Serum biomarkers and changes in clinical/MRI evidence of golimumab-treated patients with ankylosing spondylitis: results of the randomized, placebo-controlled GO-RAISE study

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Abstract

Background: In the present study, we evaluated relationships between serum biomarkers and clinical/magnetic resonance imaging (MRI) findings in golimumab-treated patients with ankylosing spondylitis.

Methods: In the GO-RAISE study, 356 patients with ankylosing spondylitis randomly received either placebo (n = 78) or golimumab 50 mg or 100 mg (n = 278) injections every 4 weeks through week 24 (placebo-controlled); patients continuing GO-RAISE received golimumab through week 252. Up to 139/125 patients had sera collected for biomarkers/serial spine MRI scans (sagittal plane, 1.5-T scanner). Two blinded readers employed modified ankylosing spondylitis spine magnetic resonance imaging score for activity (ASspiMRI-a) and ankylosing spondylitis spine magnetic resonance imaging score for chronicity. Spearman correlations (r) were assessed between serum biomarkers (n = 73) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), C-reactive-protein (CRP)-based Ankylosing Spondylitis Disease Activity Score (ASDAS), modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), and ASspiMRI scores. Serum biomarkers predicting postbaseline spinal fatty lesion development and inflammation were analyzed by logistic regression.

Results: Significant, moderately strong correlations were observed between baseline inflammatory markers interleukin (IL)-6, intracellular adhesion molecule-1, complement component 3 (C3), CRP, haptoglobin, and serum amyloid-P and baseline ASDAS (r = 0.39–0.66, p ≤ 0.01). Only baseline leptin significantly correlated with ASDAS improvement at week 104 (r = 0.55, p = 0.040), and only baseline IL-6 significantly predicted mSASSS week 104 change (β = 0.236, SE = 0.073, p = 0.002, model R² = 0.093). By logistic regression, baseline leptin, C3, and tissue inhibitor of metalloproteinase (TIMP)-1 correlated with new fatty lesions per spinal MRI at week 14 and week 104 (both p < 0.01). Changes in serum C3 levels at week 4 (r = 0.55, p = 0.001) and week 14 (r = 0.49, p = 0.040) significantly correlated with BASDAI improvement at week 14. Baseline IL-6 and TIMP-1 (r = -0.63, -0.67; p < 0.05) and reductions at week 4 in IL-6 (r = 0.61, p < 0.05) and C3 (r = 0.72; p < 0.05) significantly correlated with week 14 ASspiMRI-a improvement.

(Continued on next page)
Conclusions: Extensive serum biomarker multiparametric analyses in golimumab-treated patients with ankylosing spondylitis demonstrated few correlations with disease activity or MRI changes; IL-6 weakly correlated with radiographic progression.

Trial registration: ClinicalTrials.gov identifier: NCT00265083. Registered on 12 December 2005.

Keywords: ASDAS, Biologic, Monoclonal antibody, MRI, TNF inhibitor

Background
Magnetic resonance imaging (MRI) is now an established outcome instrument in the assessment of treatment for ankylosing spondylitis (AS), based on results of randomized, placebo-controlled studies. Such studies have shown that MRI can provide an objective assessment of response to tumor necrosis factor (TNF) inhibition in patients with AS [1, 2].

In the GO-RAISE trial of golimumab in AS (ClinicalTrials.gov identifier: NCT00265083), patients with active AS showed significant improvement in signs and symptoms after treatment with golimumab [3] that were maintained through 2 years [4]. In the MRI substudy of GO-RAISE, golimumab significantly reduced MRI-detected spinal inflammation, and these observed improvements correlated with improvement in signs and symptoms of disease [5]. Data from observational studies suggest that long-term treatment with TNF antagonists, especially if started early, may inhibit radiographic progression [6]. In another study, a clear causal relationship between the level of inflammation as assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) and radiographic progression has been established [7]. Moreover, a moderate relationship between spinal inflammation detected by MRI and syndesmophyte formation has been proven [8–11]. Therefore, we conducted additional analyses of data from the GO-RAISE trial to further assess potential relationships between serum biomarkers of inflammation and clinical measures of disease activity, as well as with spinal inflammation and fatty lesions detected by MRI.

Methods
Patients and study design
The details of the GO-RAISE study have been described previously [3, 4]. The protocol was reviewed and approved by the institutional review board or independent ethics committee at each site of this multicenter trial. (See Acknowledgements section below for further details.) All patients provided written informed consent. The study was conducted at 57 sites in the United States, Canada, Europe, and Asia. The MRI substudy was conducted at ten sites with the capability and willingness to participate. All patients enrolled at participating substudy sites were included in the MRI substudy.

GO-RAISE patients were adults with definite AS (for ≥3 months) according to modified New York criteria, a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 (0- to 10-point scale), a total back pain score ≥4 on a visual analogue scale (0- to 10-cm scale), and an inadequate response to current or previous nonsteroidal anti-inflammatory drugs (NSAIDs). Patients were randomly assigned in a 1:1:8:1.8 ratio to receive subcutaneous injections every 4 weeks of placebo, golimumab 50 mg, or golimumab 100 mg. Randomization was stratified by investigational site and screening C-reactive protein (CRP) concentration. Patients were allowed to continue stable doses of methotrexate, sulfasalazine, hydroxychloroquine, corticosteroids, and NSAIDs throughout study participation.

At week 16, patients who achieved <20% improvement from baseline in both the total back pain and morning stiffness scores entered into double-blinded early escape, such that patients in the placebo group received golimumab 50 mg, patients in the golimumab 50 mg group received 100 mg, and patients in the golimumab 100-mg group had no change to their study therapy. The placebo-controlled portion of the study ended at week 24, following which all patients who had been receiving placebo injections crossed over to receive golimumab 50 mg. Injections continued to be administered subcutaneously every 4 weeks through week 252, and the last study assessments for the period covered by the current analyses were at week 208.

Biomarker evaluations
Serum samples collected at weeks 0, 4, and 14 of the GO-RAISE trial were tested by Rules Based Medicine (Austin, TX, USA) and Pacific Biomarkers (Seattle, WA, USA) for selected markers using Luminex (Luminex, Austin, TX, USA) and enzyme-linked immunoassay platforms, respectively. The extensive list of candidate biomarkers implicated from previous studies (Additional file 1: Table S1) [12] was selected for correlation analyses with imaging and clinical endpoints, including leptin, interleukin (IL)-6, tissue inhibitor of metalloproteinase (TIMP)-1, complement component 3 (C3), intracellular adhesion molecule (ICAM)-1, CRP, haptoglobin, and serum amyloid-P.
Disease activity and progression evaluations
Clinical assessments of disease activity included the BASDAI [13] and the ASDAS employing CRP [14] determined at weeks 0, 14, and 104. MRI was employed to assess inflammation and structural changes in the spine. Serial spine 1.5-T MRI scans of the cervical, thoracic, and lumbar spine regions in the sagittal plane were acquired at baseline, week 14, and week 104 [5]. Two qualified readers who were blinded to treatment information, patient identity, and chronology of the images independently scored each sequence using modified versions of the ankylosing spondylitis spine magnetic resonance imaging score for activity (ASspiMRI-a) and the Ankylosing spondylitis spine magnetic resonance imaging score for chronicity (ASspiMRI-c) [15, 16]. ASspiMRI-a scoring of each vertebral unit (VU) was previously described [5]. For the modified ASspiMRI-c score, each VU was scored as follows: 0 (normal, no lesions), 1 (minor fatty degeneration), 2 (much fatty degeneration), 3 (one or two syndesmophytes), 4 (more than two syndesmophytes), 5 (vertebral bridging with <25% of disc length and/or bridging of one side), or 6 ( vertebral fusion with >25% of disc length and/or bridging of both sides). If a fatty lesion was present in a VU scored 3–6, it was noted. Lateral view radiographs of the cervical and lumbar spine regions were obtained at weeks 0, 104, and 208 and scored by two trained readers blinded to treatment group and chronology using the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) method [17], as described previously [18].

Data analysis
All analyses of MRI data collected through week 104 employed observed data; missing data were not imputed. Of the unique serum biomarkers tested in this trial, 73 had >80% of values below the lower limit of quantitation at baseline and are included in the analyses described herein (Additional file 1: Table S1).

A total of 4940 analyses were performed to determine Spearman correlation coefficients describing relationships between serum biomarkers at weeks 0, 4, and 14 and subsequent efficacy endpoints, including ASDAS, BASDAI, ASspiMRI-a, ASspiMRI-c (all determined at weeks 0, 14, and 104), and mSASSS (determined at weeks 0, 104, and 208). Correlations at baseline were assessed on the basis of all patients, whereas those at follow-up time points were assessed according to randomized treatment groups (placebo versus golimumab). For all postbaseline assessments, changes from baseline in biomarkers were used. Only correlations found to be statistically significant after Bonferroni multiplicity-of-testing adjustment are reported herein.

Relationships between four biomarker levels (IL-6, leptin, TIMP-1, and C3) and changes from baseline to week 104 in mSASSS were also assessed using a generalized linear model. In this model, mSASSS scores were adjusted for VUs with fat indicated via ASspiMRI-c score at baseline, because the presence of fatty lesions on MRI images is a known contributor to radiographic (mSASSS) progression [19, 20] and because these markers affect adipocytes.

Logistic regression analyses were also conducted to assess the influence of baseline and earlier (week 14) changes in biomarker levels on the development of new fatty lesions on a patient level (yes or no, i.e., not detected by MRI at baseline but detected at week 14 or week 104). In such analyses, all patients were combined, with no adjustment for treatment group or multiplicity of testing. The resulting odds ratios and 95% confidence intervals were determined.

Results
Patient analysis
One hundred thirty-nine patients had serum biomarker data, and 98 of these patients at 10 sites with MRI capability participated in the GO-RAISE MRI substudy. The vast majority of randomized patients (299 [84.0%] of 356) had pre- and posttreatment data obtained for the GO-RAISE radiographic substudy. Of these, up to 139 patients had sera collected for biomarker evaluations, and up to 125 underwent spine MRI scans. As reported previously, the demographic and baseline characteristics for the MRI substudy patients were generally consistent with those of the overall GO-RAISE patient population [5].

Correlations between baseline biomarker levels and baseline disease activity
At baseline among all patients with serum biomarker assessments (n = 98–139), significant and moderately strong correlations were observed between ASDAS and levels of the following serum biomarkers of inflammation: IL-6, ICAM-1, haptoglobin, serum amyloid-P, and C3 (r = 0.39–0.59, all p ≤ 0.01) (Table 1). As would be expected, ASDAS correlated with CRP (r = 0.66, p = 0.00) (Table 1). With respect to baseline serum markers and baseline spinal inflammation (ASspiMRI-a score) or structural lesions (ASspiMRI-c score), no significant correlations were observed.

Correlations between baseline biomarker levels and subsequent changes in measures of disease activity, radiographic progression, and spinal inflammation
Baseline leptin level was the only significant biomarker correlated with ASDAS clinical improvement at week 104 of golimumab treatment (r = 0.55, p = 0.040). Higher baseline levels of IL-6 (r = −0.63, p = 0.009) and TIMP-1 (r = −0.67, p = 0.044), but not baseline CRP,
significantly correlated with subsequent improvement in ASSpiMRI-a score (i.e., greater reduction) from baseline to week 14 of golimumab treatment (Table 2). All other correlations tested between baseline biomarkers and subsequent changes in measures of disease activity or spinal inflammation yielded insignificant relationships.

Using a generalized linear model to assess the ability of baseline serum leptin, C3, TIMP-1, and IL-6 levels to predict subsequent change in mSASSS, only baseline serum IL-6 levels were found to significantly predict change in mSASSS at week 104 ($\beta = 0.236$, SE = 0.073, $p = 0.002$, model $R^2 = 0.093$; data not shown). Results of logistic regression analyses indicated that baseline levels of inflammatory and metabolic markers leptin, C3, and TIMP-1 were statistically significant factors in the development of new fatty lesions in the spine at both week 14 and week 104 of golimumab treatment. Change from baseline to week 14 in TIMP-1 also significantly factored into the development of fatty lesions at week 104 (Table 3). Whereas most of these predictive relationships were very weak, those between higher baseline C3 levels and the seven- to eightfold lower risk of subsequent fatty lesion development were of note.

Results of a separate generalized linear model used to evaluate potential interactions between biomarkers and baseline patient characteristics show that IL-6, leptin, TIMP-1, and C3 influenced mSASSS progression independently of demographic factors of age, sex, and human leukocyte antigen B27 positivity (data not shown).

**Correlations between posttreatment biomarker levels and posttreatment measures of disease activity and spine inflammation**

Reductions in C3 observed from baseline to week 4 ($r_s = 0.55$, $p = 0.001$) and week 14 ($r_s = 0.49$, $p = 0.040$) significantly correlated with improvement from baseline to week 14 in the BASDAI score. Similarly, improvement from baseline to week 4 in serum IL-6 ($r_s = 0.61$, $p = 0.022$) and C3 ($r_s = 0.72$, $p = 0.005$) levels, as well as improvement from baseline to week 14 in serum IL-6 levels ($r_s = 0.59$, $p = 0.043$), correlated significantly with improvement in ASSpiMRI-a scores from baseline to week 14 of golimumab treatment (Table 2). All other correlations tested between posttreatment biomarker levels and posttreatment measures of disease activity or spinal inflammation yielded insignificant relationships.

**Discussion**

The search for serum biomarkers of prognostic utility in AS reflects, in part, the need for objective measures of disease activity and response to treatment, as well as the unresolved issues of pathogenesis in the disease. The

**Table 1** Correlations between baseline serum biomarker levels and baseline ASDAS

| Baseline serum biomarker | Baseline ASDAS Spearman correlation coefficient ($r_s$) | Patients (n) | $r_s$ | Bonferroni-adjusted $p$ value |
|-------------------------|--------------------------------------------------------|-------------|------|-----------------------------|
| IL-6                    |                                                        | 132         | 0.59 | 0.000                       |
| ICAM-1                  |                                                        | 139         | 0.39 | 0.011                       |
| C3                      |                                                        | 98          | 0.53 | 0.000                       |
| CRP                     |                                                        | 98          | 0.66 | 0.000                       |
| Haptoglobin             |                                                        | 98          | 0.46 | 0.010                       |
| Serum amyloid-P         |                                                        | 98          | 0.50 | 0.001                       |

**Table 2** Significant correlations between serum biomarkers and Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Disease Activity Index, and ankylosing spondylitis spine magnetic resonance imaging score for activity changes among golimumab-treated patients

| Serum biomarker, time, number of golimumab-treated patients | Spearman correlation coefficient ($r_s$), Bonferroni-adjusted $p$-value with respective outcome |
|-------------------------------------------------------------|---------------------------------------------------------------------------------|
| Leptin, Baseline, $n = 58$                                  | 0.55; 0.040                                                                     |
| Change in BASDAI from baseline to week 14, $n = 76$         | 0.49; 0.040                                                                     |
| Change in ASSpiMRI-a score from baseline to week 14, $n = 76$ | 0.63; 0.009                                                                     |
| Change in BASDAI from baseline to week 14, $n = 76$         | 0.61; 0.022                                                                     |
| Change in ASSpiMRI-a score from baseline to week 14, $n = 76$ | 0.59; 0.043                                                                     |
| Change in BASDAI from baseline to week 14, $n = 76$         | 0.49; 0.040                                                                     |
| Change in ASSpiMRI-a score from baseline to week 14, $n = 76$ | 0.55; 0.005                                                                     |

**Abbreviations:** ASDAS Ankylosing Spondylitis Disease Activity Score employing C-reactive protein, CRP C-reactive protein, C3 Complement component 3, ICAM-1 Intracellular adhesion molecule-1, IL Interleukin
structured nature of a randomized controlled trial provides more clinical uniformity in treatment regimen and outcome measures than is possible in real-world observational studies. In the present study, significant and moderately strong correlations were observed between ASDAS and levels of IL-6, ICAM-1, haptoglobin, serum amyloid-P, and C3. As expected, similar results were observed for CRP. These correlations suggest possible roles for these biomarkers in AS-related inflammation. Baseline serum IL-6 and TIMP-1, as well as reductions in IL-6 and C3, correlated with reduction in ASspiMRI-a scores. Of note, ASDAS has been shown to correlate well with ASspiMRI-a scores, and weakly with BASDAI change, among golimumab-treated patients with AS [5].

Decreases in TIMP-1 at week 14 correlated with fatty lesion development at weeks 14 and 104. The biological basis of local inflammation being associated with reparative processes in spine and local inflammation being reflected as new fatty lesions have yet to be defined, and TIMP-1 would be a candidate factor for future studies. Previously described predictors, such as insulin, matrix metalloproteinase-3, vascular endothelial growth factor, or bone resorption markers, did not significantly correlate with clinical or imaging outcomes.

Fatty lesion development (fat metaplasia) is thought to reflect postinflammation “repair” and may be a precursor of new bone formation. When assessed by logistic regression, baseline levels of inflammatory and metabolic markers leptin, C3, and TIMP-1 were statistically significant factors in the risk of development of new fatty lesions in the spine at both week 14 and week 104 of golimumab treatment, but only the relationship between higher baseline C3 levels and a seven- to eightfold decreased risk of subsequent fatty lesion development offers potential clinical utility. Both leptin and C3, the precursor of C3adesArg acylation-stimulating protein, are involved in triglyceride uptake into adipocytes and homeostasis of adipose tissue. Deficiency of leptin is associated with lipodystrophy and resistance to obesity, whereas increased C3 is linked to increased central obesity and insulin resistance [21]. Furthermore, inflammatory cytokines such as TNF-α and IL-6 stimulate production of leptin and C3, and decreased levels of the receptor for C3adesArg, C5L2 [21, 22]. Together with these properties of leptin and C3, our finding that increased baseline levels of leptin and C3 were correlated with decreased risk of vertebral fatty lesion development suggests that these are key regulators of local adipogenesis within bone tissue in AS. Although Li and colleagues also demonstrated underexpression of C3 in patients with AS (n = 6) relative to healthy volunteers (n = 6) in a preliminary search for disease-associated proteins in the sera of patients with AS [23], additional studies are needed to confirm these findings.

Limitations
A limitation of the present study is the large number of analytes, which precludes analyses such as principal component analysis or supervised cluster analysis. To guard against identifying a false-positive relationship between the large number of analytes assessed and disease activity outcomes, we employed the Bonferroni correction in the statistical modeling to account for multiplicity of testing. The crossover to active anti-TNF agent after a relatively short placebo period complicates interpretation of “placebo group” imaging data at weeks 104 and 208. These analyses are also limited by the fact that golimumab doses were combined and not assessed individually; however, given that no dose-response relationship was observed between golimumab 50 mg and 100 mg when analyzed by randomized groups at week 104 [4], the doses were combined to maximize the patient numbers in the golimumab arm. Despite this approach, there remained few patients on whom to base correlation analyses for radiographic progression and development of fatty lesions. This is an unresolved issue and should be the focus of future research in this field. Additionally, IL-6 levels can be influenced by therapeutic corticosterone use via suppression of endogenous cortisol levels [24, 25] and also by visceral fat secretion [26]; our analyses did not adjust for these potential confounders in assessing relationships between IL-6 and MRI-detected spinal inflammation and clinical measures of disease activity.

Conclusions
An extensive serum biomarker analysis in golimumab-treated patients with AS demonstrated that few biomarkers...
showed correlation with disease activity or MRI changes in multiparametric analysis. Although IL-6 weakly correlated with radiographic progression, other biomarkers found in prior studies to be significantly associated with AS imaging changes were not confirmed.

Additional file

Additional file 1: Table S1. Serum biomarker panel. Table provides a detailed list of the serum biomarkers evaluated. (DOCX 24 kb)

Abbreviations
AS: Ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASpSpMRI-a: Ankylosing spondylitis spine magnetic resonance imaging score for activity; ASpSpMRI-c: Ankylosing spondylitis spine magnetic resonance imaging score for chronicity; BAEAD: Bath Ankylosing Spondylitis Disease Activity Index; C3: Complement component 3; CRP: C-reactive protein; ICAM-1: Intracellular adhesion molecule-1; IL: Interleukin; MRI: Magnetic resonance imaging; mSASSS: Modified Storks Ankylosing Spondylitis Spine Score; NSAID: Nonsteroidal anti-inflammatory drug; r$_s$: Spearman correlation coefficient; TIMP-1: Tissue inhibitor of metalloproteinase-1; TNF: Tumor necrosis factor; VUI: Vertebral unit

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Authors’ contributions
RDI made substantial intellectual contributions to the study conception and data interpretation, helped draft and revise the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. XB made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. BH made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. DvdH made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. AD made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. XB made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. BH made substantial intellectual contributions to the study conception and data interpretation, revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Competing interests
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Ethics approval and consent to participate
The GO-RAISE study protocol was reviewed and approved by the institutional review board or independent ethics committee at each site of this multicenter trial and was conducted according to the principles of the Declaration of Helsinki and good clinical practice. All patients provided written informed consent before the conduct of any study-related procedures.

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References
1. Braun J, Landewé R, Hermann KG, Han J, Yan S, Williamson P, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum. 2006;54:1646–52.
2. Lambert RG, Salonen D, Rahman P, Inman RD, Wong RL, Einstein SG, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter,
randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2007;56:4005–14.
3. Inman RD, Davis Jr JC, van der Heijde D, Diekman L, Sieper J, Kim SJ, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008;58:9402–12.
4. Braun J, Deodhar A, Inman RD, van der Heijde D, Mack M, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis. 2012;71:661–7.
5. Braun J, Baraliakos X, Hermann KG, van der Heijde D, Inman RD, Deodhar AA, et al. Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo-controlled GO-RAISE study. Ann Rheum Dis. 2012;71:678–84.
6. Haroon N, Inman RD, Leach TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65:2645–54.
7. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis. 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis. 2014;73:1455–61.
8. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther. 2008;10(R104).
9. Maksymowycz WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum. 2009;60:93–102.
10. Rudwaleit M, Jurik AG, Hermann KG, Landewé R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis. 2009;68:120–7.
11. van der Heijde D, Machado P, Braun J, Hermann KG, Baraliakos X, Hsu B, et al. MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71:369–73.
12. Wagner C, Visvanathan S, Braun J, van der Heijde D, Deodhar A, Hsu B, et al. Serum markers associated with clinical improvement in patients with ankylosing spondylitis treated with golimumab. Ann Rheum Dis. 2012;71:674–80.
13. Garrett S, Jenkinson T, Kennedy LG, Whitehead H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21:2286–91.
14. van der Heijde D, Lee E, Kivim TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:1811–8.
15. Braun J, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum. 2003;48:1126–36.
16. Baraliakos X, Landewé R, Hermann KG, Listing J, Golder W, Brandt J, et al. Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. Ann Rheum Dis. 2005;64:730–4.
17. Greemers MCW, Fransen MJAM, van t Hof MA, Gribnau FWJ, van de Putte LBA, van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64:127–9.
18. Braun J, Baraliakos X, Hermann KG, Deodhar A, van der Heijde D, Inman R, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis. 2014;73:1107–13.
19. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowycz WP. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum. 2011;63:2215–25.
20. Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis. 2014;73:1819–25.
21. Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Biochim Biophys Acta. 2003;1609:127–43.
22. McLauren R, Kalant D, Cianflone K. The ASP receptor C5L2 is regulated by metabolic hormones associated with insulin resistance. Biochem Cell Biol. 2007;85:11–21.
23. Li T, Huang Z, Zhao L, Gu J. Serum disease-associated proteins of ankylosing spondylitis: results of a preliminary study by comparative proteomics. Clin Exp Rheumatol. 2010;28:201–7.
24. Kirvan JR, Clarke L, Hunt LP, Perry MG, Straub RH, Jessop DS. Effect of novel therapeutic glucocorticoids on circadian rhythms of hormones and cytokines in rheumatoid arthritis. Ann N Y Acad Sci. 2010;1193:127–33.
25. Spies CM, Straub RH, Cutoolo M, Buttgereit F. Circadian rhythms in rheumatology - a glucocorticoid perspective. Arthritis Res Ther. 2014;16(Suppl):253.
26. Pellegrinelli V, Rouault C, Rodriguez-Cuenca S, Albert V, Edom-Vovard F, Vidal-Puig A, et al. Human adipocytes induce inflammation and atrophy in muscle cells during obesity. Diabetes. 2015;64:3121–34.