Statin therapy for targeting cardiovascular risk in rheumatoid arthritis

Rheumatoid arthritis (RA), a prototypical immune-mediated inflammatory disease, is now definitely recognized to increase cardiovascular morbidity and mortality, irrespective of established classical risk factors. The chronic inflammatory state, a hallmark of RA, is increasingly considered to be a driving force for accelerated atherogenesis. Consequently, aggressive control of RA disease activity has been suggested to be instrumental for cardiovascular risk reduction. Currently, statins are the cornerstone of cardiovascular risk-reducing strategies. Apart from their lipid-lowering capacity, statins also exert immune-modulatory effects, which therefore may be of dual benefit in RA patients. Yet guidelines for optimal cardiovascular risk reduction in patients with RA are lacking, largely owing to the absence of randomized, clinical trial data. In this review, we focus on the pathophysiology and observational evidence of cardiovascular risk in RA, as well as the need to adjust currently employed cardiovascular risk calculators in order to accommodate the impact of chronic inflammatory disease over and above established risk factors in order to accurately predict individual cardiovascular risk in RA patients.

KEYWORDS: HMG-CoA reductase inhibitor ■ inflammation ■ rheumatoid arthritis ■ statins

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For many years, rheumatoid arthritis (RA), a prototypical immune-mediated inflammatory disease, has been attributed to increased cardiovascular morbidity and mortality, irrespective of established risk factors [1–4]. In the early 1990s, it was demonstrated that RA may shorten overall survival with mortality rates being in the range of twofold or more. It was observed that increased mortality is predominantly due to an increased rate of cardiovascular events, which is closely linked to RA disease activity [5].

At that time, the 5-year survival rate in RA patients with the poorest clinical status (approximately 40–60%) proved comparable to that of individuals with three-vessel coronary artery disease or, for example, those with stage 4 Hodgkin's disease [6]. Later studies have corroborated this increased incidence of cardiovascular events among RA patients, including a report that demonstrated an incidence rate ratio of 3.17 (95% CI: 1.33–36.36) [7]. A prospective cohort study, including approximately 115,000 healthy women who participated in the Nurses' Health Study, reported a greater than twofold higher risk of myocardial infarction among subjects who developed RA, even after adjusting for classical cardiovascular risk factors [8]. These odds especially held true for those with a disease duration exceeding 10 years, where the risk of myocardial infarction rose above 3.0 (95% CI: 1.64–5.87).

In recent years, RA therapy has significantly improved and become more intensive with stricter control of inflammation. The consequence of this approach on atherosclerosis-related death rates is striking, as elegantly demonstrated in a large cohort of approximately 3900 RA patients [9]. Among these subjects who were followed from 1980 to 1997, mortality from acute myocardial infarction witnessed an impressive decline, irrespective of trends in the general population and after adjustment for age, sex, race and disease duration. Analyses incorporating the year of birth further corroborated these findings. Interestingly, factors that may beneficially affect the cardiovascular risk profile include effective suppresion of inflammation [10], diminished use of NSAIDs [11], higher functional status and consequently, increased physical activity. Upon closer examination of the effects of current treatment modalities, in RA patients it has been demonstrated that methotrexate renders a survival benefit over conventional antirheumatic drugs, largely as a consequence of reducing cardiovascular mortality [12]. A tentative explanation for these observations involves the potent suppression of systemic inflammatory activity with ensuing recovery of patient mobility [13–16]. Accordingly, a reduced incidence of myocardial infarction was observed in RA patients

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who responded well to anti-TNF-α therapy compared with nonresponders, underlining the role of inflammation driving accelerated atherogenesis [17].

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, such as statins, have emerged as a potent class of lipid-lowering drugs and their efficacy in the prevention of cardiovascular events among various high-risk populations has been firmly established [18]. Beyond their lipid-lowering capacity, statins have also been demonstrated to exert anti-inflammatory effects, not only in atherosclerotic vascular disease, but also in a number of lipid-unrelated immune-mediated disorders with a particular reference to RA. Thus far, the molecular mechanisms involved are poorly understood. In this review, we will focus on these potential mechanisms and on the impact that statins may have on the cardiovascular risk profile in RA patients and, finally, we will suggest more stringent guidelines for cardiovascular disease prevention and statin therapy in RA.

Cardiovascular disease in RA

In RA, chronic inflammatory activity has been suggested to sensitize the vessel wall for the atherogenic impact of traditional risk factors such as dyslipidemia and diabetes. Noticeably, there is extensive overlap of inflammatory pathways and mediators between atherosclerosis and RA, characterized by the infiltration of monocyte-derived macrophages and T cells, as well as processes of post-transciptional modifications of proteins and signal-transduction pathways, for example, toll-like receptors [19].

One of the earliest changes pertains to loss of functional protection against atherosclerotic insults (endothelial dysfunction), followed by progressive structural derangements over time. With regard to functional changes, the severity of endothelial dysfunction has been demonstrated to correlate with the future risk of cardiovascular events [20]. Several groups have demonstrated that active RA is accompanied by endothelial dysfunction, which is reversible following effective resolvement of the inflammatory insult. For instance, Bergholm *et al.* demonstrated that newly diagnosed RA patients exhibit decreased flow-mediated dilation (FMD), which is indicative of decreased nitric oxide bioavailibility [21]. Of importance is that 6 months of routine anti-inflammatory therapy, effectively mitigating clinical and biochemical markers of inflammation, was accompanied by an improvement in endothelial function. Accordingly, baseline FMD was significantly impaired in RA patients [22]. During the loading phase of infliximab therapy (infliximab is a potent antagonist of TNF-α), RA patients, identified with severe and long-standing disease, responded clinically, according to the European League Against Rheumatism (EULAR) response criteria, and this was associated with simultaneous improvement in FMD. In another report, 12 weeks of infliximab therapy was followed by improvent in FMD with a concomitant reduction in systemic inflammation and disease activity scores (DAS28) in a small number of RA patients with high disease activity, despite conventional treatment [23]. More recently, reversal of endothelial dysfunction has also been reported following the initiation of ACE inhibition, thus improving vascular function in spite of unchanged inflammatory activity [24,25]. Taken together, these data implicate impaired endothelial vasomotor function being an integral part of the early disease process of RA.

Noninvasive imaging modalities allow for assessment of the atherosclerotic process at relatively early stages. Consequently, these techniques hold great promise for individual cardiovascular risk management, as well as for monitoring the efficacy of therapeutic interventions [26]. Furthermore, surrogate end points for cardiovascular disease, including FMD, intima-media thickness (IMT), intravascular ultrasound and electron-beam computed tomography, have been demonstrated to be adversely affected by cardiovascular risk factors and coronary artery disease [26,27]. Early detection of atherosclerosis progression indicates that morphological changes in the arterial wall, visualized as accelerated thickening of the carotid artery wall by B-mode ultrasonography, precede development of overt atherosclerotic lesions by approximately one to two decades [26]. The usefulness of these surrogate markers to detect early atherosclerosis in patients with RA have been emphasized recently [28]. In 47 RA patients, carotid IMT appeared thicker than in controls [29]. Patients with overt carotid atherosclerotic plaques tended to be older with a longer duration of disease, suggesting an association between age and disease duration on the one hand, and more advanced atherosclerosis on the other. In agreement with these findings, the prevalence of preclinical atherosclerosis was demonstrated to be threefold greater in RA patients (n = 94) when compared with controls that were matched for age and sex [30]. In these patients, plaque presence was associated with age, hypertension and the

use of TNF-α inhibitor therapy, but results were most likely confounded by a more severe subgroup of patients. Another study corroborated accelerated atherogenesis in 141 RA patients, revealing increased prevalence and severity of coronary artery calcification, as assessed by electron-beam computed tomography [31]. In this cohort, smoking and elevated erythrocyte sedimentation rate were alternative determinants associated with more severe coronary artery calcification. Very recently, similar findings were reported in another cohort of RA patients [32]. Once coronary artery disease (CAD) becomes manifested, RA patients exhibit a higher prevalence of multivessel disease and a greater need for revascularization than age- and sex-matched subjects without RA [33]. Consistent with this notion, angiographic scores in CAD patients have indicated that patients with RA have an increased risk of multivessel disease compared with matched controls [34]. In summary, it seems safe to assume that RA can be considered a high-risk condition for cardiovascular events, and once CAD is present, it may carry a poorer prognosis in the post-event period.

Pathophysiology of accelerated atherogenesis in RA

Accelerated atherogenesis that may be associated with RA involves both inflammation-related and noninflammatory factors. RA and atherosclerosis, to some extent, share comparable inflammatory profiles [35,36]. A wide array of inflammatory mediators contributing to active RA have been demonstrated to be associated with accelerated atherogenesis, such as TNF-α and C-reactive protein (CRP). TNF-α, a principal mediator in RA that is generated by immune cells, such as tissue macrophages and T cells, exerts potent proatherogenic effects on the vessel wall. These include cell death through apoptosis and the endothelial cell upregulation of adhesion molecules with ensuing accumulation of leucocytes in the subendothelial layers [37,38]. Alternatively, TNF-α may shift the hemostatic balance at the endothelial cell surface towards a procoagulant [39] and vasoconstrictor phenotype [40]. Recently, CRP has emerged as an important proatherogenic risk factor during the various stages of atherogenesis [41].

In this regard, it has been demonstrated in humans that systemic infusion of CRP renders the endothelium dysfunctional with ensuing procoagulant responses, particularly under hypercholesterolemic conditions [42]. Other inflammatory mechanisms that mediate the enhanced risk of developing cardiovascular disease in RA patients include the presence of certain peripheral blood $CD4^+$ T-cell subsets, which lack expression of the CD28 molecule [43]. Individuals with RA, in whom expansion of this T-cell subset with a proinflammatory phenotype and tissue damaging potential is detected [44,45], demonstrate impairment of FMD and increased IMT compared with those without, whereas blockade of TNF-α, at least partially, induces CD28 reappearance on the $CD4^+$ cell surface [43].

With regard to noninflammation-related factors, active RA has been associated with a proatherogenic lipid profile, as are other inflammatory diseases [46–50].

In treatment-naive RA patients, investigations have been conducted on whether initiation of therapy that reduces inflammatory activity would reverse the adverse lipid profile (at baseline) after 12 months [51]. Mean high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I levels increased by 21 and 23%, respectively, which is anticipated since HDL is an inverse acute-phase protein. This amelioration of the lipid profile was more pronounced in RA patients who fulfilled the ACR 20% response criteria (ACR20) and correlated significantly with the change in CRP levels as a measure of inflammatory activity. Apart from the lipid changes, RA patients had a threefold increased prevalence of the metabolic syndrome, including dyslipidemia (low HDL and high triglycerides), insulin resistance, elevated blood pressure and abdominal obesity. The major cause of this preponderance of metabolic syndrome in RA patients may, in part, relate to the decreased mobility of these patients as dictated by disease activity. Notably, the presence of the metabolic syndrome phenotype was clearly associated with the extent of coronary atherosclerosis [52].

More recently, attention has focused on the role of endothelial progenitor cells that are responsible for repair of vascular injury. In patients with overt cardiovascular disease and diabetes, the number, as well as function, of this cellular repair mechanism was impaired. Interestingly, the number of endothelial progenitor cells correlates inversely with several cardiovascular risk factors, thereby constituting a surrogate marker for vascular malfunction [53,54]. In RA, numbers of endothelial progenitor cells in peripheral blood were also found to correlate inversely with RA disease activity [55]. In experimental models of adjuvant-induced arthritis, some of these disturbances were demonstrated to respond favorably to fluvastatin therapy [56].

Collectively, the mechanisms by which RA may affect the human vasculature, and consequently contribute to the pathogenesis of atherosclerosis, are multiple by nature. High RA disease activity promotes an inflammatory endothelial phenotype combined with a proatherogenic lipid profile that, in conjunction, stimulates plaque growth and destabilization, ultimately culminating in an acute clinical event.

Effects of statins on arthritis

Statins block the conversion of HMG-CoA to mevalonate by inhibiting the rate-limiting enzyme of the mevalonate pathway, HMG-CoA reductase. The end products of the mevalonate pathway, including sterols (e.g., cholesterol) and ubiquinone (coenzyme Q), are required for a number of essential cellular functions, which include membrane integrity, steroid production, electron transport/cell respiration and (glyco) protein synthesis. In this regard, statins display potent biological effects beyond their lipid-lowering activities. Whether these are relevant in clinical terms is still the subject of intense debate. Differential effects, for instance, on leukocyte trafficking across the vascular endothelium and inflammatory responses, have been reported for the various available statins [57].

Experimental models

Statins have the capacity to attenuate the production of proinflammatory cytokines, cell proliferation and NFκB activation in (IL-1β-stimulated) fibroblast-like synoviocytes from RA patients (see **Box 1**) [58,59]. The mechanism of this anti-inflammatory effect relates to the direct inhibition of RhoA, which serves as a key regulator of TNF-α-induced NFκB activation, as well as the secretion of proinflammatory cytokines [60]. In addition, statins have been demonstrated to promote apoptosis in cultured RA synoviocytes via a mitochondrial- and caspase-3-dependent pathway and by blockage of mevalonate pathways [61]. These data are of particular importance, since inadequate apoptosis of fibroblast-like synoviocytes may lead to increased accumulation of activated immune cells in the intimal lining layer of the inflamed synovium. Furthermore, some statins have been demonstrated to inhibit the interaction between α1β2 integrin and ICAM-1, an important effect that may prevent leukocyte adhesion and infiltration at the inflammatory site [57]. The anti-inflammatory properties of statins have been reproduced in chondrocytes, suggesting a role in cartilage-protection for statins in arthritis [62]. The relevance of these *in vitro* findings have been substantiated by animal studies, supporting a favorable impact of statins on RA activity. Peroxisome proliferator-activated receptor (PPAR)α and, inversely, the protein kinase C signaling pathway, were demonstrated to be secondarily involved in the acute inhibitory effects of statins on the lipopolysaccharide-induced inflammatory response [63]. In a model of adjuvant-induced arthritis in the rat, oral treatment with atorvastatin markedly ameliorated histopathological findings and hypernociception in inflamed joints, which was paralelled by an effective blockade of neutrophil influx, reduction of proinflammatory cytokines and chemokines, as well as an increase in anti-inflammatory IL-10 (see **Box 1**) [64]. By contrast to previously described therapeutic effects, no study found attenuation of inflammatory activity by statins in a murine model of collagen-induced arthritis [65]. Last, statins have been demonstrated to attenuate bone resorption in animal models [66,67].

Box 1. Beneficial effects of statins on rheumatoid arthritis beyond lipid-lowering effects.

- Inhibition of leukocyte trafficking across the endothelium by blocking the interaction between α1β2 integrin and ICAM-1 [57].
- Attenuation of the production of proinflammatory cytokines, cell proliferation and NFκB activation in fibroblast-like synoviocytes [58,59].
- Stimulation of apoptosis of fibroblast-like synoviocytes via a mitochondrial- and caspase 3-dependent pathway and by blockage of mevalonate pathways [61].
- Cartilage protection [62].
- Inhibition of the inflammatory response through regulation of PPARα and the protein kinase C signaling pathway [63].
- Blockade of neutrophil influx and increase of the anti-inflammatory IL-10 [64].
- Inhibition of bone resorption [66,67].
- Improvement of endothelial-dependent vasomotor function [72,73].
- Enhancement of the serum lipoprotein and anti-inflammatory capacity of high-density lipoprotein [78].

RA patients

In RA patients, daily treatment with 40 mg simvastatin, administered with low-dose methotrexate and prednisone, resulted in an ACR50 response in nine out of ten individuals [68]. Simultaneously, CRP levels decreased by more than twofold following only 4 weeks of statin therapy. Apart from CRP, statin treatment for 12 weeks with stable antirheumatic therapy suppressed biomarkers of inflammation in RA individuals, involving decreases of Th1:Th2 and CD4:CD8 ratios that are associated with clinical improvement [69]. In the largest, double-blind, placebo-controlled trial so far (Trial of Atorvastatin in Rheumatoid Arthritis [TARA]), 116 patients with moderate-to-long disease duration and active disease were randomized to receive either 40 mg atorvastatin

or placebo with existing DMARD treatments [70]. In this study, statin therapy resulted in clinical improvement and reduced inflammation in the absence of serious side effects. Data from a large observational study in 4200 RA patients confirmed the concept that statin use is associated with reduced inflammatory activity and lower swollen joint counts [71].

There is accumulating evidence, from both experimental and clinical studies, supporting the immunomodulatory effects of statins, by which they may alter the clinical course of RA, including the silencing of immune-active cells, suppression of the systemic cytokine reaction/complement activation and alteration of T-cell-mediated immune responses. These anti-inflammatory effects attenuate inflammatory activity in inflamed joints, whereas they also decrease the secondary complications of inflammatory activation, including cartilage degradation and bone destruction.

Statins & cardiovascular complications in RA

The evidence that statins decrease the occurrence of cardiovascular events has been established beyond reasonable doubt. Importantly, this beneficial impact holds true accross all patient-risk categories, independent of the risk-factor profile.

Therefore, statins can theoretically be expected to benefit RA patients. Only a few clinical trials have addressed whether or not statins decrease cardiovascular events in RA. A recent study evaluated whether statins may lower cardiovascular risk by lipid lowering *per se* or by their immunomodulatory effects. In 20 RA patients with active disease, 20 mg simvastatin versus nonstatin-induced LDL lowering with ezetimibe revealed equal improvements in inflammatory markers and DAS28 activity, in spite of a clearly more pronounced LDL lowering effect in the statin group. In both arms, endothelial function improved significantly following cholesterol reduction with no differences between treatments. This small study suggests that cholesterol lowering *per se* is the major factor contributing to the previously observed benefit of statins [72]. In support of this, other studies confirmed that statin treatment predominantly improved endothelial function in patients with high inflammatory activity at baseline [73]. More recently, attention has shifted towards strategies that increase the levels of HDL, the lipoprotein particle associated with the protection against atherosclerosis. Besides its role in mediating reverse cholesterol transport, HDL has been demonstrated to be a pivotal player in attenuating inflammation as well as preserving vascular function among many other effects and HDL has been reported to reduce monocyte activation upon inflammatory stimuli and to protect rodents and humans from lipopolysaccharide-mediated cell toxicity [74–76]. Furthermore, apolipoprotein A-I has been demonstrated to interfere with the contact-mediated activation of monocytes by T lymphocytes [77]. Recently, 12 weeks of high-dose atorvastatin administered with stable antirheumatic drug therapy was demonstrated to restore the anti-inflammatory capacity of HDL in 20 subjects with active RA, whereas clinical disease activity was unaltered [78].

The paucity of statin trials in RA, as well as the small sample sizes, are indicative of the fact that little attention has been paid to adequate cardiovascular prevention in these patients. The large Heart Protection Study 2, which is evaluating the impact of simvastatin in more than 8000 RA patients in the UK, will hopefully resolve this issue [101]. Awaiting the outcome of this pivotal trial, the available data clearly support a benefit of early statin initiation in patients with RA.

Conclusion

Over the past two decades it has become increasingly clear that RA is an independent risk factor for cardiovascular events, with an impact that is over and above that of established risk factors. Since RA is a protracted disorder, the increasing focus on adequate cardiovascular prevention in RA patients is long overdue. Pathophysiologically, chronic inflammation, a hallmark of patients with (active) RA, provides a direct link between RA and accelerated atherogenesis. Therefore, first and foremost, proper management of cardiovascular risk requires aggressive control of RA disease activity. Statins are the cornerstone of cardiovascular risk-lowering strategies, offering both lipid-lowering efficacy as well as anti-inflammatory effects. Therefore, the use of statin therapy in patients with RA can be expected to both beneficially alter RA activity as well as to lower cardiovascular event rates. However, since cardiovascular risk does not often exceed 20% on a 10-year time span, routine initiation of statins in all RA patients is not recommended until the results of large randomized and controlled trials become available.

Future perspective

The authors believe that in the following years, large randomized and controlled trials, including the large Heart Protection Study 2, will provide solid data in support of the benefits of early statin initiation in patients with RA and even other immune-mediated inflammatory disorders.

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Executive summary

Cardiovascular disease in rheumatoid arthritis

- Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular events, with an impact over and above that of established risk factors.

Pathophysiology of accelerated atherogenesis in rheumatoid arthritis

- Cardiovascular complications involve inflammation-related and noninflammatory factors.

Effects of statins on arthritis

- Statins are the cornerstone of cardiovascular risk-lowering strategies.
- Statins offer both lipid-lowering efficacy as well as anti-inflammatory effects.

Statins and cardiovascular complications in rheumatoid arthritis

- Since cardiovascular risk does not often exceed 20% on a 10-year time span, routine initiation of statins in all RA patients is not recommended until the results of large randomized and controlled trials become available. Proper management of cardiovascular risk, first and foremost, requires aggressive control of RA disease activity.

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