Tumor Necrosis Factor Inhibitors May Reduce Cardiovascular Morbidity in Patients With Psoriasis

Erica B. Lee, MD; Mina Amin, MD; Jashin J. Wu, MD

The connection between psoriasis and increased major adverse cardiovascular events (MACEs) has been well studied.[1,2] Although treatment of psoriasis can improve skin and joint symptoms, it is less clear whether therapies may mitigate the increased risk for cardiovascular comorbidities. Tumor necrosis factor (TNF) inhibitors in particular have been studied with great interest given the role of TNF in vascular and metabolic functions.[3] Using a retrospective cohort design, Wu and colleagues[4] examined if treatment with TNF inhibitors in patients with psoriasis would be associated with a lower risk for MACEs compared to phototherapy. Results suggested a significantly lower hazard of MACEs in patients using TNF inhibitors vs patients treated with phototherapy (adjusted hazard ratio, 0.77; $P=.046$). Moreover, based on these findings, they calculated that treating approximately 161 patients with TNF inhibitors rather than phototherapy would result in 1 less MACE per year overall.[4]

Patients with psoriasis have been shown to have a greater noncalcified coronary plaque burden and prevalence of high-risk plaque compared to healthy patients.[5] Lerman and colleagues[5] measured the coronary plaque burden of 105 patients with psoriasis and 25 healthy volunteers using coronary computed tomography angiography. Although the patients were on average 10 years younger and had lower cardiovascular risk as measured by traditional risk scores, patients with psoriasis were found to have a greater noncalcified coronary plaque burden compared to 100 patients with hyperlipidemia. This burden was associated with an increased prevalence of high-risk plaques. Furthermore, in patients followed for 1 year, improvements in psoriasis severity were associated with reductions in noncalcified coronary plaque burden, though this finding was across all treatment modalities. However, there was no significant difference in calcified coronary plaque burden associated with reduced psoriasis severity.[5]

Moreover, Pina et al[6] conducted a prospective study evaluating the use of the TNF inhibitor adalimumab to improve endothelial function and arterial stiffness in patients with moderate to severe psoriasis. Among 29 patients, they found a significant improvement in endothelial function as measured by flow-mediated dilatation after 6 months of adalimumab therapy, with a mean increase from 6.19% to 7.46% ($P=.008$). They also reported decreases in arterial stiffness by pulse wave velocity ($P=.03$). Despite a small sample size, these findings provide 2 potential mechanisms by which TNF inhibitor therapy may reduce the risk for cardiovascular events.[6]

A retrospective cohort study evaluating data from the Kaiser Permanente Southern California health plan assessed whether TNF inhibitor therapy was associated with a lower risk for MACE in patients with psoriasis.[7] A total of 18,194 patients were included; of these, 1463 received TNF inhibitor therapy for at least 2 months. After controlling for other variables, including age at psoriasis diagnosis, sex, race/ethnicity, and other cardiovascular risk factors (eg, history of smoking or alcohol use; use of clopidogrel, antihypertensive agents, antihyperlipidemics, or anticoagulants), patients in the TNF inhibitor cohort demonstrated a significantly lower MACE hazard ratio compared to patients treated with topicals (hazard ratio, 0.80; 95% confidence interval, 0.66-0.98; $P<.05$).[7]

Conversely, a randomized, placebo-controlled trial of 107 patients found no difference in vascular inflammation of the ascending aorta and the carotids after 16 weeks of adalimumab treatment vs placebo. In this study, however, most patients had only moderate psoriasis based on a

Dr. Lee is from the Department of Medicine, Santa Barbara Cottage Hospital, California. Dr. Amin is from the Department of Dermatology, Kaiser Permanente Los Angeles Medical Center, California. Dr. Wu is from Dermatology Research and Education Foundation, Irvine, California.
Drs. Lee and Amin report no conflict of interest. Dr. Wu is a consultant for AbbVie; Almirall; Amgen Inc; Bristol-Myers Squibb; Celgene Corporation; Dermira Inc; Dr. Reddy's Laboratories; Eli Lilly and Company; Janssen Biotech, Inc; LEO Pharma; Novartis; Ortho Dermatologics; Promius Pharma; Regeneron Pharmaceuticals, Inc; Sun Pharmaceutical Industries, Ltd; and UCB. He also is an investigator for AbbVie Inc; Amgen Inc; Eli Lilly and Company, Janssen Biotech, Inc; and Novartis. He also is a speaker for Celgene Corporation; Novartis; Sun Pharmaceutical Industries, Ltd; and UCB.
Correspondence: Jashin J. Wu, MD (jashinwu@gmail.com).

mean psoriasis area and severity index score of 9.8.[8] Given studies finding higher risk burden in patients with more severe skin disease,[2] it is possible that the effect of TNF inhibitor therapy may not be as pronounced in patients with less skin involvement. There was a significant effect on C-reactive protein levels in patients receiving TNF inhibitor therapy compared to placebo at 16 weeks (P=.012), suggesting TNF does play some role in systemic inflammation, and it is possible it may exert cardiovascular effects through a mechanism other than vascular inflammation.[8]

A second double-blind, randomized trial reported similar results.[9] Among 97 patients randomized to receive adalimumab, placebo, or phototherapy, no significant difference in vascular inflammation was found after 12 weeks of therapy. In contrast, levels of C-reactive protein, IL-6, and glycoprotein acetylation were markedly reduced. The authors also reported adverse effects of adalimumab therapy on lipid metabolism with reduced cholesterol efflux capacity, a marker of ability of high-density-lipoprotein particles to perform reverse cholesterol transport, and high-density-lipoprotein particles, suggesting these effects may counteract some of the anti-inflammatory effects of TNF inhibitors.[9]

A growing body of data regarding the effect of TNF inhibitors on cardiovascular morbidity in patients with psoriasis is being collected, but no strong conclusions can be made. Given the disconnect of findings across these studies, it is possible that we have yet to elucidate the full mechanism by which TNF inhibitors may affect cardiovascular health. However, there may be additional confounding factors or patient characteristics at play. More large, prospective, randomized, controlled studies are needed to further understand this relationship.

REFERENCES

1. Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis.* 2015;74:326-332.
2. Ahlehoff O, Gislason GH, Charlot M, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med.* 2011;270:147-157.
3. Kölliker Frers RA, Bisoendial RJ, Montoya SF, et al. Psoriasis and cardiovascular risk: immune-mediated crosstalk between metabolic, vascular, and autoimmune inflammation. *Int J Cardiol Metab Endocr.* 2015;6:43-54.
4. Wu JJ, Sundaram M, Cloutier M, et al. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-α inhibitors versus phototherapy: an observational cohort study. *J Am Acad Dermatol.* 2018;79:60-68.
5. Lerman JB, Joshi AA, Chaturvedi A, et al. Coronary plaque characterization in psoriasis reveals high-risk features that improve after treatment in a prospective observational study. *Circulation.* 2017;136:263-276.
6. Pina T, Corrales A, Lopez-Mejias R, et al. Anti-tumor necrosis factor-α therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: a 6 month prospective study. *J Dermatol.* 2016;43:1267-1272.
7. Wu JJ, Joshi AA, Reddy SP, et al. Anti-inflammatory therapy with tumor necrosis factor inhibitors is associated with reduced risk of major adverse cardiovascular events in psoriasis [published online March 24, 2018]. *J Eur Acad Dermatol Venereol.* doi:10.1111/jdv.14951.
8. Bissonnette R, Harel F, Krueger JG, et al. TNF-α antagonist and vascular inflammation patients with psoriasis vulgaris: a randomized placebo-controlled study. *J Invest Dermatol.* 2017;137:1638-1645.
9. Mehta NN, Shin DB, Joshi AA, et al. Effect of 2 psoriasis treatments on vascular inflammation and novel inflammatory cardiovascular biomarkers: a randomized placebo-controlled trial. *Circ Cardiovasc Imaging.* 2018;11:e007394.