[Review article]

Increased cardiovascular risk in patients with rheumatoid arthritis: an overview

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Abstract Patients with established rheumatoid arthritis (RA) have a higher cardiovascular morbidity and mortality in comparison with the general population. It is considered to be an independent risk factor for cardiovascular disease. The purpose of this article is to describe the mechanisms responsible for accelerated atherogenesis in RA patients and to give an overview of the effects of different RA therapies (methotrexate, TNF antagonists and other biologicals).

Keywords *Cardiovascular risk – atherogenesis – rheumatoid arthritis – TNF antagonists – heart failure.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of the joints, with also a number of extra-articular manifestations, including cardiovascular disease (CVD). It is now well recognized that patients with established RA have a higher cardiovascular morbidity and mortality in comparison with the general population. The mechanisms responsible for this excess in morbidity and mortality differ from those in the general non-RA population. The prevalence and severity of a number of traditional risk factors such as arterial hypertension, dyslipidaemia, obesity and physical inactivity[1-5]is higher in RA patients. However, this does not fully explain the enhanced morbidity and mortality. In a post-mortem series of RA patients, there was less histological evidence of atherosclerosis in the coronary arteries of RA patients but more inflammation and plaque instability[6]. RA is now considered to be an independent risk factor for CVD. Immune dysregulation and sustained inflammation appear to play a major role in the development of accelerated atherogenesis[7-9]. It is therefore anticipated that therapies aimed at reducing disease activity in RA can lower the risk of CVD by reducing the burden of systemic inflammation. The purpose of this article is to describe the mechanisms responsible for accelerated atherogenesis in RA patients and to give an overview of the effects of different RA therapies (methotrexate, TNF antagonists and other biologicals).

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EPIDEMIOLOGY

Rheumatoid arthritis (RA) is a common chronic inflammatory disease causing both arthritis and systemic extra-articular manifestations. Many studies have found cardiovascular morbidity and mortality to be increased in patients with established RA, in comparison with the general population[10]. Up to 50% of this excess mortality is secondary to ischaemic heart disease, closely followed by cerebrovascular disease[11,12]. The enhanced risk of premature cardiovascular disease in RA is considered equivalent to that seen in diabetes[13] and may even predate disease onset[14].

In a cross-sectional study by Han et al. 28,208 RA patients were compared with 112,832 control subjects. The RA patients had higher rates of ischaemic heart disease (IHD) compared to control subjects (prevalence ratio 1.5, 95% CI 1.6-1.4)[15]. In a retrospective cohort study that assessed 603 patients with RA compared to

the same number of control patients, Maradit-Kremers et al. found that the RA patients were more likely to be hospitalized for acute MI (OR 3.2, 95% CI 1.2-8.7)[14]. According to a prospective cohort-study by del Rincon et al., RA patients were 4 times more likely to develop cardiovascular events like MI, stroke, or arterial revascularization (RR 4.0, 95% CI 1.3-6.4)[16].

The presentation of cardiovascular disease in RA patients differs from that in the general population. RA patients are less likely to report symptoms of angina, often leading to misdiagnosis of an acute coronary syndrome. In a retrospective cohort study by Maradit-Kremers et al., RA patients were twice as likely to experience unrecognized myocardial infarctions (HR 2.13, 95% CI 1.13-4.03) and sudden cardiac deaths (HR 1.94, 95% CI 1.06-3.55)[14]. A retrospective case-control study that compared 75 RA patients with preexisting coronary artery disease (CAD) with 128 control patients who were also diagnosed with CAD, showed that significantly more patients with RA had 3-vessel disease (RR 2.0, 95% CI 1.2-3.4)[17].

Furthermore, RA patients seem to have a worse outcome from acute cardiovascular events than the general population[18,19]. Several studies confirmed higher rates of cardiovascular death in patients with RA compared to control subjects. Thomas et al. examined 41,344 RA patients. The cardiovascular standardized mortality ratio was higher in both men (1.9, 95% CI 1.9-2.0) and women (1.6, 95% CI 1.5-1.7)[20]. Goodson et al. found an increase in cardiovascular mortality rates for women (2.0, 95% CI 1.2-3.3) whereas for men, the increase did not reach statistical significance (1.3, 95% CI 0.8-2.2)[18].

The duration of the disease plays an important role in assessing the cardiovascular risk in RA patients. In a study by Chung et al., the prevalence and severity of coronary artery calcification measured with computed tomography, was increased in patients with established RA[21]. The odds ratio (OR) for the likelihood of having more severe coronary artery calcifications in patients with established disease was 3.42 ($P = 0.002$) after adjustment for other cardiovascular risk factors.

Besides having a higher likelihood of CVD, patients with RA also seem to be at increased risk of developing heart failure, in comparison with the general population[22]. In the Rochester RA cohort, the cumulative incidence of congestive heart failure (CHF) according to the Framingham criteria at 30-year follow-up was 34%, compared with 25% in the non-RA cohort (adjusted HR 1.87, 95% CI 1.47-2.39)[23]. RA patients with CHF were less likely to have typical signs and symptoms of heart failure[24]. Hence, the treatment of CHF in RA patients was less aggressive, leading to worse outcomes compared with patients without RA. Importantly, the proportion of CHF patients with preserved ejection fraction (> 50%) was significantly higher among patients with RA than in those without, suggesting that the mechanisms of heart failure differ in people with RA in comparison with the general population[22].

PATHOGENESIS

Inflammation has been postulated to play a major role in the development and propagation of atherosclerosis and CVD in patients with rheumatoid arthritis. Many studies show the importance of inflammation and innate immunity in the pathogenesis of atherosclerosis[7,8].

The normal endothelium produces a vasodilatory response to specific stimuli (e.g. ischaemia), largely mediated by nitric oxide (NO). NO has several anti-inflammatory effects such as the inhibition of platelet aggregation and leukocyte adhesion to the endothelium, and the prevention of vascular smooth muscle cell proliferation. Endothelial dysfunction is a critical and early step in the development of atherosclerosis leading to an inflammatory cascade[25]. It is either caused by a diminished production or activity of NO, or by an imbalance of other relaxing and constricting factors, such as angiotensin-II, prostacyclin (PGI2) and endothelin-1[26-28]. In this inflammatory cascade, low-density lipoprotein (LDL) cholesterol is retained in the endothelium and becomes modified to oxidized LDL (ox-LDL). This causes endothelial activation, leading to an increased expression of adhesion molecules such as vascular adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1), as well as decreased levels of NO, and an increased release of inflammatory cytokines such as IL-1, TNF-α, CD-40 and angiotensin-II[10]. Blood monocytes attach to the adhesion molecules and become macrophages. By taking up oxidized LDL these macrophages change to foam cells, responsible for the production of more inflammatory mediators and cytokines such as IL-1, IL-6 and TNF-α, thereby continuing the inflammatory response[10]. IL-6 stimulates the production of CRP from the liver. TNF-α, a key inflammatory cytokine, has a number of pro-atherogenic effects on the arterial wall, including cell apoptosis, upregulation of adhesion molecules and endothelial cells with a more procoagulant and vasoconstrictor phenotype[29]. By recruiting mast cells, dendritic cells and eventually smooth muscle cells, a fibrous plaque is formed. This plaque can progressively grow, leading to stable angina, or can rupture, leading to an acute coronary syndrome[7,8,26-28].

The inflammatory cascade in the pathogenesis of atherosclerosis and the chronic inflammatory processes in rheumatoid joints and other tissues are very similar[30]. In both conditions, levels of IL-1, IL-6, CRP and TNF-α are elevated. In the general population, elevated levels of these inflammatory molecules are associated with an increased risk of cardiovascular events[31-33]. Given this

observation, RA-disease related inflammation has been postulated to contribute to accelerated atherosclerosis[9,34]. Indeed, markers of RA severity such as autoantibody production (RF, anti-CCP antibodies) and markers of systemic inflammation (ESR, CRP, TNF-α, IL-6) all seem to be strongly associated with an increased cardiovascular risk[35-38]. Hence, high sensitivity CRP is recently considered to be a potentially important biomarker for CAD[39]. Furthermore, elevated inflammatory molecules in RA patients may have some metabolic effects on adipose tissue, skeletal muscle and the liver, which also increase the risk of cardiovascular events by activation of the coagulation cascade and by influencing the development of traditional risk factors for atherosclerosis such as dyslipidaemia, insulin resistance and obesity[40,41].

EFFECT OF TREATMENT

In the first part of the article, we already demonstrated an increased cardiovascular morbidity and mortality in RA patients. Apart from the traditional risk factors (increasing age, male gender, smoking, hypertension, hypercholesterolaemia, diabetes), other disease-related factors play an important role in the aetiology of cardiovascular disease in these patients. Sustained inflammation appears to be the major risk factor. It is therefore anticipated that therapies aimed at reducing disease activity in RA (methotrexate and more recently biologic agents including TNF inhibitors), can attenuate atherosclerosis by reducing the burden of systemic inflammation, resulting in a decreased risk of cardiovascular disease. On the other hand, an adequate treatment of the traditional risk factors remains important. This mainly includes smoking cessation, blood pressure and lipid control, healthy diet and regular exercise.

Methotrexate

Methotrexate (MTX) is one of the cornerstones in the treatment of RA. In a large longitudinal study by Choi et al. including 1,240 RA patients, there was a 60% reduction in risk of all-cause mortality and a 70% reduction of cardiovascular deaths in patients treated with MTX[42]. Moreover, a reduced risk of cardiovascular disease in RA patients seems to be associated with the use of anti-inflammatory therapies including MTX[43]. Major side effects of MTX treatment in RA patients include hepato- and nephrotoxicity, interstitial lung disease and myelosuppression[44]. A potential effect on arterial pressure or lipid profile has not been demonstrated.

There are very few data on atherogenesis, cardiovascular disease and MTX treatment in a non-RA population. In an animal study, treatment of cholesterol-fed rabbits with MTX seemed to have an endothelium-protective effect, as there was a reduction in the size of the lesion areas, as well as the intima-media ratio, the migration of macrophages into the intima and the presence of apoptotic cells[45].

Tumour necrosis factor inhibitors

In the past decade, the treatment of RA has radically changed with the introduction of TNF antagonists. As already mentioned, TNF-α plays an important role in the pathogenesis of atherosclerosis, by exerting an effect on endothelial dysfunction, plaque formation and rupture, but also by inducing insulin resistance and

Table 1 Vascular, metabolic and clinical effects of different TNF inhibitors

	TNF-INHIBITORS		
	INFLIXIMAB	ADALIMUMAB	ETANARCEPT
Surrogate markers of atherosclerose			
Improvement of FMD	yes[51-57]	yes[51-57]	
Decrease of ccIMT	yes[58] / no[57,59]		yes[58] / no[57]
Arterial stiffness			
decrease in PWV	yes[59]		
decrease in Aix	no[60]	no [60]	no [60]
Metabolic effects			
Improvement insulin resistance	yes [61-65]	yes [61-65]	yes [61-65]
Improvement lipid profile	no [69,70]	yes [53]	yes [68]
Clinical effects			
Reduction in CVD	yes [71,74]	yes [74]	yes [71,74]
Increased incidence of heart failure	yes [76,83 (elderly)] / no[79,80,82]	yes[83 (elderly)] / no [9,82]	yes[77,83 (elderly)] / no[79,80,82]

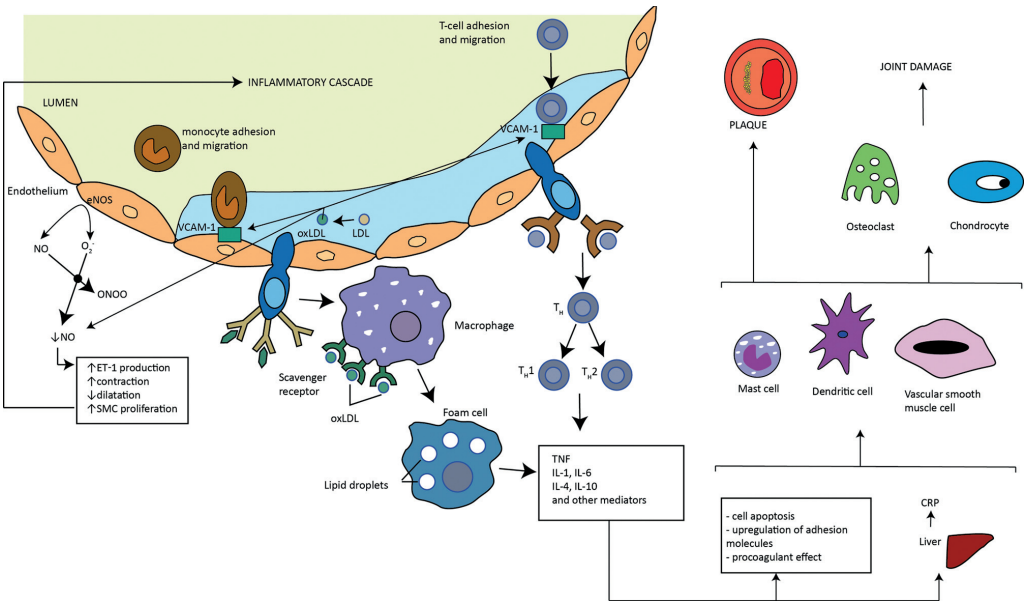

Fig. 1 Pathogenesis of plaque formation and joint damage in RA.
Monocytes and T-lymphocytes migrate into the vessel wall, where they express chemokine receptors and differentiate into foam cells and TH1 and TH2 cells, respectively. The release of TNF and other inflammatory mediators eventually leads to plaque formation and joint destruction.
Abbreviations: CRP: C-reactive protein, eNOS: endothelial NO synthase, ET-1: endothelin 1, IL: interleukin, LDL: low-density lipoprotein, oxLDL: oxidized low-density lipoprotein, NO: nitric oxide, TH: T-helper lymphocytes, TNF: tumour necrosis factor, VCAM-1: vascular cell adhesion molecule 1.

dyslipidaemia[29,40,41]. Therefore, TNF antagonists are assumed to decresease the progression of atherosclerosis, in this way leading to lower cardiovascular morbidity and mortality in RA patients. Currently, there are four available TNF antagonists: infliximab, adalimumab, etanercept, and certolizumab.

Numerous publications in the last decade suggest that TNF antagonists exert significant effects on surrogate markers of atherosclerosis and even on some metabolic and clinical parameters. Surrogate markers of atherosclerosis include endothelial dysfunction assessed by impaired flow-mediated vasodilation (FMD) of the brachial artery, carotid atherosclerosis using common carotid intimal-medial thickness (ccIMT) and increased arterial stiffness indicated by increased pulsed-wave velocity (PWV) and augmentation index (AIx). FMD and ccIMT can be assessed by ultrasonography while arterial stiffness is measured by pulse wave analysis; the higher the transit time of the pulse wave, the stiffer the vessels[46,47]. The augmentation index (AIx) is a composite of arterial stiffness and pulse wave reflection. The foregoing pulse wave is reflected back in the periphery and increases the pulse pressure in the ascending aorta; the stiffer the vessels, the higher the AIx. Endothelial dysfunction precedes overt atherosclerosis and increased arterial stiffness as well as an increased intima-media thickness of the carotid arteries are predictors of cardiovascular morbidity and mortality[48-50]. Thus, these markers could be very useful to detect early vascular changes in patients with RA.

In most available studies, treatment with TNF antagonists (infliximab and adalimumab) improved endothelial function, indicated by a significant increase in FMD. This improvement was associated with a lower disease activity and lower CRP levels[51-54]. In two short-term studies by Gonzalez-Juanatey et al. and Bosello et al., these beneficial effects of infliximab treatment on endothelial function seemed to be only temporary. After an initial improvement in endothelial function, FMD relapsed to baseline levels a few weeks after infliximab treatment[55,56]. However, the only available long-term study by Sidiropoulos et al. showed a sustained improvement of FMD after 3 months and 18 months of treatment with either infliximab or adalimumab[57]. Data regarding the effects of TNF inhibitors on carotid atherosclerosis assessed by ccIMT are rather conflicting. Del Porto et al. reported a significant improvement of ccIMT in 30 patients before and after therapy with infliximab or etanercept[58]. In contrast, Wong et al. found no change in ccIMT after treating 26 RA patients with infliximab during 56 weeks[59] and an 18-month treatment with either infliximab or etanercept in 12 RA patients did not affect ccIMT[57]. Similarly, data regarding the effects of TNF blockers on arterial stiffness assessed by PWV and AIx are inconsistent. Wong et al. described a significant decrease in aortic PWV after treating 26 RA patients with infliximab for

56 weeks[59], whereas van Doornum et al. found no change in arterial stiffness evaluated by AIx after treating 14 RA patients with either one of the three available TNF antagonists, although there was a significant improvement in disease activity[60]. A possible explanation for this variation in results is the lack of large longitudinal studies and the use of different TNF antagonists, making it difficult to compare the different studies.

TNF antagonists also have a number of metabolic effects, especially on the lipid profile and on insulin resistance. In various studies, all three available TNF antagonists have been shown to improve insulin resistance[61-65]. Results of short-term studies on the effects of biologic agents regarding dyslipidaemia are very inconsistent, with varying results using different TNF antagonists[53,64,66-68]. The short-term effects of infliximab on the lipid profile at first seemed favourable. However, in a long-term study by Nishida et al. infliximab treatment significantly increased levels of total cholesterol and HDL cholesterol after a year of treatment[69]. Similarly, in another long-term study by Popa et al. plasma levels of total cholesterol as well as LDL and the atherogenic index (AI) were higher after 6 months treatment with infliximab[70]. These results suggest that long-term therapy with infliximab may be pro-atherogenic. This may, however, not be the case for other TNF antagonists[53,67,68].

Apart from these metabolic effects and the effect on the surrogate markers of atherosclerosis, anti-TNF treatment also seems to have an influence on clinical outcome. Several studies found a statistically significant decrease in all CVD events in patients treated with TNF antagonists[71-73]. Jacobsson et al. described the age-adjusted and sex-adjusted incidence of a first CVD event in RA patients treated with TNF antagonists to be less than half that observed in the control group (RR 0.46, 95% CI 0.25-0.85, $P=0.013$)[71]. A large multinational study by Naranjo et al. found a 33% reduction (95% CI 0.53-0.85) in the risk of all CVD events and a 58% reduction in the risk of MI (95% CI 0.21-0.81, $P<0.05$) in patients treated with TNF antagonists for one year[73]. Furthermore, also the response to TNF antagonists seems to be important. Dixon et al. could not demonstrate any difference in incidence of MI in TNF antagonist users compared with control patients on a traditional DMARD, unless the response to therapy was taken into account[74]. The TNF responders had a significantly lower risk of CVD events compared to the non-responders (adjusted incidence rate ratio 0.36, 95% CI 0.19-0.69). However, when compared to MTX therapy, no additional decrease in cardiovascular risk was found in TNF antagonist users, except when TNF antagonists were used in combination with MTX. In a case-control study from a California database, use of TNF antagonists combined with MTX reduced the risk of MI by 80% (95% CI 0.05-0.88), compared with MTX monotherapy[75].

No definite conclusions can be drawn on the association between TNF antagonist use and heart failure. Early randomized clinical trials showed a significant worsening of heart failure with TNF antagonists, when used as a potential therapy for cardiac failure[76-78]. Moreover, in the ATTACH trial, a statistically non-significant increase in mortality among patients with heart failure who received infliximab therapy was found[76]. The results of more recent studies, specifically assessing the risk of cardiac failure with the use of TNF antagonists in the treatment of RA, are rather conflicting. Compared with DMARD users, and after adjusting for multiple confounders, Listing et al. found the risk of developing de novo or worsening heart failure not to be different in patients treated with TNF antagonists (adjusted HR 1.49, 95% CI 0.70-3.18, $P=0.31$)[79]. In a large USA cohort study, the risk of heart failure was even significantly lower in patients treated with TNF antagonists (2.8% in the TNF antagonist users versus 3.9% in non-users, $P=0.03$)[80]. Even after adjustment for previous cardiovascular history, no increase in heart failure in TNF antagonist users was found. Given the FDA warning following the earlier studies on TNF antagonists and heart failure, TNF antagonists were less likely to be prescribed to patients with known heart failure. However, in a case-control study that was conducted before the FDA warning, the use of TNF antagonists was associated with a lower risk of first hospitalization with heart failure (RR 0.5, 95% CI 0.2-0.9)[81]. Cole et al. found no difference in the number of admissions for cardiac failure between RA patients treated or not treated with TNF antagonists, and non-RA patients (6.7%, 8%, and 7%, respectively, $P=0.147$)[82]. In elderly patients however, TNF antagonists may increase the risk of heart failure[83]. Curtis et al. reported an increased risk of heart failure in younger patients (< 50 years of age) treated with TNF antagonists. However, this result was not statistically significant[84]. Given these inconsistent data, the British Society for Rheumatology recommends to use anti-TNF therapy with caution in patients with mild heart failure (NYHA grade 1 or 2), and not to initiate this treatment in patients with severe heart failure (NYHA grade 3 or 4). According to the same guidelines, anti-TNF therapy should be discontinued if cardiac failure develops or worsens while on treatment[85].

Other biologicals

Besides the TNF antagonists, other biologic treatments include the B-cell directed monoclonal antibody rituximab, the IL-1 receptor antagonist anakinra and the IL-6 receptor inhibitor tocilizumab. Data concerning

cardiovascular effects of these treatments are more limited than for TNF antagonists[86]. In a long-term safety analysis of RA patients receiving rituximab therapy, there was no difference in serious cardiovascular events[87]. The overall rate of myocardial infarction following rituximab therapy appeared to be consistent with rates observed in the general RA population[87]. Similarly, rates of myocardial infarction and stroke in RA patients receiving tocilizumab did not exceed expected rates in the RA population[88]. Data on the effects of new biologicals on the lipid profile are currently of particular interest. Total cholesterol, HDL, LDL and triglyceride levels increased in tocilizumab-treated patients but stabilized with continued treatment[89]. However, in preliminary data, tocilizumab treatment seems to improve insulin resistance and to decrease elevated levels of lipoprotein(a), considered an independent cardiovascular risk factor[90].

CONCLUSION

RA patients have an increased cardiovascular morbidity and mortality in comparison with the general population. The disease itself is now considered an independent risk factor for CVD. Immune dysregulation and sustained inflammation play an important role in the pathogenesis of accelerated atherosclerosis in RA patients, endothelial dysfunction being an early and critical step. It was therefore anticipated that therapies aimed at reducing disease activity could lower the risk of CVD by reducing the burden of systemic inflammation. Therapy with MTX has proven to reduce all-cause and cardiovascular mortality. TNF antagonists exert significant effects on the vascular system. Endothelial function seems to improve but in most cases this is only a transient effect. Data on the effects of TNF antagonists on carotid atherosclerosis and arterial stiffness are scarce and rather inconsistent. Long-term administration of infliximab may be pro-atherogenic. This may, however, not be the case for etanercept and adalimumab. All available TNF antagonists have been shown to improve insulin resistance. Clinically, TNF antagonists are associated with a decreased risk of all CVD events. The responders to this treatment may even have a greater benefit. Given the inconsistent data on the association between TNF antagonist use and heart failure, the British Society of Rheumatology recommends not to initiate TNF antagonists in patients with severe heart failure, and to discontinue the therapy if heart failure develops or worsens while on treatment. Data on the cardiovascular effects of other and newer biologic treatments are limited. Hence, there is a need for further research since very few evidence from RCT's and long-term studies is available.

CONFLICTS OF INTEREST: none declared.

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