Author's response to reviews

Title: Platelet-Rich Plasma vs Hyaluronic Acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial.

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Version: 2 Date: 26 October 2012

Author's response to reviews: see over
Reviewer's report
Title: Platelet-Rich Plasma vs Hyaluronic Acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial.
Version: 1 Date: 11 October 2012
Reviewer: Isabel Andia
Reviewer's report:
Major compulsory revision
The title does not reflect that this is a preliminary analysis
- The title specifically mentions “study design and preliminary results”, so that there are no doubts for the readers that these are preliminary findings.

The main outcome variable has not been identified; discussion and conclusions about OA severity and suitability of treatment are not adequately supported by the data.
- The main outcome variable has been identified, and it has also been used for the power analysis, as reported in the “materials and methods”: it is the IKDC subjective score at 12 months of follow-up. The OA severity has been assessed as inclusion criteria with imaging evaluation before starting the treatment, and this has been specified in the “materials and methods section”; and the trend observed according to OA severity has been suggested by the statistical analysis performed by a professional statistician hired for the study analysis. We are the first one to recognize and underline in the manuscript itself the limits of our analysis, so we agree we can not push conclusions beyond the actual findings. Therefore, we have been really cautious in our statements. However, we have to underline that these limits, and the value of the manuscript itself, have to be measured also against the current literature, and the reviewer itself is well aware of it, since she published also a paper on a similar application, studying 60 patients in a retrospective comparative study, almost half of the patients evaluated prospectively in this RCT. At this point of the literature our data still contribute to the scientific discussion and they still are among the most scientifically robust available, as the reviewer and all researchers in this field may recognize.

Minor essential revisions
1. Information about clinicaltrial.gov identifier is lacking
   - As correctly underlined this information is missing, and we added it in the proper section: NCT01670578.

2. Page 2, Abstract, please be explicit about “real potential of the procedure”, do you mean efficacy??
   - We actually think that potential is a wider concept than efficacy, since it comprehends also the different effect on different patients types, but in order to avoid confusion we changed this term and we wrote “efficacy”, as requested by the reviewer.
3. What is the main outcome variable? Primary and secondary outcome measures should be specified. It would be interesting to know changes of physical functioning and pain, and percentage of therapeutic responders to PRP or HA injections, and the comparison.
- The primary endpoint is IKDC subjective score improvement at the 12-month follow-up, and we specified it in the “materials and methods” section, all the other questionnaires are secondary outcome measures, and we performed the study comparison of all of them, but due to the huge amount of data in a limited space and the preliminary nature of our data we only reported what was significant. If it was not reported it was because it was not significant, as specified (however, in order not to make the text too long but to be as much informative as possible for the readers, as requested by the reviewer, we reported most of the data in a table).

4. Page 3, Background section: Please, explain “indiscriminate clinical application”; are you planning to identify responders? Attending to severity criteria?
- Yes, and this is exactly what we tried to do, analyzing the outcome in different subcategories and underlining a different trend for patients affected by different OA severity (documented by Kellgren). We wrote that through this study we would like to avoid to administer PRP to everybody (indiscriminate), because every treatment should consider advantages and disadvantages with respect to the other available treatments and be focused on the most responsive patient categories.

5. Page 4, third paragraph: PRP has rapidly evolved and there are now at least 4-5 different versions, as already described in the scientific literature. Thus it is no longer acceptable to present the clinical data without including what type of PRP was used. The authors do not describe the leukocyte content in their PRP, neither the type of PRP activator is described; these parameters clearly influence outcome. If their PRP does not contain leukocytes and/or is not activated before injection it should be explicitly reported. Please discuss limitations regarding PRP stability after freezing-thawing.
- We completely agree with the reviewer, it is important to document the characteristics of the PRP used: thus, we described our procedure in the “materials and methods” section and we also specified that we obtained a 5 times platelet concentration. Finally, we documented the presence of leukocytes, as requested. We also discussed the limitation in the “materials and methods” paragraph, as requested.

6. Page 3 and 6. This area of research is very active, clinical references in the introduction need to be updated. A multi-center level I clinical trial, should be included Sanchez et al. Arthroscopy 2012. The last paragraph in page 6 of the discussion should be changed.
- We agree, the reviewer should consider that this manuscript has been sent a few months ago, when the referred paper wasn’t published, yet. However, we now updated the literature and commented on the reference suggested.

7. Please discuss if changes in self-reported outcomes are clinically meaningful.
- Yes, we wrote: “The safety and the significant clinical improvement of this procedure were confirmed.” Of course this refers to the pre-post evaluation, as specified in the results section, whereas only a statistical tendency without clinical significant difference was found comparing the results of the two groups.”

8. Please explain better how do you establish “most appropriate clinical use”? (in page 6 last paragraph).
- We deleted this sentence to avoid any confusion, and we specified afterwards that we did not observe a significant difference in patients with more degenerated knees, so that readers can see that the main indications is for less compromised knees.

9. Discussion, page 7, first paragraph: the authors may discuss sample size before concluding about treatment efficacy in patients with early or advanced OA.

Again, I would suggest identifying % responders in both sub-groups Level of interest: An article of importance in its field Quality of written English: Needs some language corrections before being published.

- We agree, and we added this further limitation before commenting on the trend observed, as requested. For what regards responders, there are not responders vs not responders. Unfortunately the situation is more complicated, with patients having a wide range of reactions and some having a higher pain improvement, others a higher functional improvement etc… so we preferred to put mean and standard deviation instead.

- For what concerns the quality of written English, we made some improvements and we sent the article to our professional Language Consultant for appropriate English language editing.

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

- The analysis has been performed by a professional statistician.

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

Reviewer's report
Title: Platelet-Rich Plasma vs Hyaluronic Acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial.
Version: 1 Date: 18 October 2012
Reviewer: Jae-Do Kim
Reviewer's report:
This is a well written paper and interesting report on PRP vs Hyaluronic acid to treat osteoarthritis of knee. I feel the article has quite value however I have two questions.
1. In the section of Materials and Methods, there is the information about the interval of PRP injection which performed weekly. However, in your previous article, you suggested that PRP was injected at intervals of three weeks. Why did the interval of PRP injection change? Do you have any idea for changing the interval?

- This is true, we changed our injective protocol, but we can not say this was done because of scientific reasons. First of all, during the first period of our practice with PRP we were more cautious, and we preferred to have more time for observing eventually adverse events, which in the end we never found. Then there is also a more practical reason for starting to make a weekly injection cycle: in this way we could follow the HA injection cycle and have a double blinded RCT.

2. It states that “The unit of PRP was divided into 4 small units of 5ml each. One unit was sent to the laboratory for analysis of platelet concentration and for a quality test.” As I know, several growth factors such as IGF, PDGH, FGF is no less important than Platelet itself. In the Results section, the result related to platelet cell count is described. However, there is no information related to the count and any sort of growth factors. Do you have any results about this information?
We agree it would be important, but this was not part of routine quality test. However, due to the importance of this aspect, we are storing frozen samples for future evaluations (they are extremely expensive, thus requiring specific funding).

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report

Reviewer's report
Title: Platelet-Rich Plasma vs Hyaluronic Acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial.
Version: 1 Date: 19 October 2012
Reviewer: Michiel Mulier
Reviewer's report:
Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: a randomized controlled trial.
General considerations:
- Discussion: the most of the written text is about the evidence of the efficacy of PRP reported in other studies and not about the results reported in this study. This is because these preliminary results do not show any statistical evidence. In the end they only report the results of a case series of patients treated with PRP. They also do not refer to the second treatment of choice (HA) and do not refer to the evidence of the efficacy of HA as reported lately in two different meta-analysis (HA in the treatment of knee OA). Also in the introduction they do not mention this.
- We reported the available evidence of PRP use in the literature, and, as requested by the first reviewer, we also updated the description of the published studies. Beside the request of the first reviewer, we also think that this part is important, because it gives the measure to understand the importance of the available data. HA is a widely used treatment approach, and we didn't discuss it deeply since this would have required a lot of more space in the article for something that is largely known (oppositely to PRP) and that is not the focus of our paper. However, according to the request of the reviewer number 3, we also added a comment of this control group.

- The reference list is not accurate. The numbers stated in the text do not match with these in the reference list (see the last ones).
- References were updated and corrected.

- The conclusion of this study is surprisingly and I think incorrect. See discussion part.
- See comments in discussion part.

- It would be better to wait for the last 85 patients to be included before publishing these data. They do not have any hard evidence that one of the treatments had a better efficacy and they also are not able to say that these treatments are both equal in efficacy.
- This is true, but waiting all the patients to be treated and evaluated will mean that a complete study couldn’t be published before one and a half - two years, and the current literature is so full of poor studies that this data are still among the best evidences available. We agree they are not definitive and we didn’t try to hide this, on the opposite, we were the first one to underline it, starting from the title. But there is something that has to be considered and that convinced us not to wait 2 years for the publication of the complete study but to start sharing our findings with the scientific community as soon as
possible. We think that for different reasons (among these also a huge sponsor bias in this field!!!, and our data are sponsor free, since we use a laboratory made PRP that is applied for free to our patients), there is probably a too high enthusiasm and this treatment is applied widely without enough scientific evidence, and even more important without the clear understanding of what this “magic cocktail of growth factors” can really do… What our study already shows despite its preliminary nature is that there is no miracle behind, the improvement is limited! Thus, we feel that thanks to this data physicians could have a more balanced opinion with more realistic expectations when choosing to use PRP instead of other procedures, and also patients will have more correct expectations. Whereas the final results in 2 years will define more precisely the exact results obtainable, the findings of our current preliminary report have a different meaning: they increase the consciousness of the real expectations physicians and patients should have on this treatment, which is currently wrongly overestimated!

Material and methods:
- They included patients with imaging findings of degenerative changes of the joint. However, Kellgren and Lawrence grade 0 does not show degenerative signs at X-ray.
- Of course, Kellgren and Lawrence grade 0 does not show degenerative signs at X-ray, by definition. In this case the degenerative changes were documented by MRI and we specified it in the text, in the material and methods section, as suggested by the reviewer comments in order to be more precise on the patient assessment.

- How was the randomization process been performed. They do not mention this.
- Randomization was performed according to a list provided by an independent statistician: all patients underwent blood harvesting, and just before the injection cycle the physician was made aware of the treatment allocation by calling a dedicated office who was in possess of the envelopes with the treatment allocation. We clarified this in the text.

- The brand of HA is not clear. They do not mention this. Only the molecular weight is clear (1500 kDa).
- We added the brand name.

- I think the MCID of 6,7 is very low. In other studies using the VAS and Harris hip Score, minimal clinically important differences of more than 16 are calculated.
- This is partially true, for two reasons. First of all, it is for a different score. Furthermore, whereas also for IKDC subjective score 10 points are considered a safe measurement of an improvement, and both treatments documented this improvement with respect to the basal level, we felt that when comparing two treatments that both have an effect (above but close to 10 points) we couldn’t expect that, to understand if a treatment was better, 10 point difference would have been required, because in order to have this, one treatment shouldn’t have had any effect… We believe the one third of the documented mean improvement (6,7, from a pilot study) would have been a significant difference to make us decide for a treatment or another. Moreover, this numbers also required more patients to be evaluated in our power analysis with respect of other suggested differences, such as 10 or even 16, thus making the study more significant.

Maybe they could explain this a little bit better in the text.

Results:
- I think it is hard to report minor adverse effects when the first visit in the outpatient clinic is only after 2 months. You cannot rely on patients’ answers after this time. Why did they not include a diary?
The 2 months follow-up was not the only moment of adverse event collection, since we visited patients also during the second and third treatments where we could detect adverse events of the first or second injections, respectively. Moreover, patients were advised to contact us for every event, major or minor, and patients were also contacted by us between the last injection and the 2 month follow-up for organizing the visit, and this was a further opportunity to talk with the patient and assess every possible event happening after the third injection.

- How can they prove that the minor adverse effects do not compromise the overall outcome?
- We did not see any correlation from statistical analysis, but for sure we will keep analyzing this aspect in our patients to see if with a higher patients number we will be able to observe any influence.

- It is not common to write about trends and tendency in the results part of the article. Even in the discussion it is a little bit strange. You do have evidence of the efficacy of a treatment or you do not.
- Agree it is not common, and in fact this is not the mean take home message of the article, as underlined in the text. But since there is currently a lack of data, we believe it is important to give suggestions (even if based on a tendency) to limit the use of PRP to the categories of patients who at least seem to be more responsive… otherwise for the 2 years required to publish the final study physicians all around the world will believe that they can treat everybody and everything with this “miraculous cure”.

- In the literature (I think) there are no reports of intolerance to components of HA. Only complaints about pain due to the injection of HA are reported. These complaints disappear normally within a week and are most of the times due to extra-articular injection of HA. This is another problem of this study: there is no evidence that the injected PRP or HA was in all cases intra-articular. I think in a study setting it is important to be sure that the injected products are intra-articular.
- Agree. But this does not affect our study, since both procedures have been performed in the same way and thus the comparison is still valid. Moreover, patients also presented intra-articular swelling, thus suggesting that the injection was performed correctly but caused intra-articular problems.

Discussion:
- See general considerations.

- They write that in the study of Gobbi there is an increase of the KOOS, IKDC and Tegner: these are all good results. However they also write that the VAS for pain increased: this means that the results are worse considering pain. I think they made a mistake.
- We changed the text to make it clearer.

- They performed a RCT however in the discussion they report the efficacy as if there was performed a cohort series (PRP only).
- The results section starts with “when comparing the two treatments…” and then results have been reported both for PRP and HA, in the text as well as in the table.

- They conclude writing that there is no difference in efficacy in the treatment with HA and PRP, but surprisingly they suddenly they advise that the application of PRP should be
limited to patients with earlier degrees of knee OA. It is clear that the efficacy of PRP is better in this group than in the more severe affected group, but still there is no statistical and clinical difference between the two treatment groups. They also write in the introduction that PRP is much cheaper than HA (PRP is a low-cost treatment) as a treatment. Why do they not mention this in the discussion?
- Our point is that, since there is no clear difference between the two treatments, if physician would like to apply this biological approach they should at least try to limit their use (until stringer evidence will be available) to patients who seems more responsive., that is way we make this cautious suggestion.
For what regards the low-cost, this is a general statement in the introduction to underline that is a cheap way to obtain growth factors, we did not write it is cheaper than HA. Lastly, we didn’t comment on prices because the range with the currently available treatments is huge, thus making not possible to make general conclusions, and also we can not quantify the cost of our laboratory made procedure since it has always made just for research and never sold.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests