Rifaximin Approved for Hepatic Encephalopathy

BY ELIZABETH MECHCATIE

The Food and Drug Administration has approved the oral antibiotic rifaximin as a treatment to reduce the risk of developing episodes of overt hepatic encephalopathy in adults with chronic liver disease, making this the second drug approved for this indication.

Approved in 2004 for treating travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in people aged 12 and older, rifaximin is a poorly absorbed oral antibiotic derived from rifamycin, and has a broad spectrum of activity against gram-positive and gram-negative, aerobic and anaerobic enteric bacteria.

Rifaximin reduces levels of gut-derived neurotoxins such as ammonia, which is known to cause hepatic encephalopathy in patients with hepatic impairment, according to the manufacturer, Salix Pharmaceuticals, which markets the drug as Xifaxan.

The approval is for "reduction in risk of overt hepatic encephalopathy recurrence" in patients aged 18 and older. The approved dosage is one 550-mg tablet taken orally twice a day, with or without food.

Approval was based on a study comparing treatment with rifaximin to placebo in 299 patients with advanced liver disease. The study was published on March 25, the same day that the FDA announced the approval (N. Engl. J. Med. 2010;362:1071-81).

During the 6-month study, 31 of 140 patients (22%) on rifaximin and 73 of 159 (46%) on placebo had a breakthrough episode, a significant difference that represented a nearly 60% reduction in risk. Secondary end points, including the risk of hepatic encephalopathy–related hospitalizations, also were significantly reduced among those on rifaximin.

Based on the findings, the FDA's Gastrointestinal Drugs Advisory Committee voted 14-4 in February that the risk-benefit profile of rifaximin supported its approval for this indication. The panelists supporting approval emphasized that the drug's labeling should clearly inform prescribers that most of the patients (91%) who participated in the study submitted for approval were also being treated with lactulose, a drug approved in the 1970s for the indication, and that most had Child-Pugh class A or B cirrhosis.

The safety of rifaximin was uncertain when used for more severe liver disease, as was its efficacy as a single agent.

During their meeting in Silver Spring, Md., panelists said that if the drug was approved, these questions would need to be addressed in postmarketing studies, which should evaluate the safety of the drug in patients with more severe disease, those with Child-Pugh class C cirrhosis or a model for end-stage liver disease (MELD) score above 25.

The safety of chronic treatment, including the effects of long-term use on the gut flora, also was unclear, and should be studied further if the drug was approved, panelists said. Also, the clinical trial conducted by the manufacturer for this indication was for 6 months, but treatment is expected to continue until the patient undergoes a liver transplant or dies. The longest follow-up that Salix has done is an average of 1 year in patients followed in an extension study.

These concerns were reflected in the revised label, which states in the warning and precautions section that the drug should be used "with caution" in patients with severe (Child-Pugh C) hepatic impairment. The label also says that *Clostridium difficile*–associated diarrhea should be considered if a patient develops diarrhea during treatment and it does not improve or gets worse.

In the randomized, controlled study of 299 patients with advanced liver disease, treatment with rifaximin at a dose of 550 mg twice a day was compared with placebo. In the study, conducted by Dr. Nathan M. Bass of the University of California, San Francisco, and his associates, most of the patients were white, and the average age was 56 years. Patients were treated at 70 medical centers in the United States, Russia, and Canada starting in 2005.

Participants had Conn scores of 0 (two-thirds of the patients) or 1. They had had at least two episodes of hepatic

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encephalopathy, defined as a Conn score of at least 2, in the previous 6 months.

The 5-point Conn grading system is based on a clinician's subjective assessment, a concern raised by FDA reviewers. A score of 0 indicates that no abnormality was detected, whereas a score of 1 indicates trivial lack of awareness, shortened attention span, impaired addition or subtraction, euphoria, or anxiety. A score of 2 is used to indicate lethargy or apathy, disorientation to time, obvious personality change, and/or inappropriate behavior, and a score of 4 indicates coma (unable to test mental state).

Neurologic impairment was also evaluated with the Asterixis score, which ranges from grade 0 (no tremors) and grade 1 (rare flapping motions) to grade 2 (occasional, irregular flaps), grade 3 (frequent flaps), and grade 4 (almost continuous flapping motions).

The primary end point was the time to first breakthrough overt hepatic encephalopathy episode, defined as an increase of the Conn score to a 2 or higher, or an increase in the Conn score and Asterixis grade of 1 each among those with a baseline Conn score of 0.

The active drug also reduced the relative risk for hospitalization by 50%. Hospitalization involving hepatic encephalopathy was reported for 13.6% of patients on rifaximin and 22.6% of those on placebo.

Mortality was 6% (9 of 140) with rifaximin and 7% (11 of 159) with placebo; deaths were due mostly to worsening hepatic function and progression of the underlying disease.

Since the drug was approved more than 5 years ago for traveler's diarrhea, there have been five postmarketing reports of *C. difficile* colitis associated with rifaximin treatment, including one death, according to the FDA.

In addition, anaphylaxis has been identified as a notable adverse effect in postmarketing reports, and this risk is now included in the drug's label.

"These data suggest that four patients would need to be treated with rifaximin for 6 months to prevent one episode of overt hepatic encephalopathy," Dr. Bass and his colleagues said. First approved in Italy in 1985, rifaximin is now approved in 33 countries for various GI uses, including hepatic encephalopathy and adjunctive treatment of hyperammonemia, according to the manufacturer. ■

Disclosures: *The study was supported by Salix Pharmaceuticals. Dr. Bass reported receiving consulting, advisory, and lecture fees from Salix. Members of FDA advisory panels have been cleared for potential conflicts of interest related to the topic under review prior to the meeting.*

MY TAKE

Try Lactulose, Then Rifaximin

Hepatic encephalopathy, a frequent complication for patients with cirrhosis, results in disability that is generally recognized as episodes of overt confusion. Minimal hepatic encephalopathy from cirrhosis may be more difficult to recognize, because it produces less-overt complications such as impaired driving and automobile accidents.

Lactulose, a nonabsorbable disaccharide that alters colonic pH and bowel frequency, has been the mainstay of therapy for hepatic encephalopathy, although the laxative effect of lactulose can be a problem for some patients. Rifaximin, an antibiotic with limited absorption, reduces the frequency of episodes of hepatic encephalopathy in patients with cirrhosis and thus offers another therapeutic option.

Given the associated cost savings, I typically use lactulose as first-line therapy for most patients with hepatic encephalopathy, and reserve rifaximin for those who are poorly controlled or who develop significant GI side effects from lactulose.

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