

Response to the Reviewer's Comments

Reviewer #1

We appreciate your comments. Based on your comments, our manuscript is improved the scientific quality and enriched. We can reinforce the manuscript by adding more data and references. Thank you for using your precious time for us.

Below is the response to your comments.

Specific Comments to Authors:

Authors presented case study of three patients suffering from Alopecia. The study is important as cell based treatment of Alopecia needs to be optimized. The presentation of the study however has major concerns:

Response

- I agree to your opinion. The regenerative medicine requires more studies for optimization.
- We will sincerely respond to your concerns.

1. The background is very weak. It does not have enough literature to highlight gaps and build study objectives.

Response

- The background has been reinforced and references have been added.
2. Literature is not very recent. It should include latest studies. Also, more studies should be included to strengthen the manuscript.

Response

- Studies including results within the last 3 years have been added.

3. It is a case study, so it should mention if there is any clinical trial performed anywhere in the world. Some recent relevant pre-clinical studies can be included.

Response

- Unfortunately, we could not find clinical trials for the treatment of alopecia using only mesenchymal stem cells in *clinicaltrials.gov*. However, we found some case studies of alopecia treatment using mesenchymal stem cells. So, we added those case studies. Also, we added some *in vitro* and *in vivo* tests for alopecia treatment using mesenchymal stem cells. Those results were also added.
4. Limitation of the study is not mentioned. There is no data for safety of the treatment. Some toxicology studies if performed earlier should be included. Clinical manifestations / lab tests etc of the three patients or any signs of adverse reactions should be included.

Response

- In the discussion and conclusion section, the limitations of this study were mentioned while providing directions for further study.
 - The safety of the MM-UC-MSCs (minimally manipulated umbilical cord derived-mesenchymal stem cells) was assessed by testing the donated umbilical cord and contamination of the isolated MM-UC-MSCs.
 - We have added the previous research results on the safety of using the MSCs and MM-MSCs for clinical purposes.
 - We have added reports of patients about side effects during the treatment and follow-up period.
5. Detailed methods for preparation of reagents etc should be included esp the source of reagent as they should be of clinical grade. What measures were adopted to ensure the purity and quality of stem cells as they were to be used for transplantation. Some details or explanations are required for some terminologies e.g. minimally manipulated MSCs. How it is different from cultured MSCs. Are these MSCs of passage 1? These details should be provided.

ded.

Respond

- MM-UC-MSCs and injection solution were prepared and produced by ourselves, so we did not mention this. However, detailed methods for preparation and production were included in the manuscript.
 - We have included results for MSCs quality and purity.
 - We have added a definition for MM-UC-MSCs and the comparison results for minimally manipulated MSCs and cultured MSCs were also added.
6. Why only women were chosen for case study; alopecia is more common in men. Why the time points of the injections are different even within the same treatment group (sometimes weekly, sometime after 15 days). And on what basis the duration of the treatment and number of injections were decided; six months, one month, 12 months.

Respond

- It is true that androgenetic alopecia is common in men. However, we want to report the results of treatment for alopecia areata, one of the autoimmune diseases. Among our patients, patients of alopecia areata and related diseases were only women.
- We wanted to control the treatment conditions, but we did a somewhat flexible treatment depending on the patient's circumstances. The basic rule is to treat once per lesion site a week and the amount of transplantation depended on the size of the lesion area, but usually, 1ml of injection solution was used.
Patient 1 received treatment once a week or once every two weeks depending on her circumstances. Patient 2 showed treatment effects earlier than expected, so the treatment interval was changed to one month. Patient 3 was a patient from overseas, so she was treated every 2-4 weeks. For these reasons, there were variations in the number of treatments and intervals.
- Since our first purpose is to treat the patient, the duration and number of injections depended on the patient's condition.

7. It should be discussed as what could be the reason behind different time periods when the hair started to grow. Moreover, the hair growth should be quantified or at least graded as minimum, maximum and in between etc.

Respond

- The reason why the time when the hair started to grow is different is written in the discussion section. Although Patient 2 was different, Patient 1 and 3 had similar trends.
- Since there was no data about measurement at that time, we requested a visit from the patient 1 and 2 during the revision period to measure the hair density at the lesion site at that time. However, since the patient 3 lives abroad, the visit was not possible, so we could not measure it.

8. There are many grammar errors and typographical mistakes. Language editing is required.

Respond

- We revised the manuscript at the proofreading company you recommended.

Reviewer #2

We appreciate your comments. Your decision gave us great confidence and we was able to revise the manuscript with confidence. Thank you for using your precious time for us.

Specific Comments to Authors:

The manuscript is a summary of 3 case reports, well presented.

Respond

We appreciate your decision.