Peer Review File

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Reviewer A

This systemic review and meta-analysis explored safety and tolerability of combination treatment with pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis. In this study, 26% of patients discontinued treatment prematurely, and the pooled proportions of serious and any adverse drug reactions (ADRs) were 0.07 and 0.75, respectively.
This report is addressing an interesting clinical topic, but the manuscript seems to involve some issues to be resolved.

Q1. A serious limitation of the present meta-analysis is that each of the five clinical trials included involved various treatment durations. In particular, reference 18 (Ogura et al.) has a much shorter treatment period of 2 to 4 weeks, and the reviewer questions whether it should be included in the meta-analysis. Please consider this issue.

R1. We agree with your opinions. Because reference 18 (Ogura et al.) has a much shorter treatment period, we excluded this study in our analysis. We totally re-analysed the pooled proportions of discontinuation and adverse drug reactions and described the revised results in the manuscript. And we added the limitation in the discussion as the followings;
“Third, study protocols were especially heterogeneous among the selected studies. The dosing and treatment durations of antifibrotic agents among the included trials varied, which could affect the prevalence and severity of ADRs.”

Q2. The authors' discussion of the results of this meta-analysis itself (treatment discontinuation rate and ADR rates) is lacking. This is essential.

R2. I appreciate your comments. We modified and added it in the revised manuscript as the followings;
“ In pooled estimates, approximately a quarter of patients receiving combination antifibrotic agents discontinued treatment. The pooled proportions of the development of serious ADRs any ADRs were 10% and 82%, respectively. Gastrointestinal ADRs were the most frequently reported.

Since our findings could not directly compare with the outcomes of antifibrotic monotherapy, we investigated previous data using individual antifibrotic agent monotherapy. First, the adherence outcomes associated with pirfenidone monotherapy have been reported through data collected from three multinational phase 3 trials (the ASCEND trial and the CAPACITY trials) (19). Approximately 16% of patients in the pirfenidone group discontinued study treatment (19). A recent systematic review of eight reports with nine RCTs for pirfenidone monotherapy in IPF reported that the majority of patients receiving pirfenidone had ADRs, mainly nausea, diarrhea, photosensitivity, and skin rashes; most of these ADRs were mild to moderate (20). Second, the INPULSIS trials as a major study of nintedanib monotherapy reported that 24.5 % of patients discontinued treatment and 95.5% of those had ADRs (21). Diarrhea was the most frequent ADR, experienced by 62.4% of patients in the nintedanib group (21). Several retrospective studies using clinical data reported that diarrhea developed in 32–79% of patients receiving nintedanib (22).

Only one trial directly compared the safety and efficacy between combination treatment and monotherapy of antifibrotic agent (18). A open-label randomized trial reported that nintedanib with add-on pirfenidone was associated with a significant increase in the incidence of discontinuation treatment compared to nintedanib alone (35.8% vs. 17.6%, $P = 0.036$). Although the incidence of serious and any ADRs were similar between both groups (3.8% vs. 9.8%, $P = 0.220$ and 89% and 88%, $P = 0.944$, respectively), most of the reasons for discontinuation treatment in combination therapy group was ADRs. In the present study, 29% of patients discontinued combination treatment during the study period. Among these patients, the rate of discontinuation of combination treatments owing to the development of ADRs was 86.3%. The rate of discontinuation in combination therapy seemed to be relatively high compared to the rate reported in the previous major trials on pirfenidone or nintedanib individual therapy (19, 21). Further large scale RCTs directly comparing the rate of discontinuation between combination treatments and antifibrotic monotherapy is needed in the future."

Q3. Line 33, and elsewhere: the prevalence or proportions should be consistently expressed by %. (0.07⇒7%, 0.75⇒75%)

R3. Thank you for your kind comments. We changed it as "%" for the proportions.

Q4. Line 43, Highlight box, "Our findings provide clinicians with detailed data on the outcomes of combination treatments in patients with IPF":

This is rather obscure, and does not seem to be mentioned in the abstract. More specific descriptions are required.

R4. Thank you for your helpful comments. We changed it as the followings;

"Our findings provide clinicians with data on the proportions of discontinuation and adverse drug reactions of combination treatments in patients with IPF based on the current evidence."

Q5. Figures 2 and 3: Proportions or rates are easier to understand than the effect size. Please modify if possible.

R5. Thank you for your thoughtful comments. We modified the label as "proportions" instead of the effect size in the Figures 2 and 3.

Q6. What does a p value of 0.02 of Figure 2 imply? This is not mentioned in the figure legend or in the manuscript.

R6. To reduce confusion as you mentioned, we removed p-value in the Figures 2 and 3.

Q7. How do the authors define "premature" discontinuation of treatment?

R7. We appreciate your kind opinions. Premature discontinuation of treatment is an unclearly defined. We deleted "premature" in the revised manuscript.

Minor points:

Q8. Line 83; (2) is duplicated.

R8. We removed it. I appreciate your review.

Q9. Lines 158-159, and 185; Correct IPF AEs to IPF-AEs.

R9. We corrected it in the revised manuscript.

Q10. Line 266; No page description in reference #15. (Flaherty KR, Fell CD, Huggins JT, et al. Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis. Eur Respir J 2018;52:1800230.)

R10. We are sorry for our mistake. We added the page in reference #15.

Reviewer B

Q1. Please indicate the proportion of discontinuation rate in Table 1 since it is your primary aim.

R1. Thank you for your helpful comments. We added it in the Table 1.

Q2. Please be explicit in the body of the text whether full dose of with antiproliferative agent was used in combination therapy vs lower dose and whether the proportion of the discontinuation rate was different.

R2. We appreciate your important comments. We added it as the following in the results and the limitation section.

"Most subjects received the dosing of pirfenidone 1200 mg·day−1 or more and nintedanib 200 mg·day−1 or more. Among 46 patients in one study, only four received low dose pirfenidone therapy of 600-1200 mg·day−1 (16)."

"Third, study protocols were especially heterogeneous among the selected studies. The dosing and treatment durations of antifibrotic agents among the included trials varied, which could affect the prevalence and severity of ADRs."

Q3. Can the authors make any other conclusions after the analysis to help clinicians dealing with the combination use?

R3. Our findings provide clinicians with data on the proportions of discontinuation and adverse drug reactions of combination treatments in patients with IPF based on the current evidence. However, because of the absence of a control group and the small sample size, we could not draw solid conclusions. We described it in the revised manuscript.

Q4. Can the patient expect a tolerability of full dose (loading) for a certain duration and then a drop in the doses (main doses) to see maximum benefit without any discontinuation?

R4. We think that your comment for the strategy of combination therapy is critical point. Until now, the dosing strategy of antifibrotic agents for combination therapy to see maximum benefit without any discontinuation have not been studied. In the future, the dosing strategy to improve adherence to antifibrotic agents in treatment for IPF are needed in the future. We added it in the conclusion section.

Q5. Please be explicit in the text, which agent was discontinued when there was an adverse event experienced.

R5. Thank you for your thoughtful comments. We added it in the results and the discussion as the followings;

“Of the total population, the pooled proportions of discontinuation of combination treatments due to the development of ADRs was 24% (95% CI 14% to 35%; I^2 = 58.21%).”

“In the present study, 29% of patients discontinued combination treatment during the study period. Among these patients, the rate of discontinuation of combination treatments owing to the development of ADRs was 86.3%.”

Reviewer C

Q1. The topic of the manuscript is very interesting and current. Knowledge about combined antifibrotic therapy with pirfenidone and nintedanib is scarce and valuable.

The manuscript is well written, but there are no specific statements about what is new, because the term: "We identified the safety and tolerability of combination therapy in patients with IPF through a systematic review and meta-analysis of clinical trial data" is not a very general, insufficient term.

R1. I really appreciate your kind comments. We changed it in the highlight box as the followings;

“The pooled proportions of discontinuation treatments and the developments of serious and any adverse drug reactions was 24%, 10%, and 82%, respectively.”

Q2. I would also expect a more precise record of what the implication is. I would expect a reference to how the toxicity of the combination of nintedanib and pirfenidone relates to the compared monotherapy. It seems to me that at least from the work of Vancheri et al. such a comparison can be made. Does the demonstrated safety give arguments supporting the need for further research, what would these studies be like, what would they be aimed at?

This is very important clinical information and should be better described by the authors of the systematic review.

R2. Thank you for your comments. We added it in the discussion as the followings;

“Only one trial directly compared the safety and efficacy between combination treatment and monotherapy of antifibrotic agent (18). A open-label randomized trial reported that nintedanib with add-on pirfenidone was associated with a significant increase in the incidence of discontinuation

treatments compared to nintedanib alone (35.8% vs. 17.6%, $P = 0.036$). Although the incidence of serious and any ADRs were similar between both groups (3.8% vs. 9.8%, $P = 0.220$ and 89% and 88%, $P = 0.944$, respectively), most of the reasons for discontinuation treatment in combination therapy group was ADRs. In the present study, 29% of patients discontinued combination treatment during the study period. Among these patients, the rate of discontinuation of combination treatments owing to the development of ADRs was 86.3%. The rate of discontinuation combination treatments seemed to be relatively high compared to the rate reported in the previous major trials on pirfenidone or nintedanib individual therapy (19, 21). Large scale RCTs directly comparing the rate of discontinuation between combination treatments and antifibrotic monotherapy is needed in the future."

Q3. The conclusion: "...further large-scale RCTs are required to support our findings" is repeated in all earlier original papers, in the meta-analysis it would be necessary to indicate specifically what is not yet known/examined.

R3. I really appreciate your comments. We change it in the conclusions as the followings; "Because of the absence of a control group and the small sample size, we could not draw solid conclusions. And further researches for the dosing strategy of combination therapy to see maximum benefit without any discontinuation are needed in the future."

Q4. In Table 1, column one, the last publication listed is a mistake: "Vancheri C, Kreuter M, Richeldi L, et al. Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial. Am J Respir Crit Care Med 2018;197:356-63" - should be 2018 instead of 2021

R4. Tnank you for your delicate reviews. We change it as "2018" in the Table 1.