Author's response to reviews

Title: Prevalence of vertebral fractures in a disease activity steered cohort of patients with early active rheumatoid arthritis

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Author's response to reviews: see over
Answers to the reviewers

Reviewer 1:
This is a well written study extracted from the Best study and intended to determine the prevalence of vertebral fractures after 5 years of disease activity score (DAS)-steered treatment in patients with early rheumatoid arthritis.

Discretionary Revisions
The prevalence of VFs was very low which may be due to two factors that should be discussed: 1) early RA and 2) DAS steered patients well controlled with antirheumatic drugs and antiresorptives which may be different from the real world.

Answer:
We appreciate the reviewer's suggestion and have tried to underscore these issues in the discussion section.

Reviewer 2:
The authors investigated the prevalence of vertebral fractures after 5 years of DAS-steered treatment in patients with early active RA who participated the BeSt study. They found that 1) the prevalence for vertebral fracture was 15% and similar for males and females, 2) vertebral fractures were not associated with low BMD or prednisone use but advanced age and smoking, 4) patients with vertebral fracture suffer greater functional disability over time than those without vertebral fractures. This paper is important because it sheds light on the associated factors of vertebral fractures among RA patients in the real world.

Major points
1. Radiographs of the lateral thoracic and lumbar spine were available in 275 of the 508 patients (due to logistic reasons). Please specify the reasons in more detail in the Methods or elsewhere.

Answer:
We have added in the method section a more detailed description of the reasons why radiographs of the thoracic and lumbar spine were only available in 275 of the 508 patients.

2. Authors diagnosed vertebral fractures after 5 years and evaluated the DAS, HAQ, and BMD retrospectively. The study design appears to be complex. Authors should clarify the study design, state they evaluated the DAS, HAQ, and BMD retrospectively in the Methods, and discuss the shortcomings of this study design in the Discussion.

Answer:
The BeSt study is a randomized clinical trial in which data is prospectively collected. Every three months data on DAS and HAQ scores were collected and BMD measurements were performed every year. After 5 years of treatment, radiographs of the lumbar and thoracic spine were made. Our study endpoint was to determine the prevalence of vertebral fractures after 5 years of treatment. Although we evaluate the changes in DAS, HAQ and BMD from baseline to 5 years of follow-up, this does not mean the data is collected retrospectively. In general, retrospective data collection results in more bias compared to prospectively collected data. However, performing an analysis with data from baseline to 5 years follow-up with prospectively collected data is in our opinion not a shortcoming. We did add in the method section that data was collected prospectively. More details on the BeSt study design are published previously.
3. Authors state ‘-patients with vertebral fractures suffer functional impairment due to vertebral fractures or the underlying bone condition, ---’ in the Discussion. However, this is not a prospective study and high HAQ disability score during the 5 years may be associated with the vertebral fractures, although the baseline HAQ score was not significantly different between the patients with and without vertebral fractures. High HAQ disability score is reported to be associated with the risk of vertebral fractures in RA patients. Authors should cite this paper and discuss association between high HAQ score and risk of vertebral fractures in the Discussion.


Answer:
The article of Sinigaglia et al. (2000) is a cross-sectional study looking at the association between the HAQ score and the risk for vertebral fractures. Although they find that a high HAQ score is associated with the risk of vertebral fractures, it is not determined which one is caused by the other. We are the first prospective study looking at the association between HAQ scores over time and the risk of vertebral fractures. Although it is a limitation of this study that baseline radiographs of the spine are missing, we still think it is appropriate to conclude that patients with vertebral fractures might suffer functional impairment due to vertebral fractures or the underlying bone condition, since this association was independent of disease activity and age. In addition, it seems unlikely that HAQ has preceded vertebral fractures since it was previously found that HAQ deterioration is dependent on disease activity in the early phases of RA (Welsing et al, 2001).

We have discussed this article in the framework of our results.

4. Authors did not evaluate non-vertebral fractures in this study, although RA patients are likely to have not only vertebral fractures but non-vertebral fractures. Authors should state the effect of non-vertebral fractures in the Discussion.

Answer:
We did look at the presence of non-vertebral fractures in this study, but we found that there was no difference in prevalence of vertebral fractures when stratified for the presence of non-vertebral fractures. This is described in the result section.

Minor points
1. Does the term ‘GEE’ indicate generalized estimating equations in the abstract? Be sure to define all abbreviations on the first use.

Answer:
The term GEE does indeed indicate generalized estimating equations. We have changed this is the abstract.

2. Authors used both ‘vertebral fractures’ and ‘VFs in the Discussion’. They should define vertebral fractures use one or the other term consistently to avoid confusion.

Answer:
We have changed this in the manuscript and used ‘vertebral fractures’ consistently.
Reviewer 3:

This is a very interesting study. It provides insight into the bone metabolism of RA patients. This is of interest for everybody treating patient with RA. The authors did a very good job in investigating this interesting topic of fractures in early RA with aggressive targeted treatment.

- **Major Compulsory Revisions**
  1. The main problem I have is with the statistics and the presentation of the results. The authors used 2 models (GEE and mixed models) to study relationships between vertebral fractures and DAS, HAQ and BMD. Maybe this is because I am not a statistician, but I find this very confusing, because it is unclear what the final model is and why 2 models are chosen. For instance in the methods section it is written that bmd will be analysed using GEE and on the second page of the results third paragraph it is written the mean BMD predicts… in linear mixed models. I would advise to use either linear mixed models or GEE or else explain why both are used.

  **Answer:**
  We have used linear mixed models (LMM) to model DAS and HAQ over time since this model is most suitable for continuous variables. With LMM we are able to specify the correlation between measurements within a patient over time. In addition, this model is able to deal with missing data. We used the same model to look at changes of BMD over time (outcome is also continuous) between patients with and without vertebral fractures. On the other hand, we used generalized estimating equations (GEE) to model a dichotomous variable. Similar to the LMM, this model can also specify the correlation between measurements within a patient and is able to deal with missing data. We chose to look for an association between vertebral fractures and BMD and other possible confounders, such as prednisone use, bisphosphonate use, BMI etc., since these factors might also be of influence on the presence of vertebral fractures. We therefore used the 'presence of vertebral fractures' after 5 years of treatment as outcome measure and then a GEE model is more appropriate.

  We have described in the method section that LMM is used for continuous outcomes and GEE for dichotomous outcomes.

  2. The other major problem is with the lay-out of the results. They are too complex and messy. They need to be tidied to clearly state, what the outcome of this study is. The interesting finding that patients with a fracture at 5 year follow-up had a higher disease activity during the study is hidden between other negative findings and less relevant findings.

  **Answer:**
  We thank the reviewer for this remark and have slightly rewritten the results in order to give more of a ‘flow’ to the study outcomes.

- **Minor Essential Revisions**
  3. In the results percentages are given for difference between certain subgroups, please provide confidence intervals or p-values.

  **Answer:**
  We have added p-values to describe the differences between the subgroups where they were previously not reported.
4. In the discussion, please give some numbers for the occurrence of fractures in the healthy population. Also give a bit more information about the historical RA controls.

Answer:
We have added information about the occurrence of fractures in the healthy population in the discussion session. In addition, we stated that patients in our cohort are early RA and that treatment is according to a treat-to-target approach (which is different from historical RA cohorts).

5. I also feel that the discussion should concentrate more on the main outcome.

Answer:
We thank the reviewer for this excellent suggestion and have slightly rewritten the discussion.

- Discretionary Revisions
6. Form the studies cited I cannot read that BMD change predicts fractures.

Answer:
We have checked the references again and realized that we should have formulated that sentence differently, since the studies indeed only state that (lower) BMD is associated with vertebral fractures. We have changed the sentence.