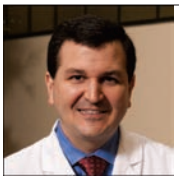
A Change is Coming



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The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Dr Torres presents information on current studies that may result in re-evaluation of historical endpoints for future PH clinical trials.

The way in which the pulmonary hypertension community will perform clinical trials in the future will be changing soon. Historically, the primary endpoint for clinical trials in pulmonary hypertension (PH) has been improvement on 6-minute walk distance (6MWD), with some trials also assessing a measure of time to clinical worsening as a secondary endpoint. In April 2012, the first morbidity/mortality study, SERAPHIN, was completed and the results were positive. This will likely change the way we perform clinical trials, and how the Food and Drug Administration (FDA) will evaluate pulmonary arterial hypertension (PAH) medications for approval.

Macitentan is a new generation of dual endothelin receptor antagonists (ERAs) with increased affinity for the ET-A receptor with a chemical structure that improves tissue penetration. This agent was studied in a Phase 3 clinical trial called SERAPHIN. This clinical trial randomized patients into 1 of 3 treatment groups: placebo, 3 mg, and 10 mg a day of oral macitentan. In the study, 742 patients were randomized 1:1:1. The patients could be on background therapy with an oral phosphodiesterase type 5 inhibitor (PDE-5i), oral prostacyclin, or inhaled prostacyclin. Global enrollment finished in December 2009, and preliminary results were available in April 2012. The primary endpoint of the study was morbidity/mortality. There was an observed risk reduction of 30% ($P=0.0108$) and 45% ($P<0.0001$) at 3 and 10 mg a day dosages, respectively. The secondary endpoints, change from baseline to Month 6 in 6MWD, and World Health Organization (WHO) functional class, were statistically significant at both dosages. A trend in favor of 10 mg dose was noted in all-cause mortality ($P=$ns). The mean exposure of the drug in the study was at least 85 weeks. There were no differences in liver function test (LFT) abnormalities compared with placebo.

The results of SERAPHIN have not yet been presented and they have not been published. Thus, there are limited data currently available on the results of the trial. It will be interesting to see what variables lead to the positive results in the trial and how close the results came to demonstrating a survival benefit. Also of interest will be any subpopulations that showed improved survival. Though the company press release suggests that macitentan did not have significant LFT abnormalities, we do not know if the Food and Drug Administration (FDA) will require regular monitoring of LFTs, as is the case for bosentan.

The results of this study will likely change the way we conduct clinical trials in the future. Most likely, the FDA will begin requiring protocols aimed at showing mortality/morbidity benefit. If this indeed becomes the new endpoint for PH clinical trials, it will be more difficult for new PAH medications to be approved by the FDA. Macitentan enrollment began in June 2008 and finished enrolling in December 2009. Preliminary results were available in April 2012, making this a nearly 4-year clinical trial. The FDA may compare new PAH study medications against the macitentan clinical trial results, and thus require large numbers of subjects to be enrolled and studied for extended periods of time as patients need time to develop events.

Currently there is another multicenter clinical trial, GRIPHON, which is evaluating a prostacyclin receptor agonist in which the primary endpoint is also mortality/morbidity. This trial is currently enrolling and preliminary results are not expected anytime soon. There are also other large PAH clinical trials being designed with morbidity/mortality as the primary endpoint. Given the small number of PAH patients in the country, it will be a challenge to enroll enough patients for these large studies, making it even more difficult for new agents to be evaluated in a timely matter.

The FDA will soon be evaluating the results of SERAPHIN. The medication has a favorable likelihood of approval given the large risk reduction rate and highly statistical P value <0.0001. How this product will be positioned and utilized in a market with 2 other ERAs, bosentan and ambrisentan, remains to be seen. One thing is fairly certain, the era of 6MWD as primary endpoint in clinical trials is most likely over.

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