Author’s response to reviews

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

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Author’s response to reviews:

Point-by-point responses to reviewers' comments

Dear Editors and the reviewers:

Thanks a lot for reviewing our manuscript and giving us an opportunity to revise our paper. We have carefully taken reviewers’ comments into consideration when preparing our revision. The constructive advice of the editors and reviewers has substantially improved our paper.

Our detailed responses to the comments are as follows:

Kohichiro Sugimura (Reviewer 1): This report is dealing with the effect of PAH-targeted therapy for PVOD patients. The reviewer thinks this topic is interesting.

Authors: Currently, the role of PAH targeted therapy in PVOD patients remains controversial, thus needing more studies in this field. We thank a lot for the reviewer’s interest in our topic.

Kohichiro Sugimura (Reviewer 1): However, this study has some criticism as described below. 1. Please add the data about the change of DLCO before and after PAH-targeted therapy.

Authors: We are sorry that we neglected to display the changes of DLCO in our previous version. In the newly revised version, we added data regarding changes of DLCO % pred and DLCO/VA % pred Pre-
and Post-PAH targeted therapies in Additional file 1: Table S1 (we moved pulmonary function test results from previous Table 1 to revised Additional file 1: Table S1 to make comparison much easier). DLCO % pred values among these patients got improved.

Kohichiro Sugimura (Reviewer 1): 2. The authors should describe the prognosis of PVOD patients in this report.
Authors: We depicted the prognosis of PVOD patients in “Clinical variables pre- and post- targeted therapies” and “General treatment and PAH-targeted therapy” in Results Section as well as in the third paragraph of Discussion Section in our previous manuscript version. The mean time from the first use of targeted therapy to the last follow up was 39.3 months, four are still in good condition, the last underwent lung transplantation in May 2018 and is still alive now. Thanks for the reviewer’s advice, we made a further discussion about the prognoses of PVOD patients in the third paragraph of Discussion Section.

Kohichiro Sugimura (Reviewer 1): 3. The reviewer is interested in the clinical course of Patient 5. Do the authors think about the possibility to misdiagnose PVOD as PAH? Please mention this issue in the discussion section.
Authors: Ten years before in 2009, the clinical features and pathophysiology of PVOD were not well understood, even though great advances such as gene detection have been made during the past years, most clinicians remain unfamiliar with this rare disease. Patient 5 was previously misdiagnosed with IPAH, thus received above PAH targeted therapies. With recent advances in imaging and genetic modalities, in combination with his clinical characteristics, we highly suspected that he suffered from PVOD, biallelic EIF2AK4 mutations were detected in June 2017, we suggested transplantation, but he himself was unwilling to undergo lung transplantation. It was not until May 2018 that he underwent lung transplantation, he is still alive now. Thanks for the reviewer’s advice, we emphasized this issue in the third paragraph of Discussion Section.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 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.
Authors: Thanks for the reviewer’s interest and positive recognition.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 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?
Authors: Currently, anticoagulation is controversial among PVOD patients. Many patients with pre-capillary PH (particularly group 4 and some in group 1, eg, idiopathic and drug-induced PAH) receive oral anticoagulants based on observational studies which suggested benefits. However, considering PVOD patients may have a risk of alveolar hemorrhage and no existing trials show benefit (PMID: 16387942), some clinicians avoid routine anticoagulation among this population. In contrast, some experts give routinely anticoagulation when low risk of alveolar hemorrhage exists. PVOD is now not an absolute contraindication to anticoagulation.
For our patients, Patient 1 was anticoagulated in consideration of his medical history of
antiphospholipid syndrome and venous thromboembolism. Patients 2/4 received anticoagulation therapies before the results of gene detection came out, considering a relatively low risk of bleeding, they were anticoagulated. For Patient 3, he was admitted for the evaluation of lung transplantation in March 2018 and was confirmed with PVOD for his clinical features in combination with following gene detection which revealed biallelic EIF2AK4 mutations, thus anticoagulation therapy was not prescribed. For Patient 5, he was misdiagnosed with IPAH in which anticoagulants were recommended based on several studies (PMID: 30545971, 24081973, 1603139, 17074918) and therefore received anticoagulants for a long period.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 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.

Authors: Sorry that we didn’t provide enough evidences proving no pulmonary edema occurred in our previous version due to limited space. Imaging was performed for all patients pre and post targeted drugs, here in our revised version, we provide representative chest X-ray and CT images of Patients 3 in Additional file 1: Figure S1, images of all patients can be provided if requested. Actually, no symptoms such as hemoptysis or pink frothy sputum occurred among our patients when given targeted drugs, arterial oxygen saturation got improved, and NT-proBNP decreased, also indicating no occurrence of pulmonary edema. Moreover, some patients (e.g. Patient 3) had no supplemental oxygen requirement and maintained oxygen saturation >95% after treatments.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 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?

Authors: In our systematic review, pulmonary edema following targeted drugs occurred in 26.7% patients (ref 2, 12, 13, 16, 19, 21-23), and epoprostenol seemed to induce pulmonary edema more frequently. But for our patients, we usually started with sildenafil or tadalafil which were proved to have better safety profiles, ambrisentan was sequentially added on if no obvious effects were observed. For severe patients, before using treprostinil (epoprostenol are unavailable in China), intravenous iloprost (for its shorter half-life period) was firstly attempted, if well tolerated, no deterioration in following chest X-ray images was observed, treprostinil was then uptitrated as we described in the Method Section “the intravenous infusion rate of treprostinil is initiated at 1.25 ng/kg/min, and was adjusted in increments of 1.25-2.5 ng/kg/min per day later”, the above strategies were not used in other case reports. The max doses of epoprostenol ranged from 2 to 29 ng/kg/min among those who did develop pulmonary edema, treprostinil used among our reported patients ranged from 15.25 to 20 ng/min/kg.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 4) Did all patients have biallelic mutations? If not, what were the mutations and could the authors provide any in-silico 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?

Authors: Yes, all patients have biallelic mutations in EIF2AK4 gene. Gene mutation sites were displayed in Table 1, gene detection reports can be sent if required. As we discussed in the second paragraph in Discussion Section, the prognoses of patients with EIF2AK4 biallelic mutations varied (PMID: 28087362, 24292273), we supposed possibly favorable effects of PAH-targeted drugs existed in certain patients harboring specific EIF2AK4 gene mutations, but this calls for further investigations.
Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Page 3, line 56: I believe it should read "met" instead of meet.
Authors: Thanks for the reviewer’s advice, we corrected this mistake in our revised manuscript.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Page 4, line 9: Definition of PAH has changed to mPAP 20. Please correct.
Authors: Thanks for the reviewer’s reminder. Although pre-capillary PH was suggested to be defined by the concomitant presence of mPAP >20 mmHg, PAWP ≤15 mmHg and PVR ≥3 WU in 6th WSPH, there are still some arguments and disaccordance about this definition, moreover, the final formal guideline has not been issued. Currently in our center in China, we are now still using the previous definition.
Additionally, PVOD patients were retrospectively enrolled in our study, and they were all diagnosed before 6th WSPH took place. Thus, we didn’t take the reviewer’s advice in our revised manuscript, but we are still grateful for the reviewer’s advice.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): 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".
Authors: Many thanks, we followed the reviewer’s advice in our revised manuscript.

Other revisions:
1. We revised the formats of our manuscript (Adjust case sensitivity and Bold in Title, Keywords, Tables and Figures; Add abbreviations under Tables) to meet the formatting rules according to the “Submission Guidelines”.
2. We changed the format of References throughout the manuscript to meet the rules.

All changes in the manuscript are indicated in the text by using track changes (Revised version with track changes was uploaded as a supplemental material).
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Thanks once again for reviewing our paper.
Yours sincerely
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