Editorial

Cardiovascular disease in rheumatoid arthritis. Importance and clinical management

Enfermedad cardiovascular en artritis reumatoide. Importancia y tratamiento clínico

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In the past 2 decades it has been shown that patients with rheumatoid arthritis (RA) have an increased cardiovascular (CV) mortality than age and gender-matched controls. This is due to the development of accelerated atherosclerosis. It has been calculated that the relative risk for developing a CV event in persons with RA is approximately double than age and gender matched persons without the disease. The increase in CV events in subjects with RA is independent of the traditional risk factors for CV events. Genetic factors such as the presence of alleles HLA-DRB1*0401 and HLA-DRB1*0404 and a chronic persistent inflammation favor the development of CV events in these persons.

Evidence of subclinical cardiovascular disease in rheumatoid arthritis

There is a series of tests that demonstrate the presence of a larger risk for heart failure and the existence of subclinical atherosclerosis in RA; these tests will be described below.

A study performed in subjects with long standing RA and without CV risk factors confirmed that subjects with RA have a greater incidence of diastolic dysfunction of the left ventricle, in addition to an increased frequency of subclinical pulmonary hypertension. These findings can explain the increased incidence of heart failure seen in these subjects.

Different tests, useful for detecting subclinical atherosclerosis, have also been confirmed as valid for corroborating the existence of accelerated atherosclerosis in subjects with RA. Among these, the evaluation of endothelial function through brachial artery ultrasound, a predictive marker of early atherosclerosis, demonstrated the existence of endothelial dysfunction in subjects with long standing RA without classic CV risk factors and also showed that endothelial dysfunction occurs in young patients with early onset RA.

Another non-invasive and useful marker of atherogenesis in RA is the determination of the width of the intima-media complex (IMC) of the carotid artery measured with commonplace carotid artery ultrasound. This group detected the presence of an abnormally high carotid IMC in subjects with long-standing RA who did not have a history of CV events or risk factors for atherogenesis, compared to controls. In addition, it was seen that in these subjects without traditional CV risk factors there was a greater incidence of atheroma plaques in the carotid area, which correlated with duration of the disease and with the presence of extraarticular manifestations in this process. It was also seen that persistently elevated C-reactive protein levels were associated to a greater IMC in subjects with long standing RA. Finally, a prognostic relationship was established between the presence of subclinical atherosclerosis in the carotid area, the CV events and long term mortality in subjects with RA. Another study confirmed, after a 5 year follow up, that the measurement of the carotid IMC has an increased predictive value, because a carotid IMC over 0.90 mm is associated to a higher risk of CV events in the follow-up of these subjects.

Influence of treatment of rheumatoid arthritis in cardiovascular events

Once evidence of a larger CV risk in RA has been established, the next step is to propose a therapeutic strategy targeting a reduction in the CV risk of subjects with this disease.

In this sense, it has been proven that active treatment of disease reduces CV mortality. Recent data has confirmed a reduction in RA mortality due to the reduction in the incidence of myocardial infarcts as a consequence of a more intensive treatment of this rheumatic disease.
Krause et al observed that subjects with RA who experimented a good clinical response with baseline methotrexate (MTX) treatment also had a reduced CV mortality than those who were resistant to this treatment. Choi et al demonstrated that in spite of having worse mortality prognostic factors, subjects treated with MTX did not present a greater rate of CV events during follow-up. Although MTX increases homocysteine values, its beneficial effects on disease activity and especially its anti-inflammatory properties would explain the reduction of accelerated atherosclerosis and, in consequence, CV mortality during RA.

Recent population studies have shown that the use of biologic drugs in subjects with RA resistant to conventional treatment reduces global mortality and CV mortality in particular in these subjects. Biologic therapy with TNF (tumor necrosis factor) blockers improves endothelial function in MTX resistant RA patients. It has also been proven that the use of rituximab in TNF blocker resistant subjects is capable of producing rapid and persistent improvement of endothelial function. Because endothelial dysfunction is a key mechanism in the development of atherosclerotic disease, improvement of endothelial dysfunction with these drugs could be a future therapeutic target in subjects with severe RA. On the other hand, although the first study did not show regression of subclinical atherosclerosis in the carotid area with the use of TNF blockers in a series of patients with severe and long-standing RA with a 3 year follow-up, another later study described a beneficial effect of these drugs, reducing significantly the carotid IMC in patients with RA.

**Influence of “non rheumatologic” treatments for the reduction of cardiovascular risk in rheumatoid arthritis**

The strict control of classic CV risk factors is a paramount importance in subjects with RA in order to reduce the global CV risk associated with this disease. In this sense the control of the lipid profile, which is frequently altered as a consequence of chronic inflammation associated to this process, is a key point to consider when treating RA. In a long-term clinical trial, statin treatment demonstrated a reduction in the clinical and biologic parameters of inflammation in subjects with long-standing RA. In addition, the use of statins has been related to an improvement on endothelial dysfunction in subjects with RA.

**Stratifying cardiovascular risk in subjects with rheumatoid arthritis**

Because RA is considered today as a clear, independent CV risk factor by itself, it is necessary to individually analyze global CV risk during the course of the disease. The use of the SCORE guideline tables for CV risk adapted for each population group in addition to the clinical evaluation of disease are 2 key points based on tests for treatment of CV risk in RA. However, there is not a unanimous recommendation based on clinical practice guidelines for the approach of this key clinical aspect at this time, for these subjects. In Spain, the start of treatment is a first step a strategy of primary CV prevention based initially on general lifestyle recommendations, a “heart-healthy” diet, weight, and blood pressure control as well as smoking cessation. In addition, in relation to the SCORE guidelines adapted for the south of Europe for subjects with RA, treatment with statins or antihypertensive medication should be initiated in those subjects with a CV SOCRE over 10%.

**Financing**

A grant from the Fondo de Investigaciones Sanitarias PI06-0024 (Spain) financed this study.

**References**


