Investigational Agent Promising for Hepatitis B

BY MARTHA KERR
Contributing Writer

BOSTON — Entecavir, an investigational oral antiviral agent, "achieves superior histologic, virologic, and biochemical improvement" in patients with e-antigen-positive chronic hepatitis B virus infection, Robert Gish, M.D., reported at the annual meeting of the American Association for the Study of Liver Diseases.

In an international phase III study, 715 patients with chronic hepatitis B who were nucleoside naive and positive for hepatitis B e-antigen (HBeAg) were randomized to receive either entecavir 0.5 mg daily or lamivudine 100 mg daily for 1 year.

"The objective here is to prevent the progression of liver disease," said Dr. Gish, medical director of the California Pacific Medical Center in San Francisco. The HBeAg wild-type strain accounts for 25%-40% of hepatitis B virus (HBV) cases.

At 48 weeks, histologic improvement had occurred in 72% of patients on entecavir, compared with 62% on lamivudine, a statistically significant difference. Histologic improvement was defined as a reduction in the Knodell necroinflammatory score of at least 2 points plus no worsening of Knodell fibrosis.

There was a significantly greater reduction in HBV DNA with entecavir than with lamivudine, with 70% of patients having unmeasurable virus levels (below 400 copies/mL) after 48 weeks on the investigational agent, compared with 38% on lamivudine. Mean HBV DNA viral log scores dropped 6.78 log10 copies/mL in the entecavir group and 5.46 log10 copies/mL in the control group. "This is unprecedented," Dr. Gish commented. "I know of no other modality that suppresses the virus to this extent."

No significant differences between the lamivudine and entecavir groups were found for the percentages of patients with seroconversion, normalization of ALT levels, or loss of HBeAg DNA.

The incidence of serious adverse events was low and equal in the two treatment arms at 7%. The most commonly reported adverse effects were headache (about 25% of both groups), upper respiratory infection (about 20% of all patients), cough in about 15%, nasopharyngitis in 14%, upper abdominal pain in 10%, fatigue in 10%, and fever in about 10%. Treatment was discontinued because of adverse events in 1% of patients on entecavir and 3% of patients on lamivudine.

Bristol-Myers Squibb Co. has submitted a new drug application to the U.S. Food and Drug Administration and a marketing authorization application to the European Medicines Evaluation Agency for entecavir that includes data from this and other phase III trials of the drug. ■

Treatment Timing Tricky for Coinfection With HIV, HCV

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — In patients coinfected with HIV and hepatitis C, the presence of HIV disease complicates the treatment of hepatitis C, and, likewise, the presence of hepatitis C complicates the treatment of HIV, Teresa L. Wright, M.D., said at a meeting on HIV management sponsored by the University of California, San Francisco.

Based on recently published studies and current U.S. and Canadian guidelines, Dr. Wright of UCSF listed some key principles in the management of patients coinfected with HIV and hepatitis C virus (HCV):

► If the patient is in an early stage of HIV disease, consider HCV therapy prior to HIV treatment.

► If the patient's HIV disease is progressing, optimize HIV control first. Then, once the patient is on a stable HIV regimen, consider HCV therapy.

If the patient's HIV disease is progressing, optimize HIV control first and then consider HCV therapy.

► Treat psychiatric disease and substance abuse, which can lead to reinfection.

► When treating HCV, peginterferon alfa-2a should be administered subcutaneously at a fixed dosage of 180 mcg once a week. Peginterferon alfa-2b should be administered subcutaneously at a dosage of 1.5 mcg/kg once per week. Two recently published studies indicate that total HCV viral suppression is more likely with either of the pegylated interferons plus ribavirin than with standard interferon plus ribavirin. Neither of the studies compared pegylated interferon alfa-2a (Pegasys) directly with pegylated interferon alfa-2b (Peg-Intron).

► Start patients on a reduced dosage of ribavirin. The guidelines recommend that the dosage of combination ribavirin should reach 400 mg b.i.d. But Dr. Wright said, "we know from a lot of experience with hepatitis C monoinfected patients that this dose of ribavirin is going to be inadequate and suboptimal, particularly in patients with genotype 1 infections. So I think most of us now are increasingly trying to get patients up at higher doses of ribavirin if tolerated." She mentioned a daily dosage of 1,000-1,200 mg.

► Especially with the higher dosages of ribavirin, patients are likely to require growth hormone support with epoetin alfa and/or granulocyte colony-stimulating factor.

► When treating HCV, avoid HIV regimens containing didanosine (Videx) because of ribavirin-associated increases in drug levels and mitochondrial toxicity.

► Monitor patients closely for side effects and drug-drug interactions.

Dr. Wright said she had no financial relationships relevant to her presentation. ■

Antiviral Tx May Cause Graft Rejection In Liver Transplant Patients With HCV

ORLANDO, FLA. — Antiviral therapy for recurrent hepatitis C infection in patients who have had orthotopic liver transplantation promotes a sustained virologic response, but also appears to contribute to a substantial number of allograft failures, Don C. Rockey, M.D., reported at the annual meeting of the American College of Gastroenterology.

Of 49 patients who had liver transplantation for chronic hepatitis C virus (HCV) infection between 1991 and 2004 and who received antiviral therapy with interferon and ribavirin for recurrent HCV, 12 had a sustained virologic response, 18 had a measurable improvement in liver test results, and 7 developed acute and/or ductopenic allograft rejection during therapy.

In each case, the development of abnormalities was associated with elimination of HCV RNA from the serum, said Dr. Rockey of Duke University, Durham, N.C. Three patients died from complications associated with profound cholestasis.

Other reports of allograft rejection during antiviral therapy in transplant patients have raised questions about the appropriateness of such treatment. Although aggressive anti-HCV therapy led to a sustained virologic response in nearly a third of the transplant patients with recurrent HCV who did not experience allograft rejection, there is an apparent tradeoff in terms of an increased risk of rejection in some patients, Dr. Rockey noted.

Large randomized, controlled studies are needed to better assess the effects of antiviral therapy on liver transplant patients, he concluded.

—Sharon Worcester

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