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Methotrexate for Cardiovascular Risk Reduction: The Right Choice?

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The causative role of inflammation in atherosclerosis and cardiovascular (CV) disease (CVD) has been well established.[1] Rheumatoid arthritis (RA), a condition associated with systemic inflammation, is included in the CVD risk calculation provided by an analysis of the national QRESEARCH database that included 2.3 million people.[2] Furthermore, in clinical practice, the most recent European guidelines clearly state that RA enhances CVD risk independent of traditional risk factors, with a risk ratio of 1.4 and 1.5 for men and women, respectively.[3] Thus, there is now considerable evidence supporting that CVD incidence is increased by about 50% in patients with RA and that one of the leading causes of increased mortality in these patients is early CVD caused by accelerated atherogenesis.[4] Therefore, the Cardiovascular Inflammation Reduction Trial (CIRT) trial aimed to assess the effect of inhibiting inflammation with low-dose methotrexate (vs placebo) on the rate of CV events in coronary patients with either type 2 diabetes or metabolic syndrome.[5]

Methotrexate is a folic acid antagonist originally developed as a chemotherapeutic drug. At low doses, it is also an effective, safe, and well-tolerated anti-inflammatory agent used in patients with RA or psoriasis.[6] Methotrexate could be a low-cost approach to reduce inflammation, that is, as an alternative to canakinumab used in the prior Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial.[7] This selection was based on observations of a substantial survival benefit, largely by reducing CVD mortality in patients with RA treated with methotrexate versus other conventional disease-modifying antirheumatic therapies in a prospective study (1240 patients).[8] However, this latter study received several criticisms. These were based on patients who, most likely at that time, had a relatively less severe form of RA as witnessed by the low number of tender joints, that is, 7.6 for the methotrexate group and 4.6 for the methotrexate-naive group, and the relatively infrequent use of prednisone (37% vs 22% in the methotrexate and methotrexate-naive groups, respectively), with essentially no use of statins (3% vs 2% in the methotrexate and methotrexate-naive groups, respectively).[8] The criticism was also directed to statistical criteria for this post hoc evaluation, that is, the mortality hazard ratio (HR) dropping from an irrelevant 0.8[9] for nonadjusted findings to a highly significant 0.4 after extensive remodeling. Indeed, in a head-to-head comparison between biosynthetic drugs, that is, tumor necrosis factor-α inhibitors, and conventional synthetic disease-modifying antirheumatic drugs, including methotrexate, these latter drugs were less effective in reducing CVD events and stroke.[10] The CANTOS trial was a randomized, double-blind, placebo-controlled study enrolling 10 061 patients with a history of myocardial infarction (MI) and residual inflammatory risk defined as high-sensitivity C-reactive protein (hs-CRP) levels $\geq$2 mg/L.[7] This trial showed that after a median follow-up of 3.7 years, canakinumab, an antibody that neutralizes interleukin (IL)-1β, significantly reduced recurrent CVD events by 15% (HR: 0.85, 95% confidence interval [CI]: 0.74-0.98, $P = .021$).[7,11]

Although not completely understood, possible beneficial effects of methotrexate on CVD may include immunosuppression as well as improved endothelial function in addition to its anti-inflammatory effects.[12] In patients with RA, methotrexate could also play antiatherogenic effects: (i) by improving the antiatherogenic function of high-density lipoprotein (HDL) particles,[13] (ii) by limiting foam cell formation, (iii) by stimulating reverse cholesterol transport,[14] and (iv) by decreasing the levels of atherogenic lipoprotein (a) and adhesion molecules (eg, E-selectin).[15] Of note, HDL quality is particularly important since functional changes rather than the cholesterol content

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of HDL particles appear to play a major role in atherogenesis.[16,17] Additional findings showed that methotrexate improved 24-hour ambulatory systolic and diastolic blood pressure and pulse-wave velocity (a marker of arterial stiffness) in patients with RA.[18]

Concerning experimental models, in cholesterol-fed rabbits, methotrexate, in combination with paclitaxel, can cause regression of atherosclerotic plaques and decrease macrophage and matrix metalloproteinase 9 presence in these lesions as well as decrease tumor necrosis factor α gene expression.[19] Conversely, in rats with adjuvant-induced arthritis, methotrexate did not improve endothelial function.[20]

The role of systemic inflammation (ie, high disease activity) contributing to accelerated CVD in patients with RA should not be ignored. It has recently been shown that, among the antirheumatic drugs used for RA treatment, methotrexate, triple combination oral therapy (methotrexate, sulfasalazine, and hydroxychloroquine), tumor necrosis factor inhibitor biologicals, and abatacept (interferes with T-cell activity) have the strongest evidence in favor of the reduction of CVD events in patients with RA, even at an older age.[21] Observational studies carried out >10 years ago were generally supportive of some CV benefit with methotrexate. Prolonged treatment with methotrexate was associated with a 15% reduction in CVD events in a cross-sectional observational study of 4363 patients with RA.[22] A systematic review of 10 observational studies involving 66 334 patients with RA, psoriasis, or polyarthritis treated with methotrexate, also indicated that this treatment was associated with a 21% reduced risk of CVD and an 18% reduced risk of MI.[23] Another systematic review and meta-analysis reported a significant decrease in CVD events with methotrexate treatment in 8 studies that included 65 736 patients with RA.[24] Finally, a meta-analysis of 7 studies with almost 24 000 patients with RA treated with methotrexate showed that such treatment is associated with a lower risk of any major acute CVD event.[25] Methotrexate treatment also appears to be associated with beneficial effects on surrogate CVD markers such as carotid intima–media thickness.[26]

The CIRT study,[5] although impressive in size and quality of data collection, was based on patients with relatively normal inflammatory biomarkers, poorly modified by treatment, thus probably reproducing the low-risk patients with RA earlier selected by some investigators. The CIRT trial after a median follow-up of 2.3 years, with a maximum follow-up of 5 years, was terminated early since the study met a prespecified threshold for futility of low-dose methotrexate therapy on the primary outcome of major adverse cardiac events (HR: 0.96, 95% CI: 0.79-1.16, $P = .67$). A first occurrence of a final event was recorded in 201 patients given methotrexate compared with 207 on placebo.[5] No significant reduction in plasma concentrations of hs-CRP, IL-1β, and IL-6 was observed.[5] Based on these results, low-dose methotrexate therapy may not have a role in the reduction of CVD events in patient populations other than those with rheumatologic diseases.[5]

Well-designed randomized clinical trials are needed to elucidate whether methotrexate decreases CVD morbidity and mortality, even in selected groups of patients such as those with RA. Also, it is clear that, even if the results of such trials are positive, methotrexate can only be a complementary therapeutic option to already established treatments for CVD prevention such as lipid-lowering drugs, antihypertensives, smoking cessation, weight loss, and so on. Namely, it has been shown that statins, for example, atorvastatin 40 mg/d, resulted not only in a significantly greater fall in low-density lipoprotein cholesterol levels than placebo but also in a 40% reduction of CVD events in patients with RA.[27] Furthermore, statins may beneficially affect RA disease activity, mainly due to their anti-inflammatory and immunomodulatory properties.[28,29] This has been already suggested more than a decade ago.[30]

Authors' Note

Dr Reiner has received honoraria for lectures from Sanofi Aventis. Dr Banach has served on the speaker's bureau and as an advisory board member for Amgen, Sanofi, Mylan, Krka, and Esperion.

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