

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).¹ 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 can indirectly affect the development of plaques by promoting Th1 cell differentiation. IL-12 induces production of reactive oxygen and nitrogen species that precipitates endothelial dysfunction. IL-12 augments the formation of atherosclerotic lesions and increases production of oxidized low-density lipoprotein antibody in the apolipoprotein E-deficient atherosclerotic model, highlighting its active role in the initial phase of atherosclerosis.^{2,3} Moreover, IL-12 deficiency or functional blockade of IL-12 reduces atherogenesis and improves plaque stability in the low-density lipoprotein receptor^{-/-} mice.⁴ IL-12 is an endogenous inhibitor of angiogenesis and may induce autoimmune myocarditis.⁵ Ablation of interleukin 23 (IL-23) seems to improve myocardial remodeling and survival post-myocardial infarction in a rodent model.⁶ Disruption of IL-12 was recently shown to improve microvascular endothelial function in a diabetes mellitus model.⁷ Finally, a recent study found that circulating IL-12 levels were predictive of long-term prognosis after acute myocardial infarction.⁸

See Article by Ikonomidis et al

The association of proinflammatory cytokines, particularly TNF- α , in patients with heart failure has long been

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recognized.⁹ However, randomized controlled trials with TNF- α antagonists were disappointing and associated with increased risk in heart failure.¹⁰ Novel therapies targeted against specific cytokines in the inflammatory cascade, such as IL-12, are currently under investigation for treatment of a variety of disorders. Ustekinumab is one of the several human monoclonal antibodies targeting the subunit (p40) of IL-12 and IL-23 that was approved by the Food and Drug Administration in 2009 for treatment of psoriasis. Recent data suggest that Ustekinumab may improve psoriasis by inhibiting IL-23 (p19 subunit), as well as IL-12, and several IL-23 inhibitors are now being tested in phase III trials in psoriasis.¹¹ Although Ustekinumab seems to be efficacious in treating psoriasis and reducing markers of chronic inflammation,¹² its potential to prevent, improve, or worsen cardiovascular syndromes remains unclear. These agents are inherently immunosuppressive, and their long-term safety, efficacy, and tolerability in subjects with cardiovascular diseases remain to be determined. For example, IL-12 knockout mice have increased susceptibility for mycobacteria and Salmonella.¹³ Based on relatively small number of cardiovascular events during follow-up, one recent meta-analysis found a potential for higher rates of major adverse cardiovascular events among patients treated with anti-IL-12/23 biological agents,¹⁴ findings that were not confirmed in other analyses.¹⁵

Ikonomidis et al, in the current issue of the journal, examined the role of IL-12 inhibition in comparison with TNF- α inhibition or cyclosporine therapy in 150 subjects with moderate psoriasis and measured their effects on left ventricular (LV) remodeling, the coronary microcirculation, arterial stiffness, and biomarkers of oxidative stress and inflammation.¹⁶ Interestingly, baseline data demonstrate that disease activity, measured by the psoriasis area and severity index, was associated with higher levels of systemic inflammation, including higher IL-12 levels and increased oxidative stress. Furthermore, higher levels of inflammation and oxidative stress correlated with the magnitude of LV strain abnormalities, B-type natriuretic peptide levels, central arterial stiffness, and coronary microvascular dysfunction. As expected, the LV strain abnormalities were proportionate to the magnitude of abnormalities in arterial stiffness, implying that the former was likely the result of the changes in arterial stiffness.

There were also interesting differences demonstrated in the pathway-specific pathophysiologic changes between the 3 agents used. Despite similar relief of psoriasis by these drugs, IL-12/IL-23 inhibition produced greater reduction in inflammation, including IL-12 levels, oxidative stress, and B-type natriuretic peptide levels compared with TNF- α blockade with etanercept or to cyclosporine. Finally, the authors show

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 echocardiography¹⁷ 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.¹⁷ 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.¹⁸ Measurement of CFR in the left anterior descending artery by transthoracic echocardiography correlates well with invasive measurements by Doppler flow wire.¹⁹ The cutoff CFR value of <2 is 90% sensitive and 93% specific for detecting significant stenosis.²⁰ As used in this study, noninvasive measurement of CFR by transthoracic echocardiography can be 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.¹⁰

Disclosures

None.

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