

## Managing a Drug's Hepatic Risks: The Bosentan Example

BY ELIZABETH MEHCATIE  
Senior Writer

ROCKVILLE, MD. — The postmarketing safety program in place for the pulmonary arterial hypertension drug bosentan resulted in a label change that describes rare cases of cirrhosis in closely monitored patients after prolonged treatment with the drug and reemphasizes the importance of monthly liver function testing in patients.

The changes in the label were announced in a "Dear Healthcare Professional" letter dated March 1, from bosentan manufacturer Actelion Pharmaceuticals US Inc., which describes a case of a female patient who was treated with the recommended dose of bosentan for 21 months. During the second year of treatment, the patient developed worsening liver function tests and eventually, developed liver failure but improved months after stopping the drug.

Bosentan was approved in 2001 for PAH (World Health Organization group I) patients, with WHO Class I or IV symptoms. A required postmarketing surveillance program was in place to monitor patients for liver damage and pregnancies as long as they are on the drug, which can cause liver damage and is teratogenic. Bosentan, an endothelin receptor antagonist marketed as Tracleer by Actelion, was approved in 2001, based on two placebo-controlled studies of 245 patients with PAH, representing 59 patient-years of treatment. The studies found that treatment resulted in improvements in exercise tolerance and delayed clinical worsening. The drug was associated with increased liver aminotransferase levels in 11% of treated subjects, which was reversible when the drug was discontinued.

Speaking at a meeting sponsored by the International Society for Pharmacoepidemiology, Dr. Eleanor Segal, vice president and head, global drug safety for Actelion Pharmaceuticals, South San Francisco, Calif., said that the hepatic risks of the drug were known, because a higher dose of the drug had been developed as an antihypertensive treatment, but was dropped because of the hepatic risks. The drug's benefits were considered higher than its risks for people with PAH, a life-threatening orphan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; other treatments have since been approved.)

The postmarketing risk management program for bosentan in the United States, the Tracleer Access Program (TAP), tracks and re-

ports to the Food and Drug Administration all adverse events related to liver injury in treated patients and the outcomes; prescribing physicians are required to enroll patients in the program, which relies on controlled distribution and patient contact to ensure monthly tests for liver enzyme changes are done.

Specifically, the distributors contact every patient on the drug before shipping their monthly supply, asking them if they have had their monthly liver function tests (LFTs), and, for female patients who are of childbearing potential, if they have had their monthly pregnancy test. If they have not, or can't remember if they were tested, the patients don't get the drug and the distributor contacts the prescribing physician.

The company is also required by the FDA to initiate a safety report for any pregnancy, any elevation in liver enzymes greater than eight times the upper limit of normal, any elevation of liver enzyme that occurred with bilirubin elevation at least two times the ULN, and any clinical liver injury associated with hospitalization, liver transplant, or death. A black box warning about the risk of liver damage and pregnancy is included in the label.

As of April, 31,000 patients had been exposed to the drug, with 21,000 patient-years of experience, Dr. Segal said.

The letter issued by Actelion describes the report of the patient whose LFTs remained near baseline during the first year of treatment on the recommended dosage of bosentan. At about 1 year, her (alanine aminotransferase (ALT) level gradually increased to 2-4 times her baseline level, which remained within normal limits, but 9 months later, she had marked elevations in aminotransferase and bilirubin levels and the drug was stopped. Aspartate aminotransferase (AST) and ALT levels remained high and bilirubin continued to increase. She developed liver failure and biopsy-confirmed cirrhosis, according to the letter, which said that the contribution of bosentan to the development of liver failure "could not be ruled out."

Eventually, the letter said, the liver failure abated, and LFTs recovered about 7 months after stopping the drug. The patient had had PAH since she was a child, had many comorbidities, and was on various drug treatments when she started bosentan.

"This case underscores the need to continue monthly monitoring for the duration of Tracleer treatment," the letter says. ■

## BP Control Key to Lupus Nephritis Care in Pregnancy

BY SARAH PRESSMAN  
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CHICAGO — Tight blood pressure control is crucial in caring for pregnant women with lupus nephropathy, but medication management must factor in potential fetal risks, Dr. Phyllis August said at a meeting on clinical nephrology sponsored by the National Kidney Foundation.

In reviewing the management strategies for pregnant women with preexisting lupus nephropathy and diabetic nephropathy, Dr. August noted that the most effective management begins even before conception. Even though preconception counseling can improve outcomes, physicians typically care for gravid women who already have significant disease.

"Overall, the outcome in pregnancy is related to the baseline blood pressure and level of renal function at the beginning of pregnancy," said Dr. August, professor of medicine at the Weil Medical College of Cornell University, New York.

ACE inhibitors and angiotensin-receptor blockers (ARBs) are vital in the treatment of lupus or diabetic nephropathy in women who are trying to conceive, but these agents are potentially quite harmful to the developing fetus, she noted.

Switching to a safer agent (such as methyldopa or labetalol) as soon as a patient misses her menstrual period to get the greatest benefit. "The overwhelming evidence for the adverse effects of ACE inhibitors and ARBs relates to second- and third-trimester exposure," she said.

Dr. August also recommended performing a cardiac evaluation before conception in women with long-standing lupus or type 1 diabetes. "Significant renal disease is as-

sociated with preeclampsia and renal complications," she noted. Chronic kidney disease also increases the risk of intrauterine growth retardation and preterm birth.

Lupus nephropathy can be quite challenging for both patients and physicians, Dr. August noted. "There is a poor outcome when the disease is active at conception," she said.

A high percentage of patients—as many as 50%-80%—will experience a disease flare during pregnancy if they have active disease at conception. On the other hand, only 10%-40% of women who are in remission at conception will have a flare.

Physicians may safely use azathioprine to treat pregnant women with lupus nephritis. Dr. August also advocated delivery during the third trimester in gravid women whose lupus nephritis is deteriorating quickly.

The mother's condition often improves quickly after delivery.

Women with lupus and antiphospholipid antibody syndrome are also at higher risk of fetal loss, arterial and venous thrombosis, renal vasculitis, and preeclampsia. Women with this syndrome may benefit from taking low-molecular-weight heparin, with or without aspirin.

Although the outlook has improved for women with certain types of chronic kidney disease who wish to bear children, the chance of a good pregnancy outcome in women with end-stage renal disease on dialysis remains poor. Women who become pregnant while on dialysis have a high incidence of adverse outcomes such as second-trimester pregnancy loss, prematurity, and congenital abnormalities. These women "should never be encouraged" to get pregnant, Dr. August said. ■

**Pregnant women with lupus and APS may benefit from taking low-molecular-weight heparin, with or without aspirin.**

## Refractory Ocular Sarcoidosis Responded to Infliximab

BY NANCY WALSH  
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AMSTERDAM — Treatment with infliximab successfully controlled refractory ocular inflammation in two patients with sarcoidosis, Dr. Boris A. Cruz reported at the annual European Congress of Rheumatology.

Ocular involvement in this granulomatous multisystem disorder is a serious complication that is associated with significant visual loss. Tumor necrosis factor- $\alpha$  plays an important pathophysiolog-

ic role in granuloma formation; anti-TNF- $\alpha$  therapy is being considered in cases that are unresponsive to corticosteroids and immunosuppressants, Dr. Cruz said.

The first patient was an 18-year-old white male who had an 18-month history of pulmonary, cutaneous, and central nervous system necrotizing sarcoid granulomatosis, a variant form of sarcoidosis. He did not respond to first-line treatment with steroids, so methotrexate was added. This ameliorated the multiorgan involvement, but severe retinal vasculitis with typical candle-wax exudate developed in his

right eye. Three 300-mg infusions of infliximab were given on days 0, 14, and 42, and the retinal lesions cleared. At 18 months, the patient remained in full remission and continued to get methotrexate plus quarterly infliximab infusions, Dr. Cruz wrote in a poster session.

The second patient was a 64-year-old white woman with an 8-year history of pulmonary, cutaneous, and ocular sarcoidosis. Ophthalmologic evaluation confirmed the presence of bilateral retinal vasculitis with capillaritis, papillitis, peripheral multifocal choroiditis, and pathologic neo-

vascularization. Her extraocular symptoms responded to steroids, but visual impairment progressed despite combined treatment with methotrexate plus intraocular steroid injections. She was given three 200-mg infusions of infliximab in the same schedule as the first patient, with clearance of all retinal inflammation and improvement of visual acuity. She too remains in clinical remission on a regimen of methotrexate and quarterly infusions of infliximab, according to Dr. Cruz of the department of rheumatology, BioCor Instituto, Nova Lima, Brazil. ■