Cardiovascular risk in rheumatoid arthritis

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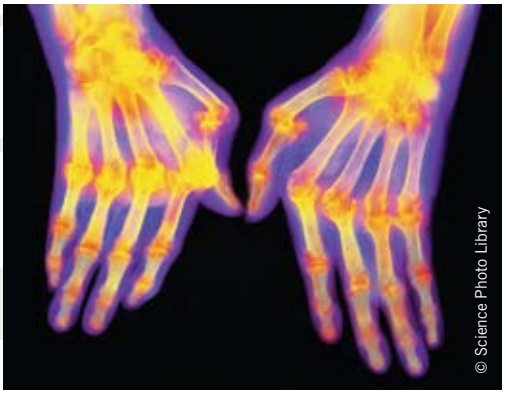
The British Society of Rheumatology have published guidelines on the management of rheumatoid arthritis, which call for an increased awareness of rheumatoid arthritis as an independent risk factor for ischaemic heart disease.[1] This increased cardiovascular risk is related to the severity and duration of inflammation, and the magnitude of additional cardiovascular risk in severe rheumatoid arthritis has been compared with that seen in diabetes mellitus.[1] Life expectancy is reduced due to an excess of cardiovascular death, with increased standardised mortality ratios ranging from 1.28 to 3.00 in rheumatoid patients compared with the general population.[2] Women with rheumatoid arthritis are twice as likely to suffer from a myocardial infarction as those without.[2] There is also an increased risk of congestive cardiac failure,[2] asymptomatic coronary heart disease and sudden cardiac death.[3]

Atherosclerosis and inflammation

It is not clearly understood why patients with rheumatoid arthritis should suffer accelerated atherosclerosis. Traditional modifiable risk factors alone are insufficient to explain the excess cardiovascular risk.[3-5] Part of the answer is that rheumatoid arthritis causes chronic systemic inflammation, which may accelerate the atherosclerotic process. Atherosclerosis is essentially an inflammatory disease, with levels of different biomarkers of inflammation such as C-reactive protein (CRP), interleukin-6, and N-terminal prohormone B-type natriuretic peptide (NTproBNP) correlating closely with subsequent cardiac events.[6] In patients with rheumatoid arthritis, inflammatory markers, disease severity,[2] and rheumatoid factor (RF) seropositivity,[7] seem to be associated with the risk of later development of atherosclerosis. This inflammation is also associated with the extent of coronary artery calcification measured by computed tomographic (CT) imaging.[8] Other non-traditional risk factors may also contribute to cardiovascular risk, and include the long-term effects of non-steroidal anti-inflammatory drug (NSAID) treatment, and the use of cyclo-oxygenase-2 (COX-2) inhibitors.



Primary care in the UK is ideally placed to assess and address cardiovascular risk factors for primary prevention in these patients for a number of reasons. It is common practice for the regular monitoring of disease-modifying anti-rheumatic drugs (DMARDs) to take place in the community, and this provides the opportunity to assess cardiovascular risk factors. Primary care already has well-established mechanisms for the assessment and follow-up of these risk factors. Physicians in primary care can audit the care of their patients and ensure that patients with rheumatoid arthritis have had a full cardiovascular risk assessment, and monitor their progress using the same chronic disease management model that is used to follow-up conditions such as hypertension and diabetes.

Managing conventional risk factors

It is important to identify those patients with rheumatoid arthritis who have conventional risk factors, such as hypertension and hyperlipidaemia, who have not already been identified and who fall within the current criteria for treatment. An assessment of cardiovascular risk using the modified Framingham Joint British Societies (JBS-2) risk assessment tables will underestimate the risk as the tables do not take into account whether or not the patient has rheumatoid arthritis. The cardiovascular risk calculator QRISK2 provides an estimate of risk using traditional risk factors and

also other risk factors such as rheumatoid arthritis, social deprivation and ethnicity. This may, therefore, provide a more accurate estimate for the risk for these patients.[9] Communication with the patient about this excess risk is important to help the decision-making process regarding additional drug therapy, and to promote any lifestyle changes that might help reduce cardiovascular risk such as dietary improvement, smoking cessation and weight reduction.

Statins play a key role in the management of cardiovascular risk in rheumatoid arthritis. The interaction of active tissue inflammation due to rheumatoid arthritis and plasma lipid levels is a complex one: there is some evidence of an association between low high-density lipoprotein (HDL)-cholesterol levels in active rheumatoid arthritis and of HDL particle dysfunction.[2] A number of studies have shown that treating people with rheumatoid arthritis with statins leads to a reduction in pro-atherogenic lipids and improvement in markers of inflammation.[2] There is a randomised, controlled trial of atorvastatin for the primary prevention of cardiovascular events in rheumatoid arthritis (TRACE-RA), but this is not due to report until 2014. The results of this trial may provide evidence for the wider usage of statins in this population than is currently recommended in the JBS-2 guidelines alone. The anti-inflammatory activity of statins may also be of extra benefit in reducing disease activity in rheumatoid arthritis. In one placebo-controlled trial of atorvastatin 40 mg in rheumatoid arthritis (TARA), there was a reduction in inflammatory markers and a modest, but clinically significant, reduction in rheumatoid disease activity after six months of treatment with atorvastatin.[10]

Other clinical trials are underway to inform decision-making regarding cardiovascular risk assessment and modification in rheumatoid arthritis. The Norfolk Arthritis Register (NOAR) collects data prospectively on a group of patients (n=1,010) with rheumatoid arthritis and has been designed with clinical outcome measurement. After 10 years' follow-up in this register, 17% of subjects had died, of which 52% of deaths were attributable to cardiovascular disease. Mortality was greatest in the group with the highest health assessment questionnaire (HAQ) score at baseline and one year, with the latter time-point the best predictor of cardiovascular mortality (hazard ratio [HR] 1.49; 95% confidence interval [CI] 1.11–1.97).[11] This register thus provides additional information to allow a more precise estimation of cardiovascular risk.

Impact of rheumatoid arthritis treatment on cardiovascular risk

In rheumatoid arthritis, the degree of inflammation correlates with the risk of cardiovascular disease, suggesting that the treatment of the inflammatory disease process could reduce this excess risk. Treatment of rheumatoid arthritis has been shown to reduce inflammation,[12] and to improve the overall lipid profile.[12-14] Several studies show that the use of DMARDs to control the disease process can reduce some of the excess cardiovascular risk. Methotrexate is the most frequently chosen DMARD,[1] and has been shown to reduce overall and cardiovascular mortality.[15] In a multi-national, cross-sectional unselected cohort-based study involving a clinical assessment and self-reported questionnaire in 4,363 patients from 15 countries, prolonged use of treatments such as methotrexate (HR 0.85; 95% CI 0.81–0.89), sulfasalazine (HR 0.92; 95% CI 0.87–0.97), leflunomide (HR 0.59; 95% CI 0.43–0.79), glucocorticoids (HR 0.95; 95% CI 0.92–0.98) and anti-tumour necrosis factor alpha (anti-TNFα) therapy (HR 0.42; 95% CI 0.21–0.81, $p<0.05$) were associated with a reduced risk of cardiovascular morbidity (angina, myocardial infarction and stroke), after adjusting for traditional risk factors.[16]

The effect of anti-TNFα therapy on cardiovascular disease has been studied in several cohort studies. A British cohort of 8,670 patients was followed up for over 18 months and those who responded clinically to anti-TNFα therapy were shown to have a reduced rate of myocardial infarction.[17] The British Society of Rheumatology has issued guidelines on the use of anti-TNFα therapy and advised that it should not be initiated in patients with New York Heart Association (NYHA) grade 3/4 heart failure and should be used with caution in patients with mild heart failure, due to concerns that its use may decompensate pre-existing left ventricular failure.[18]

Conclusion

Health professionals should be aware that rheumatoid arthritis is an independent risk factor for developing atherosclerosis and for coronary heart disease morbidity and mortality. Primary care teams should actively look for traditional cardiovascular risk factors in people with rheumatoid arthritis and be aware that tight control of risk factors is essential because of the high incidence of ischaemic heart disease in this population

Conflict of interest

None declared.

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