Managing a Drug’s Hepatic Risks: The Bosentan Example

BY ELIZABETH MECHCATIE
Senior Writer

ROCKVILLE, Md. — The postmarketing safety program in place for the pulmonary arterial hypertension drug bosentan resulted in a labeling change that describes rare cases of clinical hepatitis 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 decreased 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 or orphan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; phan disease, she said. (Bosentan was the first oral treatment approved for treating PAH; In reviewing the management strategies for pregnant women with preexisting lupus nephropathy and diabetic nephropathy, Dr. August noted that the most effective management begins with disease control even before conception. Even though preconception counseling can improve outcomes, physicians typically care for gravid women who have already significant disease.

Overall, the outcome in pregnant women with lupus nephropathy 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 missed 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 dia-

Refractory Ocular Sarcoidosis Responded to Infliximab

BY NANCY WALSH
New York Bureau

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 disease is a serious complication that is associated with significant visual loss. Tumor necrosis factor-a plays an important pathophysiologic role in granuloma formation, anti-TNF-a therapy is being considered in cases that are unresponsive to caspase-corticosteroids and immunosuppressants, Dr. Cruz said.

The first patient was an 18-year-old white male who had an 18-month history of severe ocular symptoms. He presented with a well-documented systemic sarcoidosis. He did not respond to first-line treatment with corticosteroids, so methotrexate was added. This ameliorated the multorgan 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 at the congress.

The second patient was a 64-year-old white woman with an 8-year history of pulmonary, cutaneous, and ocular sarcoidosis. She presented with panuveitis, and methotrexate was added. This confirmed the presence of bilateral retinal vasculitis with capillariai, papillitis, peripheral multifocal choroiditis, and pathologic neovascularization. Her extracocular symptoms responded to steroids, but visual impairment progressed despite combined therapy with methotrexate plus intracocular 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, Bio-

BP Control Key to Lupus Nephritis Care in Pregnancy

BY SARAH PRESSMAN LOVINGER
 Contributing Writer

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 have already significant disease.

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"Significant renal disease is associated 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 said. “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 aza-thioprine 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.

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