

Statins as early therapy to mitigate COVID-19 (SARS-CoV-2)- associated ARDS and cytokine storm syndrome – time is of the essence

Narci Teoh, Geoff Farrell

Corresponding author

Narci Teoh

*Medicine and Surgery Program, Gastroenterology and Hepatology Unit, The Australian
National University Medical School, The Australian National University, Acton, Canberra,
Australia*

Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

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1st editorial decision

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Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are
appended below. Based on their comments and evaluation by the editorial board, your work
was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-
by-point response to every comment. An exemplary rebuttal letter can be found on at
<http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use
the track changes function in the original document so that the reviewers can easily verify
your responses.

Your revision is due by May 16, 2020.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I think this is a well written and well-reasoned hypothesis paper. I do not have any additional comments and support a rapid publication.

Reviewer #2: Dear Dr. Teoh and Dr. Farrell,

Thank you for submitting this timely hypothesis paper to our journal.

I would like you to incorporate text pertaining to the effect of statins on CRP reduction, ferritin level amelioration, and decrease in WCC. Highlighting this link through previously published empirical evidence would make your hypothesis paper more compelling.

Also, I have edited the text in your manuscript, which I have attached to the reviewer report. Please use this document when preparing your revision.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Author's rebuttal

Re: Revision JCTRes-D-20-00020, 'Medical Hypothesis' for submission

Statins as early therapy to mitigate COVID-19 (SARS-CoV-2)-associated ARDS and cytokine storm syndrome – time is of the essence

Dear Professor Heger,

We are grateful to you and your team for the very prompt review of our manuscript entitled **"Statins as early therapy to mitigate COVID-19 (SARS-CoV-2)-associated ARDS and cytokine storm syndrome – time is of the essence"**. Thank you for giving us an opportunity to submit a revised version, **JCTRes-D-20-00020-R1**.

We have addressed all the comments of reviewer 2 using the track changes function in Word (document end labelled with 'track', not for publication). A clean copy of the revision is also enclosed (end labelled 'clean').

Each response to the reviewers' comments is detailed, per comment in *blue italics*. The comments and suggestions have been most helpful and has considerably improved the impact of the paper.

We hope you find the revised article now befitting the high standards of JCTR for publication.

We are,
Your sincerely,
Narci Teoh and Geoff Farrell,
The Australian National University, Canberra, Australia

Reviewers' Comments:

Reviewer #1:

I think this is a well written and well-reasoned hypothesis paper. I do not have any additional comments and support a rapid publication.

Response: The authors gratefully acknowledge the favourable comments and are pleased the logic and reasoning of the article have resonated with Reviewer #1. Thank you for supporting a rapid publication of this manuscript.

Reviewer #2:

I would like you to incorporate text pertaining to the effect of statins on CRP reduction, ferritin level amelioration, and decrease in WCC. Highlighting this link through previously published empirical evidence would make your hypothesis paper more compelling.

Response: We thank Reviewer #2 for their insightful suggestions.

The reviewer makes a salient point of including evidence of statins effectively reducing measurable inflammatory markers eg. CRP reduction, ferritin amelioration, particularly in patients.

The HARP-2 investigators did not specifically determine plasma ferritin in studying the effect of statins in ARDS however, did measure IL-6, soluble TNF-R-1. In the sub-analysis (reference 12), the HARP-2 team observed significantly higher pre-treatment plasma IL-6 and soluble TNF-R-1 in patients with the hyper-inflammatory sub-phenotype of ARDS (references 12, 13). These features are now included in the revised version (pg 2, line 12, underlined). While the HARP-2 investigators did not explicitly comment on the reduction of these markers, nor of CRP and white cell counts in their sub-analysis, they noted significant improvement in 28- and 90-day survival in statin-treated patients vs. placebo.

Notably, statins utilised in other clinical contexts such as acute coronary syndromes and stroke, have been effective in reducing serum CRP, systemic IL-1, IL-6 and TNF- α release. We have included evidence pertaining to these relevant pathophysiological vascular events in the revised manuscript (pg 2, lines 16 – 18, underlined) and appended two additional appropriate references (references 15, 16).

The revised paragraph now reads as follows:

“The utility of statins against ARDS is not new - it was tested in a prospective, randomised, doubleblind, placebo-controlled trial dubbed HARP-2.11 In patients with the hyper-inflammatory subphenotype of ARDS (high IL-6, soluble TNF-R-1), simvastatin (80 mg/day) administered enterally within 48 hours of lung injury, improved 28- and 90-day survival vs. placebo.^{12,13} Of note, simvastatin is not the most potent of statins and may not be well absorbed from the gastrointestinal tract of critically ill patients. Statins administered intravenously during coronary ischemia are more effective at decreasing infarct size than oral administration.¹⁴ Utilised in other relevant pathophysiological vascular events such as acute coronary syndromes and stroke, statins have been shown to reduce serum CRP, systemic IL-1, IL-6 and TNF- α release.^{15,16}”

Also, I have edited the text in your manuscript, which I have attached to the reviewer report. Please use this document when preparing your revision.

Thank you for your time and care in editing the text in our manuscript – again, this is exceptional attention and the authors wish to express their gratitude. The edited document was used in preparing the revision.

2nd editorial decision

17-Apr-2020

Ref.: Ms. No. JCTRes-D-20-00020R1

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: