

Peer Review File

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**Reviewer A**

1) The authors should demonstrate which statistical test was used to calculate the individual P-values.

Reply: We have added it(see Page 6, line 188-195)

2) The authors did not adjust any confounding factors. Their results do not necessarily indicate the efficacies of macitentan. Multivariate analysis to adjust for confounding factors is needed.

Reply: The datas are indicators reflecting efficacy, not the impact indicators.

Minor comments:

1) The figures and their titles do not match.

Reply: We have deleted figures due to modification.

2) line 51: The authors should mention the clinical implications from this study in " What is the implication, and what should change now?" but not limitations.

Reply: We have modified it(see Page 5, line 110-112).

Typo error:

1) line 78: "wasonducted"

2) line 130: "In the end,4A"

Reply: We have modified above all.(see Page 5, line 144)

**Reviewer B**

Major comments:

- Sample size is very small and include both patients treated in monotherapy and combination therapy, which makes it unclear if the findings related to macitentan itself or macitentan + PDE5

Reply: Our study demonstrated that there was no statistically significant difference between monotherapy and combination group, which indicated macitentan worked.

- Authors should also discuss the ESC guidelines and clarify why certain patients were treated with monotherapy (e.g., cardiopulmonary comorbidities) and how this may limit the homogeneity with those treated in combination therapy

Reply: We added this part of discussion(see Page 10, line 314.)

- Study was conducted during the peak of the COVID pandemic (April 2020-November 2021), which may have impacted the findings; authors should discuss how COVID changed the management of CTD-PAH patients at their university

Reply: We have added this(see Page15, line 494.)

- Discussion is very long and hard to read. The text should focus more on macitentan, as this is the core of the study

o Not clear why the authors repeat general information on the disease and diagnosis in the discussion, this should be already covered in the introduction and is not relevant to the study findings which are related to treatment with macitentan

o The portion on anti-inflammatory therapy is quite long and would benefit from being more targeted

o Similarly, the portion describing clinical trials could be shortened and more emphasize be put on why we needed additional data specifically for CTD-PAH

Reply: We have modified all of them.

Minor comments:

Typos: there were several typos and spacing errors throughout, this needs to be fixed (e.g., lines 58, 78, 81, 131)

Reply: We have modified all.

Abstract: Some results are included under the “Methods” header, should be under “Results”, the results should also state the overall sample size.

Reply: We have added in part of results(see Page 6, line 206.)

Implications should be more general than for the given study

Introduction: the rationale of the study could be better explained (e.g., lack of clinical trials specific to CTD-related PAH)

Reply: We have added it at the end of introduction(see Page 4, line 134.)

Methods: As the name of the university was blanked for blind peer-review, it would be good to mention in which country the study was conducted.

Reply: We have added(see Page 5, line 146.)

Line 116: Death and rehospitalization for heart failure are typically considered as markers of disease progression rather than adverse events

Reply: We have modified it(see Page 6, line 185.)

Statistical analysis: authors mentioned using paired t test to analyze before/after outcomes, but also mention using Wilcoxon rank-sum test and chi-squared test for comparison (not clear which comparisons as the tables/figures only seem to report the before/after comparison using paired t-test?)

Reply: We have modified it(see Page 6, line 188)..

Figures seem to be mislabeled

Reply: We have no figure now.

### **Reviewer C**

The article, while well-written, contains grammatical, syntax, and spacing errors. I have included sticky notes with suggested edits for improvement. **Please see the PDF.**

Reply: We have modified all.

### **Reviewer D**

The authors report a retrospective study of the efficacy and safety of macitentan use in 34 adult patients. The introduction and also the discussion gives the reader a good review of current knowledge. Results of novel PAH targeted substances, as macitentan, are important and also smaller studies could add valuable knowledge. However, I have some concerns:

My main concern about this study is: How do we know that the results report effects of macitentan and are not an effect of the PDE5i? Most of the studied patients (N=25/34) had combination treatment. The authors do not comment on this in the manuscript. I believe the study adds information about safety of macitentan use, but limited value of efficacy.

Reply: Our study demonstrated that there was no statistically significant difference between monotherapy and combination group, which indicated macitentan worked.

Moreover, we added detailed elaboration in discussion.

Other comments are:

In methods:

-Initially 40 patients were reviewed. 6 were omitted due to incomplete data and 4 due to follow up at another hospital. Finally the authors report on 34 patients. How does the equation fit together?

**Reply: We have modified it(see Page 7, line 206).**

-What dose of macitentan was given to each patient? It is stated 10 mg in the discussion, but needs to be clarified in the methods section. What dose of PDE5i was given as combination therapy? Important to know as this medication will probably add to the measured outcome.

**Reply: We have modified it(see Page 5, line 154).**

-The studied parameters for PAH are well-known and could be used as a substitute for a cardiac cath. The authors correctly comment on this in the discussion and limitations.

In tables and figures:

-Were all 34 patients included in table 1 and 2 or only some? If all patients were included I don't think its right to refer as "treatment with macitentan" only (results row 144) since most of the patients also received PDE5i.

**Reply: We have grouped the patients as monotherapy and combination groups.**

It is valuable to know how many patients were included in each statistical analysis.

-Figure 1 and 2 would benefit from adding numbers or % to make it easier to understand.

In discussion:

-In the discussion there is a long review (line 201-254) of the role and use of anti-inflammatory and immunosuppressive treatment in patients with CTD-PAH. It is interesting in itself, but does not refer to the results of the study in a way that I understand.

**Reply: We have modified it in discussion(see Page 10).**

-Further, the discussion review other studies with the use of macitentan but the results of the actual study could be more integrated and discussed.

**Reply: We have added this part in discussion(see Page 14, line 455).**

In conclusions:

-It should be added that the study report short term results and not macitentan alone.

-The authors state that "cardiac function" was improved, but there was no measurement of this. Other echocardiography parameters were measured though.

**Reply: We have modified both.**