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Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: The TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension (TRIUMPH) study open-label extension

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combination

BACKGROUND: Inhaled treprostinil improved functional capacity as add-on therapy in the short-term management of patients with pulmonary arterial hypertension (PAH). This study investigated the long-term effects of inhaled treprostinil in patients concurrently receiving oral background therapy.

METHODS: A total of 206 patients (81% women) completing the 12-week double-blind phase of the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study transitioned into an open-label extension. Patients were assessed every 3 months for changes in 6-minute walk distance (6MWD), Borg dyspnea score, New York Heart Association (NYHA) functional class, quality of life (QOL) scores, and signs and symptoms of PAH.

RESULTS: Patients were primarily NYHA class III (86%), with a mean baseline 6MWD of 349 ± 81 meters. A median change in 6MWD of 28, 31, 32, and 18 meters in patients continuing therapy was observed at 6, 12, 18, and 24 months, respectively. This effect was more prominent in those patients originally allocated to active therapy in the double-blind phase. Survival rates for patients remaining on therapy were 97%, 94%, and 91% at 12, 18, and 24 months, respectively. In addition, 82%, 74%, and 69% of patients maintained treatment benefit as evidenced by lack of clinical worsening at 12, 18, and 24 months. The most common adverse events were known effects of prostanoid therapy (headache [34%], nausea [21%], and vomiting [10%]) or were due to the route of administration (cough [53%], pharyngolaryngeal pain [13%], and chest pain [13%]).

CONCLUSIONS: Long-term therapy with inhaled treprostinil demonstrated persistent benefit for PAH patients who remained on therapy for up to 24 months.

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Several medical therapies are currently approved for the treatment of patients with pulmonary arterial hypertension (PAH). These therapies cover 3 distinct therapeutic classes and various routes of administration, including oral phosphodiesterase-5-inhibitors (PDE-5), endothelin receptor antagonists (ERA), and inhaled, intravenous, and subcutaneous prostanoids. Although a variety of treatment options

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exist, the disease remains one of progression and the outcome is invariably fatal.[1]

Because many patients do not respond sufficiently to single pharmacologic therapy, front-line combination or step-wise increase of pharmacotherapy is an option included in many standardized algorithms for treating this disease.[2,3] As part of this stepwise therapy, a common convention is to start with 1 oral agent. If targeted goals are not met after a period of time, then a second therapy is added, usually another oral or an inhaled agent.

There are a number of published studies of single-center experience and randomized trials of combination therapy that include inhaled prostacyclins.[4–7] Recently, inhaled treprostinil was demonstrated to be safe and efficacious when added to bosentan (an ERA) or sildenafil (a PDE-5 inhibitor) in PAH patients with New York Heart Association (NYHA) functional class III or IV[8] and is U.S. Food and Drug Administration-approved for combination therapy. In the pivotal multicenter double-blind study evaluating the addition of inhaled treprostinil to oral background therapy in 235 patients, the median placebo-corrected change from baseline in peak 6-minute walk distance (6MWD) was 20.0 m at Week 12 ($p = 0.0004$). In addition, quality of life (QOL) measures and *N*-terminal pro brain natriuretic peptide (NT-proBNP) improved with the addition of inhaled treprostinil.

Treprostinil is a well-characterized stable analog of native prostacyclin (PGI_2). The major pharmacologic actions of treprostinil are direct vasodilatation of pulmonary and systemic vascular beds and inhibition of platelet aggregation. Inhaled delivery of treprostinil for the treatment of PAH was developed to deliver its effects directly to the pulmonary vasculature while minimizing systemic side effects. The inhaled route of delivery is devoid of the risks, discomforts, and inconveniences associated with the parenteral administration of prostanoids.[9]

Despite the well-defined short-term efficacy of many therapeutic agents, including inhaled prostacyclins, one limitation is the lack of long-term data. Indeed, some therapies with notable efficacy at 12 weeks demonstrated waning and sub-optimal clinical effects at 1 year.[10] In light of this, long-term studies are being conducted with most new PAH therapies,[5,11,12] and maintained clinical effects must be demonstrated before these therapies become incorporated into current guideline-based therapy. As such, the goal of the present study was to observe the long-term clinical efficacy and safety of the addition of inhaled treprostinil to bosentan or sildenafil over 24 months in the TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension (TRIUMPH) trial.

Materials and methods

Patients eligible for this open-label extension had previously completed the 12-week double-blind, placebo-controlled, TRIUMPH study.[8] For patients that received the active drug for the first time during the open-label phase (ie, were randomly allocated to receive placebo in the double-blind phase), baseline data were those collected at their Week 12 double-blind visit. For patients who previously were randomized to receive the active drug in the double-blind phase, baseline data were those collected at the initial baseline visit before starting treatment in the double-blind phase. The duration of time on therapy was calculated for each patient beginning at the start of inhaled treprostinil therapy. In addition, in all patients beginning the open-label portion of study, inhaled treprostinil was reinitiated at 3 breaths 4 times daily to maintain the integrity of the initial blind.

Study visits were conducted every 3 months, which included the following assessments: peak 6MWD, performed between 10 and 60 minutes after the last inhalation, Borg dyspnea score, NYHA functional class, physical examination, evaluation of PAH signs and symptoms (specifically, edema, chest pain, orthopnea, dizziness, dyspnea, syncope, and fatigue), QOL questionnaire (Minnesota Living with Heart Failure [MLWHF]), and occurrence of adverse events. Trough 6MWD (ie, > 4 hours after dosing) was not collected in the open-label extension. The data presented here represent patients who received inhaled treprostinil for up to 2 years.

Statistical analysis

Change from baseline was calculated for data collected at 3-month intervals for 6MWD, Borg dyspnea score, NYHA class, QOL-MLWHF questionnaire, and PAH signs and symptoms. The *p*-values from the Wilcoxon signed rank test for change from baseline were calculated and are descriptive only, because no formal hypothesis tests were planned for the open-label extension. The primary end point analysis was performed without imputation of data. To address missing data from study assessments that were not conducted for any reason, an imputed analysis of last observation carried forward (LOCF) is also presented for this open-label, uncontrolled data set.

Results

Subject disposition

Results at 24 months are presented from 206 participants of the original 235 TRIUMPH patients. Of the 29 individuals who did not participate in the open-label phase, 23 (13 active, 10 placebo) discontinued before completing the double-blind phase,[8] and 6 (5 active, 1 placebo) were not transitioned into the extension by the investigator. Baseline demographics, PAH etiology, and treatment history are summarized in Table 1. The 206 patients were a mean age of 54 ± 14 years, 167 (81%) were women, and 116 (56%) were diagnosed with idiopathic PAH. Patients were on a background regimen of bosentan (69%) or sildenafil (31%). Collectively, patients received background therapy for a mean of 90 ± 74 weeks before enrollment.

The mean 6MWD at baseline was 349 ± 81 meters, and 86% of patients were at NYHA class III.

Of the 206 patients, 122 (59%) remained in the study for more than 24 months (Figure 1), and the remaining 84 of 206 participants discontinued the study because of adverse events (17%), disease progression (8%), death (5%), with-