By Samantha Alleman

Vonoprazan Vs Lansoprazole for the Treatment of Duodenal or Gastric Ulcers

Vonoprazan, a potassium-competitive acid blocker used to treat acid-related diseases, is well tolerated in Japanese patients with duodenal or gastric ulcers for up to 6 or 8 weeks of treatment, respectively, and has a similar efficacy for duodenal ulcer healing and is noninferior in terms of gastric ulcer healing compared to lansoprazole. Up to 20% of the adult Asian population has peptic ulcer disease, which can manifest in the stomach or duodenum.

Results of two phase 3, noninferiority, randomized, double-blind, double-dummy, multicenter, parallel group studies, conducted by Dr Hiroto Miwa and colleagues, were published in the January 2017 issue of *Alimentary Pharmacology and Therapeutics*. Both studies took place in Japan. The duodenal ulcer study was conducted across 76 sites between October 2011 and February 2013, and the gastric ulcer study took place across 83 sites between November 2011 and December 2012. Patients in both studies were randomized to receive 30 mg of lansoprazole or 20 mg of vonoprazan for 6 weeks (duodenal ulcer) or 8 weeks (gastric ulcer). The primary endpoint was the proportion of patients who had healed ulcers confirmed endoscopically.

Of the 372 patients in the duodenal ulcer study who were randomized to receive lansoprazole (30 mg) or vonoprazan (20 mg), 95.2% (179/188) and 92.9% (171/184) completed the treatment, respectively. Of those, all but 1 in each arm entered follow-up; 98.3% (175/178) of patients on lansoprazole and 96.5% (164/170) of patients on vonoprazan completed follow-up. The main reasons for discontinuation at either stage were protocol deviation or adverse events, the latter of which included headache, acute pancreatitis, and vomiting in the lansoprazole group (1 patient each) and dizziness, subarachnoid hemorrhage (which resulted in death), and duodenal ulcer hemorrhage in the vonoprazan group (1 patient each). Overall, 98.3% of patients receiving lansoprazole and 95.5% of patients receiving vonoprazan achieved healed duodenal ulcers. Noninferiority of vonoprazan to lansoprazole was not confirmed (95% CI, -6.400 to 0.745; *P*=.0654).

A total of 482 patients were included in the gastric ulcer study; 238 patients were randomized to receive lansoprazole (30 mg) and 244 patients were randomized to receive vonoprazan (20 mg). Within each arm, 93.3% and 92.2% of patients, respectively, completed the treatment. Two hundred three of 212 (95.8%) patients on lansoprazole and 209 of 217 (96.3%) patients on vonoprazan entered and completed follow-up. The main reasons for discontinuation from treatment and follow-up were protocol deviation and adverse events, respectively. The most common adverse events were related to gastrointestinal disorders. Overall, 93.8% of patients receiving lansoprazole and 93.5% of patients receiving vonoprazan achieved healed gastric ulcers. Noninferiority of vonoprazan to lansoprazole was confirmed (95% CI, -4.750 to 4.208; *P*=.0011).

These studies are the first randomized, controlled trials evaluating vonoprazan in patients with peptic ulcer disease. Vonoprazan was approved in the Japanese market in 2015.

Pharmacovigilance Risk Assessment Committee Confirms HBV Reactivation Risk From Direct-Acting Antiviral Use For HCV Infection

On December 2, 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency confirmed that direct-acting antiviral agents used for the treatment of hepatitis C virus (HCV) infection may lead to reactivation of hepatitis B virus (HBV). The PRAC recommends that all patients should be screened for HBV prior to beginning treatment, and patients who are coinfected with HBV and HCV should be monitored and treated consistent with current guidelines.

The confirmation is the result of a request by the European Commission on March 17, 2016 to review daclatasvir (Daklinza, Bristol-Myers Squibb), dasabuvir (marketed in Europe as Exviera, AbbVie), ombitasvir/paritaprevir/ritonavir (Technivie; marketed in Europe as Viekirax, AbbVie), simeprevir (Olysio, Janssen), sofosbuvir (Sovaldi, Gilead Sciences), and sofosbuvir/ledipasvir (Harvoni, Gilead Sciences) for the degree of HBV reactivation in patients coinfected with HBV and HCV and treated with direct-acting antiviral agents for HCV. Two other direct-acting antiviral agents were authorized in the European Union during the course of the review: elbasvir/grazoprevir (Zepatier, Merck) and sofosbuvir/velpatasvir (Epclusa, Gilead Sciences).

Approximately 30 cases of HBV reactivation have been reported thus far, and despite the low number, the PRAC recommends that these medications carry a warning in the prescribing information. On October 4, 2016, the US Food and Drug Administration issued a similar announcement regarding the risk of HBV reactivation and required a boxed warning be added to the treatments

previously listed, as well as for ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak and Viekira XR, AbbVie).

On April 14, 2016, the PRAC extended the review to include the risk of hepatocellular carcinoma. The committee concluded that further studies are needed in this area before a final decision can be determined.

The PRAC recommendations will be sent to the Committee for Medicinal Products for Human Use for a final opinion, which will be adopted by the European Commission.

Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use Associated With Iron Deficiency Risk

The use of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists for 2 or more years to inhibit gastric acid is linked to an increased risk of iron deficiency in patients without preexisting risk factors. The risk increased in relation to the strength of the acid inhibitor and decreased following discontinuation of medication. Results of the community-based, case-control study were released online on November 24, 2016 ahead of print publication in *Gastroenterology*.

For the study, Dr Jameson R. Lam and colleagues evaluated 77,046 patients diagnosed with iron deficiency between January 1999 and December 2013 against 389,314 controls. Patients with preexisting risk factors for iron deficiency were excluded from the study. Conditional logistic regression was used to estimate associations.

Within the group of patients diagnosed with iron deficiency, 3.0% (n=2343) received at least a 2-year supply of PPIs and 1.4% (n=1063) received histamine-2 receptor antagonists without PPIs. Among the control group, 0.9% (n=3354) of patients received at least a 2-year supply of PPIs and 0.6% (n=2247) received histamine-2 receptor antagonists. The risk of iron deficiency was higher in patients on PPIs (adjusted odds ratio, 2.49; 95% CI, 2.35-2.64) or histamine-2 receptor antagonists (adjusted odds ratio, 1.58; 95% CI, 1.46-1.71) for 2 or more years than in nonusers. Higher PPI doses were associated with a stronger risk, and discontinuation trended toward a weaker risk. Histamine-2 receptor antagonists did not show similar associations. A longer duration of either therapy was linked with an increased risk.

The researchers suggest that the study findings "do not recommend against acid suppression for persons with clear indications for treatment, but clinicians should exercise appropriate vigilance when prescribing these medications, and use the lowest effective dose."

Ustekinumab Effective for Induction and Maintenance Therapy for Crohn's Disease

Intravenous ustekinumab (Stelara, Janssen) led to a higher rate of response than placebo in patients with moderately to severely active Crohn's disease, and subcutaneous ustekinumab maintained remission in treatment-experienced patients, according to results of a study published in the November 2016 issue of *The New England Journal of Medicine*.

In 2 induction trials, UNITI-1 and UNITI-2, Dr Brian G. Feagan and colleagues randomly assigned patients to receive a dose of ustekinumab of either 130 mg or approximately 6 mg/kg of body weight, or placebo, intravenously. A total of 741 patients with primary or secondary nonresponse to tumor necrosis factor antagonists composed the UNITI-1 trial; 628 patients who failed conventional therapy were included in UNITI-2. Patients who completed these trials were included in the IM-UNITI trial. Patients who responded to ustekinumab (n=397) were randomly assigned to receive either 90-mg subcutaneous maintenance injections every 8 or 12 weeks or placebo. The primary endpoints for the induction and maintenance trials were clinical response at week 6 and remission at week 44, respectively.

At week 6, patients in the ustekinumab arm (130-mg dose and 6-mg/kg dose) had a significantly higher rate of response than patients in the placebo arm (UNITI-1: 34.3%, 33.7%, and 21.5%, respectively; P=≤.003; UNITI-2: 51.7%, 55.5%, and 28.7%, respectively; P<.001). At week 44, patients in the ustekinumab arm (8 and 12 weeks) had higher rates of remission than those in the placebo arm (53.1%, 48.8%, and 35.9%, respectively). Adverse events were similar among each arm in all trials.