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Original Article

Clinical science

Magnetic resonance imaging characteristics in patients with psoriatic arthritis and axial manifestations from the MAXIMISE cohort

Xenofon Baraliakos [1,*], Effie Pournara[2], Laura C. Coates [3], Victoria Navarro-Compán [4], Ricardo Blanco[5], Eamonn O'Brien[6], Barbara Schulz[2], Robert Landewe[7]

[1]Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany
[2]Novartis Pharma AG, Immunology, Hepatology and Dermatology, Basel, Switzerland
[3]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[4]Department of Rheumatology, La Paz University Hospital, IdiPaz, Madrid, Spain
[5]Divisions of Immunology, Endocrinology, and Rheumatology, Hospital University Marqués de Valdecilla, Santander, Spain
[6]Novartis Ireland Limited, Dublin, Ireland
[7]Department of Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands

*Correspondence to: Xenofon Baraliakos, Rheumazentrum Ruhrgebiet Herne, Ruhr-Universität Bochum, Claudiusstr. 45, 44649 Herne, Germany.
E-mail: xenofon.baraliakos@elisabethgruppe.de

Abstract

Objective: The current analysis of the MAXIMISE trial was conducted to investigate the presence of post-inflammatory and degenerative spinal changes and inflammatory changes in spinal processes identified in baseline MRIs and their potential for predicting differential treatment effects in a cohort of PsA patients with axial manifestations.

Methods: Baseline spinal MRIs from the MAXIMISE trial were re-read to identify additional inflammatory (spinal process), post-inflammatory, and degenerative changes, and investigate the differential treatment effect of these imaging features using logistic regression modelling.

Results: In addition to bone marrow oedema assessed at primary analysis, spinal process inflammation and post-inflammatory changes evaluated by FAt Spondyloarthritis Spine Score were documented in 11.1% and 20.2% patients, respectively. At least one type of degenerative change was noted in 64% patients, with Pfirrmann grade ≥3 (51.1%) being the most common. Combining primary and re-read MRI findings, 67.1% of patients presented with inflammatory or post-inflammatory changes while 21.2% had degenerative changes alone. Although not statistically significant, post-inflammatory changes were associated with a trend for better efficacy outcomes in terms of ASAS20, ASAS40 and BASDAI50 responses; a trend for worse outcomes was observed in the presence of degenerative changes.

Conclusion: The current analysis revealed the occurrence of additional inflammatory and post-inflammatory changes suggestive of axial PsA (axPsA) and a trend for better clinical outcomes for patients treated with secukinumab. These results elucidate the imaging characteristics and improve our current understanding of axPsA thereby supporting the interpretation of future trials.

Trial registration: ClinicalTrials.gov, NCT02721966.

Keywords: axial manifestation, degenerative changes, inflammatory, post-inflammatory, PsA

Rheumatology key messages

- Re-reading baseline spinal MRIs of PsA patients with axial manifestations revealed additional inflammatory and post-inflammatory changes.
- Inflammatory and degenerative changes are potential predictors of treatment response to secukinumab.
- The current analysis sheds further light on the role of MRI in defining axPsA.

Introduction

PsA is a chronic, heterogeneous, inflammatory musculoskeletal disorder characterized by articular and extraarticular manifestations, including peripheral arthritis, axial involvement, enthesitis, dactylitis, and skin or nail disease [1]. Even though axial disease is recognized as one of the six PsA manifestations, there is no universally accepted definition for axial PsA (axPsA), nor is there consensus on the role of MRI in the diagnosis of axPsA.

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The prevalence of axPsA varies with disease duration, and ranges from 5–28% in early stage PsA to 25–70% in long-standing disease with only 2–5% of patients presenting exclusively with axial disease [2, 3]. It is still a matter of debate whether axial PsA and axial spondyloarthritis (axSpA) are distinct entities with overlapping features [2–4]. Radiographically, the involvement of SI joints (SIJ) in axial PsA varies with normal SIJ seen in up to 35% of patients [5, 6] in contrast to axSpA [7]. Additionally, compared with axSpA, sacroiliitis in axial PsA is usually asymmetrical and unilateral, and the cervical spine is more commonly affected [8].

MRI acts as a cornerstone of diagnosis in spondyloarthritis (SpA) allowing higher resolution and visualization of both active inflammatory (bone marrow oedema [BME]/osteitis) and structural changes (erosions, fat metaplasia, bone spurs and ankylosis) than the conventional imaging [9]. Additionally, fatty lesions have been shown to follow resolution of inflammation in the spine of patients with axSpA and are considered a surrogate for structural damage progression in axSpA [10]. Pedersen *et al.* demonstrated that the FAt Spondyloarthritis Spine Score (FASSS) scoring system determines treatment outcomes and predicts the emergence of new bone growth signalling and tissue repair in SpA [11]. Furthermore, the high prevalence of degenerative changes reported in patients with SpA may delay or confound the diagnosis of axSpA or axPsA [12, 13]. Although MRI is a sensitive diagnostic modality for ascertaining axial disease in spondyloarthritis, the role of MRI in the diagnosis and classification of axPsA is still unclear. Furthermore, there is a paucity of imaging studies reporting changes in the spine and SIJ in PsA patients including inflammatory changes in posterior elements of the spine, post-inflammatory changes such as fat lesions or any type of degenerative changes.

MAXIMISE (NCT02721966) was the first randomized controlled trial (RCT) that demonstrated the efficacy and safety of a biologic DMARD in the management of axial manifestations in PsA patients with an inadequate response to NSAIDs [14]. In the primary analysis, BME in the spine and/or SIJ assessed by the Berlin score [14] was shown for around 60% of the patients. Secukinumab 300 mg and 150 mg significantly improved Berlin MRI scores *vs* placebo at week 12, providing evidence of reduced inflammation in the spine and the SIJ for patients treated with secukinumab. The current analysis from the MAXIMISE trial aimed to investigate the presence of spinal process inflammation, post-inflammatory and degenerative changes and their potential to predict a differential treatment effect in a cohort of PsA patients with axial manifestations.

Methods

Study design and patients

The details of the study design, patient inclusion and exclusion criteria, methods and primary results have been reported previously [14]. Briefly, MAXIMISE is a Phase 3b, double-blind, placebo-controlled, multicentre, 52-week trial that included patients diagnosed with PsA, fulfilling ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria with clinically diagnosed active axial disease (spinal pain ≥40/100 visual analogue scale [VAS] and Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4/10), despite the use of at least two NSAIDs over a 4-week period. Patients were randomized (1:1:1) to secukinumab 300 mg, secukinumab 150 mg or placebo; at week 12, placebo patients were re-randomized (1:1) to secukinumab 300 mg or 150 mg.

MRI scans of the spine and SIJ were performed at baseline and weeks 12 and 52 for all the patients enrolled in the study. MRIs were acquired using semicoronal and semiaxial orientation. In the primary analysis, short-tau inversion recovery (STIR) MRI sequences were used for assessing inflammatory lesions (BME using Berlin MRI score) [15]. The details of MRI of spine and SIJ including the acquisition procedure have been described previously [14]. In the current analysis, the two expert readers re-read the randomly assigned MRIs. The calibration of the readers was performed for ∼10% of the MRIs; all the other images were read only once (∼45% by each reader).

Ethics approval

This study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The MAXIMISE study was approved by independent ethics committees or institutional review boards of participating centres. All patients provided written informed consent before any study-related procedures were undertaken.

Assessments

BME by Berlin score was assessed by the primary analysis of the MAXIMISE trial [14]. The re-reading protocol included assessment of additional inflammatory changes of the spinal processes (SPi) in a binary way (present/absent), as hyperintense signal in the spinous processes in the STIR sequence and corresponding hypointense signal in the T1-weighted sequence.

'Any inflammatory change' was defined by the presence of SPi and/or Berlin score of ≥1 for the spine and/or SIJ. Furthermore, six types of degenerative changes were assessed as follows: modic lesions, Schmorl's node with or without BME, disc degeneration (herniation or marginally located high intensity zone), endplate erosion, endplate sclerosis in a binary scoring (present/absent) and degenerative disc changes assessed by Pfirrmann grading [16–18]. 'Any degenerative change' was defined as the presence of at least one of the six degenerative changes.

Additionally, post-inflammatory changes of the bone marrow were assessed by the FASSS, a scoring method that addresses the spectrum of fat lesions according to anatomical localization and phenotypic diversity in the spine [11]. Inflammatory (SPi) and post-inflammatory (FASSS) lesions on the level of a discovertebral unit were only scored if they were phenotypically related to inflammatory axial involvement, according to the readers. Lesions in the vertebral area were considered 'related to inflammatory axial involvement' if they were located at the edges of the vertebrae and without being accompanied by disc degeneration. Modic lesions, Schmorl's lesions and Pfirrmann grading were scored according to their original definitions [16–18]. In cases of doubt as to the origin of the lesion, the lesions were considered degenerative and not inflammatory, and were scored accordingly. A FASSS total score of ≥1 was the criterion for presence of 'any post-inflammatory change'.

Outcome measures, such as Assessment of SpondyloArthritis international Society 20 (ASAS20), ASAS40 and BASDAI50 responses and Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS-CRP) decrease of ≥1.1 (minimum

clinically important improvement [MCII]) at week 12 were also assessed to investigate if any of the imaging abnormalities are associated with a differential treatment effect with secukinumab.

Statistical analysis

For continuous variables, summary statistics included number of patients (*n*), mean (S.D.), minimum, lower quartile, median, upper quartile and maximum. Summary statistics for discrete variables included the number and percentage of patients in each category. A two-model approach was carried out to investigate differential treatment of predictors of ASAS20, ASAS40, BASDAI50 and ASDAS-MCII responses at week 12 in patients treated with secukinumab.

i) Interaction model 1: a logistic regression model was fitted to the data, and included interaction terms between treatment group and sex, and treatment group and nail dystrophy (informed from prior analyses) [19] as well as terms for each of the predictor variables i.e. 'age', 'smoking status' and eight mutually exclusive imaging groups (inflammatory changes; post-inflammatory changes; inflammatory and post-inflammatory changes; no changes; inflammatory and degenerative changes; post-inflammatory and degenerative changes; inflammatory, post-inflammatory and degenerative changes; and degenerative changes).
ii) Interaction model 2: a second logistic regression model was fitted to the data and included all terms from interaction model 1 and an additional interaction term between treatment group and the eight mutually exclusive imaging groups.

The log-likelihood of the two models was compared using a chi-square test to determine whether the effects of treatment depend on any of the extra predictors in model 2. If this test provided evidence against the null hypothesis at an α-level of 20% (i.e. $P \leq 0.20$), then model 1 was rejected and model 2 was considered a better fit to the data. The final model including coefficients and associated 95% confidence intervals is displayed.

A supplementary analysis with interaction models 1 and 2 was also carried out to assess any differential treatment effect for the three binary imaging groups: 'any inflammatory change', 'any post-inflammatory change' and 'any degenerative change'.

Results

A total of 485 patients were included in the full analysis set. The demographic and clinical characteristics of the study population have been previously reported [14].

Inflammatory and post-inflammatory changes

In the primary analysis ~60% of the patients had a Berlin score ≥1 for the spine and/or the SIJs. Additionally, re-reading revealed SPi for 11.1% ($n = 54$) of patients. The identified SPi by the regions of the spine are presented in Fig. 1.

Fat lesions were identified in 20.2% ($n = 97$) of patients. The mean (S.D.) and range for the FASSS total score for the study cohort was 1.8 (5.7) and 0–53, respectively. The mean (S.D.) baseline FASSS total score in the thoracic region was 1.0 (3.6) while lumbar and cervical regions had a mean (S.D.) total score of 0.6 (1.9) and 0.2 (1.2), respectively. A small proportion of patients, 1.2% ($n = 6$), had a FASSS total score of >30 (Fig. 2).

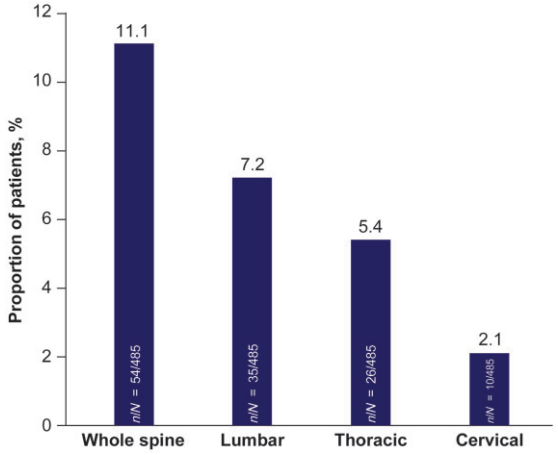

Figure 1. Spinal process inflammation by region of the spine. DVU: discovertebral unit; *N*: number of patients in full analysis set in each treatment group; *n*: number of patients with at least one DVU showing as 'present' for the associated degenerative change

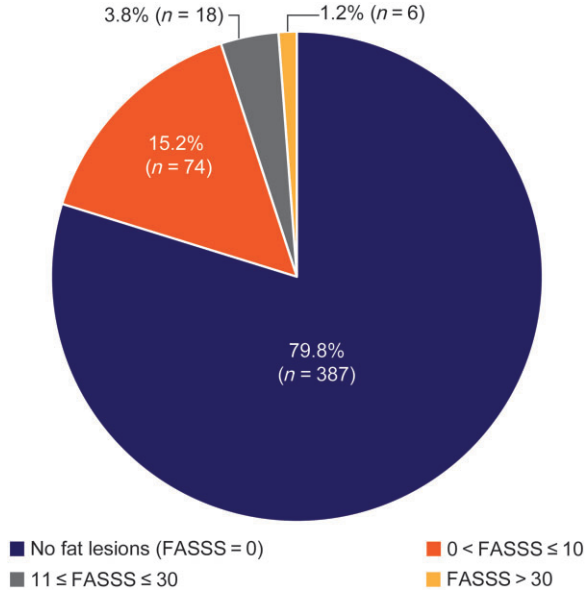

Figure 2. FASSS groups in the full analysis set

Degenerative changes

For 21.2% ($n = 102$) of the patients, only degenerative changes were identified, while 11.7% ($n = 56$) of patients had a normal MRI (Fig. 3). Approximately 64% of the patients had at least one type of degenerative change. Pfirrmann grade ≥3 ($n = 248$, 51.1%), disc herniation or high intensity zone ($n = 178$, 36.7%) and Modic changes (including Modic 1 and Modic 2) ($n = 107$, 22.1%) were the most common degenerative changes seen in whole spine (Fig. 4).

Main analysis

As the likelihood ratio test *P*-value was >0.20 for all the assessed outcome measures, we failed to reject the null hypothesis of the less complex interaction, and model 1 was

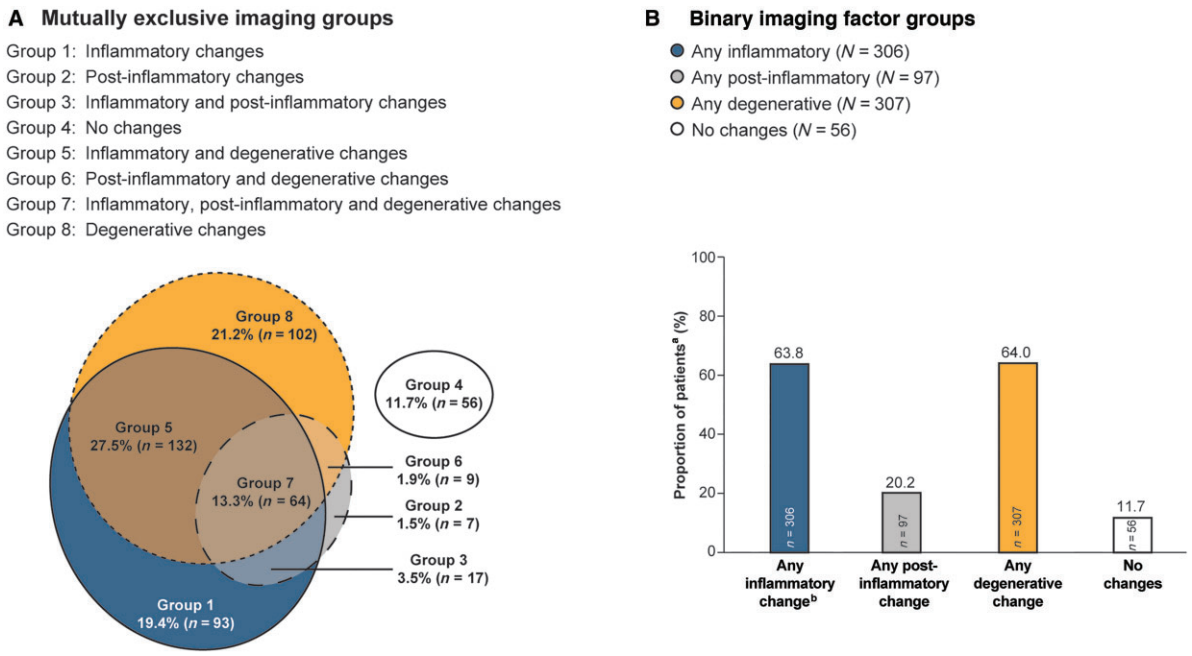

Figure 3. Distribution of patients by the type of spinal and/or SIJ MRI change, across (**A**) the eight mutually exclusive imaging groups and (**B**) the binary imaging factor groups of the supplementary analysis. [a]Proportions of patients with MRI scoring 'yes' on each of the three predictor variables: any inflammatory change, any post-inflamatory change, and any degenerative change. [b]Any inflammatory change includes positive Berlin score and spinal process inflammation. *N*: total number of patients in the imaging categories; *n*: number of patients in the mutually exclusive imaging groups

considered a better fit to the data; hence, there was no evidence of a differential treatment effect. Also, interaction model 1 did not reveal any evidence of a main effect for the eight mutually exclusive imaging groups.

Supplementary analysis

A supplementary analysis with interaction model 1 and 2 was carried out for the three binary imaging groups 'any inflammatory change' including positive Berlin score and SPi, 'any post-inflammatory change', and 'any degenerative change' (Fig. 3). The likelihood ratio test *P*-value was >0.20 for all the assessed outcome measures and, similar to the main analysis, interaction model 1 was considered a better fit to the data failing to demonstrate a differential treatment effect for any of the three imaging categories. Although not statistically significant, degenerative changes predicted poorer outcomes, while post-inflammatory changes may be associated with a higher likelihood for better outcomes, especially in terms of ASAS20 and ASAS40 responder rates at week 12. Similar observations were noted for BASDAI50 but not for ASDAS-CRP MCII responder status (Fig. 5).

Discussion

Re-reading the baseline spinal MRIs of the MAXIMISE cohort revealed fat lesions and SPi in around 20% and 11% of the patients, respectively, and demonstrated the presence of any inflammatory and/or post-inflammatory change in 67.1% of patients, a higher proportion of that identified in the initial per-protocol analysis (~60% of the patients with a Berlin score ≥1 for the spine and/or the SIJs) [14].

The unmet need to develop classification criteria and a unified nomenclature for axial involvement in PsA that would allow defining axPsA for research and early clinical recognition of axPsA to inform treatment decision making has been increasingly underlined over the past years [20]. The multicentre cross-sectional AXIS study (NCT04434885) was designed by ASAS and GRAPPA to specifically address this need and systematically evaluate the clinical and imaging manifestations indicative of axial involvement in patients with PsA [21]. This post-hoc analysis adds new imaging data from a cohort of patients with PsA and axial manifestations, thereby contributing to the body of evidence that can be considered in defining axPsA.

Existing MRI data in axPsA are limited. In a study of 125 patients from the Toronto cohort, only 44.6% of the scans presented changes compatible with SpA when considering cases with inflammatory back pain [22]. In another study, by Williamson and colleagues, the MRI scans were normal for 33% of PsA patients with clinical sacroiliitis [23]. In a cross-sectional audit of 76 MRI scans of lumbar spine and SIJ, 33 patients had a clinical diagnosis of PsA, among whom 30% demonstrated abnormalities in lumbar spine and SIJ [24]. Finally, a recent cross-sectional observational study assessing the prevalence of acute and structural changes on the MRIs of 45 PsA patients reported subchondral bone oedema, enthesitis, periarticular erosions and fat metaplasia for 37.8% of the patients. However, most of these patients presented with no clinical symptoms [25].

As recently pointed out by Braun and Landewé, the post-hoc analyses of PsA trials to investigate the efficacy of biologics on axPsA is problematic because these trials enrolled patients with peripheral arthritis irrespective of the presence of back pain or any axial symptoms [26]. In this context, the MAXIMISE cohort of 485 PsA patients with a clinical diagnosis of active axial involvement provides a unique clinical and imaging dataset to comprehensively evaluate the inflammatory, post-inflammatory and degenerative changes of baseline MRIs for the first time in conjunction with various recorded outcomes at week 12 [14]. Although MAXIMISE

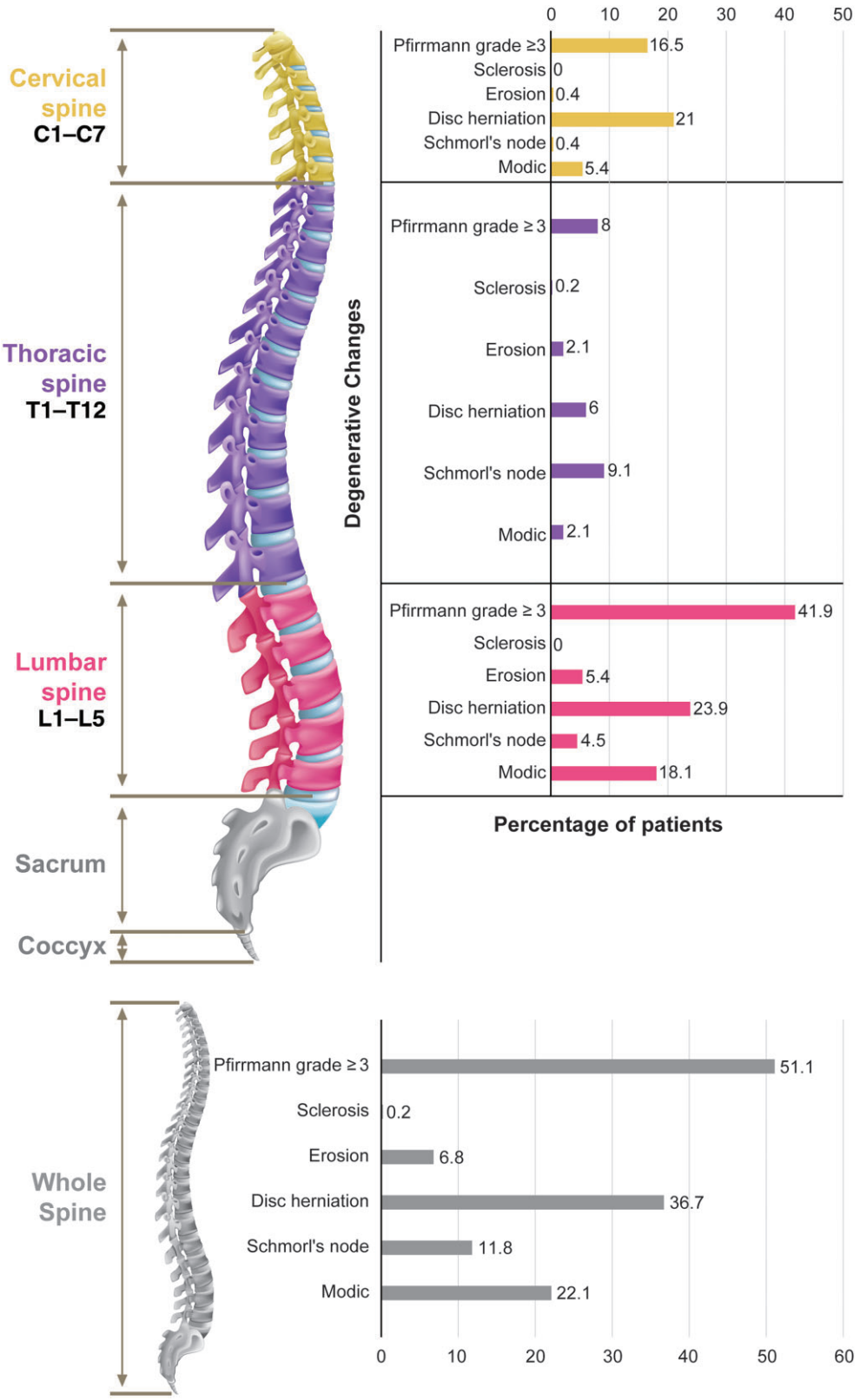

Figure 4. Degenerative changes by region of the spine; $N = 485$. The following changes such that a score of 1 for either denotes an overall score of 1 were combined as follows: Modic 1 and Modic 2; Schmorl's node with BME and Schmorl's node without BME; and disc herniation and high intensity zone. Pfirrmann grade was dichotomized at each DVU: a score of 1 or 2 was rated as 0 and a score of $\geq$3 was rated as 1. BME, bone marrow oedema; DVU, disco-vertebral unit; *n*, number of patients with at least one DVU showing as 'present' for the associated spinal degenerative change variable in the whole spine

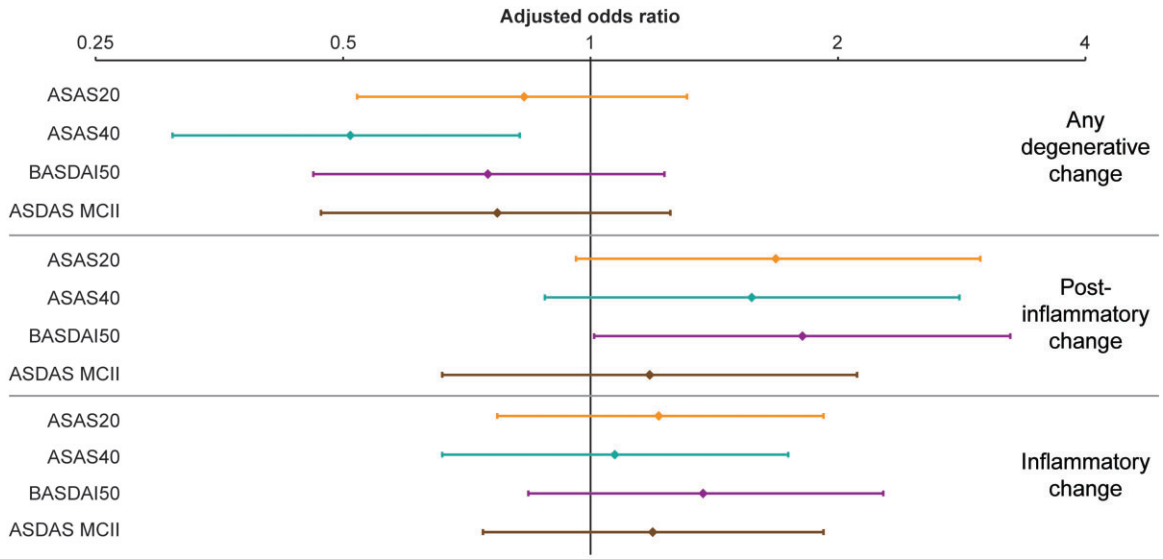

Figure 5. Logistic regression model coefficient at week 12 for ASAS20, ASAS40, BASDAI50 and ASDAS-CRP MCII. Forest plot of the adjusted odds ratio (OR) with associated 95% CI for 'any degenerative change', 'post-inflammatory change' and 'inflammatory change' as predictors for the four endpoints at week 12. The four fitted logistic regression models (one for each end point) including the interaction 'treatment × sex' and 'treatment × nail dystrophy' were determined as a better fit to the data than the ones with the additional interactions 'treatment × inflammatory change', 'treatment × post-inflammatory change', 'treatment × any degenerative change' as determined by the likelihood ratio test *P*-value. Inflammatory change = no, post-inflammatory change = no and any degenerative change = no are the reference levels for the binary predictors. The coloured points denote adjusted odds ratio (OR) point estimates and the bands denote 95% CI. The vertical line represents the null value, an OR of 1. An adjusted OR >1 indicates a higher likelihood of being a responder. The adjusted OR axis is plotted on a log scale but labelled with anti-logs

did not mandate MRI changes as an inclusion criterion, to be as close as possible to the current clinical practice, which is based on the clinical judgement of the treating physicians, MRI data were collected at baseline to assess SIJ and spinal inflammation as an exploratory end point along with the primary end point of ASAS20 response [14]. The additional rescoring features were chosen to investigate bone marrow involvement of the posterior segments of the spine and other pathologies indicating degeneration (e.g. Pfirrmann or Modic lesions). The use of the FASSS was deemed appropriate since fat lesions are reliably assessed by MRI examinations and due to the lack of reliable possibility to depict and assess erosions or new bone formation.

The present analysis not only comprehensively assessed inflammatory, post-inflammatory and degenerative changes of the baseline MRI data of 485 PsA patients with a clinical diagnosis of axial disease but also evaluated the differential treatment effect of secukinumab on ASAS20, ASAS40, BASDAI50 and ASDAS-CRP MCII for the three defined imaging groups. Although not statistically significant, baseline post-inflammatory changes might predict better outcomes while degenerative changes may suggest a negative effect on outcome measures. It is worth noting that post-inflammatory changes were scored with FASSS, a very elaborate scoring system ranging up to 456 points, and hence more exhaustive than the Berlin score and SPi. Furthermore, we need to take into account the probability of overestimating or underestimating an effect owing to the exploratory nature of the analysis. Nevertheless, identifying inflammatory, post-inflammatory or degenerative features as potential predictors of therapeutic efficacy may support the development of prediction models and eventually lead to optimized personalized treatment strategies in patients with axPsA.

The limitations of the present analysis include lack of two independent readers assessing the images to reach agreement although two very experienced experts read randomly assigned MRIs after appropriate standardization in ∼10% of the patients. Furthermore, the possibility of missing abnormalities in some locations of the spine or the presence of erosion or new bone formation that could potentially explain the lack of axPsA specific MRI findings for ∼30% of the patients cannot be ruled out. Additionally, the MRIs at week 12 were not re-read and hence the effect of treatment or any newly identified abnormalities could not be assessed. Finally, establishing the existence of differential treatment effects in RCTs is challenging because RCTs are typically sized just large enough to detect an overall average treatment effect, but the power is low for detecting true interactions. Although the two-model log-likelihood comparison approach used in the present analysis is the gold-standard frequentist method for multiplicity adjustment in subgroup analyses, caution is needed in the interpretation of positive findings [27].

Nevertheless, these results highlight the phenotypic heterogeneity of axPsA not only in terms of signs and symptoms but also in terms of imaging characteristics, indicating that the cornerstones of diagnosing the condition may be the medical history and the clinical picture of the individual patient. By shedding light on the imaging characteristics of patients with PsA with axial manifestations, these data further the current understanding of axial PsA and may lead to hypothesis generation and support the design of future trials in axial PsA.

Conclusion

Re-reading the baseline spinal MRIs from the MAXIMISE trial revealed additional inflammatory and post-inflammatory changes suggestive of axPsA, while degenerative changes were the only MRI finding in approximately one-fifth of the patients and one-tenth of the patients had no MRI changes. Although there was no significant evidence of a differential treatment effect for any of the imaging categories, the supplementary analysis

revealed interesting trends for the post-inflammatory and degenerative changes as possible predictors of treatment response in PsA patients with axial manifestations.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information. The data sets generated during and/or analysed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the study in line with applicable laws and regulations. The data may be requested by writing to the corresponding author.

Contribution statement

All named authors meet the International Committee of Medical Journal Editors (ICJME) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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