FDA Panel: Study Hepatitis B Drug in Children

Entecavir was approved for chronic HBV infection therapy in adults subsequent to the panel meeting.

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — Entecavir, an oral antiviral drug that has several advantages over currently available treatments for chronic hepatitis B, should be studied in pediatric populations, a Food and Drug Administration advisory panel recommended.

At a meeting of the FDA's Antiviral Drugs Advisory Committee last month, held primarily to review the safety and efficacy of the drug in adults, panel members recommended that the manufacturer, Bristol-Myers Squibb Co., conduct phase I and pharmacokinetic studies in children, and carcinogenicity studies in young animals.

The panel discussed potential use of entecavir—a nucleoside analogue that is a potent, selective inhibitor of hepatitis B virus (HBV) replication—in pediatric patients after unanimously agreeing (18-0) that the risk-benefit appraisal of the drug supported its approval for treating chronic HBV infections in adults. The drug was approved for adults last month within weeks of the panel meeting.

Despite concerns about a theoretical risk of malignancies in humans, the panel cited the very real risk of hepatocellular carcinoma associated with chronic HBV, safety and effectiveness data in 48-week trials of more than 1,000 patients who were either treatment naïve or refractory to lamivudine, and the lack of significant evidence of resistance to date.

In preclinical studies, the incidence of lung tumors and other malignancies was increased significantly in rodents exposed to entecavir, mostly at very high doses. To date, however, no increase in malignancies has been detected in clinical trials. Because of these findings, the FDA had asked the manufacturer to delay pediatric trials.

It would be an "enormous benefit" to have a safe and effective drug for pediatric HBV, remarked Kathleen Schwarz, M.D., director of the division of pediatric gastroenterology and nutrition, Johns Hopkins University, Baltimore. She added that more data about the carcinogenicity potential of entecavir and the effect of long-term exposure on the injured liver were needed. She recommended studies of the drug in young animals, particularly primates.

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Interferon, which is administered subcutaneously, is approved for treating hepatitis B in children aged 1 and older, but its side effects are problematic. Lamivudine (Epivir), a nucleoside analogue that is taken orally, is approved for children aged 3 and older, but the rate of lamivudine resistance is about 20% with 1 year of treatment, said Dr. Schwarz, a voting consultant to the panel. Pediatric trials of the third drug approved for HBV in the United States, adefovir dipivoxil, a nucleotide analogue that is active against lamivudine-resistant virus, are underway, she noted.

Because Bristol-Myers Squibb plans to market an oral solution, once entecavir is approved, it will immediately be used off label in children, she and others on the panel predicted. (The oral solution is intended to help with dosing issues in adult patients who have renal insufficiency.)

Dr. Schwarz and other pediatricians on the panel said they were concerned that entecavir would be used inappropriately in pediatric patients once approved, before the appropriate studies were completed. The panel chair, Janet Englund, M.D., of the division of infectious diseases at Children's Hospital and Regional Medical Center, Seattle, noted that how to dose children was not yet known. Lauren Wood, M.D., senior clinical investigator in the HIV and AIDS malignancy branch of the National Cancer Institute, Bethesda, Md., pointed out that a drug's safety and efficacy can differ greatly in children, citing an example of an HIV drug that caused bone toxicity in children, but not in adults.

Mostly urban adolescents and international adoptees in the United States are infected with HBV, and children around the world have perinatally-acquired HBV, she said. Babies with perinatally-acquired HBV have a high lifetime risk of hepatocellular carcinoma, as high as 40% in some studies, added Dr. Schwarz. And there also is a significant social stigma associated with having hepatitis B, including in young children.

The FDA usually follows the advice of these panels, which is not binding. If the drug is approved, Bristol-Myers Squibb will market entecavir under the trade name Baraclude. Approval could be imminent, because the drug is under a priority review, but had not yet been announced at press time.

The three phase III adult studies compared entecavir with lamivudine in more than 1,500 adults with chronic HBV infections and active liver inflammation, including HBeAg-negative and HBeAg-positive patients who had not been treated with a nucleoside, and HBeAg-positive patients who were refractory to lamivudine. In all three groups, a significantly greater proportion of those treated with entecavir than of those treated with lamivudine met the primary end point, histologic improvement in liver biopsy after 48 weeks of treatment. In all three groups, the mean reduction in HBV DNA was significantly greater among those treated with entecavir, and significantly more patients on entecavir had normalization of ALT levels than did those treated with lamivudine.

The safety profiles and malignancy rates were comparable in the entecavir and lamivudine-treated groups, according to the company. Entecavir also has a favorable resistance profile compared with lamivudine, according to Bristol-Myers Squibb.

During the discussion on adult use, Leonard Seeff, M.D., senior scientist for hepatitis research at the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md., said there was "no question" that entecavir is very effective at reducing viral load. "We need other treatments, and this drug has advantages that others don't—namely, at least at this point, a lower rate of mutant strains developing and no nephrotoxicity," he remarked.

Bristol-Myers Squibb has proposed a pharmacovigilance study that would aim to enroll 12,500 patients worldwide, randomize them to entecavir or another HBV drug treatment, and follow them for malignancies and progression of liver disease for 5-8 years. The panel agreed that the trial would be critical in determining whether the drug's malignancy risk would increase, and whether resistant strains would develop with a longer duration of treatment. ■

Intracranial Infection Can Mimic Hypoxic Injury on Imaging

BY SHERRY BOSCHERT
San Francisco Bureau

CABO SAN LUCAS, MEXICO — What looks like damage from hypoxic ischemic encephalopathy on neonatal brain imaging actually can be caused by intracranial infection, Robert A. Zimmerman, M.D., said at a conference on obstetrics, gynecology, perinatal medicine, neonatology, and the law.

Always correlate clinical findings and laboratory results with images of brain abnormalities to detect intracranial infections and to avoid attributing the infant's problems to hypoxic ischemic brain injury, said Dr. Zimmerman, chief of pediatric neuroradiology at Children's Hospital of Philadelphia.

He described several infections that could be confused with hypoxic ischemic encephalopathy:

▶ Acute cytomegalovirus infection, the most common intracranial infection that occurs in utero, causes fetal brain abnormalities in the second and third trimesters. Edema in the brain seen on imaging shortly after birth may simulate a toxic ischemic brain injury.

"The clinical work-up of the patient turns out to be critical" to differentiate the two, he said at the conference, sponsored by Boston University and the Center for Human Genetics.

▶ Neonatal meningitis may result from exposure to a pathogen in utero, at the time of delivery, or in the neonatal nursery.

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Both gram-negative and gram-positive bacterial meningitis can be a problem, since neonates lack a functional immune system to resist CNS infection.

Severe brain swelling secondary to *E. coli* meningitis infection can look like severe brain swelling from hypoxic ischemic brain injury, Dr. Zimmerman said.

When infection damages areas of the brain rather than causing complete brain injury, this also can be confused with hypoxic ischemic injury. Cortical infarction from infection with streptococci or gram-negative rods, for example, may be confusing.

Areas of cortical hyperintensity on imaging due to these infections can simulate damage from a partial prolonged asphyxia.

Clinical findings become extremely important in differentiating the two, he said.

Infarction of the basal ganglia due to streptococcal infection may be confused with a profound asphyxial injury, but a gadolinium-enhanced MRI can highlight changes characteristic of meningitis to help make the diagnosis.

The most severe forms of infection with *Citrobacter* or *Serratia* cause diffuse brain swelling with supratentorial necrosis due to lack of perfusion, which can look like a severe hypoxic ischemic brain injury. The clinical findings and cerebral spinal fluid analysis look quite different between the two problems, however. Close to half of patients with meningitis due to *Citrobacter* or *Serratia* also will show brain abscesses on imaging.

▶ Herpes encephalitis can result from infection in utero or from infection acquired at birth. Symptoms from infection at birth typically present as seizures and fever days or weeks after birth. Herpes encephalitis can be a focal or diffuse disease. The diffuse form of herpes encephalitis causes cytotoxic edema that can mimic a hypoxic-ischemic type of injury on imaging. Herpes usually is easily recognizable on good-quality MRI scans with diffusion studies and using gadolinium enhancement.

In general, MRI is the best modality for imaging the neonatal central nervous system; CT scans can help you look for brain calcifications, Dr. Zimmerman commented. ■