



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 57939

Title: Mesenchymal Stem Cells as Living Anti-inflammatory Therapy for COVID-19
Related Acute Respiratory Distress Syndrome

Reviewer's code: 05420105

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: United States

Manuscript submission date: 2020-07-06

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-07-07 18:34

Reviewer performed review: 2020-07-10 17:54

Review time: 2 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The present review tries to discuss the potential of mesenchymal stem cells (MSC) therapy for treating COVID-19-related ARDS-like manifestations. The authors discuss some aspects of COVID-19 pathophysiology, immunomodulatory mechanisms of MSC, and some clinical trials of cell-based therapy that are ongoing. There are several recent reviews already addressing these issues and that were not cited by the authors, both on broader aspects related to COVID-19 and on more specific to ARDS-like manifestations in the disease (e.g. doi: 10.1007/s12015-020-09999-0; doi: 10.1007/s12015-020-09973-w; doi: 10.1007/s13238-020-00738-2; doi: 10.1183/13993003.00858-2020). The present manuscript was focused on detailed immune mechanisms related to MSC actions and its applicability for reducing COVID-19 complications (e.g. cytokine storm and ARDS-like manifestations). However, the authors need to make clear what the presented novelty compared to the recently published reviews. In order to make the text more appropriate, major changes need to be made. General points: a. The language is good, but the punctuation in all text needs to be carefully reviewed. There are some phrases that do not make sense due to the punctuation, or because they have not a proper continuousness of ideas. b. Some excerpts and sentences are far too long, which makes understanding difficult. c. It is more suitable to initiate a paragraph with no abbreviation of words, using the entire term. (e.g. Introduction, line 1) d. It is not necessary to enclose abbreviations in quotation marks. (e.g. Introduction: line 3; Mesenchymal stem cell (MSC) immunomodulatory effects: line 4). e. There should be standardization of the 'MSC' term. In the abstract, it appears writing in plural with MSC abbreviation, however, in the keywords section, it appears MSCs. Structural and content points: a. In the "Abstract" section, it was cited COVID-19 symptoms such as neurological manifestations, and then they not appear in any part of the text, even nor within the topic about its



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pathology. b. In the “Introduction” section was used the term “water leakage”. Is it an appropriate term in the proposed context? c. In the topic “COVID-19 and its pathology”, a logical sequence of the content is not clear. The first paragraph of this topic would be more appropriate in the introduction section, for instance. Also, there is a lack of information about the COVID-19 general pathology, so it must be clearer than the pathology will be addressed under pulmonary aspects only. d. In the first paragraph of the topic “Recent success of MSCs for COVID-19 Patients and clinical trials” was pointed out that pharmacotherapy with chloroquine/hydroxychloroquine has promising effects on patients with COVID-19. However, the cited NIH guidelines make clear a position against the use of these drugs and point out that studies showing an improvement in patients who underwent this treatment still do not present substantial data, in addition to using a small sample size. Therefore, it would be appropriate to address these issues when discussing such treatments. Moreover, it is important to highlight the side effects of these treatments. e. In table 2 were included 25 registered clinical trials using MSC for treating of COVID-19 patients. However, there are at least 45 registered clinical trials in the clinicaltrials.gov platform, so the table should be updated. f. In the “Conclusion” section was addressed some limitations about the implementation of MSC-based therapy such as dose, delivery times, type of MSCs, efficacy, and cost-effectiveness. It would be interesting whether such limitations were better discussed throughout the text or even in the conclusion.



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Title: Mesenchymal Stem Cells as Living Anti-inflammatory Therapy for COVID-19
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Reviewer's code: 02446098

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

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Reviewer chosen by: AI Technique

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The manuscript by Feng Lin focuses on the therapeutic potential of mesenchymal stem cells for COVID-19 treatment as a living anti-inflammatory. It highlights the pathogenicity of COVID-19 and the general immunomodulatory effects of MSC and its role for cytokine storm. It also summarized the registered clinical trials of MSCs treating COVID-19 patients. The overall quality of the manuscript needs to be revised. The suggestions are as follows: Question 1: In the abstract, the author does not provide any information about the therapeutic potential of MSCs for SARS-CoV-2 or related infections. The author should add some sentences about the therapeutic potential of MSCs for SARS-CoV-2. Question 2: In the introduction, the most important point in the introduction is "Small studies have shown that MSCs can be effective in COVID-19 ARDS..." but there no references in the text. The author should add references to this information. Question 3: the introduction has only one sentence about the potential efficacy for COVID-19 and not introduce the other therapeutic strategies of COVID-19 to justify why MSCs show promise for treating COVID-19. Hence, it is suggesting to briefly introduce the different therapeutic strategies for COVID-19 and highlight the most potential point of MSCs therapy. Question 4: In the Pathology, the paragraph "Barton et al. reported two COVID-19 autopsies...", mentions SARS-CoV-2 spike protein. To be more readable and understandable, this paragraph needs more explanation of the role of SARS-CoV-2 spike protein in the pathogenicity of SARS-CoV-2. Question 5: I suggest to add the list of the most treatment options in the paragraph "Currently, drugs alone or in combination with...." the link is not working. Question 6: The subtitle "Recent success of MSCs for COVID-19 Patients" needs extensively review and cite the related works in this section. Question 7: in the figure 1 legend should include a summary of the immunomodulatory effects of MSCs on immune cells. Question 8: The



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figure has not mentioned any potential mechanism of MSCs for SARS-CoV-2. Hence, the author may refer to the possible mechanism MSCs in SARS-CoV-2 infection. Question 9: To be more understandable, it is suggested to add the specific factors regulation, whether it is up-regulated or down-regulated, etc. Question 10: The author may need to add the most related studies in table 2.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2020-07-06

Reviewer chosen by: Jia-Ping Yan

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Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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I don't have further comments.



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Position: Peer Reviewer

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Reviewer's Country/Territory: Brazil

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I have no further additional comments.