Twice-Daily PPI Reduced Laryngopharyngeal Reflux

BY DENISE NAPOLI

FROM THE JOURNAL CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

The proton pump inhibitor rabeprazole had a small but significant effect in reducing laryngopharyngeal reflux symptoms after 12 weeks of treatment, Dr. Paul K.Y. Lam and his colleagues reported in an article appearing in September.

The results are in contrast to those of previous, smaller studies that did not find PPIs to be of benefit in laryngopharyngeal reflux (LPR), wrote the authors.

This study also was one of the first to use both the nine-item Reflux Symptom Index questionnaire (J. Voice 2002;16:274-7) and the Reflux Finding Score to measure both laryngopharyngeal reflux (LPR) symptoms and physical findings.

According to Dr. Lam, of the department of surgery at the University of Hong Kong, the researchers looked at patients referred to the Voice & Laryngeal Pathology Laboratory at his institution between November 2004 and June 2007. To be included in the prospective, double-blind, placebo-controlled, randomized study, patients needed to have either hoarseness, globus (a feeling of a lump in the throat), persistent throat discomfort, or frequent throat clearing for at least 1 month in the preceding year, as well as videostroboscopic evidence of LPR with a corresponding "reflux finding score" above 7.

The reflux finding score, or RFS, is "an 8-item clinical severity scale based on findings during fiberoptic laryngoscopy" that ranges from 0, indicating no abnormal findings, to 26 (Laryngoscope 2001;111:1313-7).

Participants also had to have a negative history for any upper respiratory tract infection or allergic laryngitis in the 4 weeks prior to evaluation, and could not be younger than age 18 years, have any other laryngeal pathology, or have a history of gastroesophageal x-ray or surgery.

Patients who had been taking an acid suppressive drug any time during the month prior to enrollment were also excluded.

A total of 82 patients were randomized and completed the study at 6, 12, and 18 weeks follow-up. Overall, 42 patients took rabeprazole 20 mg twice daily for 12 weeks, 30 minutes prior to lunch and dinner (mean age, 46 years; 15 males), while the remaining 40 subjects were given placebo (mean age, 47 years; 8 males).

All patients also were taught to abstain from caffeine, alcohol, smoking, spicy food, and other potential triggers of reflux. They were advised to avoid eating less than 3 hours before bedtime and to drink plenty of water.

"The rabeprazole group had a significantly reduced total RSI score at week 6 (–3.03 plus or minus 1.05, $P = .003$) and at week 12 (–3.73 plus or minus 1.18, $P = .002$) compared to the placebo group," wrote the authors (Clin. Gastroenterol. Hepatol. 2010;8:770-6).

However, the improvement on the RSI did not persist at week 18, which was 6 weeks after the conclusion of the PPI regimen (–1.48 plus or minus 1.26, $P = .124$).

In contrast, when looking at physical improvement as measured on the RFS, the investigators found no significant difference between groups at weeks 6, 12, or 18, with significance set at the 0.01 level.

VITALS

Major Finding: The proton pump inhibitor rabeprazole significantly reduced laryngopharyngeal reflux symptoms on the nine-item reflux symptom index at week 6 and week 12 of treatment, compared with placebo.

Data Source: A study appearing in the September issue of the journal Clinical Gastroenterology and Hepatology.

Disclosures: The authors disclosed that the study was partially sponsored by the developer of rabeprazole, Esai Co. Ltd. They added that the researchers had no personal conflicts of interest.

Rather, both groups showed improvement, possibly due to the effects of education regarding abstinence from smoking, alcohol, and caffeine, although "this did not translate into significant improvement in RSI in the placebo patient group," according to the authors.

Indeed, within the rabeprazole group, Dr. Lam did find improvement from baseline at both week 12 (–2.21 plus or minus 0.64. $P = .002$) and week 18 (–3.21 plus or minus 0.57, $P = .0001$), especially relating to laryngeal and vocal cord edema.

Dr. Lam and his colleagues conceded that "despite the improvement in both RSI and RFS in the rabeprazole group at week 12, the actual change was not much (only 2.81 and 2.21, respectively)."

Furthermore, the total average scores for both the RSI and the RFS were still high even after a period of 12 weeks of therapy with rabeprazole, "with RSI score well above 10 and RFS more than 7," which was positive for a laryngopharyngeal reflux condition. ■

Linaclotide Improved Chronic Constipation in Two Trials

BY AMY SCHONFELD

FROM NEUROGASTROENTEROLOGY AND MOTILITY 2010

BOSTON – The results of two 12-week, randomized, placebo-controlled phase III trials of linaclotide showed that the drug produced significant improvement in key end points related to chronic constipation.

Quality of life self-assessments also showed a favorable response, according to Dr. Anthony J. Lembo, who reported the results of both studies in a poster presentation.

VITALS

Major Finding: Linaclotide improved bowel and abdominal symptoms linked to chronic constipation in two phase III trials. There was no rebound effect during a 4-week randomized withdrawal period.

Data Source: Two randomized, placebo-controlled trials of 642 and 630 patients.

Disclosures: Dr. Lembo and Dr. Johnston have financial ties with Ironwood Pharmaceuticals Inc., which funded the trial. All other authors are employees of Ironwood or Forest Research Laboratories.

At the same meeting, which was hosted by the American Neurogastroenterology and Motility Society, Dr. Jeffrey M. Johnston reported in an oral presentation the results of the 4-week randomized withdrawal period that followed one of the studies. The findings showed that no rebound effects were seen after linaclotide cessation.

Linaclotide is a minimally absorbed, 14-amino-acid peptide, guanylate cyclase-C agonist, said Dr. Lembo, a gastroenterologist at Beth Israel Deaconess Medical Center, Boston.

It is produced by Ironwood Pharmaceuticals Inc., which supported the studies. Dr. Johnston is the chief medical officer at Ironwood Pharmaceuticals.

Two phase III trials were conducted, one with an intent-to-treat (ITT) population of 642 patients (Trial 303) and the other with an ITT population of 630 (Trial 01). The average age was 48 years, and approximately 12% of the participants were older than 65 years. About 90% of the subjects were female.

Subjects met Rome II criteria for chronic constipation, including fewer than three complete spontaneous bowel movements (CSBMs) per week, six or fewer spontaneous bowel movements per week (SBMs), or one or fewer SBMs on the Bristol Stool Form Scale (BSFS). At baseline, subjects reported 0.3 CSBMs per week and about 2 SBMs per week.

Subjects were treated with either 133 mcg or 266 mcg linaclotide or placebo. The linaclotide groups showed significant improvement compared with placebo on the primary efficacy end point, which was the percentage of patients who had an increase of at least one spontaneous bowel movement over baseline for at least 9 of the 12 treatment weeks.

In the first trial, 39.2% of those receiving low-dose linaclotide and 37.0% of those receiving high-dose linaclotide had an increase of one or more CSBMs per week for 9 of 12 weeks compared with their baseline rate; these rates were significantly greater than the 11% rate observed in the placebo group (P less than .0001).

Similar rates were seen in the second trial (31.0% low dose, 40.1% high dose, 13% placebo).

Patients also reported improvements in other bowel and abdominal symptoms associated with chronic constipation, such as the weekly rate of CSBMs, weekly rates of SBMs, better stool consistency, less severity of straining, less bloating, less abdominal discomfort, and less constipation severity.

For example, the weekly CSBM rate rose to 2 times per week, compared with 0.5 times per week in the placebo group (P less than .0001). In both trials at both doses tested, patients taking linaclotide reported better quality of life as measured on the 4-point Patient Assessment of Constipation–Quality of Life (PAC-QOL) questionnaire.

Eighty-four percent of enrollees in each trial completed treatment. Analysis of pooled safety results from both trials showed that 7% of those receiving the low dose and 7% of those receiving the high dose of linaclotide discontinued due to adverse events, compared with 4% of those receiving placebo.

One patient who had received low-dose linaclotide died as a result of a fentanyl patch overdose unrelated to the study drug. Diarrhea was the most common adverse event reported by those receiving linaclotide, and 4% of linaclotide-treated patients discontinued due to diarrhea.

During the 4-week randomized withdrawal period, those who were treated with linaclotide during the treatment period were rerandomized to either placebo or the linaclotide dose they had received. Those who had received placebo during the treatment period received high-dose linaclotide during the withdrawal period, explained Dr. Johnston. In total, 538 patients participated in the withdrawal phase.

The investigators found that those who had first received placebo and then received the study drug in the withdrawal phase showed improvements in their constipation symptoms similar to those of the patients who had previously been treated with linaclotide.

Those who had received active treatment but were switched to placebo showed regression toward more constipation symptoms, similar to those of the patients who had previously received placebo. No rebound effect was seen after cessation of linaclotide.

Sustained improvement was seen in those treated with linaclotide during both the treatment and withdrawal periods. ■