

Long-term Entecavir Treatment in Hepatitis B Patients

According to a study reported at the 2007 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) held in Boston, Massachusetts, continuous treatment with entecavir (Baraclude, Bristol-Myers Squibb) for 4 years achieved sustained suppression of hepatitis B virus (HBV) in the serum DNA level of nucleoside-naïve patients who are hepatitis B e antigen-positive (HBeAg+). In this long-term, industry-sponsored study led by Steven-Huy B. Han, MD, of the University of California at Los Angeles School of Medicine, patients were first treated with entecavir in a blinded trial (ETV-022) for 96 weeks. After discontinuing treatment for 35 days or less, the patients were enrolled into study ETV-901 (combined entecavir 1 mg and lamivudine 100 mg/day). The ETV-901 protocol was then changed to monotherapy only (entecavir 1 mg/day).

The HBV DNA levels of a total of 108 of 146 patients in the 4-year cohort were measured by polymerase chain reaction at 192 weeks. Of these patients, only 10 had HBV DNA levels greater than 300 copies/mL. One patient in this cohort developed resistance to entecavir. The safety profile was consistent with previous reports: 90% of patients experienced some adverse event, and 13% experienced a serious adverse event. Treatment during Years 3 and 4 resulted in additional patients achieving HBeAg loss and seroconversion. Of the 108 HBeAg+ patients who were measured at 192 weeks, 91% had undetectable HBV DNA levels (<300 copies/mL). Continuous treatment with entecavir also resulted in the maintenance of alanine aminotransferase (ALT) normalization (86% at 192 weeks in the same arm).

Response in Hepatitis C Patients With Decompensated Cirrhosis

A study presented at the 2007 AASLD meeting sought to investigate whether rapid virologic response (RVR) could predict sustained virologic response (SVR) in hepatitis C virus (HCV) patients with decompensated cirrhosis who were naïve to prior combined antiviral therapy. The researchers, led by Angelo Iacobellis, MD, of the Casa Sollievo della Sofferenza Hospital in San Giovanni Rotondo, Italy, analyzed data from 94 patients with cirrhosis (96% Child-Pugh Class B) who underwent treatment with peginterferon alfa-2b (1.5 µg/kg/wk) and oral ribavirin (800 or 1,000 mg) for either 24 weeks (genotypes 1 and 4, n=50) or 48 weeks (genotypes 2 and 3, n=44). The mean patient age was 62.4±7 years.

Overall, SVR was achieved in 34 patients (36.2%), of whom 8 had genotype 1 or 4 and 26 had genotype 2

or 3 ($P<.01$). RVR was confirmed at 4 weeks follow-up in 34 patients (10 patients with genotype 1 or 4 and 24 patients with genotype 2 or 3). Four patients who achieved RVR had to discontinue therapy early due to serious adverse events. Of the total 34 patients who achieved RVR, 24 (70.6%) achieved SVR, with a significant difference between genotypes: 6 of the 10 patients with genotype 1 or 4 (60%) and 18 of the 24 patients with genotype 2 or 3 (75%; $P<.01$). Twenty-eight (82.3%) of all rapid responders who achieved SVR had a pretreatment viral load of 600,000 UI/mL or less. Among those patients who did not achieve RVR and who had genotypes 1 or 4, 48 weeks of therapy appeared insufficient to attain optimal SVR rates, according to the authors. They concluded that decompensated patients with HCV-related liver cirrhosis achieve on-treatment viral clearance at different times based on genotype and that achieving RVR could guide treatment length.

Early Viral Replication in Telbivudine Therapy for Chronic HBV

According to data presented at the 2007 AASLD meeting by researchers from the GLOBE study, an undetectable serum HBV DNA level after 24 weeks of telbivudine (Tyzeka, Novartis) therapy in chronic HBV patients is the strongest predictor of long-term outcome, for both patients who are HBeAg+ and those who are HBeAg-.

The GLOBE Study is an ongoing 2-year phase III clinical trial comparing telbivudine (600 mg/day) with lamivudine (100 mg/day) in the treatment of 1,367 adults with chronic hepatitis B. For a multivariate regression analysis of on-treatment predictive factors, patients were categorized according to serum HBV DNA level at 12 and 24 weeks and baseline ALT level. At 104 weeks, significantly more telbivudine recipients (compared to lamivudine) achieved therapeutic response. For a multivariate regression analysis of baseline predictive factors, the researchers considered age, body mass index, serum ALT, Ishak fibrosis score, serum HBV DNA level, Knodell histologic activity index score, gender, and HBV genotype. In HBeAg+ patients, baseline serum ALT levels were predictive of treatment outcome at 2 years. Baseline viremia was also found to be predictive, as serum HBV DNA levels of less than $9 \log_{10}$ copies/mL in HBeAg+ patients or serum HBV DNA levels of less than $7 \log_{10}$ copies/mL in HBeAg- patients were associated with greater efficacy and less resistance after 2 years with telbivudine therapy. By combining these baseline and on-treatment predictors, lead author Stefan Zeuzem, MD, of the J.W. Goethe University Hospital

in Frankfurt, Germany, concluded that it is possible to identify telbivudine-treated patients who will achieve the highest rate of efficacy and lowest resistance. According to Dr. Zeuzem, as patients with a high viral load at 24 weeks have poorer long-term outcomes, modification of the therapy should be considered.

Sorafenib Approved for Treatment of Unresectable Hepatocellular Carcinoma

The US Food and Drug Administration (FDA) approved a supplemental new drug application for sorafenib (Nexavar, Bayer) for the treatment of patients with unresectable hepatocellular carcinoma (HCC). FDA approval was based on data from the international phase III placebo-controlled sorafenib HCC assessment randomized protocol trial, which demonstrated that sorafenib improved overall survival by 44% in patients with HCC (hazard ratio=0.69; $P=.0006$) versus placebo. Median overall survival was 10.7 months in sorafenib-treated patients compared to 7.9 months in patients receiving placebo. No indication of imbalances was observed in serious adverse event rates between the sorafenib- and placebo-treated groups. The most commonly observed adverse events in patients receiving sorafenib consisted of diarrhea and hand-foot skin reaction.

Self-administered Reflux Questionnaire for Guiding Step-down Management

Led by Greg Rubin, MD, of the University of Sunderland in the United Kingdom, researchers compared the performance of the ReQuest in Practice questionnaire (a validated, self-administered, gastroesophageal reflux disease [GERD]-sensitive questionnaire) with the physician's clinical judgment in the step-down management of GERD. Results of this industry-sponsored study conducted in 34 general practice centers in the United Kingdom were presented at the 2007 United European Gastroenterology Week meeting held in Paris, France. Study participants were administered 40 mg daily of pantoprazole for 8 weeks followed by a reduced dose of 20 mg daily for 8 weeks.

The investigators compared the questionnaire's sum score, physician's assessment of symptoms, and patient satisfaction at 8 weeks with patient satisfaction and the questionnaire's sum score at 16 weeks. At 8 weeks, prior to stepping down to half dose, 45% of the 211 patients who completed the study were classified as relieved from symptoms by the questionnaire, whereas 54% remained symptomatic. At the 16th week, 45.2% of patients were relieved of symptoms. According to the physician's assessment, heartburn was relieved in 75.8% of patients at 8 weeks, acid regurgitation in 76.8%, dysphagia in 88.6%, and epigastric pain/discomfort in 72.5%. In the study, a patient was defined as having overall relief if the intensity

for each symptom was assessed as "none." Overall relief rates according to physician assessment were 56% at 8 weeks and 52.7% at 16 weeks. At 8 weeks, the investigator assessed 79% of patients as ready to decrease or stop treatment with 20 mg of pantoprazole. The study demonstrated that the questionnaire's sum score at 8 weeks was a better predictor of successful proton pump inhibitor dose reduction than physician assessment, as measured by positive likelihood ratio and positive predictive value. In addition, the prediction of the questionnaire's sum score at 8 weeks, with respect to symptom relief at 16 weeks, was more accurate than the physician's judgment on dose reduction. Similarly, the questionnaire sum score was a better predictor of patient satisfaction at 16 weeks than assessment by the doctor.

Computer-aided Detection Using 360-degree Virtual Dissection for Colorectal Polyps

Researchers at the Mayo Clinic in Rochester, Minnesota, conducted a feasibility study of a new computer-aided detection (CAD) software program as a first reviewer for the detection of colorectal polyps when applied to 360-degree virtual dissection image display. The results were published in a recent issue of the *American Journal of Roentgenology*. The patient population consisted of 41 consecutive patients with more than 1 polyp who underwent imaging without oral contrast material for stool tagging from a teaching file database. Using computed tomography (CT) colonography equipped with CAD software (written by one of the investigators), reviewers evaluated each possible polyp detected by the software by using virtual dissection images in conjunction with axial and 3-dimensional endoluminal views. They then compared the results with the reference standard, optical colonoscopy. Two experienced radiologists who were blinded to the reference standard findings determined whether the CAD detections were accurate. False detections were reviewed and categorized.

The investigators found the sensitivities for mid-size polyps (6–9 mm) to be 78.3% for reviewer 1 (18/23) and 91.3% (21/23) for reviewer 2. For large polyps (≥ 1 cm), the sensitivities were 94.9% (37/39) for reviewer 1 and 97.4% (38/39) for reviewer 2. Per-patient sensitivities for polyps of at least 6 mm and at least 10 mm were found to be 94.4% (34/36) and 95.1% (39/41) for reviewer 1 and 97.2% (35/36) and 97.6% (40/41) for reviewer 2, respectively. The mean number of false detections per acquisition was 4.28, most of which were from the ileocecal valve or the enema tip. The average interpretation times were 4 minutes and 26 seconds for reviewer 1 and 5 minutes and 38 seconds for reviewer 2. The authors concluded that colorectal polyp detection using CT colonography equipped with CAD and virtual dissection is feasible as a first reviewer and that detection rates are similar to

those of colonoscopy. They also noted that interobserver variability is low, interpretation times are short, and false-positive detections per patient are few.

Phosphatidylcholine for Steroid-refractory Chronic UC

According to a recent issue of the *Annals of Internal Medicine*, researchers from University Hospital Heidelberg in Germany examined whether steroid withdrawal is easier with delayed-release phosphatidylcholine or cellulose placebo in adults with chronic steroid-refractory UC. The researchers conducted a randomized, double-blind, placebo-controlled trial from March 2003 to January 2006 consisting of 60 patients with chronic steroid-refractory UC and high clinical and endoscopic disease activity index scores of at least 5. Phosphatidylcholine or placebo was administered 4 times daily for 12 weeks (for a total dosage of 2 g daily). The follow-up rate of the patients in the study was 97%. The study measured the number of patients achieving complete steroid withdrawal and either a low clinical activity index (≤ 3) or improvement in the clinical activity index score of 50% or more.

The researchers found that the primary endpoint was achieved in 15 of the 30 patients (50%) who received phosphatidylcholine and in 3 of the 30 patients (10%) who received placebo, for a difference of 40% (95% confidence interval [CI], 19–61%; $P=.002$). Twenty-four patients who received phosphatidylcholine (80%) and 3 patients who received placebo (10%) discontinued steroid therapy without disease exacerbation, for a difference of 70% (CI, 52–88%; $P<.001$). The most common adverse event was mild bloating. The authors noted the small size and short duration of the study but concluded that phosphatidylcholine reduced corticosteroid dependence more than placebo in patients with chronic steroid-refractory UC, adding that the next step involved long-term trials to evaluate the sustainability of steroid withdrawal in these patients.

The Use of Eltrombopag in HCV Patients

Researchers at Duke University Medical Center and other centers worldwide evaluated the ability of the new, orally active thrombopoietin-receptor agonist eltrombopag (Promacta, GlaxoSmithKline) to improve platelet counts and facilitate treatment for HCV infection in patients with thrombocytopenia associated with HCV-related cirrhosis. In the study, 74 patients with HCV-related cirrhosis and platelet counts from 20,000 to less than 70,000 per mm^3 were randomly assigned to receive eltrombopag (30 mg, 50 mg, or 75 mg daily) or placebo daily for 4 weeks. The primary endpoint was a platelet count of 100,000 per mm^3 or more at 4 weeks. Peginterferon and ribavirin therapy could subsequently be started, with the continua-

tion of eltrombopag or placebo for 12 additional weeks.

The investigators found that at 4 weeks, platelet counts had increased to 100,000 per mm^3 or more in a dose-dependent manner among patients for whom these data were available: in 0 of the 17 patients in the placebo group, in 9 of 12 patients (75%) in the 30-mg eltrombopag group, in 15 of 19 patients (79%) in the 50-mg eltrombopag group, and in 20 of 21 patients (95%) in the 75-mg eltrombopag group ($P<.001$). Antiviral therapy was started in 49 patients (in 4 of 18 patients receiving placebo, 10 of 14 patients receiving 30 mg of eltrombopag, 14 of 19 patients receiving 50 mg of eltrombopag, and 21 of 23 patients receiving 75 mg of eltrombopag) along with the continuation of eltrombopag or placebo. Twelve weeks of antiviral therapy with concurrent receipt of eltrombopag or placebo were completed by 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively and by 6% of patients in the placebo group. Headache was the most common adverse event during the initial 4 weeks; thereafter, the adverse events were those commonly associated with interferon-based therapy.

In Brief

A prospective study evaluated the use of a novel laparoscopic “clam shell” partial fundoplication that incorporates a modified Toupet with an anterior fundic flap for the management of medically recalcitrant GERD. The researchers concluded that this fundoplication may be considered an attractive alternative antireflux approach to Nissen fundoplication, particularly among patients at risk for postoperative dysphagia or gas bloating. (*Ann Thorac Surg.* 2007;84:1704-1709.)

Although preoperative treatment with infliximab alone does not significantly increase the incidence of postoperative complications, using both infliximab and cyclosporine A prior to colectomy in refractory UC is associated with high surgical morbidity, according to a retrospective study. (*Dis Colon Rectum.* 2007;50:1747-1753.)

A prospective, randomized, controlled, multicenter trial demonstrated that the use of extracorporeal albumin dialysis may be associated with an earlier and more frequent improvement of hepatic encephalopathy (grade 3/4). Because this 5-day study was not designed to examine the impact of the molecular adsorbent recirculating system on survival, a full assessment of the role of albumin dialysis awaits additional controlled trials. (*Hepatology.* 2007;46:1853-1862.)