

Combination Therapy Utilizing Boceprevir in Treatment-Naive Hepatitis C Patients

Preliminary results from an ongoing phase II study evaluating the investigational oral hepatitis C protease inhibitor boceprevir in combination with peginterferon alfa-2b (Pegintron, Schering-Plough) and ribavirin (Rebetol, Schering-Plough) in treatment-naive patients chronically infected with hepatitis C virus (HCV) genotype 1 were recently announced. In this study, boceprevir (800 mg TID) is being evaluated in three treatment regimens: boceprevir in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly) and ribavirin (800–1,400 mg daily) for 28 or 48 weeks; 4 weeks of peginterferon alfa-2b and ribavirin combination therapy at the doses in the first regimen followed by the addition of boceprevir to the combination for 24 or 44 weeks; and boceprevir in combination with peginterferon alfa-2b and low-dose ribavirin (400–1,000 mg daily) for 48 weeks, compared to a control of peginterferon alfa-2b and ribavirin alone for 48 weeks. The study consists of 595 patients at sites across the United States (77% of the patients), Canada, and Europe, including 491 patients in the boceprevir arms. African-Americans represent 16% of the patients, and 7% of patients in the study are cirrhotic. The primary endpoint of the study is sustained virologic response.

Patients receiving boceprevir regimens achieved a high rate of early virologic response, with 70%, 79%, and 54% of patients, respectively, having undetectable HCV-RNA at Week 12 of boceprevir therapy compared to 34% of patients in the control arm (as evaluated by the Roche Cobas Taqman 1.0 assay; lower limit of detection=15 IU/mL). Treatment discontinuations due to adverse events occurred in 12%, 9%, and 8% of the patients in the boceprevir regimens, respectively, compared to 5% of the control arm. The most common adverse events have included fatigue, headache, nausea, and anemia. There has been no increase in skin adverse events beyond that seen in the control arm. Gastrointestinal events were the most common adverse events leading to discontinuation in the boceprevir arms.

Obesity and Resolution of Heartburn

A pooled analysis of two similar randomized, double-blind studies was conducted to evaluate whether body mass index (BMI) affects heartburn resolution in patients. The results of this retrospective, industry-sponsored analysis were presented at the 2007 American College of Gastroenterology (ACG) Annual Scientific Meeting in Philadelphia, Penn., by Prateek Sharma, MD, Associate

Professor of Medicine at the University of Kansas School of Medicine, and colleagues. The analysis included 704 patients (62.4% women; mean age, 46.4 years) with nonerosive reflux disease who had been randomized to treatment with esomeprazole (Nexium, AstraZeneca) 20 mg (n=228), esomeprazole 40 mg (n=238), or placebo (n=238). All patients had experienced frequent heartburn for at least 6 months and had no evidence of erosive esophagitis, which was confirmed by endoscopy no more than 10 days prior to study entrance.

The analysis found that no apparent relationship existed between baseline heartburn severity and BMI ($P=.276$). In addition, baseline heartburn severity did not have a significant effect on heartburn resolution ($P=.985$; odds ratio [OR]=1.0; 95% confidence interval [CI], 0.97–1.03). Other than treatment, variables with a significant effect on heartburn resolution consisted of age, with greater odds of heartburn resolution with increased age ($P=.004$; OR=1.02; 95% CI, 1.01–1.03), and gender, with greater odds of resolution for men than women ($P=.028$; OR=1.50; 95% CI, 1.04–2.14). Dr. Sharma concluded that doses should be adjusted based on the symptoms of patients, not their BMIs.

Use of Analgesics in Cirrhotic Patients

According to a study presented at the 2007 ACG meeting, therapeutic doses of analgesics do not put patients with cirrhosis at increased risk for decompensation. Led by Roger Coron, MD, of Thomas Jefferson University Hospital, researchers examined the use of analgesics in 90 nonencephalopathic cirrhotic subjects hospitalized with acute decompensation events (including portal hypertensive bleeding and peritonitis) and 125 nonhospitalized cirrhotic controls. Thirty-day analgesic use and potential confounding factors for hepatic decompensation were noted, including alternative medication use and alcohol use. All controls had a history of decompensation, suggesting that cases and controls were at a roughly similar risk for decompensation due to cirrhosis alone.

Overall, 34% of patients and 44% of controls reported using analgesics over the previous 30 days, but the difference was not statistically significant. Analgesic use was not significantly associated with decompensation (adjusted OR=0.69, $P=.234$), a pattern that held true for all analgesic classes. A trend toward decompensation appeared (adjusted OR=2.02) among patients who took analgesics 4 weeks previously, but the effect was not statistically significant ($P=.112$). The authors suggested that the lack of the expected harmful effect of analgesics

could be explained by infrequent use and low doses. The trend toward higher risk for decompensation among patients who used analgesics 4 weeks previously, however, indicates that an effect may exist. Dr. Coron noted that the results were surprising, but cautioned that larger studies were warranted before prescribing analgesics to patients with liver failure who were not already using them.

Preliminary Results of AST-120 in Pouchitis

Data from the first cohort of patients from an exploratory phase II study evaluating the efficacy and safety of AST-120 (Ocera Therapeutics) in patients with active pouchitis were presented at the 2007 ACG meeting. This proof-of-concept study conducted at the Cleveland Clinic is evaluating 20 patients with active pouchitis treated with open-label AST-120, 2 g, three times daily. The primary efficacy endpoint is remission, as defined by a Pouchitis Disease Activity Index (PDAI) score of less than 7, which includes clinical, endoscopic, and histologic scores. Secondary endpoints include safety, clinical response (as measured by a decrease of PDAI of at least 3), and global quality-of-life score.

“A four-week treatment with AST-120 in patients with active pouchitis led to a significant decrease in symptoms of pouchitis and endoscopy scores in the first 10 patients enrolled in the study,” said Bo Shen, MD, principal investigator at the Center for Inflammatory Bowel Disease, Cleveland Clinic. “These results were impressive with 44.4% of the patients achieving clinical remission and 55.6% achieving a clinical response.”

Proof-of-concept trials were recently launched for AST-120 in nonconstipating irritable bowel syndrome, led by Jan Tack, MD, PhD, of the University of Leuven, Belgium, and for hepatic encephalopathy, led by Paul Pockros, MD, of the Scripps Clinic.

Computed Tomography Versus Colonoscopy in Colorectal Cancer Screening

According to a recent issue of the *New England Journal of Medicine*, researchers from the University of Wisconsin Medical School compared the diagnostic yield from primary computed tomographic colonography (CTC) screening in 3,120 consecutive adults (mean age, 57.0±7.2 years) with the yield from primary optical colonoscopy (OC) screening in 3,163 similar consecutive adults (mean age, 58.1±7.8 years) in an unrandomized study. Detection of advanced neoplasia and the total number of harvested polyps were the main outcome measures. Referral for polypectomy during OC was offered to all patients with CTC-detected polyps at least 6 mm in size. The option of CTC surveillance was also offered to patients with 1 or 2 small polyps (6–9 mm). According to established

guidelines, nearly all detected polyps were removed during primary OC, regardless of size.

During CTC screening, 123 advanced neoplasms were detected, including 14 invasive cancers, compared with 121 advanced neoplasms and 4 invasive cancers detected during OC screening. The referral rate for OC in the primary CTC screening arm was 7.9% (246 of 3,120 patients). Advanced neoplasia was confirmed in 100 of the 3,120 patients in the CTC arm (3.2%) and in 107 of the 3,163 patients in the OC arm (3.4%), not including 158 patients with 193 unresected CTC-detected polyps of 6–9 mm who were undergoing surveillance. Polyp removals in the CTC and OC arms totaled 561 and 2,434, respectively. Seven colonic perforations occurred in the OC arm, whereas none occurred in the CTC arm. The authors concluded that for advanced neoplasia, primary CTC and OC screening resulted in similar detection rates, although there were fewer polypectomies and complications in the CTC group, and that these findings supported the use of CTC as a primary screening examination before therapeutic OC.

Noninvasive Examinations for Cirrhosis

Three studies in a recent issue of *Clinical Gastroenterology and Hepatology* examined ultrasound and magnetic resonance (MR) imaging examinations as alternatives to liver biopsy in the diagnosis of liver fibrosis and cirrhosis.

Jayant A. Talwalkar, MD, of the Mayo Clinic College of Medicine, and colleagues conducted a systematic review and meta-analysis of diagnostic accuracy studies comparing ultrasound-based transient elastography with liver biopsy for detecting hepatic fibrosis. The researchers used electronic and manual bibliographic searches to identify potential studies and selected studies based on the reported accuracy of ultrasound-based transient elastography compared with liver biopsy. The meta-analysis combined the sensitivities, specificities, and likelihood ratios of individual studies. Nine studies in full publication were identified. In patients with stage IV fibrosis, the pooled estimates reported a sensitivity of 87% (95% CI, 84–90%), specificity of 91% (95% CI, 89–92%), positive likelihood ratio of 11.7 (95% CI, 7.9–17.1), and negative likelihood ratio of 0.14 (95% CI, 0.10–0.20). Among 7 studies with stage II–IV fibrosis patients, the pooled estimates reported a sensitivity of 70% (95% CI, 67–73%), specificity of 84% (95% CI, 80–88%), positive likelihood ratio of 4.2 (95% CI, 2.4–7.2), and negative likelihood ratio 0.31 (95% CI, 0.23–0.43). In both groups, diagnostic threshold bias was identified as an important cause of heterogeneity for pooled results.

In another study, Meng Yin, MD, of the Mayo Clinic College of Medicine, and colleagues performed

MR elastography in 50 patients with chronic liver disease and 35 normal volunteers and obtained MR imaging measurements of hepatic fat to water ratios to assess the potential effect of fat infiltration on stiffness-based detection of fibrosis. The researchers found that liver stiffness increased systematically with fibrosis stage. Receiver operating curve analysis showed that with a shear stiffness cutoff value of 2.93 kilopascals, the predicted sensitivity for detection of all liver fibrosis stages was 98%, whereas specificity was 99%. Receiver operating curve analysis also demonstrated that MR elastography could differentiate between patients with moderate and severe fibrosis and patients with mild fibrosis, at a sensitivity of 86% and specificity of 85%. Hepatic stiffness did not appear to be influenced by the degree of steatosis. The authors stated that based on the high negative predictive value of MR elastography, an initial clinical application may include triaging patients under consideration for biopsy examination to assess possible hepatic fibrosis.

Chen-Hua Liu, MD, of the National Taiwan University Hospital, and associates evaluated Doppler ultrasonography in the examination of the severity of hepatic fibrosis in patients with chronic hepatitis C (CHC). Consecutive, histologically confirmed patients with CHC over a 4-year period were divided into training (n=335) and validation (n=168) sets. The researchers evaluated the hepatic Doppler impedance index, splenic Doppler impedance index, and mean portal vein velocity for each patient prior to liver biopsy. Multivariate logistic regression showed that the splenic arterial pulsatility index (SAPI) and mean portal vein velocity were predictive of significant fibrosis ($\geq F2$) and cirrhosis (F4). Receiver operating characteristic analysis revealed that the areas under the curves of regression models and SAPI were comparable in predicting significant fibrosis (0.88 vs 0.87, $P=.22$) and cirrhosis (0.92 vs 0.90, $P=.12$) in the training set. In the validation set, areas under the curves of SAPI were 0.89 and 0.92 in predicting significant hepatic fibrosis and cirrhosis. The authors stated that by choosing optimized cutoff levels, 54% and 76% of the patients with significant hepatic fibrosis and cirrhosis could be predicted correctly.

Fospropofol Disodium New Drug Application

A new drug application was submitted to the US Food and Drug Administration for fospropofol disodium (Aquavan, MGI Pharma), a sedative hypnotic agent for patients undergoing brief surgical or diagnostic procedures. Data from 21 clinical studies, (1,611 patients) including a phase III trial in patients undergoing bronchoscopy, phase II and III trials in patients undergoing colonoscopy, and an open-label study in patients under-

going a variety of minor surgical procedures formed the application.

In the randomized, double-blind, multicenter, pivotal phase III trial of fospropofol disodium in bronchoscopy, the primary endpoint of sedation success was met, as well as all secondary endpoints. A total of 252 patients received either a 6.5 mg/kg dose of fospropofol disodium injection (n=150) or a control dose of 2.0 mg/kg. Among patients treated with fospropofol disodium, the sedation success rate was 88.7% compared with 27.5% of patients in the control arm (n=102; $P<.001$). The treatment success rate among patients treated with fospropofol disodium was 91.3% compared with 41.2% for controls ($P<.001$). The most frequently observed sedation-related adverse event in both arms was transient hypoxemia (15% in the fospropofol disodium versus 13% of controls). Eight patients (5%) in the fospropofol disodium arm experienced hypotension.

In the randomized, double-blind, multicenter phase III pivotal trial in colonoscopy, patients (N=312) were pretreated with fentanyl citrate (50 μ g) and then received either fospropofol disodium 2.0 mg/kg, fospropofol disodium 6.5 mg/kg or midazolam 0.02 mg/kg (2:3:1 ratio). Among those who received fospropofol disodium 6.5 mg/kg, 87% achieved sedation success, compared with 26% of patients who received fospropofol disodium 2.0 mg/kg ($P<.001$) and 69% of those who received midazolam 0.02 mg/kg. In addition, 88% of patients in the fospropofol disodium 6.5 mg/kg treatment arm achieved treatment success, defined as completing colonoscopy without requiring manual/mechanical ventilation and alternative sedative medication, compared to 28% of patients in the fospropofol disodium 2.0 mg/kg control arm ($P<.001$). The most common adverse reactions were paresthesias and pruritus.

In Brief

Capsule endoscopy is more effective in the evaluation of recurrence after surgery for Crohn's disease and is better tolerated than colonoscopy, according to a prospective study. (*Gastrointest Endosc.* 2007; 66:533-540.)

Results of a prospective study showed that both surgical resection and liver transplantation significantly improve the survival of patients with hepatocellular carcinoma, but improvements need to be made to the delivery of locoregional therapy to enhance its effectiveness. (*Liver Int.* 2007;27:1240-1248.)