

Methotrexate in Our Hearts



Undoubtedly, methotrexate (MTX) has a unique place in all rheumatologists' hearts. It holds the position of first-line treatment choice for rheumatoid arthritis (RA) in the European and North American treatment guidelines for RA^{1,2,3}. The benefit of early start of disease-modifying antirheumatic drugs (DMARD), where MTX is the most preferred, has been increasingly emphasized in the last decade. In 2010 an expert task force published recommendations aiming at maximizing patients' longterm health-related quality of life, through minimizing disease activity in RA as quickly as possible, with the goals of controlling symptoms, normalizing function, and halting radiographic progression of joint damage⁴. The treatment strategy is widely known as treat to target, and even though it has been questioned^{5,6}, it is now a cornerstone in the modern approach to RA disease activity and treatment.

In spite of the strong evidence that the drug is a good first choice for our patients, we still might not use it enough, especially when encountering the onset of RA in the elderly. Patients who develop RA at an older age have higher disease activity and disability, but experience a lesser chance of getting intensive treatment with MTX and other DMARD than their younger counterparts^{7,8}.

During the last 20 years we have also become aware that patients with RA have an increased risk of cardiovascular (CV) disease; mainly acute coronary events, but also ischemic stroke. An increased occurrence of traditional risk factors for CV disease does not fully explain the increased risk noted, and it has been suggested that inflammatory activity, and in particular, high disease activity, as seen in active RA, is partly responsible for the risk increase^{9,10,11}.

There are several reports indicating a CV risk reduction associated with MTX treatment in RA^{12,13}. The underlying mechanisms are largely unknown, but in experimental studies MTX has been observed to inhibit key proatherosclerotic cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, and IL-6¹⁴. This could result not only in control of the RA disease activity, but also in beneficial effects on endothelial function and vascular homeostasis. Depending on

the background for the observed association between disease activity and CV risk, there are thus several possible explanations for the CV preventive potential of MTX.

No trials have yet been conducted aiming to prove the "inflammatory hypothesis" with MTX treatment in RA. We still await the results from The Cardiovascular Inflammation Reduction Trial, in which patients with a high risk of a second myocardial infarction (but no inflammatory rheumatic disease) were given low-dose MTX or placebo in addition to traditional secondary preventive treatment¹⁵. In the CANTOS trial¹⁶, however, treatment with the IL-1 β inhibitor canakinumab was shown to lower the inflammation and CV events in high-risk patients who were free from inflammatory rheumatic disease. Interestingly, it did so without exerting its effect through reduction of blood lipid levels. In RA, there are observational studies on TNF inhibition and its effect on CV risk, and these studies suggest that it is not the TNF blocking agent *per se* that reduces the risk of CV disease. It is rather the effect that TNF blockers have on the disease activity that lowers the risks of CV disease in RA. In fact, those who lowered their risk the most were patients who responded to TNF treatment, as opposed to those who did not^{17,18}. The results of these studies might contribute to the understanding of the role of inflammation on CV risk in RA.

With this in mind it is interesting to read the study by Widdifield and colleagues in this edition of *The Journal*¹⁹. The study includes almost 24,000 patients diagnosed with RA after the age of 65, and the authors' main focus was to assess what effect the actual timing of MTX use has on the risk of CV disease. This is much needed because most studies on MTX and CV risk have focused on MTX as a binary variable (yes/no treatment with MTX), and have not taken into account when the treatment was given in relation to the CV event or RA diagnosis. In this cohort of patients diagnosed with RA somewhat later in life than what we usually see in our practices (mean age 75 yrs at diagnosis), only 35% were treated with MTX within the first year of diagnosis, which is a lot less than what has been reported in

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other cohorts²⁰, and the incidence of CV disease was higher than what has been reported previously. Both these aspects of course reflect the fact that the patients were older when diagnosed with RA and when followup started. Nonetheless, what the authors beautifully demonstrate is that the timepoint in their disease history when patients were treated with MTX is important; those treated within the last 12 months were at significantly lower risk of a CV event than those who had not been treated with MTX during the last 12 months. Some of this effect could be due to confounding by indication, an issue the authors address in their discussion, and that perhaps is supported by the lower prevalence of comorbidity noted in the MTX-only group. An additional novelty presented related to timeliness, is that there seemed to be a window of opportunity in CV risk prevention, not only in the prevention of joint damage, in RA. The patients who were treated with MTX during the first year of diagnosis were also at decreased risk of CV disease compared to those who were not treated, and even though the effect did not last over time and beyond MTX discontinuation, it is an interesting finding. That these patients were older when they were diagnosed than we usually see is another striking aspect. Maybe we should all ask ourselves whether we are denying our older patients the cardioprotective treatment that MTX provides and that the patients need, probably more often than patients diagnosed in their 40s.

The next step in disentangling through what pathway MTX exerts its cardioprotective effect in RA would of course be to assess the effect of MTX in relation to disease activity, and its relation to response to treatment. A clear association between response (compared with a lack of response) to MTX treatment and the risk of CV disease would support the inflammatory hypothesis, and if no association could be detected it would suggest that MTX indeed acts through other pathways than through lowering inflammation when exerting its protective effect.

Regardless, recent MTX treatment and MTX treatment during the first year of RA diagnosis seems to reduce the risk of CV disease in RA. MTX has a well-deserved place as a first-line DMARD. Maybe now is the time to give MTX its rightful place, along with statins and antihypertensives, in CV prevention in our high-risk patients with RA.

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