Author's response to reviews

Title: Whole body MR Imaging in Ankylosing spondylitis: A Descriptive Pilot Study in Patients with Suspected Early and Active Confirmed Ankylosing Spondylitis

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Cover letter (re-submitting)

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Whole body MR imaging in ankylosing spondylitis: a descriptive pilot study in patients with suspected early and active confirmed ankylosing spondylitis

Dear Dr Kouremenou

Please find below a point-by-point response to the concerns of the reviewers.

Response to reviewer’s report of Martin Rudwaleit

1. Terms “suspected early AS” and “early IBP”
Choosing a term for the early disease group proved to be a challenge. There is no universally accepted term for the early disease stage mostly as a consequence of a lack of validated diagnostic criteria. The recently proposed term “axial SpA without radiographic sacroiliitis” is most appropriate but even rheumatologists are not very familiar with it. In the first draft of our manuscript we used “suspected early AS”; the disadvantage of this term is that we can’t exclude that patients in the early disease group might develop another form of SpA in the future (e.g. psoriasis associated or enteropathic SpA). Therefore we used “inflammatory back pain” as the common denominator of the early disease group (after discussing this topic with Prof. van der Heijde of our advisory board). We are happy to adopt the version “suspected early AS”; the term has been changed throughout the manuscript.

2. Inclusion criteria of the “suspected early AS”-group
The selection criteria of the early disease group are listed in the section “inclusion criteria” (page 5). Patients were enrolled in this group if they fulfilled three criteria: BASDAI total or BASDAI item 2 of at least 4; fulfilling of at least 2 criteria of inflammatory back pain as defined in the manuscript; and at least one of the following features (line 3 to 6 section “inclusion criteria”): rapid and substantial pain relief by non-steroidal anti-inflammatory drugs, alternating buttock pain, peripheral arthritis, enthesitis, dactylitis, uveitis, HLA B27-positivity, elevated acute phase reactants, family history of AS.
Previous imaging consisted only of conventional radiography according to the recommendations by ASAS for AS cohorts (all eligible patients were included also in our national AS registry). The vast majority of patients of both groups had no previous MRI. Probably due to the small sample size of 10 patients with suspected early AS and the relatively high median BASDAI item 2 of 6.0 we found inflammatory changes in all patients of this group.
The BASDAI cut-off of at least 4 was chosen as this is one of the clinical criteria for high disease activity and for consideration of a TNFa-treatment. The frequency of MRI changes in patients with early and less active disease may differ from our results although we are not aware of MRI-studies in early AS patients having a BASDAI of less than 4.

3. Wording “about SI joints”
This wording is used in US-American publications in the field of radiology. It is possibly less used in the European literature and we are happy to change the wording as proposed.
4. Explanation of “BASDAI 2”
We added the proposed explanation on page 6, 10 and in table 1.
Medians indeed are more appropriate regarding the size of the 2 groups; table and text have been adapted.

5. Predictive value of MRI for future X-ray changes (page 14)
We fully agree with this comment. The wording of this sentence has been discussed with our advisory board (Prof. van der Heijde). The paper by Oostveen which has been quoted previously in our study will be mentioned also in this context.

Response to reviewer’s report of Maxime Dougados

1. Sample size
We agree that the sample size of this pilot study is too small to draw firm conclusions and we added an additional comment to the abstract (page 2, lines 5-6) and discussion (page 19, conclusion). A planned “validation” study with a larger sample size will hopefully allow further insights.

2. Inclusion criteria
In this pilot study we tried to include patients with a high probability of AS and we excluded patients with known psoriatic arthritis or enteropathic SpA at the time of the WB-MRI. We will change this practice for a planned validation study with inclusion of patients with any form of SpA.
In our practice MRI exams in patients with SpA are mostly asked for when there is a high disease activity or as an additional step before initiating a TNFa treatment. Thus this arbitrary limit for disease activity reflects clinical practice in our country. We added an explanation in the section “methods” (inclusion criteria, last 2 lines).
We are not aware of MRI studies in SpA with patients having a BASDAI of less than 4. We assume that the percentage of patients with MRI-abnormalities would be lower, but the correlation between clinical disease activity and acute inflammatory changes of the SI joints and the spine is discussed controversially in the literature (positive correlation cf references 19 and 28, negative findings cf references 18 and 29).
In the group with suspected early AS (early disease course), the response to NSAIDs was part of the inclusion criteria and therefore directly assessed. The percentage of patients refractory to NSAIDs in this group was 40 %.
The percentage of patients refractory to NSAIDs in the group with confirmed diagnosis can be assessed only indirectly if we assume that these are the patients initiating a TNFa treatment after the WB-MRI (the main reason for referral of patients in this group). 6/10 patients started a TNFa-therapy within a few weeks after the WB-MRI.

3. Classification criteria for the “IBP” group (according to the request of one of the reviewers re-named “suspected early AS” group)

X-ray mNY-criteria vs MRI-criteria
Together with the recent proposal by Prof. Sturrock at the Gent meeting 2006 there are now 4 scoring systems for MRI findings at the SIJ in AS. It is far beyond the scope of this pilot study to comment on these 4 proposals. The table below shows “inflammatory” bilateral signal alterations in 6/10 patients with suspected early AS not yet fulfilling the modi-
fied New York-criteria in conventional radiography. Assessing chronic SIJ changes by MRI is difficult in many cases.

One patient in this early disease group fulfilled the modified NY-criteria with onset of inflammatory back pain 9 months before the WB-MRI. This date of onset has been confirmed during the first annual follow-up exam of the observational registry. As far as I know there are a few similar patients in the Maastricht cohort of early SpA patients.

<table>
<thead>
<tr>
<th>Pat no</th>
<th>Xray mNY-crit.</th>
<th>MRI “edema”</th>
<th>MRI “chronic changes” (er=erosions or sscl=suspect. sclerosis)</th>
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</thead>
<tbody>
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<td>1</td>
<td>-</td>
<td>bilat</td>
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</tr>
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<td>3</td>
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<tr>
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<td>10</td>
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AMOR criteria: MRI changes instead of X-ray changes

General note: the questionnaire set of our national prospective observational registry of SpA patients does not allow a full scoring according to the AMOR criteria. The following items are not recorded (for several reasons including guidelines of our ethical committees): no PCR tests concerning non-gonococcal urethritis or cervicitis; no history taken concerning acute diarrhoea (but reactive arthritis recorded); no exams for balanitis.

Below is the AMOR score for each patient WITHOUT radiological findings and the corresponding MR-findings bi- or unilaterally.

<table>
<thead>
<tr>
<th>Pat no</th>
<th>AMOR score (w/o imaging and above ment. items)</th>
<th>MRI “edema”</th>
<th>MRI “chronic changes” (er=erosions or sscl=suspect. sclerosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td>3</td>
<td>7</td>
<td>bilat</td>
<td>sscl unilat</td>
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6/10 patients with suspected early AS fulfilled the AMOR-criteria (without imaging criteria). In only one of the remaining four patients a bilateral signal alteration around the SIJ has been found (and in 2 patients unilateral signal alterations).

4. SI fatty replacement of bone marrow
This is a very controversial topic with a wide variation of findings in small series of healthy volunteers, SpA-patients and a small number of studies on cadavers. As far as we know there is no large and relevant study on fatty replacement of bone marrow of SIJ in the general population.

On the other hand there are only few data on sensitivity and specificity of the so-called “inflammatory” signal alterations in SpA in SIJ. A poster by Dr. Rudwaleit and his group at the Gent congress showed “inflammatory” signal alterations of the SIJ in 8% of patients with mechanical low back pain.

5 a. Simplicity of the technique
The time for analysis and reporting to the referring physician is 15 to 20 min. A legal issue is the difficult reporting of signal alterations of internal organs.

5 b. Usefulness of the technique
This table has been added and is referred to in the section “results” (last para, page 13).

5 c. Number of figures
The 4 graphs with distributions of the MR findings have been replaced by one table.

Response to reviewer’s report of Roger Sturrock

1. Explanation of the nature of domain 2 of the BASDAI
   We added an explanation on page 6 and 10 and in table 1.

2. Reduction of the number of illustrations
   The 4 graphs with distributions of the MR findings have been replaced by one table.

This point-to-point response and the revised manuscript have been approved by all authors.

We hope to have addressed the concerns of the reviewers and we look forward to the comments on our revised manuscript by the editorial board of BioMed Central.

Best regards

Ulrich Weber, MD

Zurich 27.10.2006