

Peer-review report from both reviewers & answers

Reviewer #1: The review of Lam et al. entitled "Mesenchymal stem cell therapy for pneumonia patients", describes the therapeutic potential of MSC and extracellular vesicles derived from them, to treat respiratory pathologies, mainly COVID-19 disease caused by SARS-CoV-2 virus. The authors highlight 6 main properties of MSCs, which make them possible candidates for the treatment of lung diseases. They also describe the possibility of applying cell-free therapy based on the use of MSC-derived extracellular vesicles. In addition, the article describes the results of two recent clinical trials on the use of MSC in the treatment of COVID-19. Currently, due to the global impact of COVID-19, there are numerous publications and reviews on possible therapies for the treatment of this disease. Specifically, on the possible use of MSC and MSC-derived extracellular vesicles, several reviews on this subject have been published since the beginning of this year, as can be seen if we introduce the terms "mesenchymal stem cells" and "COVID-19" in Pubmed. However, due to the rapid progress in the knowledge of this pathology and the effort to achieve effective therapies for its treatment that is being carried out, this new review is interesting. The article is easy to read and has the positive aspect that it treats MSCs and their extra-cellular vesicles as possible therapeutic tools for the treatment of lung diseases. However, the authors should update the data they show and cite the dates when they have obtained them. This is due to the speed with which the pandemic and clinical research on COVID-19 is progressing. For example, in the introduction they indicate that COVID-19 affects more than 12,000,000 cases and 570,000 deaths worldwide. But, currently, the data according to the WHO are more than 35,000,000 cases and 1,000,000 deaths worldwide. Also, the table shown should be updated with the current data available in clinicaltrials.gov for "mesenchymal stem cells", "COVID-19" and exosomes. (<https://clinicaltrials.gov/ct2/results?cond=&term=mesechymal+stem+cells%2C+COVID-19%2C+exosomes&cntry=&state=&city=&dist=> under <https://clinicaltrials.gov/>) **(COMPLETED)**

Reviewer #2: This is an interesting review about mesenchymal stem cell for pneumonia therapy. I suggest accepting it. However, the following issues should be addressed.

1. The author should also search all data from WHO ICTRP to find all potential register trials in this field, and summary them in table. **(COMPLETED)**

1. Please also give the ID of these trials. **(COMPLETED)**

2. The review title is: Mesenchymal stem cell therapy for pneumonia patients. However, the author gives too many words about COVID-19. **(COMPLETED)** In fact, the pathogenesis of the disease should also be added. **(COMPLETED, elaborated)** The potential mechanism of stem cell should be written more. **(COMPLETED, elaborated)** I suggest the author change the title, add COVID-19 in the title **(COMPLETED, retaining as severe pneumonia and stating the causal relationships)**.

3. I note the author address is from Help Therapeutics Co. Ltd. The author did not declare the potential conflict of interest. This is most important for the current study. **(COMPLETED, grant information provided)**

4. The potential harm of the current therapy should be added. **(COMPLETED)**

5. There is still no phase 4 clinical trial, so the conclusion should be more careful. 6. Challenges and ethics should also be mentioned more. **(COMPLETED)**

I suggest the following reference:

Ma X, Wang Y, Gao T, He Q, He Y, Yue R, You F, Tang J. Challenges and strategies to research ethics in conducting COVID-19 research. *J Evid Based Med.* 2020 May;13(2):173-177. doi: 10.1111/jebm.12388. Epub 2020 May 22. PMID: 32445288; PMCID: PMC7280675. **(COMPLETED, CITED)**

7. The economic should also be mentioned for the therapy. I suggest the author read the following references: Clarke L. An introduction to economic studies, health emergencies, and COVID-19. *J Evid Based Med.* 2020 May;13(2):161-167. doi: 10.1111/jebm.12395. PMID: 32470229; PMCID: PMC7283784. Mhashilkar A, Atala A. Editorial: effective bio-economic approaches for stem cell therapy and regenerative medicine. *Curr Stem Cell Res Ther.* 2012 Jan;7(1):1. doi: 10.2174/157488812798483430. PMID: 22417633. **(COMPLETED, CITED)**

Answer for Re-Review

Thank you for pointing out a necessary update. The latest updated version has been uploaded to the interface [HERE](#) (with the statistics updated to beginning of December 2020, in a timespan of 1 year). Thank you!