Reviewer 3 v.1

Comments to the Author

Mizuki et al studied 26 patients who were administered triple oral combination therapy with macitentan, riociguat, and selexipag for the treatment of PAH. Two-thirds were treatment naïve while the rest were under some PAH medications at baseline. In the 18 patients who had available hemodynamic data, during a median follow-up period of 441 days, mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output improved by 29%, 65%, and 82%, respectively. Three-year survival rate and prostacyclin infusion-free rate since administration of all 3 drugs was 93.3% and 74.6% respectively.

This was a retrospective study and this bears significant limitations when studying the safety and efficacy of PAH targeted drug therapies. I believe that the most important finding of the study that should be mostly expressed is the subgroup analysis in treatment-naïve patients. These patients experienced a 29% decrease in the mean PAP, a 66% decrease in the PVR and a 90 increased in CO from baseline to follow-up (median 293 days). These findings should be discussed in the light of the results of the TRITON trial the only trial that has used a similar upfront triple combination (macitentan, tadalafil and selexipag). It is also strange that prostacyclin infusion was initiated in 31.8% of patients within 7 months, and no patients underwent prostacyclin infusion after 7 months. This points towards a bias of an initial high risk population of patients in which initial triple oral combination treatment was chosen.

It is important for the authors to delineate in abstract how many of treatment naïve patients the oral combination was upfront (n=10), in how many it was sequential (n=1) and how many patients were taking some PAH medications at baseline.

Authors state that “For patients who had already received other PAH-specific vasodilators at the time of enrollment, these drugs targeting the endothelin pathway, nitric oxide pathway, and prostacyclin pathway were switched to macitentan, riociguat, and selexipag, respectively”. This method has important flaws since patients are not treatment naïve and the comparison of hemodynamic and other parameters is from a baseline state in which the patient already received another vasodilation therapy.

Page 6, Did authors use the original REVEAL risk score or the updated three-category REVEAL 2.0 score?

Page 6, In the risk assessment based on guideline hemodynamics, the authors did not include SVO2.

Page 6, “The observation period was terminated when patients died, underwent prostacyclin infusion, or stopped taking macitentan, riociguat, or selexipag for any reason”. Did the authors perform the analysis of survival without taking onto account these patients?

Page 8, “Most patients were treatment-naïve (65.4%), and others were taking some PAH medications at baseline.”

Page 9, “intravenous infusion of epoprostenol was added to the triple oral combination therapy in another patient, and a subcutaneous infusion of treprostinil was added to the triple oral

combination therapy in the remaining 4 patients". Why did the authors continue to administer oral selexipag in these patients?

Page 10, please provide follow-up measurements of all hemodynamic variables apart from mPAP in the low/intermediate and high risk group.

Page 10, line 20-22 "Mean PAP at follow-up in low/intermediate risk patient was 34 (26– 21). Do you mean high risk here?

Page 10, line 22-26 "Among 5 patients who were classified as high-risk based on the guideline and needed prostacyclin infusion, 3 patients had BMPR2 mutations and 1 patient had a RNF213 25 mutation". This is a repetition!

Discussion, page 11 "Most of the low-/intermediate-risk patients and around half of the high-risk patients could be treated sufficiently with this triple oral combination therapy." This depends always on the studied population and also the follow-up period and cannot be a generalized conclusion.

In general, although the idea behind the paper has many advantages, the authors use a mix of findings in the Discussion, such as risk assessment which is not the main research question of the present study. For instance, discussing the prognostic significance of the mPAP and cardiac index, as well as echo parameters and BNP is out of the scope if this work.

Do the authors imply in the Discussion that Eisenmenger patients should be treated more aggressively with parenteral prostanoids? If yes, this is not correct.

In terms of safety, please parallel your findings with the GRIPHON trials in which patients who received triple therapy had the highest frequency of side effects.

Specific comments

Page 4, revise to "Pulmonary arterial hypertension (PAH) is a lethal disease characterized by elevated pulmonary arterial pressure (PAP) due to remodeling of the pulmonary arterial bed and right sided-heart failure".

Page 4, line 38: Add the mechanism of action of selexipag

Page 4, line 50-52: "which oral vasodilators are most appropriate for combination in such patients remain poorly documented to date". Please revise or omit since this is a single-arm study and you do not compare oral combinations in order to find the most efficient.

Page 5. How did authors acquire written informed consent from patients, since this was a retrospective study?

Page 5, calculation of cardiac index with the use of the Fick technique with a stable oxygen consumption is not supported by the PH Guidelines. This is a limitation of the study, although comparisons between baseline and follow-up hemodymanics were made using the same technique.