Protective effect of methotrexate in patients with rheumatoid arthritis and cardiovascular comorbidity

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Abstract: Rheumatoid arthritis (RA) is associated with an increased risk of premature mortality, predominantly due to increased cardiovascular disease (CVD). Systemic inflammation has been established as one of the primary drivers of accelerated atherosclerosis in RA, though other traditional and disease-specific risk factors also contribute. There is evidence that methotrexate, considered a mainstay of therapy for RA, can ameliorate some of this excess CVD risk, an effect that has not been seen consistently with other disease-modifying antirheumatic drugs. The cardioprotective action of methotrexate may occur through reducing systemic inflammation and by directly affecting some of the cellular mechanisms that lead to atherosclerosis. On the basis of this evidence, there are ongoing trials of low-dose methotrexate in patients from the general population with CVD but who do not have RA. Methotrexate reduces the overall CVD burden in patients with RA. With earlier treatment of RA and earlier use of methotrexate it is possible that we may have the capability to radically change patients' long-term CVD risk.

Keywords: atherosclerosis, cardiovascular disease, inflammation, methotrexate, rheumatoid arthritis

Introduction

Patients with rheumatoid arthritis (RA) are known to have an increased risk of premature mortality compared with the general population, primarily due to an increased incidence of cardiovascular disease (CVD), particularly coronary artery disease [Aviña-Zubieta *et al.* 2008].

The increased CVD morbidity and mortality seen in RA cannot be entirely explained by an increase in traditional risk factors [Sattar *et al.* 2003]. Disease-specific risk factors such as chronic inflammation may contribute to the excess CVD morbidity and mortality. There is evidence that both the RA and non-RA populations share many of these inflammatory mechanisms that promote premature atherosclerosis.

Methotrexate (MTX), the cornerstone therapy of disease-modifying antirheumatic drugs (DMARDs) and biological treatment of RA, has been shown to reduce the overall CVD risk,

probably by reducing the systemic inflammation that drives the development of atherosclerosis. This review explores the pathogenesis and risk factors for CVD in RA and evaluates the evidence that MTX reduces cardiovascular morbidity and mortality.

Pathogenesis and risk factors for atherosclerosis in rheumatoid arthritis

Atherosclerosis is an inflammatory disease

There is now a wealth of evidence to show that immune-mediated inflammatory mechanisms drive atherosclerosis leading to abnormal endothelial function, plaque infiltration with chronic inflammatory cells and increased risk of acute plaque rupture. These processes are accelerated by the systemic inflammation of RA. There are also clear similarities between the inflammatory vascular environment in which atherosclerosis develops and the inflammatory synovium of RA.

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This suggests common pathways may contribute to both conditions. In the general population, systemic markers of inflammation such as raised levels of highly sensitive C-reactive protein (hsCRP) [Ridker *et al.* 2004] and interleukin 6 (IL-6) [Ridker *et al.* 2002] have been shown to be independent predictors of CVD. At the intimal level, monocyte-derived macrophages and macrophage-derived foam cells [driven by inflammatory cytokines including tumour necrosis factor (TNF), granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-12] lead to atheroma formation. Atheroma plaque instability is mediated by local matrix metalloproteinase action [Morand *et al.* 2006]. Monocytes and macrophages also produce tissue factor, making the necrotic lipid core of the lesion hypercoagulable and promoting thrombus formation when lesions rupture [Plutzky, 2001].

Autoantibodies and cardiovascular risk

The presence of autoantibodies such as rheumatoid factor (RF) and possibly anticyclic citrullinated protein antibodies (anti-CCP) is associated with an increased CVD risk in RA [Goodson *et al.* 2002] and in the general population [Edwards *et al.* 2007] possibly by direct endothelial injury. Antibodies directed against oxidized low-density lipoprotein (LDL) have also been associated with CVD [van Doornum *et al.* 2002] and occur more frequently in RA than the general population [Wallberg-Jonsson *et al.* 2002], though they have not yet been proven to be pathogenic.

Procoagulable state

In addition to an inflammatory burden, RA may contribute to the thrombotic aspects of CVD through its promotion of a hypercoagulable state. Increased levels of fibrinogen, von-Willebrand factor and tissue plasminogen activator, factors that are all associated with an increased cardiovascular risk, have been noted in patients with RA [McEntegart *et al.* 2001; Wallberg-Jonsson *et al.* 2000].

Traditional risk factors

Traditional risk factors for CVD may also be more prevalent in RA. Some studies have shown that patients with RA, especially those with established disease, have an increase in traditional cardiovascular risk factors such as hypertension,

diabetes, and cigarette smoking [Bhatia *et al.* 2006].

Exercise and obesity

Disability in RA causes reduced levels of physical activity that may play a part in the increased cardiovascular risk of RA. Patients who are disabled by their arthritis are more likely to be overweight or obese [Giles *et al.* 2008], itself a risk factor for metabolic syndrome and CVD [Bray and Bellanger, 2006]. Furthermore, overweight patients with RA tend to have worse disease activity [Stavropoulos-Kalinoglou *et al.* 2009], contributing to the systemic inflammatory responses that lead to accelerated atherosclerosis.

Drug therapies

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of CVD. Corticosteroid use has been associated with an increased risk of cardiovascular events [Maradit-Kremers *et al.* 2005]. However, there may be specific interactions between the treatment and individual risk factors, such as antibody status [Davis *et al.* 2007]. Several meta-analyses have now shown that NSAIDs are associated with an increased risk of cardiovascular events [Bolten, 2006; Farkouh and Greenberg, 2009]. Naproxen appears to be the exception and does not exhibit the same increased cardiovascular risk as other NSAIDs [Rahme *et al.* 2002] and is probably risk neutral compared with placebo [Trelle *et al.* 2011]. Tight control of disease activity with MTX can reduce the overall use of corticosteroids and NSAIDs, thereby ameliorating some of the additional CVD risk that these therapies incur.

Methotrexate and cardiovascular disease

MTX has been suggested to have cardioprotective properties and data have been published regarding the effect of MTX on a variety of cardiovascular outcomes, including acute myocardial infarction (MI), heart failure and stroke. The effect of MTX on surrogate markers for CVD, such as lipid metabolism and carotid intima-media thickness (IMT), has also been investigated. These studies are summarized in Table 1.

Table 1. Summary of the effects of methotrexate in cardiovascular disease.

	Effect of MTX	Strength of effect	Oxford level of evidence
CVD			
All-cause CVD	Reduced by MTX	Strong	2a
Heart failure	Reduced by MTX	Strong	2a
Acute myocardial infarction	No conclusive evidence of benefit to date	Moderate	2a
Stroke	Trend towards reduced incidence	Moderate	2b
Cardiovascular risk factor			
Metabolic syndrome	No conclusive evidence of benefit to date	Moderate	2a
Atherosclerosis (carotid IMT)	No conclusive evidence of benefit to date	Moderate	2a
Hyperhomocysteinaemia	Increased by MTX (effect ameliorated by folic acid supplementation)	Strong	4

CVD, cardiovascular disease; IMT, intima-media thickness; MTX, methotrexate.

Methotrexate and cardiovascular morbidity

The value of MTX in preventing cardiovascular (and all-cause cardiovascular) morbidity and mortality has been investigated by several groups. A variety of composite endpoints have been used, including fatal and nonfatal MI, stroke and transient ischaemic attack.

Strong evidence of CVD benefit for MTX comes from Choi and colleagues [Choi *et al.* 2002], who reported a significantly reduced incidence of CVD mortality in a study of 1240 patients. Patients receiving MTX therapy were 70% less likely to suffer a fatal CV event [hazard ratio (HR) 0.3; 95% confidence interval (CI) 0.2–0.7] during the study (mean follow up 6 years) compared with those not receiving a DMARD. There was no demonstrable dose-dependent relationship and other non-MTX DMARD usage was not associated with a decreased risk of CVD mortality. Further evidence of benefit has been provided by several other studies also showing statistically significant reductions in CVD mortality. The reductions in CVD morbidity and mortality range from 85% to 15% [van Halm *et al.* 2006; Naranjo *et al.* 2008; Hochberg *et al.* 2008].

In contrast, Greenberg and colleagues [Greenberg *et al.* 2011] have reported data from The Consortium of Rheumatology Researchers of North America (CORRONA) group showing that MTX was not associated with a reduced

CVD risk compared with other nonbiological DMARDs. This study considered composite fatal and nonfatal cardiovascular endpoints in 10,156 patients (followed for an average of 22.9 months) and showed no significant reduction in cardiovascular outcomes compared with those receiving non-MTX DMARDs (HR 0.94; 95% CI 0.49–1.80). This study did report significant reductions in fatal and nonfatal CVD outcomes associated with anti-TNF therapies (HR 0.39; 95% CI 0.19–0.82; and HR 0.35; 95% CI 0.16–0.74 respectively). These data follow an earlier publication from the CORRONA group [Kremer, 2006] that also did not show an association between MTX use and reduced CVD events.

Methotrexate and heart failure

Patients with RA have an approximately twofold increased risk of heart failure compared with healthy controls [Nicola *et al.* 2005]. Presentation tends to be subtler and yet there is a significantly higher mortality following the onset of heart failure compared with non-RA controls [Davis *et al.* 2008]. There have been two large studies looking specifically at the association between DMARD use and heart failure. The first, a case control study of 520 patients with RA [Bernatsky *et al.* 2005] showed that current treatment with MTX (compared with non-DMARD use) conferred a 20% reduction in the risk of hospitalization for congestive cardiac failure (relative risk 0.8, 95%

CI 0.6–1.0). In the second, a cohort study of 759 patients [Myasoedova *et al.* 2011], MTX use reduced the risk of developing heart failure by half (HR 0.5, 95% CI 0.3–0.6) compared with those not receiving MTX.

Methotrexate and acute myocardial infarction

Several studies have assessed whether MTX can reduce the incidence of MI in patients with RA. One study reported a reduced risk of MI in patients receiving MTX [Naranjo *et al.* 2008], two studies showed nonsignificant trends towards reduced risk [Suissa *et al.* 2006; Radovits *et al.* 2009], and another study showed no significant difference in the risk of MI between patients receiving MTX and those not receiving MTX [Edwards, 2008]. There were significant differences in research methodology, patient demographics and duration of MTX treatment among these studies, making it difficult to draw definite conclusions about the effect of MTX in MI.

Methotrexate and stroke

There have been two publications on the incidence of stroke in patients receiving MTX. Naranjo and colleagues reported an 11% reduction in stroke when comparing patients receiving MTX with those not receiving a DMARD (HR 0.89%; 95% CI 0.82%–0.98%) [Naranjo *et al.* 2008]. The second, unpublished study did not show any reduction in stroke associated with MTX (or other DMARD) use [Endean, 2007].

Methotrexate and metabolic syndrome: obesity, insulin resistance and lipid profiles

Metabolic syndrome, a cluster of traditional cardiovascular risk factors including central obesity, insulin resistance, hypertension, raised triglyceride levels and low levels of high-density lipoprotein (HDL), has been identified as an independent cardiovascular risk factor [Reilly and Rader, 2003]. The combination of risk factors appears to confer a synergistic increase in CVD risk and is very prevalent in some RA populations (four times more common in populations from the USA with RA) [Chung *et al.* 2008].

Treatment with MTX has been shown to reduce the incidence of metabolic syndrome (as defined by the National Cholesterol Education Programme 2004 criteria) [odds ratio (OR) 0.517; 95% CI 0.33–0.80] in a study of 387

patients of whom 114 were taking MTX [Toms *et al.* 2009]. There were associated improvements in lipid parameters and fasting glucose levels but no improvement in levels of insulin resistance. A second study of 107 women with RA [Zonanan-Nacach *et al.* 2008] reported that metabolic syndrome was more common with shorter duration of MTX treatment (33 ± 1 24 *versus* 42 ± 41 months, $p=0.04$).

In contrast, two studies have shown that while RA is associated with an increased incidence of metabolic syndrome, this effect is not ameliorated by MTX use [Karvounaris *et al.* 2007; Crowson *et al.* 2011].

Methotrexate and atherosclerosis

The anti-inflammatory effects of MTX in RA may have a beneficial effect on the development of atherosclerosis as measured by carotid IMT. Several groups have investigated the potential antiatherosclerotic effect of MTX but to date no conclusive evidence of benefit has been forthcoming. Two small studies have shown statistically significant reductions in carotid IMT with combination MTX plus chloroquine therapy [Ristic *et al.* 2010] and combination MTX plus prednisolone therapy [Georgiadis *et al.* 2008] but have not assessed the effect of MTX alone. Further studies have shown no improvement in carotid IMT with MTX [Wallberg-Jonsson *et al.* 2004; Kumeda *et al.* 2002], although Turiel and colleagues were able to demonstrate improvements in coronary flow reserve; a measure of cardiac microvascular function that is a surrogate marker for preclinical coronary atherosclerosis [Turiel *et al.* 2010].

Methotrexate and hyperhomocysteinaemia

Hyperhomocysteinaemia ($>15 \mu\text{mol/liter}$) is a known risk factor for accelerated atherosclerosis and MI [Welch and Loscalzo, 1998]. It has been reported in 20–42% of patients with RA [Lopez-Olivo *et al.* 2006; Schroeksadel *et al.* 2003] and is at least partly driven by systemic inflammation. Genetic factors such as the C677T mutation also contribute [Gonzalez-Gay *et al.* 2005]. While some studies have shown an association between MTX use and hyperhomocysteinaemia [Hornung *et al.* 2004] this has not been a consistent finding. Folic acid supplementation has been shown to restore normal homocysteine levels [Schroeksadel *et al.* 2003]. In the RA cardiovascular studies in

Table 2. Summary of the effects of methotrexate on known cardiovascular risk factors in rheumatoid arthritis.

Cardiovascular risk factors	Evidence of benefit from methotrexate
Inflammation	
hsCRP	Shown to reduce levels
IL-6	Shown to reduce levels
TNF α	Shown to reduce levels
Lipids and cholesterol	
LDL:HDL	Not proven to affect
Antibodies to oxidized LDL	Not proven to affect
Cholesterol transport	Increases activity of antiatherogenic cholesterol transporter proteins
Metabolic syndrome	Trend towards reduced incidence
Procoagulable state	
Fibrinogen	Not proven to affect
Von-Willebrand factor	Not proven to affect
Tissue plasminogen activator	Not proven to affect
Other	
RF and anti-CCP	Not proven to affect
Hyperhomocysteinaemia	Not proven to affect

Anti-CCP, anticyclic citrullinated protein; HDL, high-density lipoprotein; hsCRP, highly sensitive C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; RF, rheumatoid factor; TNF α , tumour necrosis factor α .

which folic acid supplementation was considered a possible confounding factor [Choi *et al.* 2002; Prodanovich *et al.* 2005], there was no reported difference in CVD outcomes between those who received and those who did not receive supplementation.

Mechanisms of cardiovascular disease reduction by methotrexate

The exact mechanism of MTX's anti-inflammatory action in RA remains uncertain. It is probably mediated by accumulation of adenosine [Cronstein, 2010], a potent endogenous anti-inflammatory mediator, but there are also significant effects on T-cell activation [Mortia *et al.* 2006]. Systemically, MTX has been shown to reduce CRP, IL-6 and TNF α , cytokines known to drive the development of atherosclerosis [Aggarwal and Misra, 2003]. *In vivo*, MTX has been shown to downregulate foam cell production and increase expression of antiatherogenic reverse cholesterol-transport protein [Reiss *et al.* 2008].

This suggests that the antiatherogenic actions of MTX may not be confined to an anti-inflammatory effect. MTX does not appear to have a significant effect on the levels of serum LDL and HDL

cholesterol [Park *et al.* 2002] and does not appear to affect platelet function or other procoagulable factors that may be contributing to excess CVD in RA [Ridker, 2009]. These findings are summarized in Table 2.

Discussion

Most studies have tended to show a benefit from MTX in reducing the risk of CVD endpoints in patients with RA. While the studies have been heterogeneous, previous systematic reviews have consistently reported overall cardiovascular benefits with MTX [Micha *et al.* 2011; Westlake *et al.* 2010]. The evidence for benefit is strongest for a reduction in the overall CVD morbidity and mortality and weakest for stroke outcomes, though there is considerable variation in the risk reduction reported. This is most notable in the all-cause CVD mortality studies when comparing the results of Choi and colleagues and Greenberg and colleagues. Several factors are likely to explain the divergent findings for CVD outcomes, including differences in the referent population (non-DMARD use *versus* nonbiological DMARD use respectively) and differing definitions of MTX use – CORRONA assessed current MTX use while Choi and colleagues and other studies have included current or historical

use of MTX. Total duration of MTX exposure may be an important determinant of its protective cardiovascular effects. With regards to the effect of MTX on risk factors for CVD it is difficult to draw conclusions at the present time. Certainly MTX appears to have a role in preventing atherosclerosis, though the exact mechanisms are still unclear.

On the basis of this evidence there has already been one small-scale study assessing the potential for MTX to improve the outcomes for patients with heart failure who do not have RA. The METIS trial (The Effects of Methotrexate therapy on the Physical Capacity of Patients with Ischemic Heart Failure) showed a trend towards improvement in functional class (New York Heart Association) but did not show reductions in levels of CRP or composite cardiovascular outcomes [Moreira *et al.* 2009]. A second, larger study – CIRT (Cardiovascular Inflammation Reduction Trial) is currently underway. CIRT will trial low-dose MTX (10 mg weekly) in patients without RA who have stable coronary artery disease post MI and persistently elevated hsCRP [Ridker, 2009]. If CIRT can show that MTX improves composite cardiovascular adverse events then interest in anti-inflammatory treatments for CVD will surely increase.

It is noteworthy that some studies of DMARDs with an efficacy similar to MTX have also shown reduced CVD events. Naranjo and colleagues reported reductions in CVD mortality with sulfasalazine and leflunomide (HR 0.92; 95% CI 0.87–0.98; and HR 0.59; 95% CI 0.43–0.79 respectively) [Naranjo *et al.* 2008] while Van Halm and colleagues also showed a reduced CVD mortality risk with sulfasalazine monotherapy (OR 0.37; 95% CI 0.14–0.99) [van Halm *et al.* 2006]. There is evidence that treatment with anti-TNF therapy can also reduce the risk of CVD events [Greenberg *et al.* 2011; Westlake *et al.* 2011], although these findings do not appear to be as consistent as the data for MTX. The mechanisms by which these therapies modulate CVD risk are still unclear and further research is required to delineate the extent to which their action is locally mediated as opposed to simply suppressing the systemic inflammation that contributes to accelerated atherosclerosis.

The risk of developing CVD appears to be established very early in the course of RA and may already be present at the time of diagnosis

[Maradit-Kremers *et al.* 2005]. The ‘window of opportunity’ hypothesis suggests that very early inflammatory joint disease (less than 12 weeks’ duration) may differ immunologically from established inflammatory disease and that early intervention may have a beneficial long-term impact on disease progression and subsequent disability. In RA, early intervention with DMARDs and biological drugs has been shown to increase the likelihood of remission and reduce joint damage [Hyrich, 2008; Mottonen *et al.* 2002; Nell *et al.* 2004; Lard *et al.* 2001]. Furthermore, the use of MTX in very early RA has been shown to be effective [van Dongen *et al.* 2007]. Just as the window of opportunity suggests that very early treatment of RA can fundamentally alter the outcomes for patients in terms of joint disease, it is possible that earlier use of MTX may have the capability to radically change patients’ long-term CVD risk.

Conclusions

There is evidence that MTX may reduce the burden of CVD in RA. The strongest evidence of benefit exists from studies of all-cause cardiovascular morbidity and mortality. In experimental models, MTX has been shown to alter the intima-level inflammatory disease that leads to atheromatous plaque formation, although evidence of benefit is less clear in population-based studies. There is growing evidence that tight control of systemic inflammation with MTX or anti-TNF can significantly alter a person’s overall CVD risk. Whether these findings can be extrapolated to the non-RA population remains to be determined.

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Conflicts of interest statement

The authors declare no conflicts of interest in preparing this article.

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