PET-FDG for vascular imaging: a ''visual barometer'' for inflammatory risk?

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Psoriasis is a chronic immune-mediated disease affecting about 3% of the adult population in the US.[1] Although once categorized as a skin disease with no significant morbidity and mortality, studies have shown that patients with psoriasis have a higher rate of all-cause mortality, driven mainly by cardiovascular-related deaths.[2,3] Patients with psoriasis have an increased prevalence of cardiovascular risk factors including hypertension, dyslipidemia, insulin resistance, and obesity.[4–6] Even after controlling for the presence of these traditional risk factors, these patients have a higher risk of developing myocardial infarction. Given this mounting data, the most recent ACC/AHA guidelines for the primary prevention of coronary artery disease have listed psoriasis as a ''risk'' enhancing factor for atherosclerotic cardiovascular disease (ASCVD), recommending that providers discuss the risks and benefits of initiating aggressive medical and behavioral therapy with these patients.

While we applaud that psoriasis, as well as other chronic inflammatory conditions, are noted as risk enhancers for ASCVD, this recommendation leaves physicians in a quandary because not all patients with psoriasis have the same cardiovascular risk. Additional guidance is, therefore, needed to identify those at greatest risk. Overwhelming data shows that patients with severe psoriasis, defined in most studies as those patients who are hospitalized, need phototherapy, or use systemic therapy, are the most vulnerable. Large cohort studies, for example, have shown that patients with severe psoriasis have increased overall mortality risk (HR 1.5; 95% CI 1.3 to 1.7) and die 3 to 5 years younger than the general population,[7] with many dying from cardiovascular disease.[3] Patients with severe psoriasis also have a higher risk of myocardial infarction than those without psoriasis,[8] and severe psoriasis increases the 10-year risk of having major adverse cardiac events (MACE) by 6.2%.[3]

Although those with severe psoriasis are at greater risk for ASCVD and MACE, patients with mild psoriasis are not 'risk free'. In a recent meta-analysis that included > 200,000 patients, patients with mild psoriasis had a slightly increased incidence of myocardial infarction (mild: RR 1.29; 95% CI 1.02 to 1.63) and stroke (mild: RR 1.12; 95% CI 1.08 to 1.16) than patients without psoriasis.[9] The risk of ASCVD and MACE in patients with moderate psoriasis, however, is not well studied.

Unfortunately, additional biomarkers of ASCVD may be of limited utility in patients with psoriasis. The utility of high sensitivity C-reactive protein (hsCRP), for example, which is currently used to define the amount of residual inflammatory risk that remains unmodified by standard therapies, is problematic in patients with psoriasis because an elevated hsCRP may reflect inflammation in the skin or joints rather than the vasculature. Coronary artery calcification (CAC) score, on the other hand, measures coronary calcium in more mature, hard plaques. The CAC score, however, does not provide information on the extent of soft plaque burden, characterized by an abundance of inflammatory cells that is the most likely manifestation of subclinical

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disease in these patients.[10] Perhaps a better surrogate marker for ASCVD burden in patients suffering from chronic inflammatory disease(s), like psoriasis, is quantification of immune activation within the plaque in the vasculature.

FDG-PET has emerged as an important tool to detect vascular inflammation in the aorta, carotid arteries, and even the coronary arteries.[11,12] Metabolically active cells, like immune cells within plaques, take up more glucose than more quiescent cells and are, thus, more visible with PET imaging. Patients with vascular inflammation detected by FDG-PET have an increased risk of developing MACE, independent of traditional risk factors.[13] In patients with psoriasis, the degree of aortic inflammation by FDG-PET has been associated with the severity of psoriatic skin lesions[14] and correlates with atherosclerotic disease burden defined by aortic wall thickness measured by MRI[15] and coronary artery plaque build-up by CT angiography.[10,16] A handful of studies have also assessed if reducing the severity of psoriatic skin lesions leads to a decrease in surrogate imaging markers of ASCVD including FDG-PET. In a study of 25 Korean patients, treatment with ustekinumab (i.e., an inhibitor of IL 12/23 IgG1κ) reduced both the severity of psoriatic lesions as well as vascular inflammation.[17] Larger, randomized, placebo-controlled trials using such agents as adalimumab (i.e., a TNFα inhibitor) and secukinumab (i.e., an inhibitor of IL17A), however, showed no correlation. Collectively, these findings suggest that assessing the severity of psoriatic skin disease is not an accurate gauge for vascular inflammation and that treatment with biologics does not guarantee reversal of vascular inflammation.

In this issue of the Journal of Nuclear Cardiology, Boczar et al., build further on this story.[18] The investigators conducted a prospective cohort study on 42 patients with severe psoriasis, in which they utilized FDG-PET to assess the changes in aortic inflammation before and after the treatment with biologic agents (i.e., anti-TNFα, anti-IL 17 or anti-IL17/23). They compared the aortic inflammatory changes in three groups: (1) patients with severe psoriasis taking biologic agents; (2) patients with severe psoriasis taking the topical medication acitretin or phototherapy, and (3) a control group of patients with osteoarthritis. To track the changes in aortic inflammation, they measured the target-to-background ratio (TBR) in the most diseased segments of the aorta before and after 6 months of therapy. They measured TBR by obtaining a standardized uptake value (SUV) of the most inflamed section of aorta and determined the ratio of SUV to the background venous activity in the superior vena cava. Interestingly, there was no difference in the degree of vascular inflammation at baseline even in patients with osteoarthritis, a disease which is also associated with increased ASCVD risk. At the 6-month follow-up, vascular inflammation in the ascending aorta, aortic arch, and descending aorta decreased significantly in the patients with psoriasis taking biologics but not in patients with severe psoriasis who were not taking biologics and not in patients with osteoarthritis. The response to a 6-month course of biologic therapy, however, differed among patients with severe psoriasis with some patients having a reduction in FDG uptake while others having no change or even an increase in signal (i.e., therapeutic non-responders). Importantly, these non-responders have decreased myocardial perfusion reserve (MPR) on myocardium perfusion scintigraphy using ^{82}Rb PET, suggesting the development of microvascular disease in this relatively young cohort (i.e., median age was 62 years old with range 44.0 to 64.5 years).

Taken together, these results support that patients with chronic inflammatory conditions, such as psoriasis and even osteoarthritis, may have undetected and unresolved subclinical vascular inflammation that may increase ASCVD risk. These findings highlight the need to approach psoriasis, as well as other chronic inflammatory disorders, in a comprehensive manner. For psoriasis, specifically, providers should account for the systematic nature of the disease rather than just treating skin symptoms. Additionally, the correlation between a measurement of aortic inflammation and MPR further underscores the value of PET-FDG in identifying which patients with psoriasis have increased cardiovascular risk, independent of traditional risk factors and their disease severity.[13] PET-FDG can potentially serve as a non-invasive method that enables visualization of residual inflammatory risk.

While this study provides additional evidence that vascular inflammation detected by PET-FDG may be an unaddressed risk factor in the assessment of CVD risk and suggests that its clinical utility can be extended for monitoring response to biologic therapy, it is important to consider certain limitations when interpreting the results of this study. As the authors noted, this is a non-randomized, cohort study with a relatively small sample size, restricting the generalizability of these results. Additionally, the impact of each anti-TNFα, anti-IL 17 and anti-IL17/23 on vascular inflammation and MPR cannot be evaluated separately. The study also does not assess the relationship of the degree of vascular inflammation measured by FDG-PET to cardiovascular outcomes. Given these limitations, larger, prospective cohort studies are needed to answer the following important lingering questions: (1) Is inflammation in the aorta detected by FDG-PET a sensitive and specific marker for ASCVD or MACE in patients with psoriasis as well as other chronic inflammatory diseases? (2) Can

aortic inflammation measured by FDG-PET accurately predict the risk of events in the short-term (< 5 years) and long-term (> 10-year risk)? (3) Does this imaging biomarker act synergistically with the pooled cohort equations to predict ASCVD risk? (4) Does reducing the inflammation in the aorta using statins, biologics or by other means decrease cardiovascular risk?

Although FDG-PET for vascular inflammation may ultimately be too nonspecific and/or cumbersome to implement (given the need for a strict diet to overcome cardiac spillover) to be clinically useful for predicting those at high risk for ASCVD, the study gives us a potential window to a bright future. The emergence of more specific PET tracers for immune cell imaging [i.e., ^{68}Ga-DOTATE,[19] ^{18}F-FOL,[20] etc.] will pave the way for providers to deliver a more personalized method of cardiovascular risk stratification for patients with psoriasis as wells other patients with chronic inflammatory disorders.

Disclosures

The authors have no conflicts to disclose.

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