Author’s response to reviews

Title: Efficacy of subcutaneous tocilizumab in patients with rheumatoid arthritis and systemic sclerosis overlap syndrome: A report of two cases and review of the literature

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Author’s response to reviews:

Dear Editor James Mockridge

Thank you very much for your sincere handling of our manuscript and valuable pointing and suggestions to improve it made by your referees.

We have revised the indicated parts of the manuscript according to the comments of the Reviewer 1 and 2 as follows.

Sincerely,

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Reviewer 1

On the comment of [The skin response in case 1 is surprisingly good and much better than one would expect from the Toci studies. The second case is more typical. The cases are worth publishing.]

Replies to Reviewer #1

Authors are grateful to Reviewer #1 for encouraging comments. We have revised the indicated parts of the manuscript according to the comments. Corrections in the newly revised manuscript are underlined.

Please note that your review comments are shown in italic below and our replies in non-italic.

On the comment of [In the conclusion, Tocilizumab may be more effective in patients with RA and SSc overlap syndrome for which conventional treatment is inadequate. This statement is inaccurate as the authors do not state what the comparator was that Toci was more effective than.]

Reply: We have deleted “more” on page3 line13, page9 line6 and page9 line11

On the comment of [IL-6 expression is reportedly high in both the skin and serum of SSc patients, and its elevation depends on the skin sclerosis. Do the authors mean that IL-6 in the serum correlates with the skin score?]

Reply: Thank you for raising important issues. This sentence summarized ref9. However, we repeated a part of the discussion on page8 line2-6. We have deleted this sentence in the background.

On the comment of ['Sclerema' do the authors mean scleroderma mRTSS should be mRSS Figure 1 is not required.]

Reply: Thank you for raising important issues. We have changed “mRSS” in Figure 1 and 2.

Reviewer 2

Replies to Reviewer #2
Authors are grateful to Reviewer #2 for appropriate comments. We have revised the indicated parts of the manuscript according to the comments. Corrections in the newly revised manuscript are underlined.

Please note that your review comments are shown in italic below and our replies in non-italic.

Major remarks

On the comment of [Would it be possible to provide insight in the X-rays of the patients developing systemic sclerosis? Were there erosions which could be considered typical for RA (Larsen score 3+) ?]

Reply: We have attached the hand X-rays of case 1 and 2 in supplementary material for reply reviewers.

On the comment of [Some clinical pictures of the hands and the skin, before and after treatment would have been nice.]

Reply: We have attached the clinical pictures of the hands in case 1 before and 3-month after treatment in supplementary material for reply reviewers.

On the comment of [I would add in table 1 information on disease duration of RA and systemic sclerosis at the moment of tocilizumab treatment initiation.]

Reply: Thank you for raising important issues. We have added the information on disease duration of RA and/or systemic sclerosis.

Minor remarks:

On the comment of [The age of the patients at the different crucial moments in their history is somewhat unclear from the text]

Reply: At the moment of tocilizumab treatment initiation, the age of patient 1 was 74 and the age of patient 2 was 65. We have changed “Case1: 74-year-old Japanese woman at the moment of tocilizumab treatment initiation” and “Case2: 65-year-old Japanese woman at the moment of tocilizumab treatment initiation”.
On the comment of [Similarly, patient 2 underwent an arthroplasty at the age of 65, but it I'm not sure at what age she developed systemic sclerosis and was treated with tocilizumab. As a matter of fact the whole history of patient 2 is presented somewhat confusingly.]

Reply: She was diagnosed RA and underwent an arthroplasty at the age of 27. And in 2010, she was diagnosed with overlap syndrome involving RA and SSc.

We have changed “Case 2: 65-year-old Japanese woman at the moment of tocilizumab treatment initiation”

“She with a history of RA diagnosed at 27-year-old underwent right wrist arthroplasty.”

On the comment of [Om several occasions the authors use the word "sclerema". Can I assume they mean "scleredema”? Perhaps it would be a good idea to describe in more detail what is meant with this? ]

Reply: We have changed to “scleredema”.

On the comment of [TCZ is a recognized medication for arthritis.” I suppose the authors are talking about RA here, but do not understand why they mention this at this particular place in the text.]

Reply: Thank you for careful and meticulous reading of the manuscript. We have deleted the sentence of “TCZ is a recognized medication for arthritis”.

On the comment of [Since the stage of her skin thickening…” Are the authors talking about one of their cases here, or about a patient in another study?]?

Reply: Thank you for raising important issues. This sentence is referred [16]. We have changed to “Since the stage of the patient’s skin thickening was late phase…skin thickening [16]”.