Journal of Clinical and Translational Research
Peer review process file 07.202101.004

Interleukin-13 as a target to alleviate severe coronavirus disease 2019 and restore lung homeostasis

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1st Editorial decision
22-Nov-2020

Ref.: Ms. No. JCTRes-D-20-00122
IL-13 as a target to alleviate severe COVID-19 and restore lung homeostasis
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 Dec 22, 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: Very nice "medical hypothesis" put forward that centers around the role of ILC2/IL-13 in COVID-19.
Very well crafted and put together - I only have a few suggestions that could be added to make the topic stronger/broader.

--> include recent studies that link IL-33 to the severity of COVID-19
--> discuss other ILC2/type 2 immune mediators (IL-33, IL-5, IL-9, TSLP) and link it to potential anti-cytokine antibody treatments.
After these small changes I recommend publication.

Reviewer #3: The manuscript " IL-13 as a target to alleviate severe COVID-19 and restore lung homeostasis" by Lachlan Paul Deimel et al. explores recent findings indicating that IL-13 production is proportional to COVID-19 severity and proposes that excessive IL-13 contributes to the progression of severe COVID-19 and suggests that IL-13 inhibiting dugs can be used to alleviate SARS-CoV-2-associated pathology.
Overall, the manuscript is well written, and the authors provided sufficient treatment of previous literature and the hypothesis drawn is well supported by data.
Minor comments:
Reference 31 is from Preprint server. Data from preprint servers are not peer reviewed yet. Is this accepted by the journal (Data from this reference are fundamental for this medical hypothesis).

Authors' response

27th November 2020

Dear Professor Heger,
Re: Revision of JCTRes-D-20-00122

Thank you for considering our manuscript entitled "**IL-13 at the lung mucosae may govern COVID-19 pathogenesis and severity"** for publication in Journal of Clinical Translational Research. We thank the reviewers for their valuable comments and constructive feedback. We have addressed all the comments (please see below) and modified the manuscript accordingly. We have indicated all the modifications in yellow highlight and have uploaded both a clean copy and a highlighted version of the manuscript.

Kind regards,

Lachlan Deimel

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REVIEWER COMMENTS

Reviewer 1:

1. ***Question*:** Include recent studies that link IL-33 to the severity of COVID-19.

Answer: We agree that IL-33 is a crucial upstream mediator of IL-13. We have now included a sentence to reflect the recent findings exploring the role of IL-33 in COVID-19 patients. Please refer to lines 91–92. Also see answer to question 2 below.

2. ***Question*:** Discuss other ILC2/type 2 immune mediators (IL-33, IL-5, IL-9, TSLP) and link it to potential anti-cytokine antibody treatments.

***Answer*:** The reviewer raises a very valid point and we have now included a paragraph to reflect the importance of IL-33, IL-25 and TSLP in the context of ILC2 and IL-13. Please refer to lines 91–103. However, to avoid confusion we did not include IL-5 and IL-9, as these do not impact direct effects of IL-13, such as smooth muscle contraction and fibrogenesis.

Reviewer 2:

1. ***Question*:** The reviewer appreciates ILC2 derived IL-13, however, Th2 cells are also an important source and should not be neglected. Please consider revising.

***Answer*:** We have now included a sentence to reflect IL-13 production by Th2 cells and impact on viral load and adaptive immune outcomes in lines 52–54.

2. ***Question*:** Correlation of viral load and IL-13 levels (but also other cytokines) **have been described** which would be interesting to include in the discussion (https://doi.org/10.1007/s11427-020-1643-8).

Answer: Unfortunately, in the article referred by the reviewer, we have been unable to find a correlation between viral load and IL-13 (or related biomarkers) in the context of COVID-19. However, we have included several references in line 72 and also a new paragraph on other cytokines (IL-33, IL-25 and TSLP) and their relevance in lines 91–103.

3. ***Question*:** It would be informative for the reader to discuss in more details what would be the signaling and cell targets of anti-IL-13 therapy, what could be advantages and disadvantages and at which stage of disease it may/must be applied.

***Answer*:** We agree with the reviewer. To that end, we have now incorporated a sentence for clarity. Please see lines 120–122.

Reviewer 3:

***1. Question*:** Reference 31 is from Preprint server. Data from preprint servers are not peer reviewed yet. Is this accepted by the journal (Data from this reference are fundamental for this medical hypothesis).

***Answer*:** We also recognize that the paper by Donlan et al. is currently in pre-print. Importantly, we have utilized other sources that substantiate these findings: Specifically, Huagn et al 2020 showing elevated IL-13 in COVID-19 patients (ref 23) and also others that show explicit link between viral infection, IL-13 and respiratory distress status (Zizzo & Cohen (2020), ref 48).

2nd Editorial decision

Journal of Clinical and Translational Research
Peer review process file 07.202101.004

27-Nov-2020

Ref.: Ms. No. JCTRes-D-20-00122R1
IL-13 as a target to alleviate severe COVID-19 and restore lung homeostasis
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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: