Author’s response to reviews


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Author’s response to reviews:
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Dear Editor,

We submit the revised version of the manuscript entitled

Differential impact of obesity, structural severity and their combination on the efficacy of viscosupplementation in patients with knee osteoarthritis.
Post-hoc analysis of a double-blind, controlled, multicenter, randomized trial.

We took into account all the very interesting reviewers' comments.
We thank them because their relevant suggestions have greatly improved the quality of the manuscript.
We modified it in accordance with their suggestions.
The details of changes are below.
We hope that this revised manuscript meets the expectations of the editorial board and will be accepted for publication.

Best regards.

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ANSWERS TO REVIEWER #1:

I have a number of suggestions outlined below. The three main ones are (1) the discussion confuses the recommendations for those with more severe ROA - at one stage it says HA should still be used, but at other times says this group failed treatment, that HA should not be recommended for them and that it's not a viable solution in these people. This group still improved greater than the MCID, but the improvement was less than those with lower BMIs and less severe radiographic disease. The language regarding this needs to be improved throughout the manuscript. (2) I think the analyses do not reflect the aims of the paper. Quite often the study talks about identifying patient sub groups or risk factors. The type of analysis performed in this study are unable to determine these. I suggest preferably re-analysing the data using more appropriate statistical techniques, or as a last resort, removing all reference to these terms. (3) The analyses should be performed on mean change scores, or follow up adjusted scores.

A- We took into account these interesting comments. We re-analysed the data and and fully modified their interpretation. All details are given below by answering point by point to the reviewer's requirements.

Abstract

Q1-If space permits, a brief line on the stats would be helpful:
A1- The following sentences were added: Post-hoc analysis from the intent-to-treat population of a prospective, double-blind, randomized, multicentre, parallel-group trial..... Mann-Whitney or a chi-square tests were used, as appropriate, to assess the association of quantitative or qualitative factors with the patients group.

Q2-Results - do these changes account for baseline levels? And the WOMAC pain values at 6 months, are these the change in pain? I don't think reporting the raw 6 months score is necessary as the change will suffice (again, providing it accounts for baseline values)

A2- We agree with this comment. For more clarity we fully modified the § Results as following: "Forty-seven patients (28.3%) were classified as obese, 93 (56%) had OARSI score 1-2, 73 (44%) OARSI score 3, 70 (42.2%) were neither obese nor OARSI grade 3, whereas 24 (14.5%) were obese and OARSI grade 3. At baseline WOMAC pain score was not significantly different according to the patients sub-groups (p>0.05). Between baseline and month 6, WOMAC pain and function scores decreased significantly in all patient sub-groups (all p<0.01). Nevertheless the decrease of pain was twice greater in non-obese patients with OARSI 1-2 than in obese patients with OARSI grade 3 (-5.7+4.3 versus -2.8+4.3, p=0.007). At month 6, WOMAC pain sub-score was significantly lower in non-obese than in obese patients (4.9+ 4.1 versus 7.1+4.9; p=0.008) and in patients OARSI grade 1-2 versus 3 (4.8+4.3 versus 6.4+4.5; p=0.009). Furthermore, WOMAC pain sub-score at month 6 was 85.7% greater in obese/grade 3 patients than in non-obese/grade1-2 subjects (7.8+5.1 versus 4.2+4.1, p=0.001)."

Q3-I am not sure the conclusion is supported by the results - see comments in the discussion/conclusion regarding true moderator analyses that is needed to identify subgroups. And other comments about not recommending HA for these people. Also "This trial confirms that obesity and advanced stage are independent predictors of a lower response to viscosupplementation" - the analyses are unable to determine predictors as such.

A3- We agree and we fully changed the conclusion: ": In knee OA, obesity and advanced radiological score are associated with a lower response to viscosupplementation. Before considering viscosupplementation, patients who have both obesity and severe joint space narrowing should be informed of the relatively low benefits hyaluronic acid injections may provide

Introduction
Q4 - The first sentence is quite long - perhaps break into 2? And perhaps begin with a line or two about OA, symptoms, burden etc?

A4 - Done: "Knee osteoarthritis (OA) is a major cause of pain and disability in subjects over 50 years with a significant impact on physical performance and quality of life. Standard conservative therapy for knee OA includes a combination of non-pharmacological and pharmacological approaches [1-2], as none individually can be considered highly effective".

Q5 - Does viscosupplementation need abbreviating?

A5 - Viscosupplementation was no more abbreviated as VS throughout the manuscript.

Q6 - Line 7 - what is viscosupplementation? A brief explanation for readers who are unfamiliar with the treatment would be helpful

A6 - we added this short § "In the early 90s EA Balazs hypothesized that intra-articular (IA) injections of high molecular weight hyaluronic acid (HA) could restore the visco-elastic properties of the osteoarthritic synovial fluid (SF) that are altered in osteoarthritis (OA). The concept of "viscosupplementation" was born [3]".

Q7 - The EULAR recommendations are from 2003 and are out of date. I agree their use is controversial, but there are variable recommendations given across clinical guidelines (Nelson, Allen, Golightly, Goode, & Jordan, 2014). Quoting only those positive recommendations doesn't tell the true picture. For example, an uncertain recommendation was given by OARSI due to inconsistent conclusions among meta-analyses and conflicting results regarding safety (McAlindon et al., 2014), while the UK National Institute for Health and Care Excellence recommended against their use (National Institute for Health and Care Excellence, 2014). It is important to acknowledge these uncertain/negative recommendations as well, and it may help strengthen the justification for your study - variable findings because of heterogenous samples of knee OA patients.

A7 - We took into account these comments:” Nevertheless, despite its wide use in daily practice, the real efficacy of viscosupplementation remains debatable [15, 16]. There are variable recommendations given across clinical guidelines [17]. For example, an uncertain recommendation was given by OARSI due to inconsistent conclusions among meta-analyses and conflicting results regarding safety [1], while the UK National Institute for Health and Care Excellence recommended against its use [18].”
Q8- Line 19 should be "worse results"
A8- Correction done.

Q9- Line 19-24 needs a reference
A9- Ref 20, 21, 22, 23

Q10- Line 24 - please explain this previous study of yours with a little more detail
Overall the intro is quite brief but adding these changes above should help.
A10- Details are given “Eymard et al [20-23] investigated the predictors of response to viscosupplementation in 166 patients with knee OA, prospectively followed in a non-inferiority randomized controlled trial (RCT) comparing 2 viscosupplements. They showed that radiological severity and obesity were independent factors of viscosupplementation failure [23]. In the same study the percentage of patients fulfilling the OMERACT-OARSI response criteria [24], 6 months after 3 weekly HA injections, was only 41.7% in patients with both marked joint space narrowing (JSN) and obesity, while it was 87.1% in those who did not have any of these two risk factors. In patients with only one risk factor (obesity or severe JSN) the percentage of OMERACT-OARSI responders was 58.3%.”

Q11- It's not clear why you are comparing 2 HA groups. Why not saline as a control?
A11- The design of non-inferiority RCT was required by the French Haute Autorité de Santé. In France, to be reimbursed, a new viscosupplément has to demonstrate its non-inferiority versus another viscosupplément that has been demonstrated to be superior to a placebo (i.e. saline injection). In this study the comparator was Euflexxa.

Methods

Q12- Page 5, lines 19-29: please break this sentence up
A12- Done
Q13-Line 34: spell out KOFUS first. Was knee or other surgery an exclusion?

A13- Done. Planned knee and other surgery during the FU period were exclusion criteria. It has been mentioned in the manuscript.

Q14-Line 48: concomitant treatments are mentioned here but are not listed or compared between groups.

A14- There was no significant between group difference regarding concomitant treatments.

Q15-Page 6 line 17 - what/when is "each follow up visit"? This/these should be explained. Were these performed in the lab? Online or hardcopy at home?

A15- New sentence: "The follow-up visits were performed at month 3 and 6 after treatment administration. The questionnaires were fulfilled by the patients themselves in the physicians office just before the clinical examination, on a paper CRF".

Q16- Page 7 - did you control for anything in your analysis? Baseline score need to be accounted for at a minimum. And is the primary variable(s) change in pain (and function)? What data were the logistic regressions used on? And ANCOVA? The stats section would benefit from a little more explanation. Did you consider instead running a prognostic analysis, with ORs for predictors like the Altman study mentioned later? That would seem to be a stronger statistical approach than what was used - I would strongly recommend reanalysing the data using these techniques.

A16- All these analyses have been published in our previous work (Eymard et al. Obesity and radiological severity are associated with viscosupplementation failure in patients with knee osteoarthritis. J Orthop Res. 2017. doi: 10.1002/jor.23529.)

Results

Q17- Consider including a demographic characteristic table. What were the demographics of each group (e.g. BMI in the obese and non-obese groups)?

A17- Table I summarizes demographic characteristics of patient sub-groups at baseline.

Q18- Please reference Table 1 in the opening results paragraph where you talk about the data from that table.
A18- Done.

Q18- Please calculate and report (adjusted) mean difference and 95% CIs for your groups for change over time.

A18- 95%CIs have been added given in Results section.

Q19- The more appropriate outcome would be this adjusted 6-month change in pain (and function) rather than simply the 6-month value. Then you could assess each group's change in pain relative to the minimal clinically important difference (MCID) values, as well as compare mean change between groups.

A19- As, at baseline, all pain and function values were the same whatever the patient sub-group, using the adjusted 6 month change does not change any result. We agree with the second comment and we added the percentage of patients who reached the MCID threshold, in each patient subgroup (Table IV).

Q20-You could then also remove Figures 1 and 2 which aren't very informative.

A20- Figures 1 and 2 have been removed.

Discussion

Q21-Page 9 line: "…in subjects who combined THESE two risk factors."

A21- Correction done

Q22-Line 29 remove "an"

A22- Correction done

Q23- Line 34 "in the HAV-study". Perhaps amend to say in our previous study (HAV-2012) and add the reference

A23- Change done

Q24- Line 41 maybe don't say the "FLEXX trial and the extension trial" and just say the Altman et al study (I think "Altman and al" should be Altman et al).

A24- Change done

Q25-Your results showed that it was less effective in those with OARSI grade 3, and you mention that this is consistent with the Altman trial, and your other findings, but you spend just as much space (or more) justifying that it should be used in people with more advanced radiographic knee OA. Firstly, some explanation of why it was more effective in those with less
advanced disease would be helpful (like in Altman's discussion). Same with non-obese later. Secondly, given your findings don't show less effect in people with more advanced disease, consider reducing some of the content justifying why it should still be used in these patients. I understand that advanced ROA shouldn't be a contraindication, but these findings show that it is less effective in these patients.

A25- We agree with this comment. Consequently we fully re-wrote this part of the discussion: "

Q26-Page 10 lines 1-12 - this is a very long sentence. Are you able to break it up at all?
A26- Change done

Q27- Lines 20-22 The findings don't really show a risk of failure in obese people, just less effective. Consider rewording this.
A27- Change done

Q28-Lines 36-39 "the confirmation that the combination of obesity to an advanced radiographic stage is highly predictive of treatment failure" change to "the combination of obesity and advanced radiographic stage…" And again, it was not a treatment failure, just less effective - they still had a 28.6% reduction in pain which is greater than the MCID, as is pointed out in the next sentence.
A28- New sentence: "The main lesson that can be drawn from our study is that the combination of obesity and advanced radiographic stage is a predictor of a poorer effectiveness of viscosupplementation. Our data showed that the decrease of pain was two-fold greater in non-obese patients with OARSI grade 1-2 than in obese patients with OARSI grade 3. In other words, the average decrease of WOMAC pain was -58.2% in non-obese patients with OARSI grade 1-2 whereas it was only -28.6% in obese patients with OARSI grade 3. However, the latter still had a relevant reduction in pain, which remains slightly greater than the MCII threshold.

Q29-Page 11, line 9 Change "Another interesting data to point out..." to "Also of interest, WOMAC function was...." Or something similar. Line 39 change "strictly identical" to "similar" or "the same"
A29- Changes done
Q30- Line 41—53 US guided injections have been found to be more accurate and lead to greater improvements in the knee than non-guided (Berkoff, Miller, & Block, 2012). These improvements with US guidance are likely to be even greater in obese patients given their greater amounts of adipose tissue around the injection site. Perhaps cite this, and remove the line that starts with "However, in daily clinical practice knee HA injections are usually achieved without imaging guidance".

A30- New sentence: "Ultra-sound (US) guided injections have been found to be more accurate and lead to greater improvements in the knee than non-guided [40]. These improvements with US guidance are likely to be even greater in obese patients given their greater amounts of adipose tissue around the injection site. Unfortunately, in daily clinical practice, knee HA injections are usually achieved without imaging guidance. The potential impact of obesity on the risk of poor response to non-guided IA HA injections should be well known by the practitioners and encourage them to use imaging guidance."

Q31-Another limitation is the lack of a true control group. This means this study cannot perform a moderation analysis required to identify patient subgroups (e.g. see Kraemer, Wilson, Fairburn, & Agras, 2002). There was also not a prognostic analysis as mentioned earlier. This would be preferable. Page 12 lines1-2 - as mentioned this type of analysis doesn't identify a treatment subgroup of responders (a moderator analysis is needed). I suggest changing this language here, and in the abstract. Line 5 I'm a little confused because in the discussion you argue that it should still be used in those with more advance ROA

A31- We agree with all these comments. New sentence :"Lastly, another limitation is the lack of a placebo group. This means this study cannot perform a moderation analysis required to identify with certainty patients on whom treatments work and do not work and why treatments work or do not work [41]."

Q32-References

A32- All these references were added


ANSWERS TO REVIEWER #2:

Q1- A number of grammatical errors and issues with sentence structure are noted throughout the manuscript. Use of commas where stops should be used (such as in Abstract, Lines 50-52) and missing punctuation also noted.

A1-We carefully read the manuscript again and correct spelling, syntax and punctuation.

Abstract

Q2-Given the nature of the analysis perhaps "exploratory" should be added to Line 11?

A2-The word "exploratory" was added line 1

Q3-Line 37 - while most readers will be familiar with the scoring of the WOMAC function scale it may be clearer to include worse as well as higher in describing these baseline values
A3- WOMAC function data have been removed from the abstract.

Introduction

Q4- The introduction would benefit from a stronger case for why this study is needed, why the results are important and how findings can be used.

A4- We agree " Nevertheless, despite its wide use in daily practice, the real efficacy of viscosupplementation remains debatable [15, 16]. There are variable recommendations given across clinical guidelines [17]. For example, an uncertain recommendation was given by OARSI due to inconsistent conclusions among meta-analyses and conflicting results regarding safety [1], while the UK National Institute for Health and Care Excellence recommended against its use [18]. Therefore, there is a real need to identify the appropriate patients who may successfully respond to viscosupplementation [19]."

Q5-Line 5 - "first line therapies" - such as?

A5- Added '(i.e. non pharmacological modalities, analgesics, NSAIDs)

Q6- Line 7 - add "a" - "though still a matter of controversy"

A6- The full sentence has been modified " Nevertheless, despite its wide use in daily practice, the real efficacy of viscosupplementation remains debatable [15, 16]. There are variable recommendations given across clinical guidelines [17]. For example, an uncertain recommendation was given by OARSI due to inconsistent conclusions among meta-analyses and conflicting results regarding safety [1], while the UK National Institute for Health and Care Excellence recommended against its use [18].

Q7-Lines 12-15 - it would be good to elaborate on this point "ranked it as the most effective treatment for knee OA" - for which outcomes?

A7- Change: "the most effective treatment to reduce knee OA pain"

Methods
Very clear and comprehensive!

Discussion

Q8- Would be good to clarify that the outcome is self-reported physical function (in first line)

A8- New sentence: Our study showed that the decrease of the patient self-reported pain over time and the pain score 6 months after viscosupplementation, were significantly altered according to the radiographic severity and the body mass index.

Q9- Line 26 - importance of the x-ray grade for what?

A9- New sentence "The major influence of the radiographic stage on viscosupplementation efficacy is well known and has been many times underlined [20-23]."

Q10- A stronger case could be made for how these results should be used clinically.

A10- New sentence "The main interest of this trial is to allow practitioners to inform obese patients with advanced knee OA that viscosupplementation is unlikely to be sufficiently effective and that other therapeutic options, especially surgery, should be considered primarily. With such an information, patients would be able to make a choice between HA injections and other therapeutic modalities."

Q11- Tables 1 and 2 - lacks labeling / Figures 1 and 2 are not clear to interpret - y-axis needs labelling

A- Figures 1 and 2 have been removed for request of #Reviewer 1.