Author's response to reviews

Title: Evaluation of hand bone loss by digital X-ray radiogrammetry as a complement to clinical and radiographic assessment in early rheumatoid arthritis. Results from the SWEFOT trial.

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Dear editor

We hereby want to thank you for considering our manuscript “Evaluation of hand bone loss by digital X-ray radiogrammetry as a complement to clinical and radiographic assessment in early rheumatoid arthritis. Results from the SWEFOT trial”.

We have addressed all the points raised by the reviewers and added new data to the manuscript. The changes are listed below.

We have made the corresponding changes in the text, tables and figure legends according to the reviewer’s comments and suggestions and added one new reference (13).

With these modifications we believe that we have fulfilled all the reviewer’s requests and hope that our article now meets approval for publication in BMC Musculoskeletal Disorders journal.

Best regards,

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Answer to the comments:

REFEREE 1:

Reviewer: Karine Briot

C-1
Is there a correlation between systemic inflammation markers (ESR and or CRP) and radiographic damage progression?

Patients with radiographic progression (delta T-SHS > 5 during 24 months) had higher CRP and ESR at baseline, 3 and 12 months. The same trend could be seen in the whole SWEFOT trial, as we’ve reported in previous reports from SWEFOT.

C-2
Is there in this population of RA another marker (clinical or biological) able to predict radiographic progression before the hand DXR change assessed at 12 months? Authors should discuss this point clearer in their manuscript

As we mentioned on pages 7 and 8, there was no difference in radiographic progression at 24 months between ACPA positive and ACPA negative patients. Neither was any difference observed between RF positive and negative patients, between women and men or patients with radiographic damage at baseline. But patients with radiographic progression (delta T-SHS > 5 during 24 months) had higher CRP and ESR at baseline and 3 months. Previous studies have shown higher inflammation predicts more radiographic progression in RA but this is not the focus of this study.

C-3
How many patients received bisphosphonates? Did the authors take into account the effect of this treatment?

In this dataset we are unable to analyze bisphosphonate treatment at the individual patient level. During the years of this trial, bisphosphonate use overall was rather low.

REFEREE 2:

Reviewer: Elisabeth Lie

Major:

C-1:

p. 8, 2nd line of last paragraph: “T-SHS” should be changed to “Change in T-SHS” – even though “radiographic progression” is included earlier in the sentence. “Change in T-SHS” should also be included within the brackets for the comparisons of RF pos. vs. neg. and men vs. women.

Thank you for the comment. Now we have changed on page 7 as below:
“In the entire study group, there was no difference in radiographic progression at 24 months between ACPA positive and ACPA negative patients [change in T-SHS 5.04 (7.42) compared to 4.98 (5.72), p=0.28]. Neither was any difference observed between RF positive and negative patients [change in T-SHS: 7.33 (16.41) compared to 4.23 (6.33), p=0.50], or between women and men [change in T-SHS: 5.11 (11.37) vs. 4.03 (5.73), p=0.65].”

C-2
p. 8-9: Please include the OR (95% CI) for radiographic progression in patients with T-SHS >5 at 12 months vs. those with T-SHS <=5 at 12 months

Patients with T-SHS > 5 points at 12 months had significantly greater risk of radiographic progression (>5 increase in SHS) over 24 months [odds ratio 14.10, 95% CI =5.41-36.73, p<0.001 (Fisher’s exact test)] vs. those who had T-SHS ≤ 5 points.

Same analysis for radiographic progression between 12 and 24 months showed OR 9.05, 95% CI=1.99-40.95, p=0.001 (Fisher’s exact test).

Now we have added this data in the manuscript on page 8 as below:

“Patients with T- SHS > 5 at 12 months had more radiographic progression totally from baseline to 24 months [8.43 (12.93) vs. 0.93 (2.40), p<0.005 / OR 14.10, 95% CI =5.41-36.73, p<0.001 (Fisher’s exact test)] and between 12 and 24 months [1.70 (4.13) vs. 0.62 (1.78), p=0.03 / OR 9.05, 95% CI=1.99-40.95, p=0.001 (Fisher’s exact test)] vs. those who had T-SHS ≤ 5 points.”

C-3

The lack of statistical power – with only 23 patients being categorised in the group with HBL between baseline and 12 months – is an important issue with this paper and must be discussed (Reviewer 2, C-2). This is currently not discussed at all.

Now, we have added the following text in the discussion on page 14:

“Another limitation of our study was the relatively small number of patients (23 patients with HBL at 12 months) which limited the power of the study to detected small differences and associations. This small number of patients also resulted in low sensitivity.”

C-4

The numbers with HBL in each of the treatment groups should be added to figure 1 t, as reported in the response to Reviewer 2, C-2, even though the percentages are reported on p. 10.

Now we have added the number of patients in each group in figure legend as below:

“The number of patients with HBL in each therapy group: MTX responder: 2/49; Triple therapy: 12/55; MTX + INF: 9/55”
On p. 11 negative results for some results the effect of HBL on radiographic progression within the MTX mono and MTX+INF groups are reported (two last paragraphs). These results are influenced by lack of statistical power, with only 2 and 9 patients, respectively, with HBL in these treatment groups. Please modify or discuss/comment. This also holds true for the comment in the Discussion (p.13, 1st paragraph) – “In contrast, no association was seen…” – this sentence should be removed, as the authors did not have sufficient statistical power to assess this.

Thank you for the comment. Now we have deleted this sentence “In contrast, no association was seen between HBL and radiographic progression in patients with combination MTX+INF” in discussion on page 12. We have also modified the last paragraph on pages 10 and 11 as below:

“Patients with HBL had significantly greater risk of radiographic progression (>5 increase in T-SHS) over 24 months (odds ratio 3.09, 95% CI =1.20-7.79, p=0.02). This was most marked and only statistically significant in the group of patients receiving triple therapy (odds ratio 4.15, 95% CI=1.05-16-35, p=0.04), but not in the MTX monotherapy group (odds ratio 2.50, 95% CI=0.14-43.28, p=0.50) or the MTX+INF group (odds ratio 1.88, 95% CI=0.30-11.77, p=0.50), particularly due to a limited number of patients who had HBL (n= 2 and 9 in MTX monotherapy and MTX+INF, respectively).”

It is unclear for me why only 21+123=144 patients were included in the analyses for Figure 3 – while it is reported that 159 patients had data for DXR analyses. Were missing data in these 15 patients due to lack of 24-month radiographic data? Please report/clarify in the manuscript main text. (Furthermore, the response to Reviewer 1 (C-7-1) is somewhat confusing as figure 2 does not include clinical data – and in table 2 data for 144 patients is reported for radiographic progression and data for 146 patients is reported for hand bone loss.)

We had DXR analysis for 159 patients. For clinical and radiological scoring according to the SHS, we had 144 patients. In response to Reviewer 1 (C-7-1) we did not mention anything about figure 2:

“The number of patients in table 2 is unfortunately lower than in the whole group with DXR data (144 compared to 159), because there were missing values on other parameters (both clinical and radiographic) and we analyzed only those who had completed clinical and radiographic data.”

Figure 2 is a description of Radiographic progression according to the three parameters of SHS in patients with/without HBL.
Now we have added the number of patients for DXR analysis and radiographic progression on page 5.
The data about specificity/sensitivity as HBL as a predictor of radiographic progression that is given in response to Reviewer 1 in comment C-4 should be included (with % sensitivity) in the text as this is important for the clinician and also represents a limitation.

Yes, we have now added this on page 10.

Reviewer 1, C-10: I believe that x-axis of the cumulative probability plot is conventionally labeled by “Percent of patients” with scaling of 0-100% along the axis. Thus, the median radiographic progression etc. in each group can be read from the figure. Please include this.

Thank you for the comment. We have now changed figure legend 3 as follows: Radiographic progression during 24 months in patients with (n=23) and without (n=121) hand bone loss (HBL). The probability plot depicts individual radiographic progression for each patient in ascending order. As can be seen, radiographic progression is none or minimal for most patients (median: 0), but with a difference in progression between the groups at the higher end.

Discussion p. 13: The information that no patients were excluded due to severe joint damage or prosthesis should rather be moved to the results.

Now the sentence is moved to the results on page 7.

Reviewer 3, comment C-3 (and C-4): The rationale for performing/not performing, or including/not including, multivariate analysis seems very unclear. Firstly, with only 43 patients with 24-month radiographic progression, the statistical power is limited and only a few (around 4) independent variables could be included in the model. The authors state that they “do not believe that multivariate analysis is necessary”, but also report that these results will be reported separately. Please clarify. To be able to decide on (clinical) usefulness, the reader must have some information on how 12-month HBL compares to other predictors – such as 12-month radiographic score (see comment above), area under the curve (AUC) for ESR, CRP and DAS28 the first year etc., as DXR represents one extra measure, with extra costs associated.

Yes, we agree with the reviewer. We do not believe that multivariate analysis is useful because of the limited material (number of patient) in this study. The multivariate analysis will be done for whole SWEFOT population (487 patients) in a separate study. For the present subgroup of the SWEFOT trial, ACPA, ESR, CRP, baseline radiographic damage and gender did not significantly predict radiographic progression. We have described this partly on pages 7 and 8.
Minor:

C-11
p. 6: The third and fourth paragraphs both describe why the threshold of 2.5 mg/cm/month was selected for HBL, and they should be combined.

Now it is one paragraph.

C-12
Statistical analysis: The approach with doing pairwise comparisons when the ANOVA/Kruskal-Wallis p-values were statistically significant (as addressed by reviewer 1, C-6-1) should be referred to.

We have now changed the text in “statistical analysis” on page 6 as below:
“The distribution of the variables is given as the mean with standard deviation (SD). The Chi-squared test and Fisher’s Exact test were used to compare dichotomous variables between groups and the independent Student’s t-test, paired-sample T-test and ANOVA to compare continuous variables between groups (for pairwise comparison, Bonferroni test was used). For non-normally distributed data, and in particular for the radiological scores, the Mann-Whitney test and Kruskal Wallis test were used for the comparison between two and three groups, respectively. Statistical analysis was performed with SPSS 20 software (SPSS, Chicago, IL, USA).”

C-13
Please rewrite the sentence “A similar analysis for increase…” on p. 11.

Now we have changes the sentence on page 10 as below:
“The mean (SD) increase in ES was 5.42 (11.23) and 1.50 (3.73) in patients with HBL vs. those without HBL, respectively (p=0.06)”

C-14
Discussion, p. 14: […]HBL was defined as DXR-BMD change rate >= 2.5 mg/cm2/month and was used as cut-off” – please rewrite for clarity.

Now, we have deleted the last part of the sentence on page 13.

C-15
Discussion p. 15: “however, this treatment may also partly conceal the positive predictive value…” – please rewrite

Now, we have deleted the last part of the sentence on page 14.
C-16
Headers of tables 1 and 2: Please include “N=” before the numbers of patients in each of the groups

Yes, done

C-17
Tables 1 and 2: 2 decimals are given for the means and SDs for ESR and CRP. Since the values of ESR and CRP (for each patient) are given without decimals, only 1 decimal should be included for means/SDs.

The values of ESR and CRP are given now with 1 decimal in both table 1 and 2.

C-18
The answer to Reviewer 2’s comment C-11 is not satisfactory as one should be aware of numerical differences in important potential confounders (such as ESR, THS, ES) in a setting with lack of statistical power (and as THS and ES are dichotomized, p-values will typically be higher for these two variables than for continuous variables).

We have changed on page 8 as below:

“For patients with or without HBL, baseline CRP differed significantly (p=0.004) and a numeric difference was seen for ESR (p=0.12).”