Section Editor
Fernando Torres, MD

Section Editor
Deborah Jo Levine, MD

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Fernando Torres, MD, provides an update on oral prostacyclin trials.

The search for an oral prostacyclin for the treatment of pulmonary arterial hypertension (PAH) dates back to 2003, when beraprost was first studied in the United States. Unfortunately, that trial was not successful because the 6-minute walk improvement seen at 12 weeks did not persist at one year. Therefore, beraprost was not approved by the FDA for treatment of PAH. In November 2008, oral treprostinil made its debut.

FREEDOM-C was a multicenter trial adding oral treprostinil to an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor. The primary efficacy endpoint of the trial was the median change in 6-minute walk distance (6MWD) at 16 weeks relative to baseline. The placebo-corrected median change was 11 meters ($P=0.072$). The sponsoring company, United Therapeutics, speculated that the results may have been more favorable if the lower-dose 0.25 mg tablets had been available at the start of the study for easier uptitration. The patients who achieved a dose of at least 3.25 mg twice daily had a median improvement of 34 meters.

United Therapeutics then amended FREEDOM-M in 2009 to include the lower dose tablet. FREEDOM-M closed enrollment in 2010, and the company reported preliminary results in June 2011. FREEDOM-M studied the use of oral treprostinil vs placebo for the treatment of PAH on patients naïve to PAH-specific therapy. The study enrolled 349 patients, but an amendment to the study made the primary endpoint apply only to the 228 patients who had the 0.25 mg tablets available. At baseline, the patients' mean 6MWD was 330 meters; 99% of the patients were WHO functional class II or III, and 75% had idiopathic PAH while 19% had connective tissue disease.

The median improvement in 6MWD was 23 meters, compared with placebo, resulting in a P value of 0.0125. The combined 6MWD and Borg Dyspnea Score rating also improved ($P=0.0497$). Other secondary endpoints including WHO functional class, time to clinical worsening, and Borg Dyspnea Score were not statistically different from the placebo arm. The main side effects noted in the trial continue to be the common side effects of prostacyclins: headache, nausea, diarrhea, and flushing.

Given the success of FREEDOM-M, the results of a third study, FREEDOM-C(2), are eagerly awaited. This is a multicenter, randomized, placebo-controlled study adding oral treprostinil to a PDE-5 inhibitor and/or ERA. This study is very similar to the FREEDOM-C that failed to achieve its primary endpoint in November 2008. The difference is that all 313 patients in the study had the 0.25 mg and 0.125 mg tablets available. The study closed enrollment in March 2011. The preliminary results show similar disappointing results as FREEDOM-C.

In the trial, 16% of patients in the treatment arm discontinued the study drug. The primary endpoint of placebo-corrected 6MWD median change was 10 meters ($P=0.089$). The secondary endpoints of time to clinical worsening, combined 6MWD and Borg Dyspnea Score, WHO functional Class, Borg Dyspnea Score, and the Dyspnea Fatigue Index were all negative.

The overall FREEDOM Trials results, unfortunately, were that BID oral treprostinil did not lead to significant improvement in exercise capacity among patients who were receiving background PAH therapies, while the monotherapy trial was positive. These results should lead to a number of reassessments—not just about this particular medication, but also about clinical trials of oral prostacyclins and perhaps add-on therapy studies in general. Add-on therapy appears to lead to smaller placebo-corrected improvements in walk distance in general, both because the placebo groups in these studies have smaller (or no) declines in walk distance and because walk distance gains in treated patients are smaller. Nevertheless, we know many of these patients have poor long-term outcomes; alternative endpoints and/or longer studies may need to be considered. Separately, managing side effects, avoiding dropouts, and achieving adequate dosing will also likely be a key issue. It will be interesting to learn more details about dosing and outcomes in these studies.

For monotherapy with oral treprostinil, the trial was positive. We will need to wait and see if the FDA approves oral treprostinil as a monotherapy for the treatment of PH. If oral treprostinil is approved by the FDA, physician education will be needed as to the management of side effects and unwanted discontinuation of the medication. The future of this agent is still unclear and time will tell.

Correspondence: Fernando.Torres@UTSouthwestern.edu