is associated with increased cardiovascular outcomes. A large cohort study found no difference in risk of ischemic heart disease hospitalizations in patients with psoriasis compared with matched control subjects; however, this study has been noted to have possible misclassification bias, indeterminate statistical power, and questionable age stratification for outcomes. Stern and Huibregtse found that patients with very severe psoriasis have increased all-cause mortality, but severe psoriasis was not an independent risk factor for CVD. Another large study found no significant increase in risk of MI, stroke, or transient ischemic attack in patients with psoriasis, although when adjusted for age, there was a suggestion of increased MI risk for patients younger than 60 years.

However, there are numerous studies that support the association of psoriasis and CVD. Psoriasis has been found to be associated with increased risk of atrial fibrillation, ischemic stroke, and venous thromboembolism. These patients have an increased risk of atherosclerosis and diabetes, more frequent and pronounced coronary artery calcification, and lower coronary flow reserve. The disease is independently associated with higher rates of coronary artery disease at cardiac catheterization. Of note, there are possible overlapping immune pathways in both psoriasis and CVD.

Gelfand et al found that psoriasis confers risk for MI independent of traditional risk factors, especially strong in young patients, and 1 study suggests that patients with psoriasis have a worse prognosis after first MI. Furthermore, Prodanovich et al report a higher prevalence of ischemic heart, cerebrovascular,
and peripheral vascular diseases in patients with psoriasis. Mehta et al. similarly reported an increased risk of cardiovascular-related mortality associated with psoriasis independent of traditional CVD risk factors. In addition, another study found increased CVD risk and overall mortality. Abuabara et al. found patients with psoriasis to have a 6-year decrease in life expectancy; CVD was the most common cause of death.

Despite the observed association of psoriasis and CVD, a high proportion of patients with psoriasis entering trials for systemic therapy were lacking any or appropriate treatment for DM, HTN, and hyperlipidemia. A recent study reported that severe psoriasis confers an attributable risk of 6.2% on the 10-year incidence of major adverse cardiac events.

Proinflammatory cytokines in both psoriasis and atherosclerosis

Inflammation plays a prominent role in the pathogenesis of both psoriasis and atherosclerosis. Both diseases are characterized by T helper (Th)1 cytokines such as interferon-γ, tumor necrosis factor (TNF)-alfa, and interleukin (IL)-2. Interferon-γ and TNF-alfa stimulate keratinocytes to produce IL-6, IL-7, IL-8, IL-12, IL-15, and IL-18, and interferon-γ can stimulate the expression of major histocompatibility complex (MHC) class II molecules and intracellular adhesion molecule (ICAM)-1. In addition, vascular endothelial growth factor (VEGF) plays a vital role in angiogenesis, which occurs in both psoriasis and atherosclerosis.

Association of therapeutic modalities and CVD

Given the increased risk of CVD, an area of interest has been evaluating how therapeutic modalities might modulate cardiovascular risk.

Phototherapy

In 1 study, both narrowband ultraviolet (UV)-B therapy and psoralen plus UVA (PUVA) treatment gave, at week 3, a significant decrease in TNF-alfa and IL-23; IL-22 and IL-17 decreased significantly at week 6. PUVA, after 12 weeks, was found to produce a significant decrease in inflammatory cytokines and growth factors including IL-23, IL-17, and TNF-alfa. PUVA has also been shown to decrease serum levels of lipoprotein(a) but also produced an almost significant increase in apolipoprotein-B.

PUVA therapy has been reported to increase heart rate, but this may be decreased with air conditioning. Multiple studies in both PUVA and narrowband UVB therapy have failed to document notable cardiac side effects.

Systemic retinoids

Retinoids increase serum triglycerides and cholesterol, specifically by shifting high-density lipoproteins to low-density lipoproteins. One study found that acitretin caused a dose-dependent elevation in serum triglycerides and cholesterol, but this is well managed with diet and dose changes. One study showed no increase in risk of CVD with use of etretinate in patients with psoriasis.

Cyclosporine

Cyclosporine has been shown to generate reactive oxygen species and cause cell death in myocardium. It has also been shown to inhibit VEGF-dependent migration of endothelial cells and angiogenesis. However, cyclosporine is cardio-protective against reperfusion injury after MI, and reduces infarct size in animal models.

A review evaluating cyclosporine found a statistically significant increase in blood pressure (BP) in a dose-dependent fashion. Increased levels of serum triglycerides and total cholesterol were observed after 2 weeks of treatment in patients with psoriasis, and remained elevated with continued use.

Mycophenolate mofetil

In patients with pre-existing essential HTN and either psoriasis or RA, mycophenolate mofetil decreased systolic, diastolic, and mean BP. Mycophenolate mofetil treatment for 2.5 weeks decreases inflammation in carotid artery plaques. Mycophenolate mofetil exerts anti-inflammatory effects implicated in atherosclerotic plaques, and may also decrease platelet aggregation.
**Methotrexate**

In mouse models, methotrexate (MTX) decreases levels of cytokines IL-6 and TNF-alfa. Both patients with RA and psoriasis have elevated baseline homocysteine levels, associated with an increased risk of vascular disease.

Westlake et al. performed a review to determine whether MTX affects the risk of CVD in RA. Two large cohort studies in RA suggested that MTX is associated with reduced risk of cardiovascular mortality. Five studies showed evidence that the use of MTX decreased all-cause CVD morbidity including CVD, cerebrovascular disease, and atherosclerosis. One study showed a significant decrease in risk of congestive heart failure (CHF). The authors concluded that MTX use in patients with RA is associated with decreased risk of CVD morbidity and mortality.

One meta-analysis investigated the relationship of MTX and CVD. Although some studies reviewed overlapped with Westlake et al., it evaluated the heterogeneity among studies and quantified the effects of MTX on CVD. Ten observational studies were identified mainly in the RA population; only 1 included patients with psoriasis. MTX was associated with a 21% lower risk for total CVD and 18% lower risk for MI.

In contrast to these findings, a recent retrospective cohort study in patients with psoriasis and PsA found comparable rates of ischemic heart disease hospitalizations in those taking MTX versus other nonbiologic treatments.

**ASSOCIATION OF BIOLOGIC THERAPIES AND CVD**

**TNF-alfa inhibitors**

**Biomarkers of inflammation.** Treatment with TNF inhibitors (TNFi) has been shown to modify C-reactive protein, adiponectin, VEGF, and resistin. C-reactive protein is a predictor of CVD such as MI, peripheral arterial disease, and sudden cardiac death. Adiponectin has anti-inflammatory, antiatherogenic, and antioxidant properties, and VEGF may reflect inflammation and hypoxia such as in acute MI, and resistin is related to insulin resistance. Etanercept was shown to decrease levels of C-reactive protein in psoriasis and PsA after 24 weeks of treatment. There are varying results regarding the effect that TNFi have on adiponectin levels, but the largest studies suggests no association.

In the PRISTINE trial, etanercept showed no significant effects on biomarkers of cardiometabolic risk.

**Vascularity.** Studies have indicated an improvement in endothelial function upon initiation of anti–TNF therapy for RA, although only a transient improvement has been reported in some studies.

**Metabolic syndrome.** One retrospective study found that patients with RA and psoriasis receiving TNFi or hydroxychloroquine had lower risk of developing DM compared with other treatments. Etanercept has improved fasting glucose; this corresponds with previous findings that TNFi improves insulin resistance.

In a review of TNFi, an improvement in insulin resistance was reported. The effect on serum lipid levels is unclear, but there is likely no effect. In patients with RA, however, infliximab may have a short-term antiatherogenic effect. In comparison, etanercept may be less atherogenic overall as it inhibits lymphotoxin-α.

Other studies of patients with RA on TNFi have reported increases in total cholesterol and high-density lipoprotein cholesterol levels.

**Atherosclerosis.** Increased carotid intima-media thickness and arterial stiffness are independent predictors of CVD and TNFi have been shown to affect both. Treatment with TNFi in PsA decreased evidence of atherosclerosis, as measured by carotid intima-media thickness. With continuous treatment, this effect was sustained after 2 years. A larger study found that patients with PsA treated with TNFi had a lower carotid intima-media thickness, compared with traditional disease-modifying antirheumatic drugs (DMARDs). Angel et al measured arterial stiffness in patients with ankylosing spondylitis, RA, and PsA and found those receiving TNFi had a lower arterial stiffness after 3 months. Reports in patients with RA both support and refute these findings.

**Myocardial infarction.** A large cohort study compared use of systemic treatments to UVB; there was no significant difference in overall MI risk. In patients with RA, TNFi-treated patients were not found to have a lower incidence of MI compared with traditional DMARD therapy. However, when subjects were stratified by TNFi response, the risk of MI was significantly reduced in responders.

One study found a lower incidence of first cardiovascular events in patients with RA treated with TNFi. A meta-analysis investigating biologic therapies and CVD events found no significant difference in the rate of major adverse cardiovascular events (MACE), including MI, with TNFi.

Greenberg et al. examined the association of cardiovascular events with TNFi compared with DMARDs in RA. The primary study outcome was a composite of nonfatal MI, transient ischemic attack, or stroke and cardiovascular-related death. After
adjusting for age, gender, cardiovascular risk factors, and RA disease characteristics, TNFi reduced risk of the primary end point, compared with DMARDs. 130

Specifically in psoriasis, Wu et al. 131 assessed whether TNFi decreased risk of MI. Of 8845 patients, 1673 received a TNFi for at least 2 months, 2097 were naïve to TNFi and received other systemic agents or phototherapy, and 5075 were not treated with TNFi, other systemic therapies, or phototherapy. The incidence of MI in the TNFi, oral/phototherapy, and topical cohorts were 3.05, 3.85, and 6.73 per 1000 patient-years, respectively. The authors concluded that TNFi were associated with significant reduction in MI risk and incident rate compared with topicals. TNFi was associated with a nonstatistically significant lower MI incident rate compared with oral agents/phototherapy. 131

Heart failure. Heart failure is a well-known concern in TNFi therapy. Infliximab therapy of CHF was shown to increase hospitalizations, morbidity, and mortality, and is contraindicated in moderate to severe CHF, whereas etanercept did not demonstrate these effects. 132 In an analysis of etanercept in psoriasis, heart failure was rare, and increased risk was not demonstrated. 133 In a meta-analysis by Singh et al., 134 the rate of CHF was not statistically significantly different between biologics and controls.

Venous thromboembolism. Although previous data have been conflicting regarding the association of venous thromboembolism with anti-TNF therapy, 135,136 a recent study suggests that TNFi therapy is not associated with increased risk of venous thromboembolism in RA. 137

Mortality. A prospective cohort study in RA looked at all-cause mortality for those receiving DMARDs compared with TNFi. 138 There was no significant difference in mortality between groups. Two previous studies showed reduction in mortality, but these were small with potential confounding factors. 139,140

IL-12/23 inhibitors

Although IL-12 and IL-23 play important roles in the pathogenesis of psoriasis, 141 they have been implicated as potential mediators in atherogenesis. 142 Administration of IL-12 in murine models may also promote atherogenesis, 143 whereas inhibition may prevent atherosclerosis. 144

The IL-12/23 inhibitors studied include ustekinumab and briakinumab. Concern was expressed over initial analyses possibly linking briakinumab with MACE, 145,146 which led to discontinuation of all briakinumab trials in 2011. These initial analyses led to further studies to evaluate risk of MACE with this class.

A meta-analysis of controlled trials of ustekinumab or briakinumab was performed and evaluated association of MACE defined as MI, cerebrovascular accident, or cardiovascular death. 129 Although 10 MACE occurred in 3179 patients treated with IL-12/23 inhibitors, and none in 1474 placebo-treated patients, there was no statistically significant increase in the risk of MACE.

Reich et al. 147,148 demonstrated similar findings in 2 studies: 1 found no increase in MACE with up to 4 years of ustekinumab use; 147 the second found that ustekinumab confers neither a beneficial nor detrimental effect. 148 In the first study, rates of MACE showed year-to-year variability but no increasing trend over time. Cumulative rates of 0.56 and 0.46 events per 100 patient-years were reported in the 45-mg and 90-mg groups, respectively. Rates of MI or stroke were thought to be consistent expected rates in the general and psoriasis populations based on established models. 147

Therefore, most of the data on short-term use of ustekinumab suggest no positive or negative effect on occurrence of MACE, however, some authorities remain concerned. On the other hand, ustekinumab use over a 4-year period shows a clear decrease in MACE when compared with the general US population and when compared with psoriasis in Great Britain. 147

There are known limitations to the study of Ryan et al. 129; they include a lack of access to patient-level data, small number of cases of MACE, and short duration of each randomized controlled trial. It remains possible that the study may be underpowered, and therefore cannot fully determine if the IL-12/23 inhibitors increase CVD risk.

CONCLUSION

Currently, there is not enough evidence to recommend therapies for psoriasis solely based on cardiovascular impact. However, if systemic therapy is a consideration in the setting of CVD or risk, it would appear that, based on current data, TNFi and MTX offer the best evidence of benefit. As the initial clinician seen for most cases of psoriasis, the dermatologist should actively screen patients with severe disease for cardiovascular risk factors and provide appropriate counseling, treatment, referral, or a combination of these. 149

The National Psoriasis Foundation recommends the following: BP, pulse, and body mass index measurements every 2 years; fasting blood glucose and lipid levels every 5 years or every 2 years if patient has additional risk factors; and assessment of joint status at every visit. 150
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