Clinical Trials Update


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We would like to introduce you to a new section in* Advances in Pulmonary Hypertension *in which we highlight results from ongoing and recent clinical trials.

The preliminary results of several multicenter clinical trials have recently been presented. In this issue, we will focus on the results of Freedom-C, which was presented in November of 2008, as well as the Walk-PHaSST study, which was stopped early in July 2009.

FREEDOM-C: A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C SR in Combination with an ERA and/or a PDE-5 Inhibitor in Subjects with PAH.

Oral UT-15C SR is an oral prostacyclin (treprostinil) which is slowly released into the gastrointestinal tract after ingestion. The primary endpoint of this trial was to evaluate how the addition of oral treprostinil affected the 6-minute walk distance (6MWD) in patients with PAH who were already taking an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-5 (PDE-5) inhibitor. Secondary endpoints included time to clinical worsening (TTCW), Borg dyspnea scale, WHO functional class, dyspnea fatigue index, as well as others.

The study enrolled 350 patients. The median change on the 6MWD was only 11 meters at 16 weeks (p=0.07). Several secondary endpoints like TTCW (p=0.46), WHO FC (p=0.96), and Borg score (p=0.06) did not achieve statistical significance. The combined 6MWD/Borg dyspnea score (p=0.01) and dyspnea fatigue index (p=0.01) did, however, reach a statistical difference.

This was the first multicenter trial to include patients on multiple PAH medications. This is important to note as it is believed to be more difficult to show a significant change in 6MWD in patients who are taking baseline PAH medications than in those on no previous medications. Consequently, this study does show promise, as the median increase in 6MWD at 12 weeks was 13 meters (p=0.015). A major problem in this trial was the unpredicted rate at which patients dropped out of the study due to side effects. Headache and gastrointestinal intolerance were the main side effects reported. About 25% of the patients could not tolerate a dose higher than 1 mg twice a day, and 14% of patients eventually discontinued the study medication due to intolerance.

The analysis of the results indicated that the initial dose of study drug was likely too high, which contributed to side effect intolerance and thus an inability to up-titrate the drug. The fact that there was a trend toward improvement in the 6MWD and the fact that the dose could likely be better tolerated if started at a lower dose led United Therapeutics to repeat the trial with a different dosing plan. This new trial is currently enrolling patients.

Walk-PHaSST Study (NCT00492531): A multicenter, randomized, placebo-controlled clinical trial to test the safety and effectiveness of sildenafil for pulmonary hypertension in patients with sickle cell disease.

This was a 16-week, NIH-sponsored study looking at the efficacy of sildenafil therapy on exercise capacity. Secondary endpoints included changes in shortness of breath, pain crisis, pneumonia, and increased survival. The patients were randomized to receive sildenafil or placebo for 16 weeks. After that, they had the option of going into the open arm, receiving sildenafil for up to a year.

The study enrolled 76 patients. Unfortunately, after 33 patients had finished the 16-week trial, an interim safety data review showed significantly more episodes of serious adverse events in the treatment arm (38% vs 8% in the placebo arm). The most common complication was sickle cell crisis, requiring admission to the hospital. Therefore, the study was terminated prematurely for patient safety concerns.

Commentary

The results of these preliminary trials were somewhat disappointing. Freedom-C would have provided us with the first oral prostacyclin in the United States. In 2003, the lack of efficacy of beraprost was published and the medication was never taken to the FDA for approval. Thus, at this time, we still do not have an oral prostacyclin in the US market.

Walk-PHaSST study was also frustrating for the PH community. Dr. Gladwin has worked tirelessly to explore ways to improve the life of sickle cell patients who develop pulmonary hypertension. This is the second sickle cell disease trial that did not show efficacy. The first one was the ASSETT trial, which was halted early due to lack of enrollment .

Multiple clinical trials are in progress looking at the effects of various medications on pulmonary hypertension. Each issue, we will focus on a few of these trials and add updates to those we have discussed in previous issues. For more information on these trials please refer to:
http://www.nhlbi.nih.gov/
http://www.unither.com/oral-treprostinil-for-pah/ ■

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