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Editorial

Methotrexate and Cardiovascular Disease in Patients With Rheumatoid Arthritis: Insights and Novel Speculations

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Rheumatoid arthritis (RA) increases the risk for cardiovascular disease (CVD) and the risk is related to disease activity[1,2,3,4]. Groundbreaking studies on the etiology of CVD have shown that there is a strong relationship with inflammation[5,6]. Given that a core therapeutic goal in RA is to control inflammation, it is appropriate to determine if therapeutic interventions for disease activity may also favorably affect the incidence of CVD.

Because of the association of inflammation with CVD, a large therapeutic trial was conducted to determine if methotrexate (MTX) treatment in patients with a history of CVD could actually prevent new vascular events. The Cardiovascular Inflammation Reduction Trial (CIRT) was conducted in patients with a history of CVD (without RA or any other inflammatory disease) to determine if weekly MTX was associated with a decrease in new cardiovascular (CV) events[7]. The study was discontinued due to the lack of benefits of MTX on CVD reduction in this population. However, there has been much speculation regarding the reason(s) for the absence of MTX effect, including the fact that these patients did not have systemic inflammation with elevated C-reactive protein (CRP)[8].

Given the inflammatory nature of RA, it is certainly logical to posit that therapeutic interventions directed at the treatment of the underlying disease would also favorably affect the incidence of CVD in that population. Indeed, studies have shown that inhibition of both tumor necrosis factor (TNF)[9,10] and MTX[11,12,13,14,15] significantly diminishes the incidence of CVD in patients with RA.

In this issue of *The Journal of Rheumatology*, Xie and colleagues have demonstrated that MTX is also incrementally beneficial for the prevention of CVD when used in combination for patients with RA along with biologic disease-modifying antirheumatic drugs (bDMARD)[16]. As MTX is often used with bDMARD, it is of interest to determine if a CVD-protective effect of the drug is also found when used in combination with these agents. The authors used a retrospective cohort of patients between 2006 and 2015 identified from the Medicare claims database. Medicare is available for all United States citizens and is predominantly composed of older subjects. The mean age (SD) of the patients in this report was 64.6 years (12.3 yrs). The authors report that the crude incidence rates (IR) for CVD were 17.9 (95% CI 16.9–18.8) and 12.1 (95% CI 11.1–13.2) per 1000 patient-years, respectively, in MTX unexposed and exposed populations receiving bDMARD. IR were similarly diminished when MTX was combined with bDMARD for individual events of myocardial infarction (MI), stroke, MI or stroke, and a composite CVD outcome including revascularization procedures and angina.

In order to be identified as a new user of a bDMARD, patients had to have no prior use of these agents in the year prior to initiation. The diagnosis of RA was established with International Classification of Diseases, 9th revision, Clinical Modification billing codes, as were a host of comorbidities and concomitant medications. There are no direct measures of disease activity in the Medicare claims database. However, the authors used the Multibiomarker Disease Activity (MBDA) laboratory test as a surrogate for disease activity. The MBDA results are somewhat challenging to interpret as this measure was associated only with the patients in the Medicare registry in 4.87% of the population reported upon (Table 1 footnotes[16]). Xie and colleagues also used a single measure of MBDA that could have been obtained as long as 6 months prior to inclusion in the Medicare data. In addition, the ability of this laboratory measure to substitute for and accurately portray validated clinical outcomes, especially for patients with midrange results, has not yet achieved predictable

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reliability and universal acceptance. Thus, a potential weakness of the authors' report is that there was no reliable measure of disease activity in the vast majority of the population. As RA disease activity is independently associated with CVD[4], this omission is of some relevance.

The mean follow-up in the authors' report was approximately 9 months. Thus, there is the need for some longer-term observations in this population. The age distribution of patients reported is skewed towards older individuals in the Medicare database. Therefore, studies of patients with a more typical age distribution of RA will be needed to confirm these observations. The authors were unable to ascertain certain risk factors for CVD including obesity, whereas the prevalence of smoking is roughly consistent with more recent data[17] but may underestimate higher rates in the 5- to 15-year-old data the authors report.

Despite some unavoidable methodologic flaws inherent with claims data, there are certainly merits to the authors' approach, as well as their novel observation that MTX is associated with further diminution of CV events when used in combination with bDMARD. The number needed to treat (NNT) in order to avoid 1 CVD event is calculated to be 200. This number may, at first consideration, appear to be too low to justify the addition of MTX to a bDMARD if the effect of MTX on CVD risk is in fact the sole reason why the drug is being used. However, if one makes a realistic, and somewhat conservative, assumption that the "average" rheumatologist treats at least 400 patients with RA, and roughly one-half will be on a bDMARD at a given time, it is apparent that the use of MTX with bDMARD could avoid at least 1 episode of CVD per year in their RA patients. These numbers would expand greatly when the entire population of RA patients on combination treatment is considered.

There are other reasons to use MTX with bDMARD, including both its therapeutic effect as well as the inhibition of antidrug antibodies when the drug is used with monoclonal TNF inhibitors[18]. Of potential relevance to this discussion is a recent study of MTX withdrawal in patients taking tocilizumab (TCZ) that was not associated with significant clinical deterioration[19]. An examination of Xie and colleagues' Supplementary Table 1 can serve to fuel mechanistic speculations[16]. This table indicates that the IR of composite CVD events is consistently lowest for TCZ with combined incidence of MI, stroke, or fatal CVD with rates of 14.6 (95% CI 11.8–18.0) to 8.6 (95% CI 5.5–13.5) in MTX unexposed and exposed populations, respectively. Both these measures are numerically lower than the other bDMARD reported in the table, although CI do overlap. Of note, the lower incidence of CVD events compared with other bDMARD in patients taking TCZ was also consistently observed when individual categories of CVD events were examined.

Although the authors do not comment on the differences of IR and HR of CVD events across the individual bDMARD combined with MTX, it is tempting to speculate on how TCZ could provide enhanced amelioration of CVD while sharing possible mechanisms with MTX. We had previously shown that MTX is a potent inhibitor of interleukin-6 (IL-6)[20] and, as already noted, patients taking TCZ can discontinue MTX without experiencing statistical disease worsening[19]. Is it possible that the improvement in CVD events seen when MTX is combined with other bDMARD could be attributed to a partially shared mechanism of IL-6 inhibition with TCZ? IL-6 drives CRP associated with CVD[21]. As noted, the patients in CIRT did not have elevations of CRP and thus we can presume that their IL-6 levels were lower than those seen in patients with RA.

Of course, MTX exerts its therapeutic effects through a variety of mechanisms and it would be misleading to focus entirely on IL-6 inhibition to explain its therapeutic efficacy. However, this underappreciated therapeutic pathway could contribute to the drug's ability to inhibit CVD.

Thus, the juxtaposition of these apparently unconnected observations[7,16,19,20,21] is potentially hypothesis-generating. Further studies will be needed to establish the contribution of elevated levels of circulating IL-6, and its inhibition, to the beneficial effects of MTX on CVD when used as monotherapy[10,11,12,13,14,15], as well as when combined with bDMARD[16]. Janus kinase (JAK) inhibitors are also associated with potent suppression of IL-6. Long-term studies of CVD outcomes will be needed to determine if suppression of CVD, after adjustment for disease control, will also be part of the therapeutic profile of this class of drugs.

While we have focused previously on some of the potential flaws associated with claims data in an older population, it must also be acknowledged that there are also substantial positives associated with claims databases. These include very large numbers of patients with associated enhancement of statistical power, as well as overall completeness of many focused outcomes. It is also appropriate to compliment Xie and colleagues for examining for the first time the potential additional benefit of the use of MTX on CVD when used in combination with bDMARD[16]. It will be interesting to see if these same long-term benefits will extend to JAK inhibitors prescribed with and without MTX. We therefore await investigations from both claims and registry data to provide further insights on the benefits of these agents to patients with RA at risk for CVD.

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