Reviewer’s report

Title: Targeted therapy in pulmonary veno-occlusive disease: time for a rethink?

Version: 0 Date: 13 Oct 2019

Reviewer: Jose Gomez-Arroyo

Reviewer's report:

In the manuscript entitled "Targeted Therapy in Pulmonary Veno-Occlusive Disease: Time for a Rethink?", Qin Luo, Zhihong Liu et al describe the clinical history of 5 cases with EIF2AK4-mutated PVOD.

In this interesting case series report, the authors seek to provide evidence to help redefine the clinical management of patients with PVOD, based on their experience using pulmonary vasodilators in patients with clinical, histological and genetic diagnosis of PVOD.

All together the authors make a compelling argument towards the responsible use of vasodilator therapy for these patients that, at least in my experience as a clinician, has held true. Nonetheless, there are a few comments/questions that I would like be addressed:

1) Could the authors comment on the frequency of anticoagulation between your patients (80% were anti-coagulated) in comparison to the rest of case reports? Could anticoagulation play an important role in these subset of patients?
2) The authors postulate there was no pulmonary edema. However, these is a difficult statement to prove given that unless imaging was performed, we could not account for asymptomatic pulmonary edema that may have developed.
   a. Are there any imaging studies available?
   b. it would be rather informative if the authors noted a change in supplemental oxygen requirement or even changed in DLCO over time? Any of these could perhaps help support their statement.
3) How was the therapy uptitrated in your patients in comparison to other case reports that did develop pulmonary edema?
   a. How did your max doses compare to that of other patients with PAH?
4) Did all patients have biallelic mutations? If not, what were the mutations and could the authors provide any in-sillico data regarding the deleterious effect of the mutation? There are many mutations in EIF2AK4 that are not molecularly worse than others.
   a. Could these have any impact?

Minor

Page 3, line 56: I believe it shoud read "met" instead of meet.
Page 4, line 9: Definition of PAH has changed to mPAP 20. Please correct.
Page 7. Line 17-20: I would consider replacing the statement "re-hospitalized several time for drinking wine or too much water" for something related to the final problem such as "alcohol intoxication" or "volume overload".
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.

Unable to assess

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

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

Acceptable

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