Reviewer’s report

Title: The efficacy of recombinant human soluble thrombomodulin (rhsTM) treatment for acute exacerbation of idiopathic pulmonary fibrosis: A systematic review and meta-analysis

Version: 0 Date: 25 Nov 2019

Reviewer: Toru Arai

Reviewer's report:

General comments:

Kamiya et al. reviewed the manuscript written about efficacy and safety of recombinant soluble human thrombomodulin (rhTM) on acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF). AE is one of the topics in the field of IPF and rhTM is supposed to be a promising drug for AE of IPF. So this kind of review is important. I have some comments about the content of this manuscript.

Specific comets

1. Most important point is I-NSIP cases included in the paper of Abe [ref 36] was not diagnosed by SLB. So these cases could not be diagnosed as NSIP, but unclassifiable IIP. Radiologically NSIP cases showed histologically IPF in 40% cases (Sumikawa H, et al. Radiology 2014). Then I suppose it is better that NSIP cases of ref 36 is excluded.

2. I am author of ref 33. You excluded our paper showing safety and efficacy of rhTM on AE of IIP. You wrote in the manuscript, that you directly contact me and our cases of Non-IPF were unclear. I am sorry, but I do not remember your contact to me. Hence, I would like to explain our cases. All cases of our Non-IPF were Non-IPF IIPs. These cases did not undergo surgical lung biopsy. Most of the cases with non-IPF IIPs with possible UIP HRCT pattern might be IPF because Raghu et al reported that most of IIP cases with radiologically possible UIP pattern (LRM 2014) showed histologically UIP pattern. Some of non-IPF IIP cases with inconsistent with UIP pattern might be IPF. Le Rouzic reported 17% of IPF cases showed inconsistent with UIP HRCT pattern (Saecoidosis Vascular and Diffuse lung Diseases 2015). Clinically collagen vascular diseases were denied and chronic hypersensitivity pneumonia (CHP) were also denied. We included these cases in our trial because AE often occur in such cases and they result in poor prognosis (see, Arai T,et al. Respirology 2017; 22: 1363-70). I do not suppose you should include our paper (ref 33) in your investigation if you examine AE of only IPF. But I would like you to understand the aim of our study and I would you to make some comment in the discussion. In addition I would like you to modify p.12, line 17-18.

3. You mentioned Suzuki et al reported that prognosis of AE of NSIP is similar to that of IPF in ref. 20 (p.7, Line 7). I think this is not correct expression. It is true that survival of AE-IPF and AE-fibrosing ILD is similar (Fig.3 in ref. 20). However, they showed AE-NSIP did not died until day 90 (Fig. S6, online supplement in ref. 20). Number of AE-NSIP cases was only two. So I would like you to correct this part.
4. Abe et al (ref. 38) included AE of underlying IIPs with possible UIP pattern without surgical lung biopsy. In other words, they included AE-non-IPF IIPs. And this report was described in Japanese in the section of reference. Please describe in English. You can read English abstract in the WEB site of Japanese Respiratory Society.

5. Ref. 18 is a Japanese report and I cannot read the detail. Many reports about the effect of rhTM on AE-IPF were quoted in this paper. Hence, I think this report is not necessary. If you would like to quote this paper, I would like you to add the content of this paper in this manuscript and to show me the proper reason. Or I think you had better delete this paper from the reference.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
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I am the author of ref. 33. The paper showed the efficacy and safety of recombinant soluble human thrombomodulin on acute exacerbation of idiopathic interstitial pneumonia. Then I might have non-financial competing interests in relation to this paper. However, I suppose my comment to this paper is reasonable. I would like the editors to judge my review.

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