EDITORIAL

Inflammation as a Treatment Target after Acute Myocardial Infarction

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Inflammation is widely believed to play a central role in the pathogenesis of atherosclerosis and acute coronary events.[1,2] Although treatments with proven benefits for secondary prevention of coronary artery disease (e.g., statins and aspirin) appear to have salutary effects on inflammation, the identification of an effective treatment specifically targeting inflammation has been elusive.[3] The Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) provided encouragement that targeting inflammation may be an effective treatment in chronic coronary artery disease. In CANTOS, canakinumab, a monoclonal antibody inhibiting interleukin-1β, reduced the level of high-sensitivity C-reactive protein and resulted in a modestly lower risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke than did placebo.[4] Results were driven by a lower risk of nonfatal myocardial infarction, and there was a higher incidence of fatal infections among canakinumab-treated patients than among patients who received placebo, arousing concerns about risk–benefit trade-offs. Subsequently, nonspecific antiinflammatory treatment with methotrexate in the Cardiovascular Inflammation Reduction Trial (CIRT) showed no reduction in the level of high-sensitivity C-reactive protein and no benefit with regard to cardiovascular outcomes,[5] leaving open the question of whether direct intervention on inflammation can improve cardiovascular outcomes.

With this backdrop, Tardif and colleagues[6] now report in the *Journal* the results of the Colchicine Cardiovascular Outcomes Trial (COLCOT), which tested low-dose colchicine, an antiinflammatory agent clinically used to treat gout and pericarditis that works by inhibiting tubulin polymerization and microtubule formation, for secondary prevention after acute myocardial infarction. The investigators randomly assigned 4745 patients (mean age, 61 years) to receive either colchicine (0.5 mg daily) or placebo at a mean of 13.5 days after myocardial infarction; the median follow-up was 22.6 months. Participants had a high prevalence of guideline-recommended treatment: percutaneous coronary intervention for the index myocardial infarction in 93% of the patients, and the use of dual antiplatelet therapy and statins in 98% and 99%, respectively.

The risk of the primary composite end point (death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization) was lower in the colchicine group than in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02), but this result was driven predominantly by lower risks of angina and stroke. A significant effect on death from cardiovascular causes or myocardial infarction was not shown. Overall, the incidence of adverse events or serious adverse events was similar in the two groups; however, some known gastrointestinal side effects of colchicine, including nausea, were more frequent in the colchicine group, as were pneumonias. However, unlike in CANTOS, no deaths from infection were reported in COLCOT, and the incidence of septic shock in COLCOT was low and similar in the two trial groups.

Although vital status was known in 99.5% of the patients in COLCOT, 1.9% of the patients were lost to follow-up and 0.6% withdrew consent. Fur-

thermore, nearly 19% of the patients in both treatment groups stopped receiving colchicine or placebo prematurely (median treatment duration among patients discontinuing the trial regimen early, 7.1 months [interquartile range, 1.9 to 14.6] for colchicine and 6.1 months [interquartile range, 1.6 to 14.4] for placebo). This high percentage of patients discontinuing the trial regimen, combined with unknown end-point status for 2.5% of the patients, could have obscured the true cardiovascular treatment effect or adverse-event profile. Results of a secondary per-protocol efficacy analysis were only modestly more favorable (hazard ratio, 0.71; 95% CI, 0.56 to 0.90), but these findings should be interpreted with caution because numerous biases may be at play in such nonrandomized comparisons; trial interpretation should principally be informed by the primary intention-to-treat analysis. Regardless, the modest benefit driven by a soft end point of hospitalization for angina and revascularization does not support the routine use of colchicine for secondary prevention without a better understanding of the absence of effect on death or myocardial infarction.

An interesting observation in this trial was the lower risk of stroke in the colchicine group than in the placebo group. Similar findings were reported in a systematic review and meta-analysis of four other randomized trials of colchicine.[7] Whether this reflects a unique mechanistic effect of colchicine in the cerebrovasculature or is simply the play of chance is a question for further investigation.

With the report of COLCOT, where does this leave us with inflammation as a therapeutic target? Direct inhibition of interleukin-1β with canakinumab reduced the level of high-sensitivity C-reactive protein as expected but resulted in only a modest composite efficacy benefit driven by myocardial infarction with a worrisome infection risk; nonspecific antiinflammatory treatment with methotrexate had no effect on the high-sensitivity C-reactive protein level or cardiovascular outcomes; and colchicine, which acts through a unique mechanism, did not lower the high-sensitivity C-reactive protein level more than placebo did in the small subgroup of patients with available data but had a modest composite efficacy benefit, albeit driven predominantly by an angina end point. These observations do not lessen the overall importance of inflammation in atherosclerosis, nor should they halt efforts to find more effective antiinflammatory agents with better side-effect profiles. However, they should encourage us to revisit whether inflammation itself is the best treatment target or whether opportunities exist to identify and better understand pathophysiological processes or mediators that incite inflammation and drive atherosclerosis in order to intervene further upstream.

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