Cardiovascular Risk in Rheumatoid Artritis. ¿Up to What Point?

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Is There an Increase in Cardiovascular Morbidity and Mortality in Rheumatoid Arthritis?

Patients with rheumatoid arthritis (RA) have an increase in mortality by any cause, confirmed in the majority of studies, with a ratio between observed deaths and expected deaths that varies between 0.8 and 3. This data has been fundamentally been evidenced in older, almost always seropositive RA cohorts,[1] with a longer evolution and followed mainly in tertiary care centers, which gives an idea of the severity of the disease, and that in more recent cohorts, probably related to a better general medical assistance and an earlier treatment of RA, these findings are not always confirmed.[2] Of the causes of mortality, cardiovascular (CV) causes seem to predominate,[3] even though it is difficult to statistically demonstrate that the studied cohort is not ample enough.[4] Among other things, it is difficult to demonstrate why the CV cause is also predominant in the general population mortality and there have to be very large differences to detect them, even if this has been described in some studies.[4]

When the incidence of CV episodes in RA has been studied, comparing them to control population, an increase generally has been shown. Nonetheless, many of these studies have been carried out in tertiary care centers, where patients with more severe illness and a longer evolution time are sent, although there has also been an increase in the frequency of CV complications in RA treated in primary care settings,[5] even observing that the risk of myocardial infarction (MI) appears before the diagnostic criteria for RA are fulfilled.[6] The EMECAR[7] cohort, which represents a mixed RA population of hospitalized and outpatients, has been unable to demonstrate that there are more CV episodes than those expected in a population of equal gender and age, and there are several studies unable to show that the ratio of hospitalizations due to CV causes is larger than expected for a control population without arthritis.[8] This contradiction between an increase in the CV mortality which does not always correspond to an increased incidence in the CV episodes, can have a physiologic explanation apart from a relationship to risk factors that have not yet been studied adequately. Everyday there is more data that shows that patients with RA have accelerated atherosclerosis, with arterial rigidity and an increment in the vascular resistance that affects the coronary arteries in a very extended form and also affects peripheral vessels.[9,10] If, paradoxically, with such an extension of atherosclerosis there are no more CV episodes, it is possible that either the patients with RA die with greater frequency or immediately alter their first CV related hospitalization,[11] or else have less pain or interpret angina pain in a different manner and due to this would not seek specialized attention and have silent MI and sudden death more frequently.[6]

Do Patients With Rheumatoid Arthritis Have More Cardiovascular Risk Factors?

Classic CV risk factors must be taken into account. This does not mean that there is a confirmed increase in these risk factors in RA due to reasons different from patient gender and age. The EMECAR[7] cohort analysis indicates that the CV risk factors are not more frequent than expected in the Spanish population with RA than in the general population of equivalent age and gender, except in the case of tobacco use. Smoking is both an etiologic and prognostic risk factor in RA[12] apart from a sufficiently contrasted CV risk factor. The recently discovered relationship between the shared epitope, citrulinated autoantibodies or rheumatoid factor and tobacco clearly support our radical posture against smoking in RA.[13] There are emerging CV factors, greatly related with inflammatory processes. The value of C reactive protein (CRP) is a clear independent prognostic factor of CV mortality, even in patients without RA.[5,14] Rheumatoid factor multiplies up to six times the risk of dying due to a CV cause in RA, but is

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also associated with an elevated risk of CV death in subjects without RA.[15] Homocysteinemia seems to play a fundamental role in patients treated with methotrexate, especially in the ones not receiving folic acid supplements.[16]

It seems clear that the morbidity and mortality of CV origin is not completely explained by the traditional CV risk factors.[17] If the truth is to be told, everyday there is more data that show that severity of illness is the real protagonist in the CV type comorbility in RA. The inflammatory process is key in the development of accelerated atherosclerosis that occurs in patients with RA, and is related with the endothelial dysfunction as well as with the immunologic factors.[4] In the same manner, the presence of an elevated joint count is also a clear predictor of CV mortality.[18]

What Is the Influence of Treatment?

Part of this CV mortality could be related to some treatments in RA. The non-steroidal anti-inflammatories, be them coxibs or not, have a certain relationship with the incidence of MI, especially when taken for prolonged periods of time, the case in many RA patients.[19] Glucocorticoids, by diverse mechanisms, favor the development of atheroma plaques, something that is stronger than the anti-inflammatory, and therefore beneficial effect, that they could have.[20] Methotrexate produces an increase in homocysteinemia, unless folic acid supplementation is taken on the day after taking methotrexate, something that can reduce even CV mortality.[21]

Another part of CV mortality in RA could be related to the lack of treatment of the CV comorbidities. It has been shown that when treating a chronic illness, the probability of treating the comorbidity diminishes significantly. In RA it has been shown that the probability of taking prophylactic aspirin is 30% less than in patients without arthritis,[22] apart from the fact that the traditional CV risk factors are treated insufficiently.[23] It is true that the therapeutic compliance for a CV illness is low in patients with various medications therefore emphasis should be placed on reminding the patients of their importance.

Curiously, the control of CV risk factors can improve RA. The case of tobacco and its relationship with severity has been mentioned, both in CV illness as in arthritis. Statins improve the CV prognosis by optimizing the lipid profile, but also diminish the incidence of osteoporotic fractures and have a discreet beneficial effect over inflammatory activity.[24] It seems, on the other hand, that the efficacious treatment of RA reduces morbidity and mortality due to CV causes.[21,25] Incapacity in patients with RA has been progressively diminishing since 1977 to 1998, even before the appearance of of new therapeutic agents. This significant decrease was attributed to a shift to a more aggressive therapeutic attitude, especially to the increase in disease modifying drugs and more concretely, methotrexate. The appearance of methotrexate has represented not only a change in the incapacity of patients with RA but also has had a clear impact on mortality.[21] Every day there are more studies that support the beneficial role of the anti tumor necrosis factor (TNF) drugs over certain vascular risk factors. In spite of the scarcity of data, a recent study[26] has shown how, after correcting for different variables, including the duration of follow-up and the severity of RA, patients treated with biologics presented less first ischemic CV episodes compared to patients that had not received biologic treatment. This suggests that the possible beneficial effect of the TNF antagonists over the inflammatory process can also have a protective effect on the development of CV episodes.

What Must Be the Attitude of a Rheumatologist?

The rheumatologist is the main health provider of patients with RA. He or she must be able to stop the inflammatory process and care for the vital prognosis, and therefore must be well acquainted with the comorbility associated with RA. Evidently the emphasis put on CV protection Hill depend on the baseline risk, both on the population and the individual levels. Among CV risk factors, tobacco is one of the most frequently taken into account. But one must not forget other risk factors that tend to alert us such as male gender, older age and having a previous CV event. In this last case, one must not forget acetylsalycilic acid at an anti-aggregating dose with a prophylactic intention. Homocysteinemia is easy to combat ensuring an optimal folic acid value, especially if the patient is taking methotrexate.

The adequate selection and treatment of traditional CV risk factors and a better control of the joint inflammatory process can lead to a significant reduction in the morbidity and mortality due to CV causes in patients with RA.

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References

1. Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis Rheum. 2002;46:2010-9.
2. Kroot EJ, van Leeuwen MA, van Rijswijk MH, Prevoo ML, van´t Hof MA, van de Putte, et al. No increased mortality in patients with rheuma-

toid arthritis: up to 10 years of follow up from disease onset. Ann Rheum Dis. 2000;59:954-8.
3. Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O´Dell J, Pincus T. Making an impact on mortality in rheumatoid arthritis: targeting cardiovascular comorbidity. Arthritis Rheum. 2004;50:1734-9.
4. Goodson N. Coronary artery disease and rheumatoid arthritis. Curr Opin Rheumatol. 2002;14:115-20.
5. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year follow-up study of a primary care-based inception cohort. Arthritis Rheum. 2005;52:2293-9.
6. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005;52:402-11.
7. González-Álvaro I, Carmona L, Balsa A, Sanmartí R, Belmonte MA, Tena X. Patterns of disease modifying antirheumatic drug use in a Spanish cohort of patients with rheumatoid arthritis. J Rheumatol. 2003;30:697-704.
8. Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis. 2005;64:1595-601.
9. del Rincón I, Haas RW, Pogosian S, Escalante A. Lower limb arterial incompressibility and obstruction in rheumatoid arthritis. Ann Rheum Dis. 2005;64:425-32.
10. Warrington KJ, Kent PD, Frye RL, Lymp JF, Kopecky SL, Goronzy JJ, et al. Rheumatoid arthritis is an independent risk factor for multi-vessel coronary artery disease: a case control study. Arthritis Res Ther. 2005; 7:R984-91.
11. van Doornum S, King B, Brand C, Sundarajan V. Mortality rates following a first acute cardiovascular event. A comparison between rheumatoid arthritis patients and the general population [abstract]. Arthritis Rheum. 2005;52:2.
12. Masdottir B, Jonsson T, Manfredsdottir V, Vikingsson A, Brekkan A, Valdimarsson H. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. Rheumatology (Oxford). 2000;39:1202-5.
13. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, Kloppenburg M, de Vries RR, le Cessie S, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLADRB1 shared epitope alleles. Ann Rheum Dis. 2006;65:366-71.
14. del Rincón I, Williams K, Stern MP, Freeman GL, O´Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis Rheum. 2003;48:1833-40.
15. Jacobsson LT, Knowler WC, Pillemer S, Hanson RL, Pettitt DJ, Nelson RG, et al. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum. 1993;36:1045-53.
16. Landewe RB, Breedveld FC, Dijkmans BA. Methotrexate treatment and mortality in rheumatoid arthritis. Lancet. 2002;360:1095-6; author reply: 1097-8.
17. del Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44:2737-45.
18. Jacobsson LT, Turesson C, Hanson RL, et al. Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. Arthritis Rheum. 2001;44:1170-6.
19. García Rodríguez LA, González-Pérez A. Long-term use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. BMC Med. 2005;3:17.
20. del Rincón I, O´Leary DH, Haas RW, Escalante A. Effect of glucocorticoids on the arteries in rheumatoid arthritis. Arthritis Rheum. 2004;50:3813-22.
21. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173-7.
22. Colglazier L, Wolfe F, Michaud K. Rheumatoid arthritis (RA) patients are less likely to be treated with prophylactic aspirin despite an increased risk of myocardial infarction. Meeting of the American College of Rheumatology [abstract]. 2005.
23. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2005;52:722-32.
24. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363:2015-21.
25. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med. 2003;115:371-6.
26. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005;32:1213-8.