The Role of Biologic Therapy for Psoriasis in Cardiovascular Risk Reduction

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The cardiovascular comorbidities associated with psoriasis have been well documented; however, the mechanism by which psoriasis increases the risk for cardiovascular disease (CVD) remains unclear. Elevated systemic inflammatory cytokines and mediators may play a key role in their association, which prompts the questions: Do systemic medications have a protective effect? Do patients on systemic antipsoriatic treatment have a decreased risk for major adverse cardiovascular events (MACEs) compared with untreated patients?

We believe the shared inflammatory processes involved in psoriasis and atherosclerosis formation are potential targets for therapy in reducing the incidence of CVD and its associated complications. A growing amount of evidence suggests cardioprotective effects associated with antipsoriatic treatments such as tumor necrosis factor (TNF) inhibitors and methotrexate. Gkalpakiotis et al[1] demonstrated a reduction in serum E-selectin (mean [standard deviation], 53.04 [23.54] ng/mL vs 35.32 [8.70] ng/mL; $P<.001$) and IL-22 (25.11 [19.9] pg/mL vs 12.83 [8.42] pg/mL; $P<.001$) after 3 months of adalimumab administration in patients with moderate to severe psoriasis. Both E-selectin and IL-22 are associated with the development of atherosclerosis, endothelial dysfunction, and an increased incidence of CVD. Similarly, Wu et al[2] demonstrated a statistically significant reduction (−5.04 mg/dL [95% confidence interval [CI], −8.24 to −2.12; $P<.01$) in C-reactive protein in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis after concurrent use of methotrexate and TNF inhibitors.

Solomon et al[3] compared the rate of newly diagnosed diabetes mellitus among psoriasis and rheumatoid arthritis patients treated with TNF inhibitors, methotrexate, hydroxychloroquine, and other nonbiologic disease-modifying antirheumatic drugs. The authors' findings suggest that those who take a TNF inhibitor (hazard ratio [HR], 0.62; 95% CI, 0.42-0.91) and hydroxychloroquine (HR, 0.54; 95% CI, 0.36-0.80) are at lower risk for diabetes mellitus compared to those treated with nonbiologic disease-modifying antirheumatic drugs. Conversely, the methotrexate (HR, 0.77; 95% CI, 0.53-1.13) cohort did not show a statistically significant reduction in diabetes risk.[3]

Pina et al[4] revealed improvement in endothelial function after 6 months of adalimumab use in patients with moderate to severe psoriasis. To evaluate the presence of subclinical endothelial dysfunction, the authors assessed brachial artery reactivity by measuring flow-mediated dilation and carotid artery stiffness by pulse wave velocity. Patients showed an increase in flow-mediated dilation (mean [SD], 6.19% [2.44%] vs 7.46% [2.43%]; $P=.008$) and reduction in pulse wave velocity (6.28 [1.04] m/s vs 5.69 [1.31] m/s; $P=.03$) compared to baseline measurements, indicating an improvement of endothelial function.[4]

Ahlehoff et al[5] observed for improvements in subclinical left ventricular dysfunction in psoriasis patients after treatment with biologics. Using echocardiography, they assessed for changes in diastolic function and left ventricular systolic deformation (defined by global longitudinal strain). Of patients who received 3 months of biologic therapy (TNF inhibitor or IL-12/23 inhibitor) and maintained at minimum a

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psoriasis area and severity index 50 response, all demonstrated an improvement in diastolic function (mean [SD], 8.1 [2.1] vs 6.7 [1.9]; $P<.001$) and global longitudinal strain (mean [SD], −16.8% [2.1%] vs −18.3% [2.3%]; $P<.001$). Of note, patients who did not achieve a psoriasis area and severity index 50 response at follow-up did not exhibit an improvement in subclinical myocardial function.[5]

Moreover, a Danish nationwide study with up to 5-year follow-up evaluated the risk for MACE (ie, cardiovascular death, myocardial infarction, stroke) in patients with severe psoriasis receiving systemic anti-inflammatory medications and nonsystemic therapies including topical treatments, phototherapy, and climate therapy.[6] Compared to nonsystemic therapies, methotrexate use (HR, 0.53; 95% CI, 0.34-0.83) was associated with a decreased risk for cardiovascular events. However, a protective decreased risk was not found among patients who used systemic cyclosporine (HR, 1.06; 95% CI, 0.26-4.27) or retinoids (HR, 1.80; 95% CI, 1.03-2.96). Any biological drug use had a comparable but nonsignificant reduction of cardiovascular events (HR, 0.58; 95% CI, 0.30-1.10). After multivariable adjustment, TNF inhibitors were associated with a statistically significant decreased risk for cardiovascular events (HR, 0.46; 95% CI, 0.22-0.98; $P=.04$) compared to nonsystemic therapies. The IL-12/23 inhibitor did not demonstrate this relationship (HR, 1.52; 95% CI, 0.47-4.94).[6]

Lastly, Wu et al[7] compared the risk for MACE (ie, myocardial infarction, stroke, unstable angina, transient ischemic attack) between patients with psoriasis who received TNF inhibitors or methotrexate. The TNF inhibitor and methotrexate cohorts were observed for a median of 12 months and 9 months, respectively. After adjusting for potential confounding factors, they found a 45% reduction (HR, 0.55; 95% CI, 0.45-0.67) in cardiovascular event risk in the TNF inhibitor cohort compared with the methotrexate cohort. Notably, analyses also showed comparatively fewer cardiovascular events in the TNF inhibitor cohort throughout all time points—6, 12, 18, 24, 60 months—in the observation period. Regression analysis revealed an 11% reduction in cardiovascular events (HR, 0.89; 95% CI, 0.80-0.98) with each additional 6 months of cumulative TNF inhibitor exposure.

The current sum of evidence suggests cardioprotective effects of TNF inhibitor and methotrexate use. However, given the cumulative systemic toxicity and inferior cutaneous efficacy of methotrexate, TNF inhibitors will likely play a more significant role going forward. The role of methotrexate may be for its simultaneous use with biologic therapies to limit immunogenicity. Newer biologic agents such as IL-12/23 and IL-17 inhibitors have not yet been as extensively studied for their effects on cardiovascular risk as their TNF inhibitor counterparts. However, because of their shared ability to target specific immunological pathways, it is plausible that IL-12/23 and IL-17 agents may exhibit cardioprotective effects.[8]

Patients with psoriasis should be counseled and educated about the increased risk for CVD and its associated morbidity and mortality risk. Screening for modifiable risk factors and recommending therapeutic lifestyle changes also is appropriate. Future studies should help define the role of specific systemic drugs in reducing the risk for CVD in patients with psoriasis. Despite the expanding amount of evidence in the current literature implicating the use of TNF inhibitors for cardiovascular risk prevention, there is still a need for long-term, randomized, placebo-controlled trials to provide more authoritative evidence-based recommendations.

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