Reviewer's report

Title: Biomarkers related with bone turnover: extensive evaluation in a cohort of patients with ankylosing spondylitis

Version: 2 Date: 17 May 2012

Reviewer: Nouran Abaza

Reviewer's report:

1- Major Compulsory Revisions
1.a - Title
The word biomarkers in the title is not enough to describe the molecules studied in this work as most important molecules OPG and RANKL are better described as cytokines or regulators of bone formation and resorption (bone turnover).
The suggestion is to substitute the word biomarkers by biomarkers and cytokines (or regulators) of bone turnover.
1.b - Abstract
Results
Add important results concerning increased OPG level in active AS patients and its correlation with activity as all this appear suddenly in the conclusion without any mentioning in results.
Conclusion
The level of OPG and its correlation with disease activity is mentionned here for the first time while it should be in results and preserve conclusion for brief interpretation such as that the increased OPG in active AS patients reflects ectopic new bone formation and on going inflammation.
1.c - Background
In the 2nd paragraph line 9 substitute the word biomarkers by biomarkers and cytokines (or regulators) of bone turnover. Same in line 11.
1.d - Results
Add the results of OPG correlation with disease activity in the correlation analysis as it is the most important in the study as clearly stated in the conclusion.
1.d - Discussion
In the 1st paragraph line 8,9 here the OPG correlation appears with no previous notion about it in the results so kindly add it in results and also it needs explanations: OPG level in AS patients were found to be lower during inactivity which might contribute to osteoporosis noted as lowered BMD detected at femur in these patients as there is a lack of proper inhibition of osteoclastogenesis by the OPG effect that hinders the interaction of RANK-RANKL essential for maturation and activation of osteoclast precursors. On the other hand, the
increased OPG level during disease activity might lead to new bone formation as it inhibits osteoclastogenesis. This bone formation in AS is known to be ectopic but still the molecular dysfunction that makes it as such needs to elucidated. Finally the OPG level was found in our study to be lower in anti-TNF treated patients, which might lead the decrease of new bone formation and inflammation. Also add that DKK-1 increased level in anti-TNF treated patient leads to diminished osteoblastogenesis and hence bone formation via its inhibitory effect on Wnt signalling pathway.

In the 2nd paragraph line 14, 15

Low OPG level is expected to be associated with increased osteoclastogenesis due to the lack of its competitive inhibition with RANK over RANK-L. Here the authors mentioned in line 14,15 that is associated with decreased osteoclastogenesis what is the explanation. Accordingly in line 15, 16 they mentionned anti-TNF therapy to be associated with osteoblastic activity. The results of patients on anti-TNF therapy in this study showed lowered OPG and increased DKK-1 which should favor osteoclastogenesis and decrease bone formation respectively as explained before.

1.e - Conclusion

In the 1st paragraph line 2 the OPG correlation with disease activity is mentionned here for the first time while it should be added to the results and also similar to comment in abstract the explanation or interpretation should be added.

2- Minor Essential Revisions

2.a - Suplement document 1
Line 8: change "These is" by "This is"

2.b - Table 1
BMD unit by g/cm2
might add the standard deviation SD
BASMI, BASFI, BASDAI not mentionned in the table so no need to there abbreviation detailed below the table

2.c - Table 2
BCE detailed bone collagen equivalent

2.d - Table 3
detailed abbreviation of BASDAI

2-e - Conclusion
line 1 change OP into OPG

1. Is the question posed by the authors well defined?
Yes, but please add the word cytokines or regulators as mentioned in my comment on title instead of the word biomarkers alone.

2. Are the methods appropriate and well described?
Yes
3. Are the data sound?
Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
Mostly except those needed in comments
6. Are limitations of the work clearly stated?
Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes
8. Do the title and abstract accurately convey what has been found?
Not accurately, an alternative would be: Biomarkers & cytokines of bone turnover in ankylosing spondylitis and the conflict of bone formation versus osteoporosis: who acts when?
9. Is the writing acceptable?
Yes

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
'I declare that I have no competing interests'