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Low-dose methotrexate does not reduce risk of cardiovascular events

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When it comes to reducing inflammation to decrease the risk of heart disease and stroke, results from the much-anticipated Cardiovascular Inflammation Reduction Trial (CIRT) indicate that targeting the right inflammatory pathways in at-risk patients is crucial. Last year, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that the interleukin-1? inhibitor canakinumab both targeted a specific inflammatory pathway and consequently lowered rates of heart attack and cardiovascular death. By contrast, the findings from CIRT showed that low-dose methotrexate neither inhibited that same inflammatory pathway nor reduced major adverse cardiovascular event rates. These results were presented by Paul Ridker, MD, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, during the American Heart Association Scientific Sessions 2018, and published simultaneously in The *New England Journal of Medicine*.

"The contrasting results between these two contemporary clinical trials demonstrate the importance of considering the mechanistic diversity of inflammatory pathways and of approaches to their inhibition," said Ridker. "Understanding these differences will be crucial for future studies targeting inflammation in atherosclerosis."

Prior to CIRT, observational studies had suggested that low-dose methotrexate, an inexpensive and effective drug widely used to treat rheumatoid arthritis and other inflammatory diseases, might reduce rates of cardiovascular events. The federally-funded CIRT was designed to

rigorously test whether low-dose methotrexate could effectively reduce risk of major adverse cardiovascular events—that is, heart attacks, stroke and cardiovascular death. In parallel, Ridker and colleagues also designed and conducted CANTOS, sponsored by Novartis, to test the same outcomes for canakinumab, a drug that specifically targets interleukin-1β. Interleukin-1 is a pro-inflammatory cytokine that, if over-produced, results in increased inflammation throughout the body as well as elevated levels of interleukin-6 and high sensitivity C-reactive protein (hsCRP), two critical biomarkers of inflammation.

CIRT and CANTOS were both randomized, double-blind, placebo-controlled trials, and both enrolled stable but high-risk atherosclerosis patients. CANTOS, however, was designed to include only patients with persistently elevated hsCRP levels. CIRT did not employ this criterion, and the average hsCRP level for the population was well within the normal range. CIRT enrolled 4,786 North American patients with prior heart attack or multi-vesselcoronary disease who additionally had either type 2 diabetes or a metabolic syndrome. The trial stopped after a median follow-up of 2.3 years.

Unlike canakinumab as used in CANTOS, low-dose methotrexate as used in CIRT did not reduce the inflammatory pathway leading from interleukin-1 to interleukin-6 and on to hsCRP. Concordantly, and in contrast to canakinumab, low-dose methotrexate did not lower cardiovascular event rates compared to placebo. The team reports that 201 patients taking methotrexate suffered a major cardiovascular event compared to 207 patients taking the placebo. Yet, methotrexate was associated with elevations of liver enzymes, reductions in leucocytes and hematocrit, and a higher incidence of non-basal cell skin cancers.

"The results from CIRT and CANTOS, when considered together, tell us something critically important: Not all inflammation is the same, and not all drugs that target inflammation are the same," said Ridker. "While it is

disappointing that an inexpensive drug like methotrexate did not have the effects we previously saw in CANTOS, the results from CIRT shed crucial light on the underlying biology that connects inflammation with cardiovascular disease. The divergent trial results provide a clear roadmap to guide our efforts going forward."

Despite its wide clinical use, the biological mechanisms underlying the anti-inflammatory effects of methotrexate in rheumatoid arthritis and other inflammatory conditions remains poorly understood. Drugs such as colchicine and oral NLRP3 inhibitors that may intersect with the interleukin 1 to interleukin-6 to CRP pathway are currently under investigation or in development.

"CANTOS and CIRT provide the cardiovascular community proof-of-principle that specific targeting of the interleukin-1 to interleukin-6 pathway of innate immunity is crucial for preventing atherothrombotic events. The research goal now and the clinical need of our patients is to find inexpensive and widely applicable agents that can safely target this pathway," Ridker said.

Provided by Brigham and Women's Hospital