Bosentan's Long-Term Safety in PAH Endorsed

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STOCKHOLM — An Internet-based postmarketing surveillance program has provided reassurance regarding the long-term safety of bosentan in routine clinical practice for treatment of various subgroups of pulmonary arterial hypertension.

The experience with this novel Internet-based data collection system has been so favorable that the system deserves broader consideration as a possible new model for widespread postmarketing surveillance—and not just for orphan drugs such as bosentan (Tracleer), the nonselective dual endothelin receptor antagonist that is the only approved oral treatment for pulmonary arterial hypertension (PAH), Jørn Carlsen, M.D., said at the annual congress of the European Society of Cardiology.

The program, known as the Tracleer Excellence Post Marketing Surveillance (TRAX PMS) program, was set up by Actelion Pharmaceuticals in cooperation with the European Agency for the Evaluation of Medicinal Products.

Liver abnormalities were a particular focus in the surveillance program. That's because in the clinical trials that led to bosentan's marketing approval, 12.7% of treated patients developed elevated liver enzyme levels greater than three times the upper limit of normal. Although regulators approved bosentan on the grounds that its clinical benefits trumped the safety concerns as they were understood at the time, they also sought additional data on the drug's long-term effects on the liver.

In less than 2.5 years, the TRAX PMS program enrolled nearly 5,000 patients treated with bosentan in 18 European countries. Mean exposure time to the drug was 39 weeks, for a total of more than 3,400 patient-years of follow-up on bosentan. To put the resultant accrued wealth of safety data in context, Dr. Carlsen of the Rigshospitalet, Copenhagen, said the pivotal trial that led to bosentan's marketing approval featured just 59 patient-years of follow-up.

The interactive Internet-based surveillance program provided prescribing physicians with treatment and safety-monitoring algorithms, and also collected what Dr. Carlsen termed "safety signals"—data on adverse events, hospitalizations, deaths, and reasons for drug discontinuation.

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DR. CARLSEN

"This is a new way of looking at drugs after their introduction," he observed.

In the total group of nearly 5,000 treated patients, 7.7% developed liver enzyme levels in excess of three times the upper limit of normal. In the overall PAH population, the risk was greatest during the first 3 months of therapy and declined with time. Half of the affected patients required permanent discontinuation of treatment. Roughly 30 continued to have elevated enzymes after discontinuation; however, there were no cases of fatal or permanent clinical hepatic injury.

Dr. Carlsen presented additional data on liver enzyme elevation rates in three subgroups of patients in TRAX PMS: 5.5% in the 470 patients with chronic thromboembolic pulmonary hypertension (CTEPH); 2.8% in 579 patients with PAH associated with congenital heart disease; and 8.4% in 1,583 with idiopathic PAH.

The mean time on bosentan before liver enzyme abnormalities occurred was 127 days in the CTEPH group. That was longer than in patients with idiopathic or congenital heart disease–associated PAH.

Session cochair Marc Humbert, M.D., Ph.D., said he was surprised to learn from TRAX PMS that as many as 10% of bosentan-treated patients in Europe are on the drug for CTEPH, a condition that develops in 0.5%-4% of patients with acute pulmonary embolism when their thrombus fails to resolve, leading to sustained pulmonary artery obstruction. An increasingly popular curative surgical procedure for CTEPH is pulmonary thromboendarterectomy, noted Dr. Humbert of Université Paris-Sud. Dr. Carlsen replied that these CTEPH patients were among the many that surgeons deem unacceptable candidates for the complex operation.

"If you refer 100 patients to surgery, only about 50 will be eligible," he said. ■

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