Psoriasis, Biologics, and Cardiovascular Disease: The Heart of the Matter

A relationship between increased cardiovascular events in patients with psoriasis has implications for management of this chronic disease.

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Since the association between occlusive vascular disease and psoriasis was proposed in the 1970s, a myriad of epidemiological studies has confirmed a relationship between psoriatic inflammation, namely psoriasis and psoriatic arthritis, and adverse cardiovascular events. This relationship is complex and was considered initially to be due to the higher prevalence of preexisting underlying cardiovascular risk factors in such patients. Psoriasis patients are often obese and have concomitant dyslipidemia, insulin resistance, and hypertension—all components of metabolic syndrome. Such patients are more likely to be smokers, consume alcohol, and have higher plasma homocysteine levels, which is an independent risk factor for cardiovascular disease. Up to 30 percent of patients with psoriasis have concomitant psoriatic arthritis, increasing their risk of cardiovascular disease, similar to other inflammatory arthritides. However, psoriatic inflammation remains an independent risk factor for cardiovascular disease even after adjusting for preexisting cardiovascular risk factors.

Additional findings on psoriasis comorbidities report age and sex disparities in cardiovascular risk factors compared to the general population. Women with psoriasis tend to have a higher prevalence of metabolic syndrome than men. However, younger males with psoriasis are at higher risk for cardiovascular disease compared to the general population and even to older hyperlipidemic patients. Research prompted by these findings into the molecular pathophysiology of psoriasis and atherosclerosis shows common inflammatory pathways for both disease states. In a United Kingdom population-based study, severe psoriasis correlated with a 6.2 percent increase in major adverse cardiovascular events (MACEs) over 10 years. Subsequently, current data validates a well-established association between psoriasis and psoriatic arthritis as independent risk factors for cardiovascular disease and atherosclerosis, as well as mortality due to coronary heart disease.

The recognition of a relationship between increased cardiovascular events and patients with psoriasis presents a critical need for improved treatment and management of psoriasis with special attention to comorbidities. Severe psoriasis with involvement of greater than 10 percent body surface area decreases a patient’s life span by as many as three to four years. Given the common underlying inflammatory pathways found in psoriatic cutaneous plaques and atherosclerotic plaques, one could conclude that treatment of the skin may ameliorate MACEs in psoriasis. However, conventional psoriasis treatments have various unfavorable cardiovascular side effects. Methotrexate therapy, for example, is associated with increased homocysteine levels. This effect may be reduced with concomitant use of folic acid. Cyclosporin can increase blood pressure, triglycerides, and cholesterol levels depending on the dosage and duration of therapy. Similarly, increased triglyceride and cholesterol levels have been reported with acitretin therapy.

In patients with severe psoriasis with involvement of greater than 10 percent body surface, life span may be decreased by as much as three to four years. Current data not only point to the efficacy of biologic therapy in reducing cardiovascular disease, but also their safety in psoriatic patients, both in regards to MACEs and congestive heart failure.

**the bottomline**
The advent of biologic treatments, such as inhibitors of tumor necrosis factor-alpha (TNF-α) and interleukins (IL)-12/23, IL-17, and IL-23, has revolutionized the management of psoriasis from an immunological perspective. The efficacy of these treatments in skin disease is highly desirable. Multiple studies have depicted a decrease in cardiovascular events in psoriatic patients treated with biologics compared to patients not treated with systemic therapies or topicals only.20-22 Furthermore, comparisons of different systemic therapies have shown an overall favorable effect on cardiovascular events with biologic therapies.23 There is ongoing research into comparisons of various systemic therapies and their effects on cardiovascular risk reduction. Current data point to the efficacy of biologic therapy in reducing cardiovascular disease, as well as their safety in psoriatic patients, both in regards to MACEs and congestive heart failure.22 We provide a literature review of the current evidence on the safety and efficacy of biologics in psoriatic disease with cardiovascular comorbidities.

**TNF-A INHIBITORS**

TNF-α inhibitors are associated with significantly reduced cardiovascular risk compared to both methotrexate and phototherapy.20,24-26 The protective effects are cumulative and more prominent in patients with more severe psoriasis.27 TNF-α plays a role in promoting inflammation, insulin resistance, endothelial dysfunction, metabolic syndrome, and atherogenesis.

TNF-α inhibition promotes insulin sensitivity, exhibited in a prospective study on adalimumab in psoriasis patients without diabetes.28 Inhibition of TNF aids in restoration of endothelial function as well as coronary microvascular function and flow, particularly in patients with skin symptoms responsive to anti-TNF-α therapy.30 This effect was exemplified in a study on etanercept using the number of circulating endothelial cells (CEC) as a measure of endothelial dysfunction. CEC level was significantly decreased after six months of therapy.31

TNF-α inhibitors can decrease serum cardiovascular biomarkers. E-selectin, a biomarker indicative of endothelial dysfunction and associated with increased risk of atherosclerosis, was shown to decrease after treatment with adalimumab in just 12 weeks.32 Etanercept has been shown to reduce the inflammatory marker, C-reactive protein, regardless of statin therapy in psoriasis patients.24 Etanercept has also been shown to reduce cardiovascular disease by improving autonomic dysregulation of the cardiovascular system via decreased heart rate variability.33 Therefore, the anti-inflammatory properties of TNF-α inhibition ameliorate the cardiovascular burden of psoriasis.

Infliximab, in particular, has been shown to increase vascular wall shear stress, and close monitoring is recommended if used in patients with congestive heart failure.34,35 However, a recent meta-analysis did not find any difference between placebo in rates of MACEs with infliximab among other biologics.22 Considering all this data, TNF-α inhibitors are plausible treatment options for psoriasis with the aim of concomitant improvement of cardiovascular events and risk factors.

**IL-12/23 INHIBITORS**

The greatest concern for cardiovascular safety of biologics was raised in regard to IL-12/23 inhibitors (ustekinumab) during clinical trials. Overexpression of IL-12/23 is a common pathway between psoriasis and atherosclerosis and concluding that this class of medications increases the risk of adverse cardiovascular events is difficult to rationalize. Nevertheless, Phase 2 and 3 placebo-controlled studies on ustekinumab showed an increased risk of MACEs compared to placebo (five reports in ustekinumab arms compared to zero in the placebo group).36 Tzellos, et al. have proposed optimization of cardiovascular risk factors before initiating IL-12/23 inhibitors in psoriasis patients with multiple cardiovascular risk factors,37 although this is not supported by concrete evidence. The inability to draw a solid conclusion regarding cardiovascular adverse events of IL-12/23 biologics is attributed to limitations of statistical analyses as well as an incomplete understanding of immunological pathways concerning psoriasis and atherosclerosis.38

Further clinical trials and longer duration of therapy did not confirm the association of IL-12/23 inhibitors with increased cardiovascular risk. They found the risk of cardiovascular events to be similar to that of the general population.36 Reich, et al. concluded that treatment with ustekinumab has neither a beneficial nor harmful effect on risk of serious cardiovascular events in psoriasis patients. In a 52-week Phase 3 trial of ustekinumab, one cardiovascular adverse event was reported in the 90mg ustekinumab arm compared to none in the 45mg and placebo groups.39

A recent Phase 4 randomized clinical trial assessed aortic vascular inflammation (AVI) using 18F-2-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). A transient decrease in AVI was observed in the treatment group by week 12 but did not remain significantly low compared to placebo at 52 weeks. Levels of IL-1b, IL-17a, IL-18, IL-6 and TNF-α, all of which are markers associated with modification of atherosclerotic events, were significantly lower at the end of week 52.40 Currently, there is no evidence to confirm that IL-12/23 inhibitors increase the risk of serious cardiovascular events, and they might have beneficial anti-inflammatory effects. Future clinical trials are needed to confirm cardiovascular risk reduction effects of IL-12/23 inhibitors.
IL-17 INHIBITORS

IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab) are currently approved for the treatment of moderate to severe plaque psoriasis and can be further classified by the target of their inhibition. Secukinumab and ixekizumab inhibit IL-17A, a pro-inflammatory cytokine. Brodalumab inhibits the receptor of this cytokine, IL-17 receptor A (IL-17 RA). The role of IL-17 in cardiovascular events is not yet fully established, however, both anti- and pro-atherogenic effects have been observed with IL-17, likely due to its complex interactions with other cytokines.41

In a pooled analysis of 10 randomized psoriasis clinical trials, MACEs were seen more frequently in the secukinumab group compared to etanercept and placebo. However, when adjusted for baseline cardiovascular risks after 52 weeks of treatment, the rates were comparable in all treatment groups.42 In an observational study from a Danish registry comparing adalimumab, etanercept, infliximab, secukinumab, and ustekinumab for two years, secukinumab had the highest number of adverse cardiovascular events compared to others. However, the absolute numbers were still low (four cases representing two percent of patients). Additionally, patients receiving secukinumab reported more cardiovascular risk factors at baseline.43

Von Stebut, et al. measured endothelial function by flow mediated dilation (FMD) in patients receiving secukinumab for 52 weeks. Increased FMD was reported in both patients receiving the secukinumab 150mg dosing as well as 300mg.

Fresh Take: Psoriasis Treatment Today

With Alice B. Gottlieb, MD, PhD

The advent of biologics has changed the way psoriasis is treated, but access to these highly effective drugs remains an issue, says Alice B. Gottlieb, MD, PhD, Clinical Professor in the Department of Dermatology, Icahn School of Medicine at Mt Sinai and the Medical Director of Mount Sinai-Union Square in New York City.

"Biologics have changed the course of this disease. Today we aim for clearance in psoriasis and control of signs and symptoms, improvement in quality of life and inhibition of radiographic progression in psoriatic arthritis (PsA). We didn't have any hope of that years ago," she tells Practical Dermatology. Dr. Gottlieb's team was the first to demonstrate in a randomized, double blind, placebo controlled study in 2001 that monotherapy with tumor necrosis factor inhibitors cleared psoriasis.1

Unfortunately, "Writing prescriptions for biologics increases practice overhead and decreases revenue because the prior authorization work, patient education, and injection training are not reimbursed and require hiring of additional personnel. As a result, many dermatologists prescribe biologics only when they absolutely have to," she says.

Change needs to happen at the payer and provider level, and drug costs need to decrease in order to improve access to these medications for all psoriatic disease patients, Dr. Gottlieb says. "Patients need to be aware that they can get clear skin and that there are drugs that can make psoriatic arthritis much, much better," she says. "Many dermatologists may not inform their psoriasis patients about the full range of options, so patients have to do the research themselves." Dr. Gottlieb often directs her patients to the National Psoriasis Foundation website for more information on treatment choices.

Many dermatologists don’t ask psoriasis patients about joint involvement or PsA, which is the most common comorbidity of psoriasis. The American Academy of Dermatology-National Psoriasis Foundation psoriasis guidelines state that dermatologists should ask about PsA in every psoriasis patient, educate patients on the signs and symptoms of PsA, and make sure that if PsA is suspected treatment is promptly initiated by themselves or by a rheumatologist.

Many times payers dictate what treatments should be tried. Current biologic options include tumor necrosis factor (TNF), Interleukin (IL)-17 and IL 23 blockers.

The good news is that the psoriasis and PsA treatment pipelines are robust, Dr. Gottlieb adds. Bimekizumab (UCB) is a humanized IgG1 monoclonal antibody that inhibits both interleukin-17F and interleukin-17A. "It could be a game changer, but we have to see what will happen in trials," she says. "I am excited about oral tyrosine kinase 2 (Tyk2) inhibitors in psoriasis," she says. The topical category has been stagnant and devoid of innovation for a while, but Tapinarof (Dermavent) is under development for plaque psoriasis and atopic dermatitis and could be the next big thing if studies pan out. Tapinarof is an investigational therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in Phase 3 development in the US.

References:
dosing, compared to placebo. Although this increase was not statistically significant compared to placebo, it was clinically relevant. This is due to the finding that each one percent increase in FMD decreases cardiovascular risk by 13 percent. Additionally, there was a statistically significant 2.1 percent increase from baseline in FMD in psoriasis patients after 52 weeks. These findings delineate the safety of secukinumab for use in psoriasis patients with cardiovascular risk factors as well as a potential beneficial effect which is yet to be confirmed in further studies.

An analysis of seven ixekizumab clinical trials with 4,209 patients showed MACES comparable to etanercept in the first 12 weeks of treatment. Although rates of MACEs were increased in the 60-week treatment extension, the differences were not statistically significant upon adjustment for baseline cardiovascular risk factors. This was similar to the secukinumab trials in which the patients in the treatment arm exhibited more cardiovascular risk factors and comorbidities at baseline.

A Phase 3 randomized clinical trial of brodalumab resulted in five MACEs, three in patients rerandomized to placebo after treatment and two in the placebo group. The incidence of MACEs in patients treated with brodalumab was not statistically significant.

Collectively, the data on IL-17 inhibitors point to their cardiovascular safety in the treatment of psoriasis. There is a potential beneficial role of IL-17 inhibition in decreasing cardiovascular comorbidities in psoriasis patients which would be better determined with longer post-marketing surveillance of this class of drugs.

**IL-23 INHIBITORS**

IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab) are the most recently approved biologics in the treatment of moderate to severe plaque psoriasis. In a recent study with three-year data on guselkumab, the rate of MACES in patients receiving guselkumab was no greater than in patients treated with adalimumab, nor did the rate increase over time. In a post-hoc analysis of two randomized clinical trials on tildrakizumab, the safety and efficacy of tildrakizumab did not differ in patients with metabolic syndrome vs those without metabolic syndrome. In a clinical trial of risankizumab for the treatment of plaque psoriasis, two cases of cardiac side effects were reported, both of which occurred in patients with preexisting cardiovascular risk factors. Safety conclusions however, could not be made due to the small number of patients and short duration of the trial. Long-term data on the safety of IL-23 inhibitors is not yet available, however, their safety profile across all serious adverse events has been shown to be promising.

**OBJECTIVE MEASURES FOR CV RISK DETERMINATION**

Objective measures of cardiac inflammation can help us better understand the effects of biologics on the cardiovascular system. Coronary computed tomography angiography (CCTA) has been utilized to visualize coronary plaques and to determine their characteristics in psoriasis patients. Epicardial adipose tissue thickness has also been proposed as a cardiovascular-risk determinant in such patients. Patients with psoriasis were found to have a higher non-calcified coronary plaque burden as well as increased number of high-risk plaques, similar to older patients with hyperlipidemia. Both of these indices improve after one year of systemic treatments that ameliorate skin disease and improve Psoriasis Area and Severity Index (PASI) scores. Systemic treatments assessed included methotrexate, TNF-a inhibitors, IL-17 inhibitors, and IL-12/23 inhibitors; plaques were assessed using CCTA. These findings were reproduced in an additional study of 290 patients with severe psoriasis treated with TNF-a inhibitors, IL-17 inhibitors, and IL-12/23 inhibitors undergoing CCTA at baseline and after one year of treatment. In patients receiving phototherapy or topical treatment, coronary artery disease had progressed and coronary plaques were infiltrated with lipids, while lipid rich plaques and necroses had decreased in the treatment group.

CCTA was used in a different study to assess changes in perivascular fat attenuation index (FAI), a marker of subclinical atherosclerosis and coronary inflammation, both before and after treatment with TNF-a, IL-17 and IL-12/23 inhibitor biologic therapies. A statistically significant decrease in perivascular FAI was seen after one year of treatment in patients who had PASI score improvements. This effect was independent of a decrease in markers for metabolic syndrome, namely lipids, blood glucose, and body mass index. Perivascular FAI did not decrease in patients treated with phototherapy or topical treatments. Ultimately, this data confirms the increased cardiovascular inflammation in psoriasis patients and the positive effect of biologic therapy on halting the progression as well as mitigation of inflammation.

**CONCLUSION**

The use of biologic therapies is associated with a favorable safety profile as well as increased efficacy in alleviating skin disease when compared to alternative treatments, making this class of medications an ideal option in systemic treatment of psoriasis. From a cardiovascular perspective, biologics could be a superior option considering the cardiometabolic burden of conventional systemic psoriasis treatments. Research is ongoing into the clinical outcomes of biologic therapy in psoriasis. Utilization of objective measurements for cardiovascular risk determination, including serum cardiometabolic biomarkers and imaging modalities...
for vascular inflammation, could shed light into the safety of biologics in cardiovascular disease as well as their efficacy in mitigating cardiovascular risk. ■

To learn more about the link between psoriasis, cardiovascular disease, and whether biologics improve cardiovascular disease, consider attending the inaugural 2020 San Diego Dermatology Symposium from May 29-31, 2020 at the InterContinental San Diego where Dr. Wu will discuss more in depth. sddermsymposium.org

Dr. Wu is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Dr. Reddy’s Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, Valeant Pharmaceuticals North America LLC.

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