

Orphan Drug Status Granted to AST-120 for Pouchitis

The US Food and Drug Administration (FDA) recently granted orphan drug status to AST-120 (Ocera Therapeutics) for the treatment of pouchitis, a frequent and severe complication in colectomy patients with a J-pouch. Positive preliminary results from an exploratory phase II trial for AST-120 in the treatment of active pouchitis were presented at last year's American College of Gastroenterology Meeting. There are currently no FDA-approved drugs for pouchitis. AST-120 is an oral agent known to adsorb bile acids and bacterial toxins, as well as mediate inflammation in the gastrointestinal tract. In addition to the phase II trial that is currently ongoing in patients with active pouchitis, AST-120 is also being evaluated in a phase III trial in fistulizing Crohn's disease (CD).

Natalizumab Approved for Treatment of Moderate-to-Severe CD

The FDA recently announced the approval of a supplemental Biologics License Application for natalizumab (Tysabri, Elan/Biogen Idec) for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD who have evidence of inflammation and have had inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of tumor necrosis factor (TNF)- α .

Approval was based on clinical trials including ENCORE, in which natalizumab was shown to induce response and remission in patients with moderately to severely active CD. After 12 weeks of therapy, 60% of natalizumab patients achieved response compared to 44% of placebo patients, and at both Weeks 8 and 12, 48% of natalizumab patients sustained response compared to 32% of placebo patients ($P < .005$ for both). Among patients who experienced inadequate response to earlier treatment with TNF- α inhibitors, 38% attained sustained response at Weeks 8 and 12.

In ENACT-2, an additional year of natalizumab therapy sustained response and remission among patients who initially responded to natalizumab after 3 months in ENACT-1. Of patients who responded in ENACT-1, sustained response during ENACT-2 was observed in 61% of patients receiving natalizumab at every visit through an additional 6 months, compared to 29% for

placebo. This difference was also sustained through 12 months of additional therapy (54% vs 20%). Remission was sustained at every visit with an additional 6 or 12 months of natalizumab in 45% and 40% of patients, respectively, compared to 26% and 15% of patients receiving placebo ($P < .005$ for all comparisons). Among patients who had prior failure to TNF- α inhibitors, response and remission were sustained at every visit through an additional 6 months of natalizumab in 52% and 30% of patients, respectively. Among patients taking steroids and in whom response was attained, approximately two thirds were able to discontinue steroids within 10 weeks of beginning tapering.

Natalizumab has been associated with rare cases of progressive multifocal leukoencephalopathy, and other serious adverse events have included hypersensitivity reactions (eg, anaphylaxis) and infections. Serious opportunistic and other atypical infections have been seen in natalizumab patients, some of whom were taking concurrent immunosuppressants. Herpes infections were also slightly more common in natalizumab patients. In multiple sclerosis (MS) and CD trials, the incidence and rate of other serious adverse events, including serious infections, were similar in patients taking natalizumab and those taking placebo. Common adverse events in the natalizumab MS trials include headache, fatigue, infusion reactions, urinary tract infections, joint and limb pain, and rash. Other common adverse events in the natalizumab CD trials include respiratory tract infections and nausea. Clinically significant liver injury has also been cited in natalizumab patients in the postmarketing setting.

Prevalence of Eosinophilic Esophagitis in Patients With Dysphagia

Led by Ganapathy A. Prasad, MD, of the Mayo Clinic, Rochester, Minnesota, researchers conducted a prospective study to evaluate the prevalence of eosinophilic esophagitis (EE) as well as its clinical and endoscopic predictive factors in patients undergoing evaluation for dysphagia. The study, which was published in a recent issue of the *American Journal of Gastroenterology*, examined 376 outpatients (age range, 18–60 years) undergoing endoscopy for dysphagia at the Mayo Clinic in Rochester, Minnesota between June 2005 and June 2006. Patients completed the validated Mayo Dysphagia Questionnaire (MDQ). If no cause of dysphagia was endoscopically

evident or if there were endoscopic findings suggestive of EE, biopsies were obtained from the midesophagus. The presence of more than 20 eosinophils/high-power field was used to define EE, and the predictors of EE were identified by performing logistic regression.

Among the 376 patients who participated in the study, 238 patients (63%) completed the MDQ and 222 patients (59%) underwent midesophageal biopsies, of which 33 (15%; 95% confidence interval [CI], 6–12%) had histologic evidence of EE. Ten of the 102 patients (9.8%) who appeared endoscopically normal had histologic evidence of EE, whereas 8 of 21 patients (38%) who had endoscopic changes suggestive of EE had histologic evidence of EE. Predictive factors of EE included younger age, endoscopic features suggestive of EE, absence of proton pump inhibitor use for reflux, and history of food impaction lasting for more than 5 minutes. The authors subsequently concluded that midesophageal biopsies from normal-appearing mucosa should be obtained in all patients with unexplained solid food dysphagia, as this guideline may diagnose EE in approximately 1 in 10 cases.

Baclofen for Maintenance of Alcohol Abstinence in Patients With Liver Cirrhosis

According to a recent issue of the *Lancet*, researchers at the Catholic University of Rome in Italy conducted a randomized, double-blind, controlled study to evaluate the efficacy and safety of baclofen in achieving and maintaining alcohol abstinence in patients with liver cirrhosis. The study population consisted of 148 alcohol-dependent patients with liver cirrhosis who were referred to the Institute of Internal Medicine in Rome, Italy between October 2003 and November 2006. Of these patients, 84 were randomly assigned to either oral baclofen (30 mg daily) or placebo for 12 weeks after alcohol detoxification. Primary outcome was defined as the number of patients who achieved and maintained alcohol abstinence, and measures of this outcome included total alcohol abstinence and cumulative abstinence duration (assessed at regular follow-up visits using reports of family members, patients, blood examinations, and urine examinations). Relapse was determined by alcohol intake of more than 4 daily drinks or overall consumption of 14 or more weekly drinks over a period of at least 4 weeks.

Intention-to-treat analysis showed that among the 42 patients in the baclofen arm, 30 (71%) achieved and maintained abstinence compared with 12 (29%) of 42 in the placebo arm (odds ratio, 6.3; 95% CI, 2.4–16.1; $P=.0001$). The number of patients who discontinued treatment did not differ between the baclofen (6/42; 14%) or placebo (13/42; 31%) arms ($P=.12$). The dura-

tion of cumulative abstinence was approximately 2-fold higher in patients in the baclofen arm than in those in the placebo arm (mean, 62.8 [SE 5.4] vs 30.8 [5.5] days; $P=.001$). There was no evidence of hepatotoxicity. In addition, reductions from baseline in international normalized ratio, alanine aminotransferase, bilirubin, and gamma-glutamyltransferase levels and increases from baseline in albumin levels were significantly greater in patients in the baclofen arm. These patients also scored significantly lower on standardized measures of alcohol craving. The authors concluded that baclofen is efficacious at aiding alcohol abstinence in alcohol-dependent patients with liver cirrhosis and that as the drug is well tolerated, it could play an important role in treatment of these individuals.

Phase III Trials Announced to Evaluate Telaprevir

Phase III evaluation of telaprevir, (VX-950, Vertex) an investigational oral inhibitor of hepatitis C virus (HCV) protease was recently announced. The primary pivotal trial will focus on the evaluation of 24-week telaprevir-based therapy and will enroll approximately 1,050 treatment-naïve, genotype 1 HCV patients randomized equally across 3 treatment groups (approximately 350 patients per group). The study will be conducted in approximately 100 centers worldwide, including the United States and the European Union. The study groups will include: 24 weeks of therapy, with telaprevir dosed at 750 mg every 8 hours for 12 weeks in combination with standard doses of pegylated interferon alfa-2a (PEG-IFN) and ribavirin (RBV) for 12 weeks, then continuing for another 12 weeks with PEG-IFN and RBV alone; 24 weeks of therapy, with telaprevir dosed at 750 mg every 8 hours for 8 weeks in combination with standard doses of PEG-IFN and RBV for 8 weeks, then continuing for another 16 weeks with PEG-IFN and RBV alone; and a control arm with standard doses of PEG-IFN and RBV dosed for 48 weeks.

Patients in both telaprevir groups who attain rapid viral response (RVR), defined as undetectable (less than 10 IU/mL) viral levels by the end of Week 4, and who remain undetectable at Week 12 will receive 24 weeks of treatment. Patients in these treatment groups who do not meet the RVR criteria but are undetectable at Week 24 will continue with PEG-IFN and RBV for a total of 48 weeks.

In addition, a second controlled clinical study will be concurrently conducted as part of the registration program for a treatment-naïve indication. The objective of this study will be to develop additional sustained viral response (SVR) and relapse rate data with 48 weeks of treatment that confirms the results from phase II studies

and provides additional evidence to support the 24-week regimen in the phase III trial. The design of the study is currently being finalized but is expected to enroll approximately 400–500 patients (including patients in the control group).

The primary objective of the two studies will be to evaluate the percentages of patients in each study group who attain SVR, defined as undetectable (less than 10 IU/mL, as measured by the Roche TaqMan assay) HCV RNA 24 weeks after the completion of dosing. SVR data are expected from both studies by mid-2010.

Tumor Size and Survival Rates for Pancreatic Cancer

Researchers at Saint Louis University and the M.D. Anderson Cancer Center in Houston investigated the link between tumor size and survival rates for pancreatic cancer. The study, which was published in a recent issue of *Pancreas*, examined 65 patients (average age, 67; male, n=38) diagnosed with pancreatic cancer at the M.D. Anderson Cancer between December 2000 and December 2001.

Median survival after diagnosis was 17.2 months for patients with tumors of 20 mm or smaller; 12.3 months for patients with tumors 21–25 mm; 8.5 months for patients with tumors 26–30 mm; and 7.6 months for those with tumors larger than 30 mm. Of those patients with tumors 20 mm or smaller, 2 were still alive after 48 months, whereas none of the patients with tumors larger than 30 mm were alive after 36 months.

The authors pointed out that the group of patients with the smallest tumors and the highest survival rates were relatively small in number (n=12, 18%). In contrast, the largest group of patients (n=27, 42%) had tumors larger than 30 mm. In addition, the average tumor size of patients in the study was 32.9 mm, above the threshold of the lowest survival rate. That figure is roughly comparable to an average tumor size of approximately 30 mm among pancreatic cancer patients in general, according to the study.

“Even though it seems intuitive and was supported by preliminary observations from earlier studies, for the

first time we now have evidence that a progressive decrease in the size of a pancreatic tumor at the time of diagnosis improves patient outcomes rather dramatically,” said Banke Agarwal, MD, Associate Professor of Gastroenterology at the Saint Louis University School of Medicine and lead author of the study. Dr. Agarwal emphasized that researchers will need to focus on further investigation into identifying groups of people who should be screened early for pancreatic cancer, such as those with a family history of pancreatic cancer, a group that is currently under active investigation, or elderly people recently diagnosed with diabetes or depression, who have been shown to have a higher likelihood of pancreatic cancer, according to preliminary data from other studies.

In Brief

According to a case-control study and a validation case-control study, the epidermal growth factor (EGF) gene polymorphism genotype was associated with risk for development of hepatocellular carcinoma in liver cirrhosis through modulation of EGF levels. (*JAMA*. 2008;299:53-60.)

In a prospective international multicenter study, the addition of autofluorescence imaging to high-resolution endoscopy increased the detection of both the number of patients and the number of lesions with early neoplasia in patients with Barrett esophagus. The false-positive rate of autofluorescence imaging was reduced after detailed inspection with narrow-band imaging. (*Gut*. 2008;57:167-172.)

In a retrospective chart review, limited duration intravenous cyclosporine therapy in the treatment of inflammatory bowel disease was frequently associated with adverse events, though the majority were minor and responded to dose adjustment. Although not all severe adverse events can be clearly attributed to cyclosporine use alone, its high incidence suggests that vigorous monitoring by experienced clinicians at tertiary care centers may be required. (*Am J Gastroenterol*. 2008 Jan 2 [Epub ahead of print].)