Reply to: Bone marrow oedema on sacroiliac/spine MRI: is it really a sign of objective inflammation warranting treatment?

Sirs,

We appreciate the opportunity to respond to the comment by Esatoglu and Hatemi on our article “Non-radiographic axial spondyloarthritis patients without initial evidence of inflammation may develop objective inflammation over time” (1). Their main concerns were about the specificity of magnetic resonance imaging (MRI) of bone marrow edema (BME) lesions for detecting active inflammation in patients with axial spondyloarthritis (axSpA), as well as the value of MRI for monitoring disease activity.

Regarding the question of the specificity, it is important to keep in mind that the patients in our analysis were drawn from the ABILITY-1 study, in which all enrolled patients had a rheumatologist diagnosis of non-radiographic axSpA (nr-axSpA) and in addition fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA and were experiencing clinically active disease (ASAS total back pain score ≥4 and a Bath Ankylosing Spondylitis Disease Activity Index ≥4), despite the previous use of at least 1 non-steroidal anti-inflammatory drug (NSAID) (1). Since the design of the ABILITY-1 study, it has become well known that MRI inflammation may result after physical forces at enthesal sites (such as the area of the sacroiliac joints, but also other musculoskeletal areas) for many reasons which are not yet completely understood (2). Therefore, it is neither possible nor justifiable to directly compare our patients with the healthy military recruits in the study by Varkas et al. (3) that Esatoglu and Hatemi cite. In addition to the well-defined clinical phenotype of the ABILITY-1 study participants, the procedures for imaging were carefully designed to ensure the highest possible specificity. Experienced, well-trained central readers evaluated all images after internal calibration and agreement to exclude lesions that were suspected to occur for reasons other than SpA, such as lesions that were in the extremely superior part of the sacroiliac joint, which are considered to be more likely mechanical than inflammatory. In contrast, these BME findings appear to have been included in the paper by Varkas et al., as shown in Figure 1 of their article. In practice, such lesions are being excluded from use for identification of SpA patients.

Our subanalysis did not evaluate the effect of adalimumab on axial BME, as it has been previously reported for the ABILITY-1 study that adalimumab treatment compared with placebo resulted in significant decreases in spine and sacroiliac joint inflammation in patients with nr-axSpA (4). With respect to the effect of etanercept treatment on BME in the study by Rudwaleit et al. (5), one needs to take into account that the majority of patients included had established structural damage in the sacroiliac joints and fulfilled modified New York criteria for ankylosing spondylitis (AS), which may show a different pattern of inflammation compared with the nr-axSpA of patients in ABILITY-1, who did not fulfill these criteria. In addition, patients in the study by Rudwaleit et al. were evaluated after 6 weeks of placebo-controlled treatment with etanercept, only half of the time period evaluated in ABILITY-1, and it is currently unknown what the expected time course for resolution of BME with effective therapy is. We therefore believe that the results of these studies are not comparable.

Concerning the value of MRI in monitoring disease activity in nr-axSpA and informing treatment decisions, we fully agree with Esatoglu and Hatemi (who give the historical cautionary example of avascular necrosis of the hip) that an abnormal MRI finding, in the absence of symptoms, should not prompt biologic therapy. Indeed, guidelines and product labels restrict the use of biologic drugs in patients with nr-axSpA to those with clinically active disease despite treatment with NSAIDs who also have an objective measure of inflammation (6-10). Having an objective measure, rather than relying solely on symptoms, prevents indiscriminate use of biologics in this patient population. MRI is an objective measure whose results may constitute part of the evidence for identifying which patients should receive advanced therapy. Again, all patients in the ABILITY-1 study had symptoms of active disease at baseline, and patients with axSpA who have persistent symptoms are suitable candidates for follow-up and additional treatment options. As the burden of axSpA on patients is considerable, with significant levels of pain (11), every effort should be made to manage the condition effectively over time. Esatoglu and Hatemi speculated that it would be of more interest to examine changes in inflammation during adalimumab treatment and whether those changes were correlated with changes in disease activity. As we have noted, the first question was answered by the reports that showed significant improvements in inflammation as assessed by MRI among patients with nr-axSpA. Similarly, significant improvements in spine and sacroiliac joint inflammation were also demonstrated with adalimumab compared with placebo in another study in patients with AS (4, 12). Likewise, the association between changes in inflammation assessed by MRI and disease activity was tested in a pooled analysis of etanercept or adalimumab treatment compared with placebo in patients with active axSpA, which found significant correlations, although only in patients with disease duration of <4 years (13).

In summary, the purpose of our study was to assess changes in objective inflammation over time in well-categorized nr-axSpA patients who had not received prior biologic treatment. We do not claim that MRI inflammation always indicates active disease in patients with nr-axSpA; as all ABILITY-1 study patients had clinically active disease at baseline, this hypothesis cannot be addressed with our data. What our article showed was that nr-axSpA patients who initially present with clinically active disease, but without an objective indication of inflammation, may later develop an objective finding that then qualifies them for more advanced treatment. Among patients with clinically active disease who do not initially exhibit an objective measure of inflammation and who remain symptomatic over time, we continue to support re-testing for objective inflammation at a later time point as an appropriate approach to patient management.

X. BARALIAKOS1, MD, PhD
J.K. ANDERSON2, DO, MS
1Rheumazentrum Ruhrgebiet Herne, Ruhr-University, Bochum, Germany;
2Immunology Clinical Development, AbbVie Inc., North Chicago, IL, USA.

Please address correspondence to: Dr Xenofon Baraliakos,
Rheumazentrum Ruhrgebiet, Ruhr-University Bochum, Claudiastrasse 45,
Herne 44649, Germany.
E-mail: xenofon.baraliakos@elisabethgruppe.de
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References