Significance of structural changes in the axial skeleton in patients with axial spondyloarthritis: how important are lesions in the sacroiliac joint?

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ABSTRACT

Inflammatory back pain (IBP) is a characteristic clinical symptom of patients with axial spondyloarthritis (axSpA) that is caused by inflammation in the axial skeleton. In early disease stages the sacroiliac joints (SIJ) are most often affected, the spine usually at later stages. In many but clearly not all cases of axSpA new bone formation in form of syndesmophytes and ankylosis occur in the further course of the disease. Function and mobility may be impaired by both, inflammation and structural changes. In clinical trials outcome parameters most often used refer to pain, disease activity, function, mobility and global health but many researchers are also interested in radiographic progression in the axial skeleton of patients with axSpA. This viewpoint discusses the relevance of structural changes in the SIJ in comparison to the spine and in relation to functional outcomes and mobility.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that manifests primarily in the axial skeleton, initially mostly in the sacroiliac joints (SIJ), later spreading to the spine in many but not all cases. The disease is characterised by inflammation and new bone formation in the axial skeleton and other entheseal sites. These pathologies are mostly assessed and detected by conventional radiography (CR) and MRI. Tumour necrosis factor inhibitors (TNFi), IL-17 antagonists (IL-17i) and Janus kinase inhibitors are shown to be efficacious in patients with axSpA including clinical signs and symptoms and reduction of axial inflammation as assessed by MRI. Another important outcome is radiographic damage, in axSpA usually appearing in form of syndesmophytes and ankylosis in the axial skeleton, for example, in the SIJ and the spine.

Disease modification in axSpA

The concept of disease modification, defined as retarding or stopping structural damage by antirheumatic drugs (DMARDs) originally coming from rheumatoid arthritis (RA) does not have a very solid basis in axSpA because randomised placebo-controlled trials are lacking and because only low rates of radiographic progression in the spine as assessed by CR and scoring with mSASSS have been reported for the bDMARDs TNFi and IL-17i while data on tsDMARDs are underway. However, a reduction of erosions and ankylosis in the SIJ as assessed by MRI during bDMARD and tsDMARD treatment has recently also been reported in axSpA patients. While studies looking at radiographic changes in the SIJ in early disease have already been published a while ago there is now a new report on such changes from the Swiss cohort which is well known because the authors have already provided more retrospective evidence that TNFi have decelerating effects on radiographic spinal progression in axSpA which is related to a decrease of inflammation as suggested by reduction of C reactive protein (CRP) levels.

Indeed, the situation is quite complex. Therefore, it seems mandatory to put the data into perspective. About 15 years ago, we had asked the question: ‘what is the most important outcome parameter in ankylosing spondylitis?’ In this editorial, we challenged the view that radiographic progression is more or equally important as compared with disease activity, pain and function. Last year, we discussed the relevance of small changes in MRI erosion counts in patients with axSpA treated with bDMARDs and tsDMARDs mainly related to their relevance for patient-reported outcomes.

The radiographic course of axSpA

The recent developments regarding radiographic progression in axSpA are a very good
reason to think about the nature of structural damage and disease modification in this disease that affects the SIJ early in the course and extends later to the vertebral column where all three spinal segments can be involved.

There are two main targets of disease modification in axSpA: (1) osteodestructive changes such as erosions and (2) osteoproliferative changes such as syndesmophytes and ankylosis. After the early hypothesis that the sequence of events is inflammation—erosion—fat metaplasia—bone formation the situation now seems to get more complicated because follow-up MRI studies have repeatedly shown that in the vast majority of cases the cause of new bone formation cannot be detected. Nevertheless, several factors predictive of bone formation have been identified showing that sex, smoking and almost all structural changes in the SIJ and the spine are predictive of radiographic progression as assessed by mSASSS, and there is strong evidence that spinal inflammation as assessed by MRI and increased CRP levels are also predictive while this is not the case for sacroiliac inflammation because, at least small changes are not specific for axSpA and more extensive inflammatory changes in the SIJ, in combination with HLA B27, were shown to predict development of structural changes in the SIJ.

**What about the natural course of radiographic progression in axSpA?**

We do know that there is quite some variability in radiographic spinal changes in follow ups on both, the individual and the group level, however, persistently high disease activity as assessed by ASDAS is clearly associated with more radiographic (mSASSS) damage. An increase of one ASDAS unit was shown to lead to an increase of 0.72 mSASSS units within 2 years in that study, and patients with inactive disease had an mSASSS increase of about 5 points in 10 years.

In cohort studies, about one-third of patients already have syndesmophytes at baseline, and mean mSASSS scores vary depending on disease duration. In patients with about 10 years of disease duration the mean mSASSS (range 0–72) is between 10 and 15. In patients treated with bDMARDs such as TNFi and IL-17i the mean change in mSASSS within 2 years has usually been below 1. Importantly, vertebral erosions play only a minor role in the development of structural spinal changes, and those seem to very rarely occur in nr-axSpA—even though some patients classified as nr-axSpA have no definite structural changes in the SIJ but may have syndesmophytes (which may also be due to the limited reliability of the detection of such changes in the SIJ).

The situation for the SIJ is different for several reasons. It is currently increasingly discussed whether radiographic scoring should be replaced by MRI (figure 1) because it is at least as good regarding structural changes, much better in terms of active inflammation, and it does not require ionising radiation. However, the progression of radiographic changes in the SIJ by at least one grade after 2 years is known to only occur in a small percentage of patients with early axSpA, and an elevated CRP was a strong positive predictor of structural progression in the SIJ. Indeed, MRI scores for such structural...
SIJ changes are characterised by a floor effect indicating that the measure has a low limit for potential responses and many scores are near this limit. Thus, the range of SIJ MRI scores (data calculated from the original publication by Maksymowycz) for fat metaplasia, erosions and ankylosis is limited to not more than 12% within 2 years in GESPIC, and even lower in other cohorts such as DESIR. Finally, there are no solid predictors for rapid progression to date. The well reported and established influence of age has to be taken into account when evaluating structural changes in SIJ, while the significance of other structural changes in the SIJ which also occur in the normal population is less clear.

Another interesting question in this regard is the observation of increasing backfill in the SIJ in axSpA patients on DMARD treatment. What is this? A repair mechanism like in RA? The starting point for (more) ankylosis? In any case it is not clear what impact this observation has or will have for the patients.

In any case, it is now increasingly clear that, for diagnostic purposes, the combination of bone marrow oedema and erosions is the best option. The influence of age has to be taken into account when evaluating structural changes in SIJ, while the significance of other structural changes in the SIJ which also occur in the normal population is less clear.

The important issue of replacing CR by low-dose CT in detail is beyond the scope of this editorial—even though there is increasing evidence that it does capture the whole spine (in contrast to CR and scoring with the mSASSS) and it is more sensitive to change.

What about the consequences of structural changes related to function and mobility?

There is evidence that both, inflammation and structural changes in the spine, have an impact on function and mobility. In a 10-year study on TNFi-treated patients a with both, r-axSpA and nr-axSpA, physical function as assessed by the Bath AS functional index (BASFI) and the Bath AS spinal mobility score (BASMI) remained stable over time despite radiographic spinal progression, and no association between changes in mSASSS and BASFI was found, while syndesmophytes (mSASSS) seemed to exert more influence on spinal mobility (BASMI) over time. The data of that study showed that an increase of 20 and 12 mSASSS points over time would be responsible for an increase of one BASFI or one BASMI point, respectively. In a paper on the GESPIC cohort, statistical analyses adjusted for structural damage in the spine as assessed by mSASSS, disease activity (BASDAI) and gender, revealed an independent association of a sacroiliitis sum score with BASFI and BASMI. Change by one radiographic sacroiliitis grade in one joint was associated with BASFI/BASMI worsening by 0.10/0.12 points, respectively, independently of disease activity and structural damage in the spine. These data show that there is a minimal almost neglectable direct effect of structural SIJ changes on function and mobility.

CONCLUSIONS

The clinical value of detecting a decrease or increase of structural changes in the SIJ in much detail is not very clear at present, even though higher degrees of such changes are associated with more radiographic progression in the spine. Nevertheless, it is reassuring that anti-inflammatory therapies do rather decrease such changes in the SIJ—even though it seems very clear that the reduction of inflammation and bone formation in the spine is much more important from the patients’ point of view because of their impact on spinal function and mobility.
As previously mentioned, I would like to propose to get rid of the term nr-axSpA for diagnosing patients. This term should only be used for classification purposes. Especially in patients with syndesmophytes but no clear radiographic changes in the SIJ use of this term doesn’t make sense. Of course, SIJ need to be evaluated for more or less structural changes to assess the disease status of patients (according to their symptoms) but why should we determine a radiographic state in the SIJ methodologically known not to be very reliable that, in addition, is subject to change? Of interest, in a study on axSpA patients with a symptom duration of less than 2 years, nearly half of the patients already had structural changes in the SIJ—suggesting that the concept nr-axSpA has limited value for identifying early patients. Indeed, it seems more interesting to look at the time period between the onset of typical symptoms and the first appearance of structural changes in the SIJ, for example, to assess how fast structural changes develop. Finally, I think it’s time to replace CR of the SIJ by MRI since it is the better imaging technique to detect inflammatory and structural changes (figure 1) in the SIJ.

Correction notice
This article has been updated since it was first published online. The caption to figure 1 has been updated and reference 53 has been moved to the last paragraph.

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REFERENCES
26. Bennett AN, McGregor D, O’Connor S, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically


