Spinal mobility in the cervical and lumbar spine correlates with magnetic resonance imaging findings for inflammatory and structural changes in patients with active ankylosing spondylitis

X. Baraliakos[1], K.G.A. Hermann[2], S. Xu[3], E.C. Hsia[3], J. Braun[1]

[1]Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Germany; [2]Radiology, Charité Universitätsmedizin, Berlin, Germany; [3]Janssen Research & Development, LLC, Spring House, PA, USA.

Abstract

Objective

We aimed to assess relationships between single Bath Ankylosing Spondylitis Metrology Index (BASMI) components and corresponding spinal segment magnetic resonance images (MRI) in anti-tumour-necrosis-factor-treated AS patients.

Methods

Using available MRI and BASMI data from the GO-RAISE trial (n=91 patients), MRI scores for active inflammatory (ASspiMRI-a) and chronic structural (ASspiMRI-c) changes in cervical and lumbar spine segments were compared with BASMI cervical (cervical-rotation [CR] angle, tragus-to-wall [TTW] distance) and lumbar (lumbar flexion [LF], lateral-lumbar-flexion [LLF]) spine component scores (linear definition). Generalised linear models were employed to assess relationships between BASMI components and ASspiMRI-a/ASspiMRI-c measurements at baseline and for week-14 (golimumab/placebo groups) and week-104 (all golimumab-treated) change scores.

Results

Baseline lumbar ASspiMRI-a scores correlated with LF and LLF (β=0.231 and 0.238, respectively; both $p<0.01$), while this was less prominent for ASspiMRI-c scores and LLF (β=0.142, $p=0.04$). A significant but weak correlation was found between changes from baseline to week 104 in cervical spine ASspiMRI-c score and TTW distance among all treated patients (β=0.161, $p=0.003$).

Conclusion

Detailed assessments indicated baseline spinal mobility impairment in patients with active AS correlated weakly with MRI-detected lumbar spinal inflammation; correlations with chronic, structural damage/changes were very weak. Improved, less variable MRI and spinal metrology assessments are needed for future clinical research.

Key words

ankylosing spondylitis, biologic, tumour necrosis factor, spinal mobility, BASMI, MRI, inflammation

Xenofon Baraliakos, MD
Kay Geert A. Hermann, MD, PhD
Stephen Xu, MS
Elizabeth C. Hsia, MD, MSCE
Jürgen Braun, MD

Please address correspondence and reprint requests to:
Xenofon Baraliakos,
Rheumazentrum Ruhrgebiet Herne,
Ruhr-University Bochum,
Claudiusstr. 45,
44649 Herne, Germany.
E-mail:
xenofon.baraliakos@elisabethgruppe.de

Received on April 12, 2019; accepted in revised form on July 8, 2019.

ClinicalTrials.gov. registration number: NCT00265083.
Registered December 12, 2005.
Trial initiated December 13, 2005.

Funding: this study was funded by Janssen Research & Development, LLC and Merck/Schering-Plough.

Competing interests: no non-financial conflicts of interest exist for any authors.
X. Baraliakos has received research support and/or consultancy/speaker fees from AbbVie, BMS, Boehringer Ingelheim, Celgene, Chugai, Janssen Biologics, Novartis, Pfizer, Sandoz, and UCB.
K.G.A. Hermann has received honoraria for educational lectures from Abbott, Janssen Research & Development, MSD (Schering-Plough), Pfizer (Wyeth), and UCB.
E. Hsia is a full-time salaried employee of Janssen R&D, LLC, a Johnson & Johnson (J&J) pharmaceutical company, and owns stock/stock options in J&J.
S. Xu is a full-time salaried employee of Janssen R&D, LLC, a J&J pharmaceutical company, and owns stock/stock options in J&J.
J. Braun has received honoraria for talks, advisory boards, paid consultancies and grants for studies from AbbVie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Chugai, EBEWE Pharma, Janssen, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis, and UCB.

Introduction

Ankylosing spondylitis (AS), a chronic systemic inflammatory disorder primarily involving the sacroiliac joints and the spine, is characterised by inflammation, pain, stiffness, and fusion of the axial skeleton. Resultant spinal immobility leads to limitations in physical functioning, work disability, and impaired quality of life.

Tumour-necrosis-factor (TNF)-antagonism leads to improvement in spinal inflammation assessed by magnetic resonance imaging (MRI) and spinal mobility assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI) (1-3). BASMI-assessed spinal mobility has been reported to correlate with imaging outcomes on the group level. For example, in a subanalysis of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort, spinal mobility impairment in AS was found to be independently determined both by irreversible spinal damage and by reversible spinal inflammation, with spinal mobility impairment being more influenced by spinal inflammation in early disease, and by structural damage in later disease (4).

To further our understanding of these relationships, we employed data from the GO-RAISE trial, which assessed the anti-TNF agent golimumab in patients with active AS and included both clinical and MRI evaluations (2, 5). We analysed the relationships between single components of the BASMI and MRI scores of corresponding spinal segments at baseline, week 14 (golimumab and placebo-treated), and week 104 (all golimumab-treated) in AS patients.

Methods

This study was conducted in compliance with the Declaration of Helsinki. Governing ethical bodies at each of 57 participating sites approved the GO-RAISE study protocol. All patients provided written informed consent. Details of the GO-RAISE patient eligibility criteria and study conduct have been reported (5, 6). Briefly, patients had AS diagnosed using the modified New York criteria (8) and presented with active disease at study onset. Active disease was defined by the presence of both Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, (7)) and total back pain visual analogue scale scores ≥4 (range: 0–10).

GO-RAISE (ClinicalTrials.gov Identifier: NCT00265083) was a phase 3, multicentre, placebo-controlled, double-blind trial in which enrolled patients were randomised (1:1.8:1.8) to receive subcutaneous placebo, golimumab 50 mg, or golimumab 100 mg at baseline and every 4 weeks (q4wks) (6). The study was fully placebo-controlled from week 0 through week 16. Per study design, all patients received double-blind active treatment with golimumab 50 mg or 100 mg q4wks from week 24 through week 100.

Spinal mobility was assessed using the BASMI based on a linear method (8). The BASMI linear incorporates five clinical measurements that reflect axial mobility, including tragus-to-wall distance ([assessment result in cm – 8 cm]/3 cm), lumbar flexion/modified Schober ([7.4 cm – assessment result in cm]/0.7 cm), cervical rotation angle ([89.3° - assessment result in degrees]/8.5°), lateral lumbar flexion ([21.1 cm – assessment result in cm]/2.1 cm), and maximal intermalleolar distance ([124.5 cm – assessment result in cm]/10 cm). The average score of the five assessments yields the BASMI linear result, which ranges from 0–10.

Serial MRI scans of the cervical spine (CS) and lumbar spine (LS) were obtained at baseline (within the 4-week period preceding the first dose of study medication), week 14, and week 104. MRI scans were acquired in the sagittal plane using 1.5T-scanners with T1-weighted, fast (turbo) spin-echo, and short tau inversion recovery (STIR) methodology.

Two qualified, experienced, independent readers, blinded to treatment information, patient identity, and image chronology, scored each MRI sequence. Cervical and lumbar vertebral units (VUs) were evaluated and scored for activity, *i.e.* hyperintense bone marrow lesions ("bone marrow oedema/osteitis") by STIR, and for erosions using the AS Spine MRI-active (ASspiMRI-a) and a modification of the AS Spine

MRI-chronic (ASspiMRI-c) scores as noted below (2, 9, 10). For ASspiMRI-a scores, VUs were scored at each time point as follows: 0 (no bone marrow oedema/erosions), 1 (minor bone marrow oedema involving ≤25% of the VU, no erosions), 2 (moderate bone marrow oedema involving >25% but ≤50% of the VU, no erosions), 3 (major bone marrow oedema involving >50% of the VU, no erosions), 4 (minor erosion involving ≤25% of the VU with minor bone marrow oedema), 5 (moderate erosion involving >25% but ≤50% of the VU with bone marrow oedema), or 6 (major erosion involving >50% of the VU with bone marrow oedema). For the modification of the ASspiMRI-c score, each VU was scored as follows: 0 (normal, no lesions), 1 (minor fat metaplasia, <25% of VU), 2 (much fat metaplasia ≥25% of VU), 3 (1-2 syndesmophytes), 4 (>2 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). Weighted kappa statistics were generated to assess agreement between Readers 1 and 2.

For both ASspiMRI-a and ASspiMRI-c scores, baseline values and changes from baseline at week 14 (placebo- and golimumab-treated patients) and week 104 (all golimumab-treated patients) were compared with BASMI values for the CS (cervical rotation angle and tragus-to-wall distance) and LS (lumbar flexion and lateral lumbar flexion) questions at the same time points via generalised linear modelling (GLM) and calculation of regression coefficients. Correlation analysis of spine MRI with the fifth BASMI component, *i.e.* intermalleolar distance, was not performed because it relates to hip mobility. MRI data were analysed using the mean of the two readers' respective CS and LS scores. If one reader's score was missing, the other reader's score was used; if both readers' scores were missing, patient data were considered missing. Observed data from patients with baseline and ≥1 postbaseline scores were included in these analyses.

GLM analysis of BASMI individual question change scores (Y; converted to linear range of 0–10) and MRI segment inflammation change from baseline (X) also was performed. These analyses were adjusted for baseline age, sex, disease duration, individual baseline BASMI question scores, golimumab duration, and BASDAI scores. Given that the association between radiographic damage of the spine and spinal mobility impairment in AS has been established (6), the baseline modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (14) also was included in the model. Numerical scores derived from radiological changes identified from the assessments of the lateral view of the CS were applied as adjustment factors for tragus-to-wall distance and cervical rotation angle, while those from LS assessments served as adjustment factors for lumbar flexion and lateral lumbar flexion). Similar GLM analyses were conducted to assess the effect of gender (X) on BASMI change scores (Y) at weeks 14 and 104. These analyses were adjusted for baseline age, sex, disease duration, Invidia baseline BASMI question scores, baseline mSASSS (CS for tragus-to-wall distance and cervical rotation angle and LS for lumbar flexion and lateral lumbar flexion), treatment duration, baseline BASDAI scores, and ASspiMRI-a (or ASspiMRI-c) change scores indicating either cervical or lumbar spine segment inflammation at weeks 14 and 104.

Table I. Generalised Linear Model[a] of baseline BASMI individual questions (Y) on MRI segment inflammation (X). All patients.

ASspiMRI score type/Spinal segment type/BASMI measurement	All patients			
	#of patients	Beta estimate	*p*-value[b]	R^2
ASspiMRI-a score at baseline				
Cervical spine, inflammation at baseline				
BASMI - Tragus-to-wall distance (Q1)	91	0.149	0.301	0.45
BASMI - Cervical rotation angle (Q3)	91	0.082	0.633	0.49
Lumbar spine, inflammation at baseline				
BASMI - Lumbar flexion (Q2)	91	0.231	**0.004**	0.35
BASMI - Lateral lumbar flexion (Q4)	91	0.238	**0.006**	0.47
ASspiMRI-c score at baseline				
Cervical spine, structural at baseline				
BASMI - Tragus-to-wall distance (Q1)	91	0.034	0.352	0.45
BASMI - Cervical rotation angle (Q3)	91	0.010	0.813	0.49
Lumbar spine, structural at baseline				
BASMI - Lumbar flexion (Q2)	91	0.055	0.389	0.26
BASMI - Lateral lumbar flexion (Q4)	91	0.142	**0.040**	0.44

[a]GLM model employed for calculation of R^2 values adjusts for baseline age, sex, disease duration, individual baseline BASMI question scores, baseline mSASSS (CS for tragus-to-wall distance and cervical rotation angle and LS for lumbar flexion and lateral lumbar flexion), treatment duration, and baseline BASDAI scores.

[b]*p*-values shown in **bold** are statistically significant.

ASspiMRI-a/b: ankylosing spondylitis spine MRI activity/chronicity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CS: cervical spine; GLM: generalised linear modelling, LS: lumbar spine; mSASSS: modified Stokes Ankylosing Spondylitis Spine Score; Q: question; R^{2-}: regression coefficient derived from GLM modelling.

Results

Patient population

A total of 356 patients were randomly assigned to treatment, 98 of these patients at 10 study sites with MRI capability participated in the GO-RAISE MRI substudy (2), and 91 patients had both MRI and BASMI data available for analysis. Patient disposition through week 104 of the GO-RAISE trial has been reported (5). The demographic and baseline characteristics for the MRI substudy patients were generally consistent with those of the overall GO-RAISE patient population (2).

Reader agreement

Kappa statistics indicated moderate agreement between readers for ASspi-

Table II. Generalised Linear Model[a] of BASMI individual question (Y) on MRI segment inflammation (X) change scores. Golimumab-treated patients.

BASMI measurement question (change score -Y)	Spinal segment type/ASspiMRI score type (change score -X)	Visit	n	Beta estimate	*p*-value[b]	R^2
Tragus-to-wall distance (Q1)	Cervical spine inflammation					
	ASspiMRI-a	Week 14	79	-0.011	0.891	0.28
		Week 104	66	0.002	0.982	0.13
	ASspiMRI-c	Week 14	79	0.028	0.514	0.29
		Week 104	66	0.161	**0.003**	0.26
Lumbar flexion (Q2)	Lumbar spine inflammation					
	ASspiMRI-a	Week 14	79	0.091	0.387	0.21
		Week 104	66	0.021	0.800	0.30
	ASspiMRI-c	Week 14	79	0.152	0.526	0.21
		Week 104	66	-0.010	0.953	0.30
Cervical rotation angle (Q3)	Cervical spine inflammation					
	ASspiMRI-a	Week 14	79	-0.194	0.167	0.29
		Week 104	66	0.104	0.387	0.25
	ASspiMRI-c	Week 14	79	0.091	0.205	0.28
		Week 104	66	0.008	0.920	0.24
Lateral lumbar flexion (Q4)	Lumbar spine inflammation					
	ASspiMRI-a	Week 14	79	0.035	0.737	0.19
		Week 104	66	0.076	0.208	0.29
	ASspiMRI-c	Week 14	79	-0.034	0.888	0.19
		Week 104	66	-0.123	0.311	0.29

[a]GLM model employed for calculation of R^2 values adjusts for baseline age, sex, disease duration, individual baseline BASMI question scores, baseline mSASSS (CS for tragus-to-wall distance and cervical rotation angle and LS for lumbar flexion and lateral lumbar flexion), treatment duration, baseline BASDAI scores, and ASspiMRI-a (or ASspiMRI-c) change scores indicating either cervical or lumbar spine segment inflammation at week 14/104.
[b]*p*-values shown in **bold** are statistically significant.
ASspiMRI-a/b: ankylosing spondylitis spine MRI activity/chronicity, CS: cervical spine, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, GLM: generalised linear modelling, LS: lumbar spine, mSASSS: modified Stokes Ankylosing Spondylitis Spine Score, Q: question, R^2: regression coefficient derived from GLM modelling.

MRI-a and ASspiMRI-c scoring at week 14 (0.53 and 0.45, respectively) and week 104 (0.45 and 0.46, respectively).

Baseline correlations

At baseline, ASspiMRI-a scores of the LS, but not the CS, correlated with lumbar flexion (β=0.231, *p*=0.004) and lateral lumbar flexion (β=0.238, *p*=0.006) scores. At the same time, baseline ASspiMRI-c scores of the LS weakly correlated only with lateral lumbar flexion scores (β=0.142, *p*=0.040) (Table I).

Change score correlations

No significant correlations were found in the short term between week-14 ASspiMRI-a or ASspiMRI-c change scores and individual BASMI question change scores among golimumab-treated patients. For week-104 change scores among patients who were now all receiving golimumab, a weak but significant correlation was observed between ASspiMRI-c in the CS and tragus-to-wall distance (β=0.161, *p*=0.003) (Table II). In most of the modelling analyses for change scores, no statistically significant effect of baseline age, gender, disease duration, mSASSS score (CS/LS), treatment duration, or baseline BASDAI was observed, except that CS mSASSS was a significant adjustment factor for the change in the BASMI cervical rotation score from baseline to week 14 and week 104 (data not shown).

Discussion

This is the first report on a correlation between inflammatory and chronic spinal lesions as seen by MRI and detailed assessments of spinal mobility in patients with active AS before and after treatment with anti-TNF. The MRI results are consistent with earlier reports on patients with active AS, which showed that both inflammation as assessed by MRI and structural changes as assessed by conventional radiographs contribute to impairments of spinal mobility (4). In view of the limitations of the mSASSS (*i.e.* assessment of anterior vertebral edges only, poor correlation at the individual level with spinal mobility) (10), we included in our analysis a modified ASspiMRI-c chronicity score that captured structural lesions in anterior and posterior VUs, as well as the extent of fat metaplasia within each VU. These results extend prior data by demonstrating, in the lumbar spine, significant correlations of spinal MRI activity and chronicity scores before anti-TNF treatment was started, with detailed spinal mobility measures. We were unable to confirm across BASMI measures that age, gender or radiographic score consistently contribute to impaired spinal mobility, as described by Machado and colleagues (4). Finally, the present study is also the first of which we are aware to evaluate correlations between change scores in BASMI components and spine MRI scores. In comparison to the baseline correlation analyses, those between change scores in mobility and ASspiMRI-a/c at the segment level were much weaker and inconsistent.

A limitation of the study may be the low inter-evaluator agreement of the MRI scores, which we explain with

the overall described low reliability of evaluating structural lesions, especially new bone formation, on MRI examinations (11). In addition, the sensitivity to change of the ASspiMRI-c score has not been defined to date, and the present slight modification of the score is being used for the first time in correlation analyses with BASMI components, although relationships between it and serum biomarkers have recently been assessed in patients with AS (12).

In conclusion, detailed assessments indicated baseline spinal mobility impairment in patients with active AS correlated weakly with MRI-detected lumbar spinal inflammation as well as with chronic, structural damage/changes. Whether such correlations will improve by the usage of imaging techniques that assess structural changes in small sites such as facet joint evaluation by low-dose computed tomography (13), remains unclear. Overall, the usage of different imaging techniques such as conventional radiographs, computed-tomography or MRI may serve for evaluation of different aspects of clinical outcomes, based on the individual patient´s situation (14). For evaluation with MRI, improved, less variable MRI and spinal metrology assessments are needed for future clinical research.

Acknowledgments

The authors thank the patients, the investigators and the study personnel who made this trial possible, and also Michelle Perate MS, a paid consultant of Janssen Scientific Affairs, LLC, who helped prepare the manuscript.

The authors also thank the following Institutional Review Boards/Ethics Committees: China Medical University Hospital Instituted Review of Board 9F, Taichung, Taiwan, Republic of China; Comité de Protection des Personnes Ile-de-France III, Hôpital Tarnier-Cochin 89, Paris, France; Commissie Medische ethiek van de Universitaire Ziekenhuizen KU Leuven/ U.Z. Gasthuisberg, Leuven, Belgium; Ethikkommission der ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der WWU Münster, Münster, Germany; Human Experiment and Ethics Committee, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, Republic of China; HUS Helsingin ja Uudenmaan sairaanhoitopiiri, Medisiininen eettinen toimikunta, Biomedicum Helsinki, HUS, Finland; Institution Review Board, Biomedical Research Institute, Seoul National Universithy Hospital, Jongro-gu, Seoul, South Korea; Institution Review Board, Dong-A University Hospital Clinical Research Center, Seo-Gu, Busan, South Korea; Institutional Review Board, Guro Hospital, Korea University Medical Center, Guro-Gu, Seoul, South Korea; Institution Review Board, Hanyang University Hospital, Sungdong-Ku, Seoul, South Korea; Institution Review Board, Pusan National University Hospital, Seo-Gu, Busan, South Korea; Institutional Review Board, Seoul St. Mary's Hospital/The Catholic University of Korea, Seocho-gu, Seoul, South Korea; Joint Institution Review Board. No. 201, Taipei. Taiwan, Republic of China; METC azM/UM Maastricht, Maastricht, The Netherlands; Western IRB, Olympia, WA.

Key messages

- In anti-TNF-treated AS patients, baseline spinal mobility impairment correlated weakly with MRI-detected lumbar spinal inflammation.
- Correlations between spinal mobility impairment and chronic, structural damage/changes on MRI were weak.
- Less variable MRI and spinal metrology assessments are needed for future clinical research.

Data availability

The data that support the findings of this study are available from Janssen Research and Development, LLC, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Janssen Research and Development, LLC.

References

1. BRAUN J, BRANDT J, LISTING J *et al*.: Treatment of active ankylosing spondylitis with infliximab: A randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-93.
2. BRAUN J, BARALIAKOS X, HERMANN KG *et al*.: Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo- controlled go-raise study. *Ann Rheum Dis* 2012; 71: 878-84.
3. DOUGADOS M, BRAUN J, SZANTO S *et al*.: Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: Results from a 12-week open-label extension of the spine study. *Rheumatology* (Oxford) 2012; 51: 1687-96.
4. MACHADO P, LANDEWÉ R, BRAUN J, HERMANN KG, BAKER D, VAN DER HEIJDE D: Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. *Ann Rheum Dis* 2010; 69: 1465-70.
5. BRAUN J, DEODHAR A, INMAN RD *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.
6. INMAN RD, DAVIS JC JR, VAN DER HEIJDE D *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: 3402-12.
7. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK 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.
8. VAN DER HEIJDE D, LANDEWÉ R, FELDTKELLER E: Proposal of a linear definition of the bath ankylosing spondylitis metrology index (basmi) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis* 2008; 67: 489-93.
9. BRAUN J, BARALIAKOS X, GOLDER W *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.
10. BARALIAKOS X, LANDEWÉ R, HERMANN KG *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.
11. BRAUN J, BARALIAKOS X, GOLDER W *et al*.: Analysing chronic spinal changes in ankylosing spondylitis: A systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004; 63: 1046-55.
12. INMAN RD, BARALIAKOS X, HERMANN KA *et al*.: Serum biomarkers and changes in clinical/mri evidence of golimumab-treated patients with ankylosing spondylitis: Results of the randomized, placebo-controlled go-raise study. *Arthritis Res Ther* 2016; 18: 304.
13. DE KONING A, DE BRUIN F, VAN DEN BERG R *et al*.: Low-dose ct detects more progression of bone formation in comparison to conventional radiography in patients with ankylosing spondylitis: Results from the sias cohort. *Ann Rheum Dis* 2018; 77: 293-9.
14. KILTZ U, BARALIAKOS X, REGEL A, BUHRING B, BRAUN J: Causes of pain in patients with axial spondyloarthritis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 107): S102-7.