Author's response to reviews

Title: Effectiveness of Low-Dose Doxycycline (LDD) on Clinical Symptoms of Sjogren’s Syndrome: A randomized, double-blind, placebo controlled cross-over study

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Author's response to reviews: see over
Dear Editor,

Enclosed please find our revised manuscript “Effectiveness of Low-Dose Doxycycline (LDD) on Clinical Symptoms of Sjögren’s Syndrome: A randomized, double-blind, placebo controlled cross-over study.” (MS ID: 4240773711444654). We truly appreciate the comments and constructive criticism from the reviewer. We have now made all the corrections suggested by the reviewer to the manuscript, figures and figure legends, and responded to the comments (please see below).

We hope that the manuscript is now suitable to be published in *Journal of Negative Results in Biomedicine*. If there is need for additional corrections, please don’t hesitate to contact me.

Sincerely,

Leo Tjäderhane

RESPONDING AUTHOR

RESPONSE TO REVIEWER’S COMMENTS

We would like to thank the reviewer for her/his interest towards our study and the constructive comments that certainly helped us to improve the quality of the manuscript. Below, please find detailed response to those comments.

Response to the Major comments from the reviewer:

1) The reviewer raises a question about the low number of patients included into the study. This question certainly is valid and warrants explanation. The screening and selection of the patients were based on the patients records of the Department of Rheumatology in Oulu University Hospital, Oulu, Finland, and included all the patients with diagnosed SS in the Central hospital area. As described in Materials and Methods, 44 patients were screened, 27 fulfilled the inclusion criteria 22 chose to take part to the study. The main point is that we contacted all the SS patients in the hospital district and all that were available for the study were included. The same patient population has been used in previous studies, in which the number of participants has varied from 26 to 30, the fluctuation of the numbers being caused by natural fluctuation of the patients available at the certain study periods (for the list of references of these studies, please see the end of this letter).

The low number and its possible effect on the outcome of statistical significance has now been discussed in the Discussion, page 6, as follows: “The lack of clinically significant findings in this study may also be affected by the low number of patients (22 patients) involved, even though all the patients in the patient records of Northern Ostrobothnia Hospital District (Oulu University Hospital, covering 12 % of Finland’s surface area) with SS diagnosis were included into screening. Another study with larger patient population, requiring multi-center study, would be needed for the final conclusion in this matter.”

We appreciate that the reviewer also found our conclusion that further larger studies with LDD on subjective symptoms are not justified is correct, since organization of multi-center study with a high possibility of no benefits to the patients is simply neither practical nor ethical.

Response to the Minor comments from the reviewer:
2) The misspelling of “doxycycline” in page 5, line 11 of the Discussion, has now been corrected.

3) On Page 6, on the 3rd last line, misspelling of “LLD” has now been corrected to “LDD” as pointed out by the reviewer.

4) In the reference list, reference 26 (Preshaw et al) has now been corrected, as it was previously numbered as 27 (two references were given number 27). In the text, reference number 26 was used when referred to Preshaw et al. The text has now been rechecked to ensure correct use of references numbers, as suggested by the reviewer.

5) The reviewer found the letters used to describe statistical significances in figure 4 unclear. Figure 4 has now been redrawn to use lines and asterisks to improve the clarity, as suggested by the reviewer. The figure legend has been modified accordingly (page 14).