Reviewer’s report

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

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Reviewer: Takuma Isshiki

Reviewer's report:

Reviewer comment
General review:

As prognosis of IPF-AE is extremely severe, new treatment strategy is required. Recently several reports indicated the possibility that rhTM treatment would be beneficial for the prognosis of AE-IPF. However, as authors mentioned in the manuscript, almost all of the studies were retrospective studies and the study population was small. Since AE-IPF is relatively rare manifestation and the prognosis was severe, conducting RCT seems to be difficult. Therefore, meta-analysis of these studies might be helpful to interpret the usefulness of the treatment.

1. I have one concerned about the selection of clinical trials. The authors exclude one trial among the reports because of lack of the clear diagnosis of non-IPF (Arai T et al, Respirology 2019 ). This study was conducted only in multicenter and the number of patients was relatively large among the reports. Moreover, as you know, the precise diagnosis of IIPs was often hard even in the experts. The prognosis of control group in this study was similar to other reports. Therefore, I guess the population of this study was not much different from other groups. Since authors included the study of NSIP patients (Abe et al, 2015), I suppose including the study in analysis is reasonable and support the certainly of currents study.

2. Previous studies reported the prognostic factors of AE-IPF. Baseline FVC, DLco, fibrotic markers, CRP, P/F at the onset of AE-IPF and so on were reported to be the clinical markers. Therefore, authors should be described the difference of these markers between two groups.

3. As authors mentioned in the manuscript, thrombomodulin has either anti-inflammation effect or anti-coagulant function. Several reports reported that HMGB-1 was upregulated in the lungs of animal models of lung inflammation and fibrosis and lungs of AE-IPF patients. Moreover, the HMGB-1 levels in peripheral blood were reported to be the prognostic marker of AE-IPF. Describe the association between HMGB-1 and AE-IPF would be support the positive effect of rhTM treatment in AE-IPF.

4. Among these reports in the meta-analysis, low molecule weight heparin (LMWH) was used in some part of the patients in control group. Are there any differences of outcome in rhTM treated patients and LMWH treated patients?
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.

I am able to assess the statistics

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