Clinical Trials Update


Fernando Torres, MD


Deborah Jo Levine, MD

Section Editors: **Fernando Torres, MD**, and **Deborah Jo Levine, MD**

The Clinical Trials Update was created as a way to highlight new and ongoing research trials that are evaluating therapies for pulmonary arterial hypertension (PAH). In this issue we highlight 2 multicenter trials that recently led to FDA approval for 2 new PAH therapies: PHIRST-1 and TRIUMPH-1.

The PHIRST-1 Study[1] (Pulmonary Arterial Hypertension and Response to Tadalafil [an orally active phosphodiesterase type-5 inhibitor]) was a 16-week randomized, double-blind, placebo-controlled trial including patients with either idiopathic PAH or associated PAH. Patients enrolled in the study were either PAH-treatment–naïve, or on background therapy with the endothelin-receptor antagonist bosentan. All patients (whether naïve or on bosentan) were randomized to receive placebo or tadalafil at doses of 2.5, 10, 20, or 40 mg orally daily.

The primary outcome measure was the placebo-corrected change from baseline to Week 16 in 6-minute walk distance. Secondary outcomes included WHO functional class, time to clinical worsening, Borg dyspnea score, and quality of life measures. Hemodynamic measurements were obtained in a subset of patients. Patients completing the study could enter a long-term extension trial.

A total of 405 patients with PAH were evaluated, and randomization was stratified for baseline walking distance, type of PAH, and bosentan use. The majority of patients had symptoms of WHO functional class II or III. Of these patients, 53.5% (n=216) were on baseline bosentan.

There was a dose-dependent improvement in the 6-minute walk distance with tadalafil; however, only the 40 mg dose showed a statistically significant improvement ($P<0.01$). In the total group the mean placebo-corrected effect was 33 meters. In the bosentan-naïve group the treatment effect was 44 meters, and in the bosentan-treated group the treatment effect was 23 meters.

There was no statistically significant difference between the groups with regard to WHO functional class. There was an improvement in time to clinical worsening in the tadalafil 40 mg group compared to placebo, but this was not statistically significant. There was no difference in the Borg dyspnea score between the tadalafil and placebo groups. There was a statistically significant improvement in the quality of life score in patients on tadalafil. In the 93 patients for which hemodynamic data were collected, there were statistically significant improvements in the mean pulmonary arterial pressure, pulmonary vascular resistance, and confidence interval in the tadalafil 20 and 40 mg daily groups. No changes were seen on the systemic blood pressure.

All doses of the tadalafil were well tolerated. The most common adverse events were headache, myalgia, and flushing. Most adverse events were reported as mild or moderate. Of the 341 patients who completed the 16-week study, 334 entered the long-term prospective extension study. This trial provides evidence of the safety and efficacy of the orally active phosphodiesterase type-5 inhibitor, tadalafil, at a dose of 40 mg once daily. The effects seen on exercise and hemodynamics are comparable to other drugs approved for PAH. Of note, just over 50% of the patients enrolled in this study were already on background therapy with the endothelin receptor antagonist bosentan. This group also showed improvements (although to a lesser extent then the patient-naïve group). This is important as it lends support for the use of combination therapy in PAH.

The results of the TRIUMPH-1 study were presented at ATS 2008. The study examined the effects of adding inhaled treprostinil to background medical therapy of either an endothelin receptor antagonist (bosentan) or a phophodiesterase type-5 inhibitor (sildenafil). The study medication was delivered through a multipiece device called the OptiNeb® (United Therapeutics, Silver Spring, MD). The medication is inhaled during 4 sessions per day. Each session consists of 3 to 12 puffs and takes 3 to 5 minutes from beginning to end of each treatment. The study's primary end point was a change in 6-minute walk distance. There were 235 patients who participated in this double-blind, randomized (1:1), placebo-controlled study. At the end of 12 weeks, the placebo-corrected improvement in 6-minute walk was 20 meters at peak ($P<0.0006$) and 14 meters at trough ($P<0.01$) of the study drug. Clinical worsening, change in NYHA class, and Borg dyspnea score were not significantly changed. Given that the change in 6-minute walk was highly statistically significant, the medication appears safe; the FDA approved the use of inhaled treprostinil with only one study. Inhaled treprostinil is currently indicated in the US to increase walk distance in patients with NYHA Class III symptoms associated with WHO Group I PAH.

Though some may argue that such a small change in 6-minute walk may not be worth a medication that requires 4 sessions per day, it is notable that the improvement was seen while patients were already on background therapy (endothelin receptor antagonist or phosphodiesterase type-5 inhibitor). The most common side effects (≥10%) seen with inhaled treprostinil in the placebo-controlled clinical study were cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, and diarrhea.

Address for reprints and other correspondence: Fernando.Torres@UTSouthwestern.edu, levinedj@uthscsa.edu

These 2 trials led to the approval of 2 new agents for the treatment of PAH. Both drugs appear to be efficacious and well tolerated. Also, both of these agents are approved at dosing intervals that are less frequent than other agents in the same categories. Over the next few months, we will observe the evolution of the inhaled prostacyclin market with the current inhaled iloprost (available in the US since about 2003). It will also be interesting to see how tadalafil fits within the phosphodiesterase type-5 category, alongside the current phosphodiesterase type-5 inhibitor sildenafil.

Reference

1. Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894-2903.

NHLBI Support of PH Research

The American Recovery and Reinvestment Act of 2009 (ARRA) provided an opportunity to enhance NHLBI support of cardiovascular and cardiopulmonary disease. The scientific community studying PH and related pulmonary vascular diseases competed extremely well for this support. As a result, 6 Challenge Grants were awarded by the Division of Lung Diseases, NHLBI. ARRA-funded projects explore important basic and translational investigations into pulmonary vascular biology, novel disease development hypotheses, and new treatment modalities and measures of treatment efficacy.

Examples of exciting new research on PH therapy in particular include projects that are:

- Identifying novel ways to deliver vasodilators to the pulmonary circulation
- Using stem-cell based drug delivery methods to test novel treatments
- Using nanotechnology to image lung vessels in order to deliver disease-modifying drugs directly to pulmonary vascular lesions
- Identifying treatment-responsive biomarkers in pediatric patients suffering from idiopathic PH

ARRA funding has provided significant investments into furthering our understanding of the lung's circulation, how this vital circulation becomes diseased, and how we can better identify and treat diseases of the lung vasculature including PH. For further information on NHLBI support of PH research, please contact the Division of Lung Diseases' Program Director in Lung Vascular Research:

Timothy M. Moore, MD, PhD
Division of Lung Diseases
NHLBI, NIH
6701 Rockledge Drive
RKL II, Suite 10042
Bethesda, MD 20892
(301) 435-0222