Author’s response to reviews

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

Authors:
Qin Luo (luoqin2009@163.com)
Qi Jin (drjinqi@foxmail.com)
Zhihui Zhao (1250167892@qq.com)
Qing Zhao (zhaoqingfw@aliyun.com)
Xue Yu (yuxuefw@foxmail.com)
Lu Yan (Ripple_Yan@163.com)
Yi Zhang (med-zhangyi@foxmail.com)
Changming Xiong (xiongcm2000@163.com)
Zhihong Liu (zhihongliufuwai@163.com)

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Author’s response to reviews:

Point-by-point responses to reviewers' comments

Dear Editors and 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 reviewers has substantially improved our paper.

Our detailed responses to the comments are as follows:

Kohichiro Sugimura (Reviewer 1): The reviewer has no more comments.
Authors: We feel deeply happy that we have eliminated the reviewer’s concerns about our previous manuscript. Thanks once again for reviewing our paper.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Could you speculate why would DLCO get better? Do you think it is dependent on better RV function? Improved vascular perfusion? Both? None?
Authors: As we know, severe reduction in the DLCO to less than 50% of the predicted value is quite common in PVOD, which might be explained by a reduction in capillary blood volume from a compromised pulmonary vascular bed and poor membrane diffusion as a result of interstitial oedema (PMID: 27009171). After treatments, our patients got their conditions stabilized or improved without lethal pulmonary edema occurrence, their right ventricle size, TAPSE, sPAP and ejection fraction all
got improved, we speculate better DLCO was associated with better RV function as well as improved vascular perfusion since RV function and pulmonary blood flow are mutually interactive, the exact mechanism remains to be explored.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Regarding anticoagulation: I think it will be useful to include the fact that most patients were anticoagulated, particularly because we do not know the significance of venous thrombosis in patients PVOD - I believe a regular reader would benefit from the small piece of discussion added to the reviewer comments regarding the dichotomy of treatment.
Authors: We agree with the reviewer that the significance of venous thrombosis in patients PVOD remains unclear. Thanks for the reviewer’s advice, we make a brief discussion about anticoagulation therapy in the third paragraph of Discussion Section, and hope this will bring benefits to our readers.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Regarding pulmonary edema: Excellent. I believe it adds relevant information even if imaging is not included. Please add these findings in the final publication.
Authors: Thanks for the reviewer’s praise and advice, we have added evidences showing no pulmonary edema occurred in the paragraph “General treatment and PAH-targeted therapy” in the Results Section.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Regarding therapy and its association with pulmonary edema. I think a short comment on how different your regimen was compared to other case reports is relevant.
Authors: Epoprostenol was used in many other case reports, but treprostinil was rarely used. However, epoprostenol is unavailable in China, thus we commonly use iloprost and treprostinil instead. We initiated treprostinil at 1.25 ng/kg/min, and adjusted in increments of 1.25-2.5 ng/kg/min per day later. Before using treprostinil for severe patients, intravenous iloprost for its short half-life period was firstly attempted. The above strategies were not used in other case reports. These differences were depicted in the fourth paragraph of Discussion Section.

Jose Gomez-Arroyo, M.D, Ph.D (Reviewer 2): Excellent work. I look forward to citing your findings!
Authors: We thank the reviewer for his praise.

To meet the journal requirements for submission, we provide ages as age-ranges instead of exact ages in Table 1, provide heading for "Declarations" and for the "Figure Legends" and include a statement in Funding section describing the role of the funding body.

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).

Thanks once again for reviewing our paper.

Yours sincerely
Qi Jin, on the behalf of the authors. Center for Pulmonary Vascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Road, Xicheng District, Beijing, 100037, China. E-mail: drjinqi@foxmail.com.