Reviewer’s report

Title: Clinical effects of direct hemoperfusion using a polymyxin B-immobilized fiber column in clinically amyopathic dermatomyositis-associated rapidly progressive interstitial pneumonias

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Reviewer: Nathan Hambly

Reviewer's report:

Firstly, I would like to thank Okabayashi and colleagues for their submission. The manuscript represents a case series of patients with amyopathic dermatomyositis presenting with an acute ILD flare managed with a direct hemoperfusion polymixin-B immobilized filter.

The data presented is valuable and significantly contributes to the existing medical literature in this field. Particularly valuable is the new data detailing the extremely poor prognosis associated with anti-MDA-5 antibodies in this affected cohort. Unfortunately, in comparison to previous retrospective case series involving patients with acute exacerbations of ILD, the presented data do not demonstrate a measurable benefit of the PMX-DHP.

I will outline a series of major and minor suggestions regarding the manuscript in its current format:

Major

Background

1. Could the authors describe in more detail the histologic pattern of RPIP? Is this similar to DAD or is this term specific to CADM? Please provide supporting references.

2. Need to clarify the strength of literature supporting the use of PMX-DHP in other forms of RPIP such as IPF. I believe that the majority of the data is from retrospective uncontrolled cohorts? What was the value seen in these trials from a clinical perspective?

3. I think it needs to be stated that this is an investigational technique rather than a standard of care. Could the authors provide more detail regarding the mechanism by which PMX-DHP is thought to have benefit in RPIP?
Methods

1. At present there is no control arm where patients did not receive PMX-DHP. Is it standard of care in your institution to treat all patients with RPIP in such a fashion. It would be valuable to have a control group of CADM related RPIP without

Conclusion

1. I think the major conclusion of this article should be that the RPIP in anti-MDA-5 CADM is associated with very poor prognosis. Feel the scope of the article should be directed at this rather than the PMX-DHP non-effect.

Minor:

Background

1. Need reference for the statement that CADM patients frequently develop RPIP

2. Anti-tRNA synthetase antibodies are commonly associated with fibrotic ILD. Why was a similar association with acute respiratory failure or acute exacerbation not observed?

Methods

1. Describe in more detail the protocol used for PMX-DHP. The number of sessions, frequency, etc.

Results

1. Should describe whether patients were treated with lung protective strategy, were antibiotics empirically prescribed as per the recommendation for AE-IPF?

2. Numerical difference in LDH levels does not appear to be clinically relevant between survivors and non-survivors in comparison to ferritin. Do the authors agree?

3. Why is it relevant that serum LDH correlate to serum ferritin? Serum ferritin is not a validated biomarker for ILD flares. Should be correlated to clinical outcomes.

4. Need to introduce what HMBG-1 is earlier in the manuscript
5. I am a little confused as to the relevance of comparing non-validated biomarkers in LDH, ferritin, and platelet count to the anti-MDA-5 status. What is the value of making this comparison given its clinical relevance and the very small sample size used.

Discussion

1. Results suggest that anti-MDA-5 it is not only an important prognostic marker but an important pre-disposing biomarker. Are patients with CADM more predisposed to being MDA-5 positive

2. Far too much text in the conclusion regarding the potential value of non-specific biomarkers

**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.

No

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

No

**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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