ABSTRACT

Objective. Although the efficacy of combined treatment targeting pulmonary arterial hypertension (PAH) has been suggested to be preferable, the comparative efficacy of combination therapy versus monotherapy in connective tissue disease (CTD)-associated PAH (CTD-PAH) remains undetermined. We performed a meta-analysis regarding this topic.

Methods. The Cochrane Library, MEDLINE, PubMed, and EMBASE databases were searched for randomised controlled trials (RCTs) that directly compared the efficacies of combination therapy and monotherapy targeting PAH in patients with CTD-PAH. The risk of the clinical worsening of PAH and changes in 6-minute walk distance (6MWD) were evaluated. The Mantel-Hansel method was used to pool the results with a random-effects model.

Results. Six RCTs with 963 patients were included. The results of the meta-analysis showed that combination therapy significantly reduced the risk of clinical worsening events by 27% (pooled relative risk of 0.73, 95% confidence interval [0.60–0.89], p=0.002) with no significant heterogeneity (I²=13%, Ph=0.33) and tended to increase 6MWD by 21.38 m (95% CI [-20.38 to 63.14]; p=0.32; F=58, P=0.09). No significant heterogeneity was indicated with funnel plots.

Conclusion. Combination therapy targeting PAH may confer preferable therapeutic efficacy compared with monotherapy in patients with CTD-PAH as evidenced by a more remarkable reduction in the risk of clinical worsening and a probable improvement of exercise capacity in these patients.

Introduction

Despite advances in diagnosis and treatment in recent decades, pulmonary arterial hypertension (PAH) remains an important cause of morbidity and mortality worldwide. Pathophysiologically, PAH is characterised by a progressively increasing pulmonary vascular resistance (PVR) and pulmonary artery pressure, which ultimately lead to right-heart failure and death (1-3). The aetiologies of PAH have been considered to be multiple, and substantial number of patients with PAH (25–30%) have associated connective tissue disease (CTD-PAH) (4, 5). As a major complication of CTD, CTD-PAH has been indicated as a predictor of mortality in patients with CTD (6).

Currently, several specific medications have been proven to show efficacy for patients with PAH, and the treatment targeted the important pathological factors involved in the pathogenesis of PAH, such as endothelial dysfunction. Notably, various medications including phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostaglandins, soluble guanylate cyclase stimulators, and a selective prostacyclin receptor agonist (6, 7) that have been proven to be effective in patients with PAH may also have a favourable influence on endothelial function. However, despite the application of the above potential medications, the prognosis of patients with CTD-PAH remains poor. For example, patients with systemic sclerosis associated-pulmonary arterial hypertension (SSc-PAH, accounting for nearly 75% of CTD-PAH (8)) may have worse survival than those with IPAH (1, 9). Therefore, improved therapeutic strategies for CTD-PAH continue to have clinical significance.
In addition to the development of novel treatments, a combination of available medications has been proven to represent an important therapeutic strategy for many chronic diseases, including PAH. Notably, combination therapy for overall PAH may exert a more favorable influence on exercise capacity, hemodynamic status and clinical prognosis compared with monotherapy (1, 2, 10-12), which is recommended by current international guidelines for the management of PAH (13).

Accordingly, although a substantial number of randomised controlled trials (RCTs) and meta-analyses have proven the efficacy of combination therapy compared to monotherapy in PAH (1, 11, 14-16), the efficacy of combination therapy in patients with CTD-PAH alone, particularly for those with SSC-PAH, remains unclear. In addition, although pilot observational studies and small-scale RCTs are available (8, 17, 18), large-scale RCTs that evaluate the therapeutic efficacy of combination therapy in CTD-PAH are rare (19, 20).

Furthermore, the results of previous observational studies and RCTs are not always consistent, which highlights a need for a systematic review and meta-analysis to overcome the inadequacy of statistical power of individually included small-scale trials. Therefore, this study performed a meta-analysis to compare the efficacy of combined and monotherapy in patients with CTD-PAH.

Methods
Search strategy
We searched the Cochrane Library, MEDLINE, PubMed, and EMBASE for RCTs that compared combination therapy versus monotherapy of PAH-target therapies for patients with CTD-PAH published from 1990 through January 2017. Subgroup studies of CTD-PAH patients in PAH studies were also included. Search terms were designed to provide maximum sensitivity in detecting trials in PAH. We also manually searched reviews, guidelines, retrieved article references, and conference abstracts from relevant scientific meetings. However, we excluded conference abstracts because the data therein are often preliminary and have not been thoroughly peer reviewed. The search was restricted to the English language (a detailed search strategy is shown in Supplementary file 1).

Study selection
Studies were included if they met all of the following criteria. (1) Prospective RCTs assessing the efficacy of PAH-target combination therapy compared with background monotherapy in adult patients with CTD-PAH; (2) Reported the clinical outcomes of interest; (3) Follow-up duration was at least 12 weeks; (4) Specific therapies for PAH, including prostaglandins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (ambrisentan, bosentan, and macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil, and vardenafil), soluble guanylate cyclase stimulators (riociguat) and selective prostacyclin receptor agonists (selexipag) were applied. Studies were excluded if they met either of the following criteria: (1) case reports or reviews; (2) nonclinical trials; (3) animal experiments; (4) no comparison of combination therapy vs. monotherapy; (5) not in PAH patients or did not include the data of CTD in the subgroup analysis of PAH; (6) unable to extract data from the literature.

Data collection and quality assessment
Data were extracted independently by two reviewers using a standard form that included study characteristics (author name, publication year, and sample size), intervention, control, study design and methodology (randomization, blinding, and loss to follow-up), and outcomes. Results were compared, and any disagreements were resolved by consensus. If the same studies were reported in several papers, the analysis was limited to the largest cohort unless the necessary data had appeared only in another paper. If there were incomplete data in the published article, the corresponding authors or the sponsors were contacted directly for the information required. The primary endpoint of interest was the risk of clinical worsening (defined as a combination of all/PAH-cause death, admission to hospital, lung transplantation, atrial septostomy, treatment escalation including initiation of prostaglandins, symptomatic progression, etc.), which is summarised in Table II. The secondary outcomes were to assess whether combination therapy improved changes in exercise capacity (6MWD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), World Health Organization (WHO) functional class or New York Heart Association functional class, or cardiopulmonary hemodynamics, if possible.

Two reviews independently evaluated the validity of the selected studies. We assessed the quality of the included RCTs according to the standard criteria of The Cochrane Collaboration, which assessed random sequence generation, allocation concealment, blinding and incomplete outcome data, selective reporting and other bias. According to criteria of The Cochrane Collaboration, studies were divided into three categories: (1) low risk of bias – low risk of bias for all key domains; (2) unclear risk of bias – unclear risk of bias for one or more key domains; and (3) high risk of bias – high risk of bias for one or more key domains.

Statistical analysis
Due to the heterogeneity of the component studies, we used the Mantel-Haensel random-effects model to estimate the pooled risk ratios (RRs) with their 95% confidence intervals (CIs) for dichotomous outcomes data. For continuous outcomes data, mean differences were calculated. Forest plots were created when possible. All tests were two-tailed, and a p-value <0.05 was considered statistically significant. Inter-study heterogeneity was measured using Q statistics (p<0.01 was considered heterogeneous) and I² statistics (I²>50% was considered heterogeneous). Publication bias was assessed by funnel plots. All statistical analyses were performed using RevMan v. 5.2 (The Nordic Cochrane Center).

Results
Study selection
A total of 219 articles were identified by initial literature searching after removing duplicate studies (Fig. 1). No fur-
other articles were retrieved by manual searching. After reviewing the titles and abstracts to exclude irrelevant articles, 38 articles were reviewed in full-text for eligibility. Subsequently, 32 articles were excluded primarily because they were not comparative studies between the efficacies of combination therapy vs monotherapy, not in PAH patients or not including subgroup data of CTD-PAH. Finally, 6 studies (19-24) were eventually included in the meta-analysis. All included trials were randomised, prospective and placebo-controlled trials.

**Characteristics and quality evaluation of the trials**

Overall, we included 6 RCTs with 963 patients with CTD-PAH. The characteristics of the included RCTs are shown in Table I. The follow-up duration of the selected trials ranged from 12 weeks to 79 weeks. For the RCTs, the most basic characteristics, such as the distribution of genders of the patients and the proportions of patients with SSc, could not be estimated because we were unable to access the original data. Of the included RCTs, five trials were designed to investigate the effect of sequential add-on PAH-specific combination therapies, while only the AMBITION study (19) assessed the effect of upfront (initial) combination therapy of endothelin receptor antagonists compared with PAH-target monotherapy in adult patients with PAH. The medications added-on in each study were phosphodiesterase-5 inhibitors (n=1, PHIRST 2011 (24)), endothelin receptor antagonists (n=2, SERAPHIN 2013 (22); COMPASS-2 2015 (21)), a soluble guanylate cyclase stimulator, riociguat (n=1 PATENT-1/2 2016 (20)), and a selective prostacyclin receptor agonist, selexipag (n=1, GRIPHON, 2015 (23)).

The definition of clinical worsening is in accordance with the definitions used in the original RCTs (Table II). All included studies had a low risk of bias.

**Pooled analysis of clinical worsening**

The clinical worsening of the CTD-PAH patients was reported in four trials (21, 21-23). The pooled results with a total of 833 patients indicated that clinical worsening occurred in 35.5% (296 of 833) of participants: 29.8% (136 of 456) in the combination therapy group and 42.4% (160 of 377) in the monotherapy group. The meta-analysis results showed that combination therapy significantly reduced the risk of clinical worsening events by 27% (pooled RR 0.73 [95% CI, 0.60-0.89], p=0.002), with no significant heterogeneity between the included studies (I²=13%, Ph=0.33) (Fig. 2). Further subgroup analyses according to the incidences of the components of the clinical worsening outcome, such as mortality or nonfatal clinical worsening end points, could not be performed due to a lack of available data. Funnel plots (Fig. 3) showed that there was no significant publication bias in the analysis of clinical worsening.

**Pooled analysis of changes in exercise capacity**

Data for analysing the exercise capacity of combination therapy were available from 3 trials (19, 20, 24), which included 168 patients in the group of combination therapy and 107 patients in monotherapy. Compared with monotherapy, PAH-target combination therapy was associated with an improvement of exercise capacity as evidenced by the increment of 6MWD by 21.38 m (95% CI, -20.38 to 63.14; p=0.32; I²=58, Ph=0.09) compared to monotherapy, although this was not statistically significant (Fig. 4). Funnel plots (Fig. 3) showed that publication bias may exist in the analysis of clinical worsening.

**Other outcomes referred in selected studies**

Studies were not powered to examine the differences of other outcomes (e.g., haemodynamics status, WHO function class and NT-proBNP) with restricted data. Therefore, these outcomes were
Combination vs. monotherapy in CTD-associated PAH / J. Pan et al.

Table I. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/total patients (%)*</th>
<th>Follow-up duration (weeks)</th>
<th>Baseline therapy</th>
<th>Therapeutic arm</th>
<th>Females (%)</th>
<th>WHO functional class (%)</th>
<th>Outcomes</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT-1/2, 2016</td>
<td>111/443 (26%), 70 (63%)</td>
<td>12 weeks, 2 years</td>
<td>ERA (59.5%), non-parenteral prostaglandins (10.9%), both (1.1%)</td>
<td>Riociguat 2.5 mg tid</td>
<td>98 (88%)</td>
<td>I (5%), II (36%), III (57%), IV (2%) (data missing for 1 patient)</td>
<td>Primary: 6MWD Secondary: PVR, NT-proBNP, WHO functional class; TTCW; BIDS; EQ-5D and LPH questionnaires</td>
<td>Low risk</td>
</tr>
<tr>
<td>AMBITION, 2016</td>
<td>187/500 (37%), 118 (SSc-PAH)</td>
<td>79 weeks*</td>
<td>Ambisentan 10 mg/d or tadalafil 40 mg/d</td>
<td>Ambisentan 10 mg/d + tadalafil 40 mg/d</td>
<td>165 (88.2%)</td>
<td>II (48/187, 25.7%), III (139/187, 74.3%)</td>
<td>Primary: time to first adjudicated clinical failure. Secondary: (data not shown): change from baseline at week 24 in NT-proBNP level, satisfactory clinical response to therapy**, 6MWD, BIDS, and WHO functional class</td>
<td>Low risk</td>
</tr>
<tr>
<td>COMPASS-2, 2015</td>
<td>88/334 (26%)</td>
<td>16 weeks</td>
<td>Sildenafil (100%)</td>
<td>Bosentan 125 mg bid</td>
<td>NA</td>
<td>NA</td>
<td>Primary: time to first morbidity or mortality event†</td>
<td>Low risk</td>
</tr>
<tr>
<td>GRIPHON, 2015</td>
<td>334/1156 (29%)</td>
<td>71 weeks†</td>
<td>ERA, phosphodiesterase-5 inhibitors, or both, treatment naive ††</td>
<td>Selexipag 200-1060 μg twice daily</td>
<td>NA</td>
<td>NA</td>
<td>Primary: First event of death or a complication related to PAH‖</td>
<td>Low risk</td>
</tr>
<tr>
<td>SERAPHIN, 2013</td>
<td>224/742 (30%)</td>
<td>6 months</td>
<td>Non-parenteral prostaglandins, phosphodiesterase-5 inhibitors, treatment-naive</td>
<td>Macitentan 3 mg (n=73) per day</td>
<td>NA</td>
<td>NA</td>
<td>Primary: time to first event related to PAH or death from any cause Secondary: 6MWD; WHO functional class; death due to PAH or admission to hospital for worsening PAH up to the end of treatment period (analysed in a time-to-event analysis), death from any cause up to the end of the study</td>
<td>Low risk</td>
</tr>
<tr>
<td>PHIRST, 2011</td>
<td>19/87 (22%)</td>
<td>16 weeks</td>
<td>Bosentan (53%), treatment-naive (47%)</td>
<td>Tadalafil 40 mg (n=9) or 20 mg (n=10) per day</td>
<td>NA</td>
<td>NA</td>
<td>Primary: 6MWD Secondary: WHO functional class, TTCW, BIDS, hemodynamic measurements</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Notes: *Number of CTD patients/overall patients (%) †PATENT-1/2: PATENT-1 was a 12-week, randomised, double-blind, placebo-controlled, Phase III trial to study the efficacy of riociguat for the treatment of PAH. PATENT-2 is a 2-year, open-label, long-term extension study that includes patients who completed PATENT-1 without ongoing study drug-related serious adverse events. 70 patients received the PAH-specific pretreatment: ERA and/or non-parenteral prostaglandins. ‡Mean duration of study treatment was 63.7 and 70.7 weeks for the patients receiving placebo and selexipag, respectively. **10% improvement in 6MWD compared with baseline, with improvement in or maintenance of WHO functional class I or II symptoms and no events of clinical worsening before or at the week 24 visit. ††defined as time to death from any cause, hospitalisation for worsening PAH or start of intravenous prostanol therapy, atrial septostomy, lung transplant, or worsening PAH. †‡The mean duration of the study was 63.7 and 70.7 weeks for the patients receiving placebo and selexipag, respectively. †††Since 80% of patients were on background therapy and subgroup analyses were not available, analyses were performed for the whole population. †‡‡Disease progression, worsening PAH resulting in hospitalisation, initiation of parenteral prostanol therapy or oxygen therapy, lung transplantation, or atrial septostomy. †††worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanooids, lung transplantation, or atrial septostomy. CTD: connective tissue disease; PAH: pulmonary arterial hypertension; ERA: endothelin receptor antagonist; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; TTCW: time to clinical worse; BDS: Borg dyspnea Scale; EQ-5D: EuroQoL Group 5-Dimension self-report questionnaire on QoL; LPH: living with pulmonary hypertension; SSc-PAH: systemic sclerosis associated PAH; NA: not available.

descriptively reported and may be regarded as exploratory. In the studies of AMBITION, a mean reduction in NT-proBNP from baseline was greater in patients receiving combination therapy versus monotherapy [-60.4% vs. -43.1% (103 vs. 84)] in overall CTD-PAH patients. A similar improvement was also found in PATENT-1/2 trial, which showed that riociguat could improve PVR (-135±157 vs. -45±222 dyn ·s ·cm⁻²; 41 vs. 12), cardiac index (0.5±0.6 vs. -0.2±0.5 (L/min ·m²; 41 vs. 12) and NT-proBNP (274±2576 vs. 54±778 pg/mL; 66 vs. 17) to a greater extent in the combination group versus monotherapy in the CTD-PAH population.

Discussion
In this study, by pooling the results of available clinical trials, the results of
our meta-analysis demonstrated that combination therapy targeting PAH was associated with a significantly reduced risk of clinical worsening in CTD-PAH patients compared with monotherapy. Moreover, combination therapy may also be associated with a favorable change of exercise capacity as measured by the results of 6MWD, although this was not statistically significant. These results suggested that combination therapy targeting PAH may confer better therapeutic efficacy compared with monotherapy in CTD-PAH patients.

Efficacy in CTD-PAH vs. IPAH

Findings from numerous previous RCTs (25-27) and meta-analysis (1, 2, 10-12) support that risk reduction (approximately 35%-38%) and exercise capacity improvement was more remarkable in overall PAH patients than those who received PAH-target combination therapy compared with monotherapy. However, whether this is consistent in patients with CTD-PAH deserves further confirmation. Notably, the results of several large-scale cohort studies have indicated that patients with CTD-PAH are usually associated with poor prognosis despite intensive treatment (5, 9).

In summarising the outcomes of phase III RCTs of target therapies for PAH submitted to the US Food and Drug Administration (FDA), Rhee et al. (9) reached the conclusion that treatment was less effective in CTD-PAH compared with IPAH in terms of increasing 6MWD (difference in the treatment effect of Δ6MWD: -17.3 m, 90% CI[-31.3 to -23.3], p=0.043) and preventing clinical worsening (p for interaction =0.012). Our study showed similar results, indicating that the reduction of RR for clinical worsening is 27% in CTD-PAH patients who received combination PAH targeting therapy as compared with monotherapy (in comparison with an approximate 35%-38% reduction in overall PAH patients) (1, 2, 10). This is important because clinical worsening has been approved to be an evidence-based end-point in studies of treatment efficacy in PAH despite an inconsistent definition (1). We also found that combination therapy tended to improve the exercise capacity as evi-
denced by an improvement of 6MWD of 21.38 m. However, a meta-analysis regarding the influence of combination therapy on 6MWD had significant heterogeneity, and the results were not statistically significant. This was most likely caused by the limited studies being combined. Interestingly, although changes in the 6MWD in PAH patients have been associated with a change in the risk of clinical worsening (28, 29), subsequent studies did not support that changes in 6MWD were an inappropriate surrogate marker of disease progression, and 6MWD may not predict clinically relevant events such as all-cause death, hospitalisation, or lung transplantation (1, 30). Therefore, the influence of combination therapy on 6MWD in patients with CTD-PAH needs to be confirmed in future large-scale clinical trials.

Recent studies (9, 31) tried to explain the attenuated response in CTD-PAH compared with idiopathic PAH. Firstly, patients with CTD-PAH tended to be older, were more likely female, had lower exercise capacity and carbon monoxide diffusion capacity levels at the baseline, and experienced adverse events more frequently than patients with IPAH or heritable PAH. Secondly, patients with CTD-PAH, especially SSc-PAH, are more likely to have pulmonary venous changes in addition to the characteristic pulmonary arterial changes observed in IPAH. They also tend to have extrapulmonary complications, such as arthritis, limited mobility, and deconditioning [32, 33]. Moreover, additional comorbidities, such as interstitial lung disease and recurrent aspiration resulting from esophageal dysmotility, may also affect clinical outcomes and treatment response in patients with CTD-PAH (34). Therefore, it is important in clinical practice to initiate PAH targeted therapy in patients with CTD-PAH immediately after diagnosis, and combination therapy may be preferable, according to the results of our findings.
Efficacy in sequential vs. initial combination therapy

Combination therapy is the use of two or more classes of agents simultaneously and has theoretical appeal because the modulation of several signaling pathways by combing drugs may improve outcomes without increasing drug toxicity (8, 35). Combination therapy may be sequentially added on or initially combined up front. Up to now, studies that compared the efficacies of sequential and upfront combination therapy in PAH (36) are rare. BREATHE-2 study (n=33) investigated the efficacy of initial combination therapy with epoprostenol and bosentan compared to epoprostenol which failed to demonstrate any difference between the groups. The AMBITION study (37), which is also included in our meta-analysis, provided the most compelling evidence to date for an upfront oral combination therapy strategy in PAH, including CTD-PAH (19). The results of this study showed that patients with WHO function II beffited most from the upfront combination (HR 0.21 (95%CI 0.07-0.63; p=0.005)), suggesting that the clinical benefits of this upfront strategy may be maximal when used early in these patients. However, it did not conclusively demonstrate that upfront therapy was superior to sequential therapy based on the study design. A pilot study on an initial triple combination (intravenous epoprostenol, bosentan and sildenafil) in 19 WHO functional class III-IV patients provided preliminary evidence of long-term benefits of upfront triple combination therapy in patients with severe PAH (38). Based on the above findings, it could be hypothesised that initial (upfront) combination may be a better choice for PAH patients with III-IV class of WHO function, severe hemodynamic impairment, extremely in CTD-PAH for better treatment benefits. Further studies are needed to evaluate whether the efficacy of sequential and upfront combination is different in selected PAH patients.

Safety

Our meta-analysis failed to compare the safety of combination therapy and monotherapy in the specified CTD-PAH population with the restricted data. In the subgroup analysis of CTD-PAH from AMBITION (19), no further increased risk of safety issues was noticed in the combination group of the CTD-PAH subset. Specifically, the incidence of adverse events (AEs) was more frequent with initial combination therapy than monotherapy, but these were limited to common AEs including peripheral edema, headache, etc., and serious adverse events (SAEs) and AEs leading to a permanent discontinuation of the study drug were balanced. Analysing the data of 10 RCTs of therapies for PAH from the US FDA, the risk of AEs was higher among patients with CTD-PAH assigned to active therapy compared with those receiving placebo than IPAH (OR: 1.57, 95%CI [1.00-2.47] vs. OR: 0.94, 95%CI [0.69-1.26]; p for interaction = 0.061); however, there was no difference in the risk of SAEs in the analyses. Despite the higher occurrence of AEs in patients with CTD-PAH, the risk of drug discontinuation due to an AE was similar to that in IPAH (p for interaction = 0.27) (31). Notably, the higher occurrence of treatment-related AEs in patients with CTD-PAH did not translate into an increased risk of drug discontinuation due to an AE. This may indicate that treatment-related AEs in patients with CTD-PAH, although greater in number, were not sufficiently severe to warrant treatment discontinuation. Alternatively, it could be well-tolerated when appropriate preventive measure was applied to minimise the occurrence and impact of AEs. Obviously, the safety outcomes regarding the combination therapy in patients with CTD-PAH warrant further evaluation.

Limitation

Our study has limitations that should be considered when interpreting the results. Firstly, the restricted numbers of RCTs and small sample size of the study included may lead to heterogeneity and overestimated beneficial effects over the limited studies (39). We also pooled data from the subgroup analysis of the PAH population and not the specified CTD-PAH studies; thus, some baseline data were incomplete. Only the AMBITION study and PATENT-1/2 study further explored the difference in outcomes in the individual CTD-PAH population. However, the end-point of the above two trials was different for analysis merging because clinical failure was defined as a primary outcome in the AMBITION study, while the change in 6MWD was the primary outcomes in the PATENT-1/2 study. Secondly, our meta-analysis pooled data from studies comparing different combinations of pulmonary vasodilators. However, not all target agents were included. The 6 included trials assessed the additional effect of phosphodiesterase-5 inhibitors (n=1 PHIRST; 2011), endothelin receptor antagonists (n=3, AMBITION 2015; SERAPHIN, 2013; COMPASS-2, 2015), a soluble guanylate cyclase stimulator, riociguat (n=1 PATENT-1/2 2016), and a selective prostacyclin receptor agonist, selexipag (n=1, GRIPHON, 2015), while oral or inhaled prostaglandins were not included. Although current guidelines indicate that any form of the combination of two or more classes is acceptable, difference exist regarding the pharmacologic efficacy and safety profiles among the individual agents and the order in which the drugs were added within each of these combinations. Moreover, no head-to-head trials of different combinations have been performed, and it may be difficult to achieve with the few published studies aiming at the CTD-PAH population. Finally, the inconsistent presentation of 6MWD, the different duration of the trials, and the difference of CTDs at baseline may also contribute to heterogeneity in the meta-analysis.

In conclusion, the results of our meta-analysis indicated that combination therapy targeting PAH may confer preferable therapeutic efficacy compared with monotherapy in patients with CTD-PAH as evidenced by a more remarkable reduction in risk of clinical worsening and a probable improvement of exercise capacity in these patients. Because the prognosis in patients with CTD-PAH is worse than overall PAH, initial combination therapy may improve the clinical outcome outcomes in the CTD-PAH population.
References


