Pulmonary arterial hypertension (PAH) is characterized by vascular remodeling and cellular proliferation that leads to narrowing and obstruction of small pulmonary arteries. The arteriopathy is clinically manifest as increased pulmonary vascular resistance and elevation of pulmonary arterial pressures. PAH is considered a progressive vasculopathy that ultimately leads to right heart failure and death. Although there is no cure for PAH, current pharmacological therapies have improved morbidity, and in some cases, mortality. The current 3-year survival for patients with PAH managed with state-of-the-art multiple drug therapy remains troubling at ≈58%.1 This is slightly better than in the 1980s, when there were no approved treatments.

In PAH endothelial dysfunction and platelet activation causes an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A2 production. Prostacyclin has both vasodilatory and antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Prostacyclin synthase levels are decreased in pulmonary arteries of patients with PAH.2 An imbalance between these two arachidonic acid metabolites favoring thromboxane A2 plays an important role in the pathogenesis of PAH.3 This imbalance is addressed by the exogenous administration of prostanoids as therapy in advanced PAH.

Epoprostenol was the first prostacyclin used in the treatment of PAH. Intravenous epoprostenol improves hemodynamics, functional capacity, and survival.4,7 The second-generation prostanooid, Treprostinil, which has a considerably longer half-life (4.5 hours versus 4–6 minutes for epoprostenol),3 can be administered subcutaneously, intravenously, or by inhalation, and also improves pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH.3,11 Prostacyclin remains a mainstay of PAH therapy and is the only therapy with a proven survival benefit.12,17 Limitations of prostacyclins are the delivery systems and the inherent complications of a chronic central venous tunneled catheter, subcutaneous infusion site inflammation and pain, and the limited ability to escalate dose with inhalational therapies. Nevertheless, prostacyclins remain the treatment of choice in patients with severe PAH. There is growing evidence that earlier use of prostanoids may benefit patients with mild-to-moderate disease.14

In spite of growing evidence that the use of prostanoids improves both morbidity and mortality, they remain underused. There is a clear impact of underprescribing of prostacyclins on mortality15; in fact, half of the patients who die with PAH die never having been treated with a prostacyclin. An effective well-tolerated oral approach would have a tremendous impact on delivery of what is consider the most effective therapy for patients with PAH.

In the current issue of Circulation, Jing and colleagues16 present the results of the recently completed FREEDOM-M trial, a double-blind, randomized, placebo-controlled, parallel-group study comparing the twice daily administration of oral treprostinil with placebo in de novo PAH patients not receiving any background PAH therapy. The study drug dose was titrated based on each patient’s clinical response and tolerability. The study was designed to assess the safety and efficacy of oral Treprostinil based on the primary end point of change in 6-minute walk distance (6-MWD) over 12 weeks of therapy in patients with access to 0.25-mg tablets at randomization. Secondary efficacy end points included changes in 6-MWD at Weeks 4, 8, and 11, World Health Organization functional class, Borg Dyspnea Score, dyspnea-fatigue index, signs and symptoms of PAH, and clinical worsening, which represent the current standard approach to clinical trials in PAH. The authors found that there were significant improvements in 6-MWD, with >50% of subjects treated with study drug improving by ≥20 m, and >30% of patients improving their 6-MWD >50 m. The therapy was well tolerated, and side effects were typical of prostacyclin treatments.11,17 In contrast to previous clinical trials,18–20 there was no significant treatment effect on the incidence of clinical worsening. However, the overall incidence of clinical worsening was quite low.

Previous studies of oral Treprostinil have shown variable results. The first completed oral Treprostinil study was the FREEDOM-C trial; a randomized, double-blind, placebo-controlled trial that included 354 PAH patients who were considered optimized on effective background PAH therapy that included an endothelin receptor antagonist, a phosphodiesterase-5 inhibitor, or both. Patients were administered oral Treprostinil or placebo over the 16-week trial. The majority of patients were World Health Organization functional class III of mixed etiologies as in the FREEDOM-M trial. A nonsignificant treatment effect was observed at Week 12, with a placebo-corrected median change of 11 m (P=0.07).
Patients who achieved a week-16 twice-daily oral Treprostinil dose of 1.25 to 3.25 mg and 3.5 to 16 mg experienced a greater change in 6-MWD (18 and 34 m, respectively) than patients who achieved a twice-daily dose of <1 mg or discontinued because of adverse events (4 m).21 In the current study there also appeared to be a correlation between dose and 6-MWD treatment effect. A further analysis of the FREEDOM-C data suggests that the inability to dose titrate was a limiting issue that muted the overall treatment effect. Of the 174 patients who received active drug, 135 completed the study, 25 patients discontinued because of an adverse event, and 33 patients were unable to titrate their dose >1 mg twice daily. Accordingly, 58 (33%) patients in the active treatment group did not maintain a dose of oral Treprostinil >1 mg twice daily, which appeared to be a suboptimal dose.

One of the key differences in the study by Jing et al is the ability for a more gradual dose titration that was better tolerated. It appeared that relatively rapid dose titration in earlier studies limited to 1-mg increments may have a negative result for the first phase III trial of oral treprostinil; many patients dropped out, and few were able to escalate dose to therapeutic levels. This led to the development of lower strength tablets used in the current study.

This and several other recent trials of new therapies in PAH illustrate the growing challenge of conducting studies in a complex orphan disease.22 The FDA has yet to approve oral Treprostinil, having questioned the clinical importance of the 6-MWD in previously released FREEDOM-M data, the inability to demonstrate an improvement in time to clinical worsening in any study of oral Treprostinil, and the inability to show a significant improvement in 6-MWD in the FREEDOM-C studies (personal communication, United Therapeutics). Our usual approach to phase III trials in pulmonary vascular disease needs to be reconsidered. In the West it has become nearly impossible to do a de novo placebo controlled trial, which is why an increasing number of trials are being done in countries that have limited treatment options. If we continue to use our traditional outcome measures in studies requiring background therapy, it is hard to envision how much more we can squeeze out of a 6-MWT, or how much impact we can have on clinical course in a 12- to 16-week time frame. We may be setting the approval bar out of reach. Fortunately, along with advances in our understanding of the science of PAH, there are increasing efforts toward the development of improved clinical trial design. The introduction of new trial design will require collaboration between academic investigators, clinicians, regulatory agencies, and the pharmaceutical industry.22,23

The study by Jing et al16 presents encouraging data that support using an oral prostacyclin as effective first line therapy for patients with PAH. This study does not provide confirmation that oral prostacyclin is more or less effective than other oral therapies. It is also not clear whether the effects on survival seen with escalating doses of IV prostacyclin will be seen for oral versions. Nevertheless, availability of an oral prostacyclin would address very important aspects of the care of these complex patients, including the ability to provide the benefits of prostacyclin therapy to a broader population of patients with PAH. Providing prostacyclin therapy earlier in the course of PAH could limit or delay the need for more complex delivery systems and the inherent complications of those systems.

Disclosures

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References


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