Interleukin Antagonists
Have We Found the Right One to Block? Are Cardiovascular Effects of Biologic Therapies Similar?

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There is strong experimental and clinical support for a causal role of immune dysregulation and inflammation in atherosclerosis and heart failure. Atherosclerotic lesions are infiltrated by monocytes, macrophages, and T lymphocytes (predominantly Th1). Cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), are released by the infiltrating inflammatory cells and stimulate adhesion molecule expression. IL-6 can downregulate nitric oxide production and further worsen endothelial dysfunction. Progression of this inflammatory response is primarily regulated by specific patterns of cytokine expression. Interleukin 12 (IL-12) is a proinflammatory cytokine produced by many cell types, including monocytes, neutrophils, dendritic cells, macrophages, and smooth muscle cells in plaques. In addition to its primary role in initiation of cell-mediated immunity, IL-12 is an endogenous inhibitor of angiogenesis and may induce autoimmune myocarditis. Ablation of interleukin 23 (IL-23) seems to improve myocardial remodeling and survival post-myocardial infarction in a rodent model. Disruption of IL-12 was recently shown to improve microvascular endothelial function in a diabetes mellitus model. Finally, a recent study found that circulating IL-12 levels were predictive of long-term prognosis after acute myocardial infarction.

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that Ustekinumab-mediated blockade of IL-12/IL-23 resulted in greater improvement in arterial stiffness, coronary flow reserve (CFR), and ultimately LV strain measurements compared with either cyclosporine or TNF-α blockade. Moreover, the magnitude of improvement correlated with the improvement in systemic indices of oxidative stress and inflammation, particularly circulating IL-12 levels.

Speckle-tracking echocardiography myocardial strain imaging estimates subclinical changes in LV contractile function that are often not reflected as changes in LV ejection fraction. However, strain imaging may be influenced by race, ethnicity, sex, aging, and cardiovascular risk factors that were at least partially accounted for in this study. CFR measures the capacity of the coronary microcirculation to dilate in response to increased myocardial demands and can be assessed both invasively and noninvasively. CFR measurement by transthoracic echocardiography has several advantages because it is noninvasive, easily available at the bedside, inexpensive, and avoids radiation. Measurement of CFR in the left anterior descending artery by transthoracic echocardiography correlates well with invasive measurements by Doppler flow wire. The cutoff CFR value of <2 is 90% sensitive and 93% specific for detecting significant stenosis. As used in this study, noninvasive measurement of CFR by transthoracic echocardiography can be a useful measure of coronary microvascular function but may not be obtainable in all subjects.

In summary, this study further highlights the important link between systemic inflammation and oxidative stress precipitated by chronic inflammatory diseases, such as lupus, rheumatoid arthritis or psoriasis, and subclinical vascular disease, measured as microvascular dysfunction or large arterial compliance, and ultimately the impact of these changes on myocardial function. Although the impressive beneficial effects of IL-12/IL-23 blockade on these measures has been demonstrated, whether this will result in improvement in the risk of adverse cardiovascular outcomes in populations with systemic inflammatory states remains to be determined. Importantly, the safety of these agents in patients with overt cardiovascular diseases, particularly postacute coronary syndromes and heart failure, will need to be assessed because surrogate marker improvements have not necessarily been predictive of safety in previous studies.

Disclosures

None.

References


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