

Can tetracyclines ensure help in multiple sclerosis immunotherapy?

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1st Editorial decision
31-Mar-2020

Dear authors,

Your submission entitled "Can tetracyclines ensure help in Multiple Sclerosis immunotherapy?" has been reviewed by the Editorial Board. Although the editors see merit in your work, the manuscript is being returned to you for the following reason(s):

- [X] The English language needs to be polished considerably.
- [] The manuscript length is not proportional to the amount of presented data.
- [] The conclusions of the manuscript are not supported by the data.
- [] Improper statistical analyses are performed.

See my additional comments at the bottom of this email.

Please address the above issue(s) prior to resubmitting your work and contact the Editorial Office at info@jctres.com if you have any questions regarding your submission.

Kindest regards,

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

2nd Editorial decision
14-May-2020

Ref.: Ms. No. JCTRes-D-20-00018R1
Can tetracyclines ensure help in Multiple Sclerosis immunotherapy?
Journal of Clinical and Translational Research

Dear Dr. Rapôso,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below. Please note that the editorial office would like you to address the following items:

- 1) Please polish the language to meet standards of the journal;
- 2) Please provide novel information to a maximum extent so as to have it qualify as "timely."

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jun 13, 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: The manuscript is a review on the concept of using tetracyclines for the treatment of multiple sclerosis. The manuscript while interesting is in need of major modifications so as to enhance its supportive content and presentation of relevant material.

Major comments:

1. In the initial section the authors may wish to expand on the strengths and weaknesses of available drugs and cost as a burden to its users.
2. The introductory paragraph could be better written and presented and outline the sections to be covered. Also, the use of the term multifunction antibiotics is not best. Maybe pleiotropic antibiotics. Also, for example when you denote their clinical use you need to outline those approved by agencies such as the FDA and then possible "other" uses that are common in the clinical setting (not experimental).

3. An additional table may be considered where the authors list pre-clinical studies that provide evidence (positive or negative) for their broader efficacy on a range of diseases.
4. Sentences such as "has shown many actions in some pathways, among which" are too broad and need to be better written and defined. Same for the sentence "properties that are very helpful for different approaches".
5. The review needs to address most importantly long-term use, dosing schemes, formulations, and also the status for their use in children which has expanded as per FDA approvals. An emphasis for the use of Dox in malaria would be worthwhile.
6. Various sections need a review for the proper writing in English.
7. Pertaining to the section on MMPs the authors may wish to include additional pre-clinical and clinical studies (with greater detail) where MMP activity occurs in excess and where tetracyclines have demonstrated positive effects. For example, gingivitis is the most well documented application where excess MMP activity occurs (leading to gingiva destruction) and where this class of drugs is approved and this is not mentioned.
8. The section on inflammation needs to be divided into a) reactive oxygen species scavenging action, 2) suppression of cytokines and, 3) modulation of inflammatory cells (dendritic cell section to be included here). Also, relevant pre-clinical and clinical examples should be included for example sepsis and ARDS, dengue fever etc.
9. Figure 2 should be improved to have visual elements be better presented and also in the labeling as it is difficult to denote.
10. The clinical trials section may wish to be categorized for diseases such as cardiovascular, neurological, etc. this section should be the last before the conclusions.

Reviewer #2: The purpose of this review is unclear. As described on page 4 by the authors, the first-line drugs are IFN-beta and glatiramer acetate, followed by the second-line agents including fingolimod and natalizumab. It was also reported that rituximab, an anti-CD20 mAb, was effective in reducing clinical relapses and gadolinium-enhancing brain lesions. Without describing the relationship between these drugs and tetracycline, this review article provides little information to readers. Do the authors believe that the combination therapy with the first- or second-line drugs and tetracycline shows more beneficial effects? If so, it should be precisely described and discussed.

Description regarding pharmacokinetic and MMP inhibition effects (Chapters 2.1, 2.3 and 2.6) of tetracycline should be trimmed because these descriptions are not so important in this review.

In the clinical trial section, statements that are unrelated to MS and EAE should be deleted. MS clinical trials (Refs. 106, 108 and 110 etc.) should be introduced in more detail. In line with this, a large part of Table 1 should be deleted.

Remember the title of this article. "Can tetracycline ensure help in multiple sclerosis immunotherapy?" The reviewer wants to know whether tetracycline administration really helps treatment of MS patients. The present manuscript does not answer this question.

The authors must delete a large part of tetracycline introduction and add descriptions regarding the relationship between presently used drugs and tetracycline.

Too many references.

Reviewer #3: This paper review recent data involving the tetracyclines Minocycline and Doxycycline and their therapeutic potential in MS, the paper is well written and informations correctly discribed. I do not have more comments and for me the review can be published in the present form.

Reviewer #4: The authors review the pleiotropic properties of tetracyclines and their potential as therapies in Multiple Sclerosis.

1. The first sections could be more focused on MS, as opposed to the multitude of immune-modulating effects of tetracyclines.
 2. The clinical trial section is quite limited, as there is not much new information in this respect in the field.
 3. The manuscript should be revised for typos and language.
 4. Figures and tables are well crafted.
 5. There is perhaps too much emphasis on pharmacokinetic considerations.
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Authors' response

Can tetracyclines ensure help in Multiple Sclerosis immunotherapy?

Responses to reviewers

We thank all the reviewers for their suggestions. This helped us improve the manuscript. All comments are replied point by point below.

Reviewers' comments:

Reviewer #1: The manuscript is a review on the concept of using tetracyclines for the treatment of multiple sclerosis. The manuscript while interesting is in need of major modifications so as to enhance its supportive content and presentation of relevant material.

Major comments:

1. In the initial section the authors may wish to expand on the strengths and weaknesses of available drugs and cost as a burden to its users.

R: At the end of the section these questions about the regular treatment have been included. It can be viewed on page 5.

2. The introductory paragraph could be better written and presented and outline the sections to be covered. Also, the use of the term multifunction antibiotics is not best. Maybe pleiotropic antibiotics. Also, for example when you denote their clinical use you need to outline those approved by agencies such as the FDA and then possible "other" uses that are common in the clinical setting (not experimental).

R: We tried to organize better the central ideas with the recommendations in an introductory paragraph on page 3. The name of the tetracyclines paragraph was replaced as advised.

3. An additional table may be considered where the authors list pre-clinical studies that provide evidence (positive or negative) for their broader efficacy on a range of diseases.

R: An additional table summarizing the experimental studies was added to the study leaving the older table for clinical trials only. It can be viewed on pages 16 and 19.

4. Sentences such as "has shown many actions in some pathways, among which" are too broad and need to be better written and defined. Same for the sentence "properties that are very helpful for different approaches".

R: Sentences like that were removed and re-written.

5. The review needs to address most importantly long-term use, dosing schemes, formulations, and also the status for their use in children which has expanded as per FDA approvals. An emphasis for the use of Dox in malaria would be worthwhile.

R: We prefer to focus on the autoimmune area to restrict the review field, although your mention of malaria is completely welcome to further analysis.

6. Various sections need a review for the proper writing in English.

R: We apologize for this misunderstanding, another minacious review in text grammar was performed.

7. Pertaining to the section on MMPs the authors may wish to include additional pre-clinical and clinical studies (with greater detail) where MMP activity occurs in excess and where tetracyclines have demonstrated positive effects. For example, gingivitis is the most well documented application where excess MMP activity occurs (leading to gingiva destruction) and where this class of drugs is approved and this is not mentioned.

R: We prefer to dedicate attention to trials in a specific section, just describing the effects reported focusing on the MMPs.

8. The section on inflammation needs to be divided into a) reactive oxygen species scavenging action, 2) suppression of cytokines and, 3) modulation of inflammatory cells (dendritic cell section to be included here). Also, relevant pre-clinical and clinical examples should be included for example sepsis and ARDS, dengue fever etc.

R: Accepting the great advice, we divided the anti-inflammatory section into three subsections likely described above, that can be perceived in the pages 10 to 13

9. Figure 2 should be improved to have visual elements be better presented and also in the labeling as it is difficult to denote.

R: Figure 2 was remodeled on page 14 to improve visual understanding and to be more organized and the label was re-written to be more efficient in the image guidance.

10. The clinical trials section may wish to be categorized for diseases such as cardiovascular, neurological, etc. this section should be the last before the conclusions.

R: The DC's section was moved to a subsection in anti-inflammatory section, page 13, and the clinical trials section was improved with more details and information from each trial and the text and table in the section was used organized by the categories reported above (pages 14 to 20).

Reviewer #2: The purpose of this review is unclear. As described on page 4 by the authors, the first-line drugs are IFN-beta and glatiramer acetate, followed by the second-line agents including fingolimod and natalizumab. It was also reported that rituximab, an anti-CD20 mAb, was effective in reducing clinical relapses and gadolinium-enhancing brain lesions. Without describing the relationship between these drugs and tetracycline, this review article provides little information to readers. Do the authors believe that the combination therapy with the first- or second-line drugs and tetracycline shows more beneficial effects? If so, it should be precisely described and discussed.

Description regarding pharmacokinetic and MMP inhibition effects (Chapters 2.1, 2.3 and 2.6) of tetracycline should be trimmed because these descriptions are not so important in this review.

R: We think all information to base our judgment matters and it lies to a study that can provide all information about the disease and how the medicine proposed can work, so, to reach this, maybe more interesting to the readers if the study contains the sections mentioned, just for the more comfortable experience of knowledge having these data summarized in the same paper.

In the clinical trial section, statements that are unrelated to MS and EAE should be deleted. MS clinical trials (Refs. 106, 108 and 110 etc.) should be introduced in more detail. In line with this, a large part of Table 1 should be deleted.

R: The clinical trials section was improved with more details and information from each trial. The text and table in the section were organized by disease categories, and the pre-clinical studies were removed and mentioned in a proper space. The table has now a dedicated space to MS in clinical trials, and EAE in pre-clinical (pages 14 to 19).

Remember the title of this article. "Can tetracycline ensure help in multiple sclerosis immunotherapy?" The reviewer wants to know whether tetracycline administration really helps treatment of MS patients. The present manuscript does not answer this question.

R: We apologize if the message received does not able to transmit our intentions, but we believe that providing this data and showing the studies, the readers will be capable to develop themselves a judgment. However, your consideration was very useful to a deep

think about our text, and an improvement in the Conclusion section and all sections were added to show more precisely our affirmative thoughts about the central questions and title of this study.

The authors must delete a large part of tetracycline introduction and add descriptions regarding the relationship between presently used drugs and tetracycline.

R: For a review study we provide to the reader all the considerations of the drug that led us to this path, and through the sections, they can build a thought about it and can increase the debate.

Too many references.

R: MS is a very delicate subject, and to answer the title, we need a strong theoretical reference, this explains the larger number of studies consulted for the elaboration of this review, in our fixes a few numbers of references were removed, however the most important is that we did not deny any credit to the authors of the studies consulted.

Reviewer #3: This paper review recent data involving the tetracyclines Minocycline and Doxycycline and their therapeutic potential in MS, the paper is well writted and informations correctly discribed. I do not have more comments and for me the review can be published in the present form.

R: Thank you for your consideration and the compliments, we improved the quality of the study and hope that readers can feel the same that you said.

Reviewer #4: The authors review the pleiotropic properties of tetracyclines and their potential as therapies in Multiple Sclerosis.

1. The first sections could be more focused on MS, as opposed to the multitude of immune-modulating effects of tetracyclines.

R: We think that the MS section can bring information enough to base the discussion ahead, however in the clinical trial section (improved) you can see more about MS in a practical aspect (pages 14 to 19).

2. The clinical trial section is quite limited, as there is not much new information in this respect in the field.

R: The section was improved and divided into pre-clinical and clinical trials keeping more focus in each type of study, and dividing these sections through the disease categories related to each trial (pages 14 to 19).

3. The manuscript should be revised for typos and language.

R: We apologize for this misunderstanding, another minacious review in text grammar was performed to fix mistakes and avoid this situation.

4. Figures and tables are well crafted.

R: The both were improved, we are thankful for your compliment, hope readers can think the same (pages 13 to 20).

5. There is perhaps too much emphasis on pharmacokinetic considerations.

R: We apologize for this impression, besides the pharmaceutic institution that we are, improvements were made to avoid this interpretation and lead the reader to a more complete exposure of the subject without any emphasis on sections that not are the central point of the studies.

3rd Editorial decision
27-Oct-2020

Ref.: Ms. No. JCTRes-D-20-00018R2
Can tetracyclines ensure help in Multiple Sclerosis immunotherapy?
Journal of Clinical and Translational Research

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:

Reviewer #1: None