

Positive 12-Week Interim Analysis Results for Danoprevir

Data from a 12-week interim analysis of the ATLAS trial, which evaluated the use of the investigational protease inhibitor danoprevir (Roche) for treatment of hepatitis C virus (HCV), were presented at the American Association for the Study of Liver Diseases 61st Annual Meeting held recently in Boston, Massachusetts. Study participants consisted of noncirrhotic, treatment-naïve adults (most with genotype 1 HCV) who had serum HCV RNA levels of at least 50,000 IU/mL and no advanced fibrosis. Pegylated interferon alfa-2a plus weight-based ribavirin was administered to all subjects, who were randomized to 12 weeks of placebo or 1 of 3 danoprevir arms: 300 mg every 8 hours, 600 mg every 12 hours, or 900 mg every 12 hours. Depending upon whether rapid virologic response was achieved, patients continued on standard therapy for an additional 24 or 48 weeks. Efficacy was defined as an undetectable HCV RNA level (<15 IU/mL). At week 2, levels were undetectable in 52% of the 300-mg arm, 57% of the 600-mg arm, 62% of the 900-mg arm, and 0% of the placebo arm. Week 4 showed progressions to 73%, 86%, 86%, and 7%, respectively, and week 12 analysis yielded undetectable levels in 88%, 89%, 92%, and 43%, respectively. Viral resistance was seen mainly in the 300-mg arm (in 2 patients at week 2 and 5 patients at weeks 4 and 12); the 600-mg arm had only 3 cases by week 12. Resistance was not seen in the 900-mg arm due to considerably less cumulative exposure; emerging toxicity led to discontinuation of that dosing regimen. Patients with HCV genotype 1A accounted for all cases of resistance.

Low-Dose Aspirin Reduces Colorectal Cancer Risk

As reported in the October 22nd early online publication of *The Lancet*, researchers examined follow-up data from 4 randomized trials in the United Kingdom and Sweden assessing the use of aspirin for primary and secondary vascular event prevention and 1 trial evaluating various aspirin dosages in order to examine the impact of aspirin on colorectal cancer risk over a 20-year period. Two trials randomized patients to 75 mg of aspirin daily or placebo, 1 trial evaluated 300 mg versus 1,200 mg daily versus placebo, 1 trial examined 500 mg of aspirin daily versus no aspirin, and the last trial randomized patients to 30 mg or 283 mg of aspirin daily. In the aspirin-versus-control trials, colorectal cancer was found in 391 of 14,033 patients (2.8%) and death occurred in 240 patients during

a median follow-up period of 18.3 years. Aspirin decreased the 20-year colorectal cancer risk (incidence hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.60–0.96; $P=.02$; mortality HR 0.65, 95% CI 0.48–0.88; $P=.005$). Where available, subsite data analysis showed a reduction in colorectal cancer risk in the proximal colon (incidence HR 0.45, 95% CI 0.28–0.74; $P=.001$; mortality HR 0.34, 95% CI 0.18–0.66; $P=.001$), though not in the distal colon (incidence HR 1.10, 95% CI 0.73–1.64; $P=.66$; mortality HR 1.21, 95% CI 0.66–2.24; $P=.54$; for incidence difference $P=.04$ and for mortality difference $P=.01$). Benefit rose with treatment duration; aspirin use of 5 or more years decreased proximal colorectal cancer risk by roughly 70% (incidence HR 0.35, 95% CI 0.20–0.63; mortality HR 0.24, 95% CI 0.11–0.52; both $P<.0001$), along with rectal cancer risk (incidence HR 0.58, 95% CI 0.36–0.92; $P=.02$; mortality HR 0.47, 95% CI 0.26–0.87; $P=.01$). For disease prevention, 75 mg of aspirin daily was as effective as higher doses, though fatal colorectal cancer risk was greater with 30 mg compared to 283 mg of aspirin daily during long-term follow-up in 1 trial (odds ratio 2.02, 95% CI 0.70–6.05; $P=.15$).

Entecavir Approved for Treatment of Chronic Hepatitis B Virus With Decompensated Liver Disease

Based upon data from ETV-048, a randomized, controlled, open-label, ongoing, phase IIIb study, the US Food and Drug Administration approved the supplemental New Drug Application of entecavir (Baraclude, Bristol-Myers Squibb) for chronic hepatitis B virus (HBV) treatment in adults with decompensated liver disease. The study evaluated 1 mg of entecavir once daily versus 10 mg of adefovir (Hepsera, Gilead) once daily in this patient population and found that, at 48 weeks, entecavir demonstrated greater viral suppression than adefovir. Study participants were either treatment-naïve or had undergone prior treatment with lamivudine or interferon-alfa. At baseline, patients had a mean serum HBV DNA level of 7.83 \log_{10} copies/mL and a mean alanine aminotransaminase level of 100 U/L; 54% were hepatitis B e antigen positive; and 35% were lamivudine resistant. A primary endpoint was the percentage of patients who had an undetectable HBV DNA viral load (<300 copies/mL); 57% (57/100) of the entecavir arm versus 20% (18/91) of the adefovir arm achieved an undetectable viral load at 48 weeks. Adverse reactions included peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%).