Drug Pipeline for Hepatitis B Treatment Said to Be Prolific

BY BRUCE JANCIN
Denver Bureau

HONOLULU — The future of chronic hepatitis B therapy will look much like HIV treatment today: multidrug combinations aimed at thwarting development of resistant viral strains, Dr. Paul J. Pockros predicted at the annual meeting of the American College of Gastroenterology.

"All of us in gastroenterology are going to have to deal with antiviral resistance. I think we're headed this way both for hepatitis B and hepatitis C. We're going to be akin to the HIV doctors. There are 21 HIV drugs available, and their resistance profiles dictate how they're used, with drugs in different classes being used together. And that's really what many of us have started doing in dealing with hepatitis B," said Dr. Pockros, head of the division of gastroenterology/hepatology at the Scripps Clinic in La Jolla, Calif.

One of the major lessons hepatologists have learned from the HIV treatment experience is that sequential antiviral monotherapy is not the way to go. It results in creation of drug-resistant strains that can be transmitted to other individuals. That lesson was strikingly brought home by the experience with lamivudine, a nucleoside analog that was the first oral antiviral agent approved for chronic hepatitis B.

When lamivudine (Epivir) received marketing approval in 1998, it was quickly adopted as a first-line therapy because it is orally administered and has far fewer side effects than subcutaneous interferon-alfa-2b (Intron-A), then the only other treatment option.

Unfortunately, as the years went by, the full scope of the lamivudine resistance problem became apparent. After 1 year, 20% of treated patients developed viral resistance to the drug. After 2 years, it was 38%. After 3 years, 49%. And after 4 years on lamivudine, 67% of treated patients had resistant virus. The clinical consequences include rebound of serum hepatitis B DNA, a reduced seroconversion rate, elevated serum liver enzymes, and reversal of histologic improvement.

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Viral resistance has been much less of a problem with the two oral antiviral agents approved since lamivudine. The rate of resistance after 4 years on adefovir dipivoxil (Hepsera) monotherapy is 18%. The resistance rate after 1 year on the nucleoside analog entecavir (Baraclude) is 0% in lamivudine-naive patients and 7% in lamivudine-resistant individuals.

"My own view is that lamivudine will drop out of the picture because we have a better nucleoside analog now. It's not cheaper, but it's certainly better in its efficacy, and it causes less resistance," said Dr. Pockros, who is on the speakers' bureaus for Gilead Corp., Bristol-Myers Squibb Co., Idenix Corp., and Roche.

With the 2005 marketing approval of pegylated interferon-alfa-2a, physicians can now choose from five agents for the treatment of hepatitis B. Many more are in the developmental pipeline.

"I think we'll end up with 10 drugs for hepatitis B, possibly even more, and we'll use combination therapy—either a combination of a nucleoside and a nucleotide analog, like adefovir and lamivudine, to minimize resistance, or a combination of one of those drugs and pegylated interferon," he predicted.

Four drugs are in or have completed phase III clinical trials for hepatitis B. Two—emtricitabine (Emtriva) and tenofovir (Viread)—are already marketed for HIV. The others are the nucleotide analog telbivudine and pegylated interferon-alfa-2b. In addition, at least 11 agents are in phase II trials.

American patients and physicians clearly prefer oral therapy even though the approved agents must often be prescribed indefinitely, but in Europe, pegylated interferon-alfa-2a has become the leading first-line hepatitis B therapy. ■

Antidepressants Safe in End-Stage Liver Disease

SAN FRANCISCO — Antidepressants were safe and moderately effective in a study of 368 patients with end-stage liver disease, Dr. Jayant A. Talwalkar reported.

Little is known about the effects of antidepressants in patients with end-stage liver disease. The prevalence of depression was 41% in this population, higher than the estimated 30% in the general population. The mean age of the depressed patients was 54 years, and 44% were women, Dr. Talwalkar wrote in a poster presented at the annual meeting of the American Association for the Study of Liver Diseases.

The investigators reviewed the records of all patients who underwent a formal psychiatric consultation as part of their evaluation for a liver transplant. The patients were treated at one institution during a 2-year period.

Of the 150 patients identified as depressed, 44% had a prior history of depression and 83% were eligible for pharmacologic therapy for their depression. Antidepressants were prescribed for 83% of the 125 eligible patients, for a mean duration of 13 months.

Treated patients showed no significantly increased rates of worsening serum liver biochemistries, compared with the 264 patients who did not use antidepressants. The rates of development of new complications also did not differ between these two groups, reported Dr. Talwalkar of the Mayo Clinic, Rochester, Minn., and his associates.

"Pharmacologic therapy was not associated with a greater frequency of hepatic decompensation in patients with end-stage liver disease," he wrote. The most common antidepressants prescribed were selective serotonin reuptake inhibitors, used by 83% of treated patients; 34% of patients required a change in antidepressant therapy or additional drugs for depression. Citalopram was used by 46% of patients, paroxetine by 20%, sertraline by 12%, and trazodone by 10%.

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DR. TALWALKAR

Dr. Talwalkar has received research funding from Pfizer Inc., the manufacturer of sertraline.

Antidepressant-related adverse events, reported in 21% of treated patients, included somnolence in 10%, nausea or diarrhea in 6%, and dry mouth in 3%.

The main causes of liver disease were hepatitis C infection, alcohol abuse, a combination of the two, and nonalcoholic steatohepatitis. The liver disease caused fatigue in 51%, pruritus in 10%, ascites in 70%, hepatic encephalopathy in 40%, hepatocellular carcinoma in 8%, and a prior variceal hemorrhage in 16%. Overall, 24% of patients were using β-blockers.

—Sherry Boschert

HBV Suppression at 6 Months Predicts Treatment Success

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The extent of hepatitis B viral suppression after 6 months of therapy predicts treatment efficacy and the risk of developing resistance at 1 year, Dr. Ching-Lung Lai said at the annual meeting of the American Association for the Study of Liver Diseases.

A study of 1,367 patients with chronic hepatitis B virus (HBV) infection and viral DNA levels greater than 6 $\log^{10}$ copies/mL found that more than 95% of those with undetectable viral levels after 6 months of drug treatment had undetectable levels after 1 year of treatment.

Patients with detectable HBV at 6 months had more variable outcomes at 1 year, with higher viral loads at 6 months linked to increased risks for detectable virus, viral breakthrough, and development of drug resistance at 1 year, said Dr. Lai, chief of gastroenterology and hepatology at the University of Hong Kong, and his associates.

"Now we can actually adjust the patient's treatment" by adding or changing drugs if HBV remains detectable at 6 months, he suggested. "Early viral suppression at 6 months is an ideal thing to aim for in the treatment of chronic hepatitis B."

The main purpose of the phase III, randomized GLOBE study was to compare the efficacy of the investigational anti-HBV drug telbivudine with lamivudine during 2 years of treatment. The temporal relationship between early viral suppression and 1-year outcomes was seen in both treatment groups, but telbivudine worked better to suppress the virus, Dr. Lai said. He is a consultant for and has received funding from Idenix Pharmaceuticals, which is developing telbivudine in collaboration with Novartis Pharma AG.

The relationship between early viral suppression and good 1-year outcomes applied regardless of whether patients were positive or negative for hepatitis B e-antigen (HBeAg) at baseline.

For the analysis, patients were divided into four groups based on viral load at 6 months, as measured with polymerase chain reaction: patients with undetectable levels (below 300 copies/mL), fewer than 3 $\log^{10}$ copies/mL, 3-4 $\log^{10}$ copies/mL, or more than 4 $\log^{10}$ copies/mL.

Among HBeAg-positive patients, HBV DNA was undetectable at 1 year in 91% of patients with undetectable levels at 6 months but in only 5% of patients with more than 4 $\log^{10}$ copies/mL at 6 months. In HBeAg-negative patients, HBV DNA was undetectable at 1 year in 94% of those with undetectable levels at 6 months and in 10% of patients with more than 4 $\log^{10}$ copies/mL at 6 months.

Viral breakthrough by 1 year was seen in fewer than 1% of patients who had undetectable HBV DNA at 6 months, regardless of HBeAg status. Breakthrough occurred by 1 year in 14% of HBeAg-positive patients and 24% of HBeAg-negative patients who had more than 4 $\log^{10}$ copies/mL of HBV DNA at 6 months.

At baseline, all patients had compensated liver disease and ALT levels at 1.3-10 times the upper limit of normal. ALT levels normalized by 1 year in 88% of HBeAg-positive patients and 81% of HBeAg-negative patients who had undetectable HBV DNA at 6 months, indicative of improved liver function. In comparison, ALT levels normalized by 1 year in 53% of HBeAg-positive patients and 41% of HBeAg-negative patients who had a viral load of more than 4 $\log^{10}$ copies/mL at 6 months.

In each of the viral load categories, telbivudine achieved greater viral suppression and led to less drug resistance, compared with lamivudine, he added. ■