Reviewer’s report

Title: S100A4 is elevated in axial spondyloarthritis: a potential link to disease severity

Version: 0 Date: 01 Feb 2019

Reviewer: Zofia Guła

Reviewers report:

Major points:
1. Authors hypothesized that S100A4 protein may participate in the formation of syndesmophytes in patients with axSpA. Considering that S100A4 is a negative regulator of bone remodeling, one would expect that in patients with osteoproliferation (long lasting SpA with syndesmophyte and ankylosis) the level of S100A4 is lower than in healthy control. Some experimental studies showed more pronounced osteoblast differentiation in SA100A4 knockout mic, deficient of S100A4. However, in all groups of axSpA the level of S1004A was significantly higher than in healthy control. The levels of S100A4 were lower in axSpA patients with more bone formation, as demonstrated by the presence of syndesmophytes, compared to axSpA patients with no spinal involvement, but the difference was no longer significant after adjustment for disease duration, sex, age, BASDAI and CRP. It is though difficult to find clear link between the levels of S100A4 and osteoproliferation in axSpA.
2. The subsequent groups of patients are relatively small, and they differ in use of biologics - 55% in SpAII group vs 0 and 6% in other two groups. We cannot exclude the potential influence of the treatment on the level of S100A4. It would be interesting to see the level in SpAII group without biologic treatment.
3. What is the possible explanation for decrease of S100A4 during the disease?

Minor points:
1) Why did the Authors choose for the analysis exclusively the S100A4 and the DKK1? It is hard to believe that they did not measure more proteins regulating bone turnover, eg. Wnt, BMP, RANKL, OPG?
2) All allusions of causality should be removed. Although this may be an interesting hypothesis, the study design precludes all inferences of causality.
3) The use of ASDAS is currently more "desirable" than BASDAI, so please consider ASDAS or both.
4) The Authors must remove the both meaningless and misleading linear trends from correlation graphs.
4. p.4: S1004 or S100A4 - is this the same molecule?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**

Please indicate the quality of language in the manuscript:

Acceptable

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