Editorial
Rheumatologists, take heart! We may be doing something right
Ronald F van Vollenhoven

Rheumatology Unit, the Karolinska Institute, Department of Rheumatology, The Karolinska University Hospital, Reumatologen D2-1, 17176 Stockholm, Sweden

Corresponding author: Ronald F van Vollenhoven, Ronald.van.Vollenhoven@ki.se

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Abstract

In the present issue of *Arthritis Research & Therapy* data are presented suggesting that antirheumatic therapies decrease the risk of cardiovascular disease in patients with rheumatoid arthritis. The QUEST-RA group, a large international collaboration, analyzed data on 4,363 patients in a cross-sectional manner. Traditional risk factors were all significantly associated with cardiovascular events, and the presence of extraarticular disease significantly increased the risk, confirming a previous publication. The most interesting analysis in this study suggests that effective antirheumatic treatment, with traditional disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, or anti-TNF biologics, reduces the risk of cardiovascular disease in rheumatoid arthritis. Some methodological issues are discussed, however, and confirmatory studies are suggested.

Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular disease. It is not yet known if antirheumatic treatments can modulate this risk in a favorable manner.

In the present issue of *Arthritis Research & Therapy* Naranjo and colleagues present data suggesting antirheumatic treatments do modulate this increased risk [1]. The authors present on behalf of the QUEST-RA group, a large international collaboration involving 48 rheumatologists in 15 countries. Data were collected on 4,363 patients with RA in a cross-sectional manner, from patients and physicians by recall and chart review. From this large dataset, the authors were able to determine a number of facts. The patient population was quite typical for established RA, and 9.3% of these patients reported having had cardiovascular disease or events (heart attack and angina, coronary heart disease, coronary by-pass surgery, and stroke were included, but only if they occurred after RA had developed). The presence of traditional risk factors was ascertained and, by comparing patients with and without a cardiovascular event, most of these risk factors could be confirmed: higher age, male sex, hypertension, smoking (ever), diabetes, and hyperlipidemia were all significantly associated with the risk for cardiovascular events. A more interesting finding was that the presence of extraarticular disease clearly increased the risk of cardiovascular events, confirming a previous publication by Turesson and colleagues [2].

The real importance of this study, however, may lie in the final analysis, presented in Table 5 of their paper, which intends to determine to what extent antirheumatic treatment modulates the risk of cardiovascular disease [1]. To achieve this, the authors collected data from the physicians on the treatments (glucocorticoids, conventional disease-modifying antirheumatic drugs [DMARDs], and biologics) given to the patients with start and stop dates. They then used the duration of treatment for each drug in each patient separately as an independent variable in a multivariate analysis where potential confounders were also included, including age and sex, other traditional risk factors, and disease activity by the Disease Activity Score as well as the Health Assessment Questionnaire disability index. These analyses all show a negative relationship between the length of treatment with conventional DMARDs and the risk of cardiovascular events; that is, longer duration of treatment with, say, methotrexate was associated with a somewhat lesser risk than a shorter duration of treatment with the same agent. The risk reduction was quantitatively strongest with leflunomide, and was statistically significant in the most stringent analysis for all but two of the drugs under study. A significant but weaker relationship was also found, rather surprisingly, with glucocorticoids, and, more in line with current expectations, a stronger relationship with anti-TNF biologics (other biologics were not assessed). The authors cautiously interpret these data as suggesting that effective antirheumatic treatment reduces the risk of cardiovascular disease in patients with RA.

DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

This may well be true. The current study design – a retrospective cross-sectional review based in some part on patient recall – and using internal comparisons rather than a control group, however, are not ideal to address this issue. In particular, the use of length of treatment as the variable of interest raises both conceptual and technical issues. The conceptual question is whether the length of time that a patient stays on a treatment is a good indication that the patient had good disease control during that time. Obviously this is not necessarily true at the individual level, but at the group level this approach may work reasonably well – as demonstrated in a number of studies, including studies of survival on drugs [3,4] and a study of radiological progression in the first 2 years of disease [5].

The technical issues are more formidable. First of all, and as the authors themselves admit, the study is subject to left-censoring: those patients who died of a cardiovascular event could obviously not contribute data. One interpretation of the study is therefore that antirheumatic therapy does not change the risk of a cardiovascular event, but increases the risk that the event will prove fatal! Obviously this is a cynical interpretation if there ever was one, but it may serve to underscore the difficulties with retrospective studies. Another problem is that the length of each treatment is restricted by the duration of the disease itself: those patients with the shortest disease duration at inclusion would also be more likely to contribute shorter treatment courses than those with the longer disease duration. But, importantly, this particular problem would make the results go the other way, so that the criticism in fact strengthens the conclusions. A final concern worth mentioning is a channeling bias: it is conceivable that patients were given antirheumatic therapies based in part on the perception of risks associated with these agents for that particular patient, and cardiovascular risk factors might have played in that decision. An example would be that leflunomide would be chosen less often for patients with hypertension, or that glucocorticoids would be avoided in patients with diabetes. When the authors controlled for these known risk factors, however, the association between treatment and risk was generally maintained.

Taking these data at face value, it is quite striking that almost all of the antirheumatic therapies investigated provided a benefit. This would strongly argue against a specific pharmacologic effect separate from the antirheumatic effect, but rather supports the idea that this efficacy is conveyed by decreasing the immune-mediated inflammatory process underlying atherogenesis [6] and/or plaque instability [7].

The final message of Naranjo and colleagues' paper, and one that should be encouraging to those of us managing patients, is that our insistence on the sustained use of appropriate antirheumatic therapies, while not always the most popular with patients, has been the right approach all along – not only with a view on the rheumatic disease itself, but also for the cardiovascular complications.

In summary, the possibility that antirheumatic therapy decreases the risk for cardiovascular complications is tantalizing. The current study, while not exactly proving this point, adds a further measure of support to the concept, and suggests that it must now be formally addressed, either by a rigorously designed and implemented prospective cohort approach or by a controlled clinical trial.

Competing interests
The author declares that they have no competing interests.

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