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Short communication

The impact of delayed treatment on 6-minute walk distance test in patients with pulmonary arterial hypertension: A meta-analysis

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ABSTRACT

Background: The impact of treatment delay in stable patients with pulmonary arterial hypertension (PAH) remains unaddressed.
Methods: This meta-analysis included six datasets of PAH therapies with randomized-controlled trials (RCT) and corresponding open-label extension (OLE) studies. We evaluated the change in 6MWD at 1 year in the OLE studies by active treatment versus ex-placebo group. The ex-placebo group (i.e., the patients randomized to placebo in the RCT and ultimately treated with active therapy in the OLE) represented the "delay-in-treatment" population.
Results: Patients with a treatment delay of 12–16 weeks in PAH targeted therapy had an improvement in 6-minute walk distance (6MWD) test at 1 year, but this improvement did not amount to the same degree of improvement as their initially treated counterparts. The difference in 6MWD was 15 m to 20 m at 1 year.
Conclusion: A short-term delay in PAH targeted therapy may adversely affect functional capacity in patients with PAH. This meta-analysis provides some insight as to whether earlier treatment would benefit stable patients with PAH.

1. Introduction

Despite advances in pulmonary arterial hypertension (PAH) targeted therapies, patients with this progressive and fatal disease often experience delays in diagnosis as well as delays in treatment.

The adverse prognostic impact of late referral for parenteral prostanoids and the consequent delay in such treatment has been demonstrated in a monocentric study by Badagliacca et al. [1], but the importance of treatment delay in stable naïve patients remains unaddressed. This is an important clinical issue as current guidelines suggest either monotherapy or upfront combination therapy for treatment-naïve PAH patients in World Health Organization functional class (WHO FC) II or III [2]. The monotherapy approach, however, may delay the start of combination therapy by at least 4 to 6 months since time of first evaluation.

In the present meta-analysis, we address the impact of delayed treatment on functional capacity by analyzing the treatment arms of randomized controlled trials (RCTs) that were followed by an open-label, long-term evaluation. Our working hypothesis was that patients with a delayed start in PAH-targeted therapy during the open-label phase would not achieve the same level of 6MWD in the long term compared with their peers who started the active treatment during the blinded phase.

2. Methods

We identified the pivotal RCTs for each of the approved PAH targeted therapies, as these studies included both an active arm and a placebo arm. In addition, these particular trials would have consistency in terms of study designs and data reporting, based on the regulatory requirements for approval (e.g., 6MWD as an efficacy endpoint). From these studies, only studies with data reported for an open-label extension (OLE) phase were considered. We surmised that patients randomized to placebo in the RCT would have ultimately been treated with active therapy in the OLE; therefore, these ex-placebo patients could represent the "delay-in-treatment" population. Lastly, we included only trials that reported 6MWD in the OLE stratified by active and ex-placebo groups at the end of the study.

Our search yielded a total of 6 datasets, including BREATHE-1 OLE, ARIES OLE, PATENT-2, PHIRST-2, FREEDOM OLE, and TRIUMPH OLE [3–8]. These studies evaluated bosentan, ambrisentan, riociguat, tadalafil, oral treprostinil, and inhaled treprostinil, respectively. Data analyzed from each study consisted of estimates of change in 6MWD at 1 year in the OLE studies by active treatment versus placebo group. Notably, the baseline 6MWD for the placebo group was reported differently among the OLE studies. In our analysis, for "Subset 1" (BREATHE-1 OLE, ARIES OLE, PATENT-2, and PHIRST-2), the results for this endpoint were based on a comparison against the baseline 6MWD in the pivotal

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RCTs. For "Subset 2" (FREEDOM OLE and TRIUMPH OLE), they were based on the baseline 6MWD reported before active treatment in the OLE trials. Results are therefore presented as separate models. A general fixed-effect parametric approach [9] was used to calculate the overall estimate of treatment difference measured as change in 6MWD at 1 year between active arm and ex-placebo.

3. Results

The six datasets included in the analysis comprised a total population of 1157 patients. From these datasets, four RCTs were 12 weeks in duration (ARIES-1/-2, PATENT-1, TRIUMPH-1, FREEDOM-M) [10–13]; the others were 16 weeks in duration (BREATHE-1, PHIRST, FREEDOM-C, FREEDOM-C2) [14–17]. Across these studies, baseline 6MWDs ranged from a mean of 330 to 368 m and were generally reflective of a patient population in predominantly in WHO FC III and, to a lesser extent, WHO FC II. A small percentage of patients were in WHO FC IV. Three RCTs included only PAH-treatment-naïve patients (ARIES-1/-2, FREEDOM-M, BREATHE-1) [10,13,14], whereas in the other studies, active therapy could be added on to stable background PAH therapy [11,12,15–17].

Fig. 1 shows summary statistics for each study, and the results of the fixed effects meta-analysis. The overall fixed-effects estimate of mean difference in change in 6MWD from pivotal RCT baseline, or "Subset 1," is 14.6 m (95% CI [5.6–23.5]) ($P = 0.0015$). The overall fixed effects estimate of mean difference in change in 6MWD from baseline before first active dose, or "Subset 2," is 20.5 m (95% CI [10.4–30.7]) ($P = 0.0001$). Both show a statistically significant difference in change in 6MWD at 1 year between the active arm and ex-placebo arm.

4. Discussion

To our knowledge, this is the first study reported in the literature to quantify the impact of delayed treatment with PAH targeted therapy on 6MWD, looking across classes of approved therapies and their respective OLEs. We found that patients with a short-term delay (12–16 weeks) in PAH targeted therapy had an improvement in 6MWD at 1 year, but this improvement did not amount to the same degree of improvement as their initially treated counterparts.

Based on our analysis, the difference in 6MWD ranges from 15 to 20 m at 1 year, which is quantitatively relevant if we consider that in the randomized-controlled phases of PAH trials the differences in 6MWD between study intervention and placebo/control at the end of 12 or 16 weeks ranged from 20–60 m in treatment-naïve patients [10,11,13–15] to 10–25 m in patients who were already on background PAH therapy [12,15–17]. With upfront combination strategy, Galie et al. [18] found a significant treatment difference of about 25 m with ambrisentan–tadalafil versus monotherapy at 24 weeks, and this improvement in 6MWD was associated with a significant long-term reduction in mortality/morbidity events. In a pooled analysis of 10 RCTs, even though change in 6MWD did not explain a large proportion of the relationship between treatment and clinical outcomes, an increase of 10 m was found to significantly reduce the risk of clinical events at 12 weeks [19]. Also, from a clinical perspective, the inability of patients with delayed treatment to achieve an additional 15- to 20-m improvement in 6MWD could have important clinical consequences, as the capacity to achieve a certain 6MWD threshold has been demonstrated to have prognostic value either alone or in combination with other indices [20–22].

A limitation of this study is that, due to incompleteness in data reporting, we could not be more inclusive of all RCT and OLE studies for the PAH targeted therapies, which would have increased the robustness of the analysis. Although we had representative agents from each class of targeted therapy (including prostacyclin analogues [treprostinil], endothelin receptor antagonists [bosentan, ambrisentan], phosphodiesterase type-5 inhibitors [tadalafil], soluble guanylate cyclase stimulators [riociguat]), sitaxsentan, sildenafil, iloprost, and beraprost were not included due to the incompleteness of data reporting (i.e., some studies did not report 6MWD in the OLE, and others did not stratify these results by active versus ex-placebo). Further, newer approved agents, such as macitentan and selexipag, have been studied in long-term morbidity-mortality trials, and there are no data from OLE studies. For this same reason, studies that evaluated use of upfront combination therapies could not be included. Importantly, the use of OLE study data limits our meta-analysis in confirming a point estimate for a treatment effect. OLE studies are, by definition, unblinded and exclude subjects who discontinued for any reason (including clinical worsening, declining to continue despite doing well on therapy, etc.). Another limitation is that our meta-analysis focused on change in 6MWD, as this endpoint was used as the primary endpoint in most pivotal RCTs. Functional capacity evaluated by 6MWT is not a strong surrogate for morbidity/mortality; thus, our analysis is unable to address whether the same phenomenon would also occur with harder endpoints that have been evaluated in more recent trials [18,23,24]. Certainly, additional insight may have been garnered by looking at longer term event-based outcomes, such as clinical worsening; however, differences in definitions and/or reporting of these endpoints across the OLE studies as well as the variable nature as to when an event will occur precluded assessment of these data in our meta-analysis. Lastly, our meta-analysis was limited to an evaluation timeframe of 1 year, based on available OLE data. Therefore, it is unknown if the ex-placebo patients would have eventually caught-up at a later date.

In conclusion, results from our meta-analysis show that a short-term delay (12 to 16 weeks) in PAH targeted therapy has adverse impact on functional capacity as measured by 6MWD in the longer term. Patients

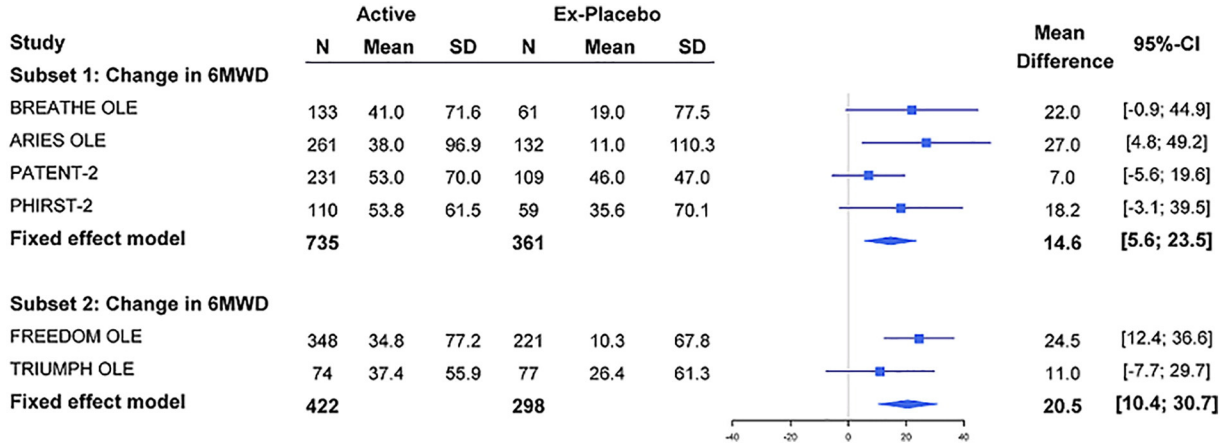

Fig. 1. Fixed-effects estimate of mean difference in change in 6MWD.

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with a delay in PAH targeted therapy do not "catch up" to their earlier treated counterparts over the first year of treatment and, therefore, the benefit of earlier treatment may not be recouped, at least during this timeframe. It is not known if patients with a delay in therapy can or will eventually catch up at a later date. Additional studies that assess the impact of delayed treatment on clinical outcomes such as clinical worsening and survival would be of interest.

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CDV has received fees for serving as a speaker, consultant, and an advisory board member for Actelion, Bayer, Dompè, GSK, Italfarmaco, Lilly, MSD, Pfizer, and United Therapeutics. RB has received fees for serving as a speaker and consultant for Bayer, Dompè, GSK, MSD, and United Therapeutics. CRM, YR, and ACN are employees of United Therapeutics. RLB has received fees for serving as a consultant for Bayer and United Therapeutics, and has received research support from Actelion, Bayer, Geno Pharmaceuticals, Gilead, IKARIA, and United Therapeutics.

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