Reviewer’s report

Title: Improvement in symptoms and signs in the forefoot of patients with rheumatoid arthritis treated with anti-TNF therapy

Version: 1 Date: 17 March 2010

Reviewer: Martijn Steultjens

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This study provides important preliminary evidence on the effectiveness of anti-TNF therapy for specific foot-related symptoms in RA patients.

A particular strength of the study is the use of ultrasound (US) imaging to provide high-quality data on inflammation and joint damage in the foot.

Since this study used an uncontrolled design with a fairly low sample size in which patients were not blind to the treatment they received (I assume, see comment a. below), the usual caution with interpreting these results applies: neither the natural course of the disease and its symptoms nor the placebo effect or similar phenomena were controlled for. Therefore, this study’s results do not conclusively show that anti-TNF drugs are effective in improving foot status in RA.

Nevertheless, within the confines of the chosen design, this study was generally performed well and does present important findings. There are however some issues that require clarification, which would fall under the ‘major compulsory revision’ type comments:

a. “A blinded...design was utilized” (Method, line 1). I assume this refers to the fact that all assessors were blinded to each other’s examination results, but that patients were not blinded to the fact that they were receiving anti-TNF medication. And with regard to the follow-up measurement, were all assessors, and the US assessor in particular, also blinded to their own baseline assessment of the individual patient being assessed? Please clarify.

b. The target population for the study is defined as “all patients with RA...who were starting anti-TNF therapy” (p.4, 2nd paragraph). Later, the study sample is described as being initially N=32 with one drop-out. It is unclear whether the N=32 comprised all eligible consecutive patients as per the target population description, or if there were patients fitting the target population profile who were excluded or excused themselves from participation with only the most willing and fitting patients actually enrolling in the study. As such, it is difficult to judge if these findings can be generalized to the wider RA population. It would therefore be good to also have a flow chart showing on how many patients met the basic inclusion criteria (confirmed diagnosis of RA, and starting anti-TNF therapy) during the inclusion period, how many were excluded by the researchers, how many declined the invitation to participate themselves, and how many finally
enrolled in the study.

c. A second aspect of describing the sample concerns study attrition. The authors claim all but one of the 32 participants completed the study. However, available US data are reduced from 60 feet at baseline to apparently 52 feet at follow-up. Also, the specific US Doppler measurements were down to N=18 at follow-up from N=22 at baseline. This suggests at least partial drop-out was an issue with some patients not completing all follow-up measurements. This should also be incorporated and clarified in the flow chart mentioned under b.

d. An interesting characteristic of the study sample was the disease duration of 11 +/- 10 years (range 1-39), which is labelled as ‘homogenous’ by the authors. I fail to see what is homogenous about the sample’s disease duration given SD and range. These figures also suggest that the distribution was skewed with relatively few patients with a long disease duration and relatively many early RA patients. Later on in the manuscript, the term ‘homogenous’ is qualified as meaning patients ‘at the same stage of treatment’. However, this does not necessarily imply that these patients are also at the same stage in their disease. Please clarify and justify the use of the term ‘homogenous’ in this paper.

e. Some of the most intriguing findings of the study concern the change over the 12 weeks in synovitis and bursal hypertrophy as assessed by US. For both impairments, a number of joints change from present to absent, but there are also joints in which signs of inflammation appear during therapy. The authors suggest the latter may be the result of increased mechanical stress following higher or more frequent loading of the joint as patients feel better and become more mobile. Another possibility is that to some extent US findings will vary over time due to the imperfect reproducibility of US measurements, resulting in joints being identified as inflamed at follow-up but not baseline without this reflecting any change in the joint’s actual status. Is there any evidence in the literature on the reproducibility and other clinimetric properties of US in RA feet? If so, please include this in the Discussion to strengthen the case for the mechanical stress theory. If not, random measurement error in US should be acknowledged as a possible cause for the presented results.

f. Overall, although the drug therapy is clearly effective, after 12 weeks of medication disease activity is still high, foot inflammation highly prevalent and patient function still affected. The authors comment that 12 weeks may be too short a period to find more improvements, although to my knowledge 3 months is a generally accepted term to assess anti-TNF treatment response. But how do these findings compare to other literature on anti-TNF effectiveness? Was treatment response in general (i.e., DAS, VAS-wellbeing) better or worse than could be expected? And, more importantly, did foot symptoms improve more or less than what has generally been reported for other joints such as the hands, knees etc.?

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests