CLINICAL TRIALS UPDATE

Recent Phase 3 Results

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The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Deborah Levine, MD, examines the PATENT-1 study results, findings from CHEST-1, and outcomes of the SERAPHIN trial.

Three important Phase 3 clinical trial findings have recently been published regarding treatment of pulmonary hypertension (PH): PATENT-1 described the results of treating patients with riociguat for pulmonary arterial hypertension (PAH); CHEST-1 reported findings on the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) with riociguat; and SERAPHIN discussed using macitentan for PAH.[1-4]

Riociguat is a soluble guanylase cyclase (sGC) stimulator that, when bound to nitric oxide (NO), enhances synthesis of cyclic guanosine monophosphate (cGMP), which promotes vasodilatation and decreases proliferation, fibrosis, and inflammation. Riociguat has a dual mode of action: it sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding and it also directly stimulates sGC via a different binding site, independently of NO. Macitentan is a dual endothelin-receptor antagonist (ERA) that was developed by modifying the structure of bosentan to increase efficacy and safety. It is characterized by enhanced tissue penetration and receptor binding capability.

PATENT-1

PATENT (Pulmonary Arterial Hypertension sGC-Stimulator Trial) is a 12-week, double blind, randomized, placebo-controlled international multicenter trial. The inclusion criteria listed were: pulmonary vascular resistance (PVR) >300 dyn/sec/cm^5, mean pulmonary artery pressure (mPAP) ≥25 mm Hg, and a 6-minute walk distance (6MWD) of 150-450 m. Patients were included if they had either been receiving no other PAH therapy or if they were receiving either ERAs or nonintravenous prostanoids for PAH (50% of patients were receiving no other therapy, 44% were receiving an ERA, and 6% of patients were receiving nonintravenous prostanoids). Patients were required to be on these medications at stable doses for at least 90 days. A total of 443 patients were randomly assigned to receive riociguat 3 times daily (TID) with dose titration to 2.5 mg TID, placebo TID, or riociguat TID with capped titration at 1.5 mg TID. The patients receiving the dose capped at 1.5 mg TID were not included in the efficacy analysis.

The primary endpoint was change in the 6MWD from baseline until the end of the study (12 weeks). Secondary endpoints included changes in the PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization (WHO) functional class, time to clinical worsening, Borg scores, and quality of life scores.

There was a statistically significant improvement in 6MWD at Week 12 in the riociguat group (+30 m) compared with the placebo group (-6m), for a total change of 36 meters. This effect was seen across both patients on and not on prior PAH therapy. Both PVR and NT-proBNP levels decreased significantly. The time to clinical worsening was increased and the Borg score improved in the riociguat group. These benefits of the riociguat group were maintained at 24 weeks, seen in the long-term extension study (PATENT-2). There was no increased frequency of adverse events or discontinuations in the riociguat group as compared to placebo.

These results reflect patients who were both on prior PAH therapy and those who were receiving no other therapy. In those patients not on prior therapy, the increase in 6MWD may be considered modest. However, in patients on prior therapy, improvements were similar to those in other trials (ie, PHIRST and BREATHE-1). The results also reflect that riociguat appears to be a safe therapy with a novel mechanism of action to add to the armamentarium of therapies for patients with PAH.

CHEST-1

CHEST-1 (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With CTEPH) was a 16-week, multicenter, randomized, double blind, placebo-controlled international trial to evaluate riociguat in patients with CTEPH (Group 4 PH). Patients with either technically inoperable CTEPH or patients who had undergone pulmonary endarterectomy but had persistent or recurrent PH were included in the trial.

Inclusion criteria were: PVR >300 dyn/sec/cm^5, mPAP ≥25 mm Hg, and a 6MWD of 150-450 m. Patients were excluded if they had received an ERA, phosphodiesterase type 5 (PDE-5) inhibitor, or NO donor 3 months prior to the study. The primary and secondary endpoints were identical to the PATENT-1 trial. A total of 261 patients (173 riociguat, 88 placebo) were randomly assigned to receive either placebo or riociguat (1, 1.5, 2, or 2.5 mg) TID, and the dose was titrated over the course of 8 weeks.

There was a statistically significant improvement in 6MWD at 16 weeks in the riociguat group compared to placebo (46 m difference). PVR and other hemodynamic parameters (mPAP, cardiac output) improved significantly when compared to placebo, as well as significant decrease in the level of

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NT-proBNP, and improvements in WHO functional class. There was no significant difference in the incidence of clinical-worsening events between the riociguat and placebo groups (2% vs 6%; $P=0.17$).

CHEST-1 demonstrates that riociguat appears to be a safe oral therapy for patients with inoperable CTEPH and for those with persistent PH after endarterectomy. Keeping in mind that patients should always be evaluated for CTEPH and that surgery must be the first option whenever possible, it would be a welcome additional treatment for these patients.

SERAPHIN

The SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) trial is the pivotal Phase 3 study designed to evaluate the efficacy and safety of macitentan. To date, SERAPHIN is the largest and longest conducted randomized, controlled study in PAH patients. SERAPHIN is unique among PAH trials in that it included a clearly defined primary endpoint of morbidity and all cause-mortality of treatment vs placebo, making it the first event-driven Phase 3 trial in PAH.

The primary endpoint was a composite endpoint from the time of initiation of treatment to the first occurrence of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous (IV) or subcutaneous (SC) prostanoids, or worsening of PAH. Secondary endpoints included improvement in the 6MWD and improvement in WHO functional class at 6 months, death due to PAH or hospitalization for PAH up to the end of treatment, and death from any cause up to the end of treatment and up to the end of the study. Laboratory data were assessed at Months 3 and 6, and 6 months after until the end of treatment.

Seven hundred forty-two patients were randomized 1:1:1 into 1 of 3 treatment groups: placebo, 3 mg, and 10 mg a day of oral macitentan. Use of PDE-5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine were all allowed. Any of these therapies had to be at a stable dose for at least 3 months. Any SC or IV prostanoids were excluded. Inclusion criteria were: patients 12 years of age and older who had idiopathic PAH, heritable PAH, or PAH related to connective tissue disease, repaired congenital systemic to pulmonary shunts, HIV, or drug or toxin exposure; 6MWD of 50 m or more, and in WHO functional class II, III, or IV.

In this study, macitentan showed a significant decrease in the morbidity and mortality endpoint. The composite endpoint of death due to PAH or hospitalization showed a significant treatment effect with macitentan (mostly driven by lower hospitalization in the macitentan groups). A trend in favor of the 10 mg dose was noted in all-cause mortality. The worsening of PAH was the most frequent primary endpoint event. The effect of macitentan on this endpoint was observed regardless of background therapy for PAH. The secondary endpoints, change from baseline to Month 6 in 6MWD, and WHO functional class were statistically significant at both dosages. Macitentan was well tolerated in the study. The overall incidence of adverse events reported and treatment discontinuations was similar across all groups. The incidence of serious adverse events was lower in patients treated with macitentan compared to placebo. Compared to placebo, a higher proportion of macitentan-treated patients had nasopharyngitis, headache, and anemia. There were no differences in liver function test abnormalities compared to placebo. In addition, no difference in edema was observed between macitentan and placebo.

This study is novel in its morbidity/mortality endpoint. The design, the duration of the study, and the results bring up the important issue of whether this trial establishes a new baseline of how we evaluate new therapies for chronically progressive diseases such as PAH.

All 3 of these important trials were published in the last 2 months in the *New England Journal of Medicine*. The FDA is currently reviewing the results of these studies for consideration for approval for treatment of PH.

References

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