CLINICAL UPDATE

Current Developments in the Treatment of Functional Dyspepsia

Highlights in Functional Dyspepsia Treatment From Digestive Disease Week 2017

May 6-9, 2017 • Chicago, Illinois

Caraway Oil/L-Menthol Plus Common Functional Dyspepsia Medications Is Safe and Effective

The use of a caraway oil/L-menthol, site-specific targeting formulation (COLM-SST; FDgard, IM HealthScience) was safe and effective in patients who were already taking usual functional dyspepsia (FD) medications, according to the results of FDREST (FD Reduction Evaluation and Safety Trial). This study compared the use of COLM-SST and commonly available FD medications vs placebo and commonly available FD medications. These findings were presented in a poster by Dr William D. Chey and colleagues at Digestive Disease Week (DDW) 2017.

Patients were eligible if they fulfilled the Rome III criteria for FD and had at least moderate symptoms on at least 4 days during a screening period of 14 days. Each capsule of the tested formulation contained 25 mg of caraway oil and 20.75 mg of L-menthol. Patients received 2 capsules of COLM-SST or placebo in the morning and evening (30-60 minutes prior to a meal) with water for 28 days. The formulation or placebo was taken in addition to any existing FD medications (eg, proton pump inhibitors, H2 receptor agonists, anticonvulsants, beta blockers, antihistamines, antidepressants/tricyclic antidepressants, pain modulators, antacids). A 14-day washout was needed for prohibited medications such as antiemetics, prokinetics, cholinergics, antidiarrheals, sedative hypnotics, nonsteroidal anti-inflammatory drugs, narcotic analgesics, oral heartburn and gas relief agents, probiotics, and antispasmodics. These agents were only allowed 48 hours after the first dose and with approval by the medical monitor. Patient demographics and FD symptom subgroups did not significantly differ between the COLM-SST and placebo arms.

In total, 100 patients were enrolled. Patients taking COLM-SST plus usual FD medications experienced a decrease in symptoms at 2 to 14 days and at 15 to 28 days. In addition, this arm was numerically superior to the placebo arm in all measures. At day 28, clinical global impressions were much or very much improved in 61.2% of the COLM-SST arm vs 48.9% in the placebo arm. The COLM-SST arm experienced no serious treatment-emergent adverse events and fewer nonserious treatment-emergent adverse events than the placebo arm.

Chey WD, Lacy BE, Cash BD, Epstein M, Shah SM. Randomized controlled trial to assess the efficacy & safety of caraway oil/L-menthol plus usual care polypharmacy vs. placebo plus usual care polypharmacy for functional dyspepsia (FD). Presented at: Digestive Disease Week; May 6-9, 2017; Chicago, IL. Poster Sa1618.

Improvement Reported in Postprandial Distress or Epigastric Pain Syndromes With Caraway Oil/L-Menthol Plus Usual Medications

Approximately three-quarters of patients with postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS) experienced substantial improvement after 4 weeks of COLM-SST plus commonly available FD medications, compared to approximately half of the placebo group. These findings, which came from FDREST, were presented in a separate poster by Dr William D. Chey and colleagues at DDW 2017.

Patients with FD can be placed into PDS or EPS subgroups, per Rome III criteria. For this study, patients with PDS had to report a global overall symptoms (GOS) score of at least 5 for sensation of pressure, heaviness, or fullness, whereas patients with EPS had to report a GOS score of at least 4.5 for epigastric pain or discomfort. Treatment, which lasted 28 days, consisted of COLM-SST (50 mg of caraway oil and 41.5 mg of L-menthol) or placebo in the morning and evening plus usual FD medications (defined previously). In addition, a washout

period was needed for prohibited medications, also as described previously.

In total, 34 patients with FD fulfilled the criteria for PDS, and 39 patients with FD fulfilled the criteria for EPS. At day 28, clinical global impressions improved much or very much in 78% of patients with PDS and 72% of patients with EPS who received COLM-SST plus commonly available FD medications, compared to 50% (P=.09) and 40% (P=.046) of the placebo arms, respectively. Patients with PDS in the COLM-SST arm experienced a statistically significant decrease in sensations of pressure, heaviness, or fullness vs the placebo group at 24 hours and were objectively better, although not statistically significant, vs the placebo arm in all measures at 2 to 14 days and 15 to 28 days. In addition, patients with EPS who were taking COLM-SST experienced a statistically significant decrease in epigastric pain or discomfort symptoms at 24 hours and were objectively better, although not statistically significant, vs the placebo arm in all measures at 2 to 14 days and 15 to 28 days.

Chey WD, Lacy BE, Cash BD, Epstein M, Shah SM. Efficacy of caraway oil/L-menthol plus usual care vs placebo plus usual care, in functional dyspepsia patients with post-prandial distress (PDS) or epigastric pain (EPS) syndromes: results from a US RCT. Presented at: Digestive Disease Week; May 6-9, 2017; Chicago, IL. Poster Sa1619.

Functional Dyspepsia Symptoms Improve Within 24 Hours With Caraway Oil/L-Menthol Plus Usual Medications

At 24 hours, significant symptom relief was seen in patients with EPS as well as patients with PDS who received COLM-SST plus commonly available FD medications, according to findings from FDREST that were presented in a poster by Dr Brian E. Lacy and colleagues at DDW 2017. To the investigators' knowledge, this is the first time that rapid relief of FD symptoms has been seen with a product, even when used as an add-on treatment.

As previously mentioned, 100 patients were enrolled in this trial who fulfilled the Rome III criteria for FD. Patients with at least moderate symptoms for at least 4 days during the screening period (14 days) were randomized to 2 capsules of COLM-SST or placebo in the morning and evening. Each COLM-SST capsule contained 25 mg of caraway oil and 20.75 mg of L-menthol. COLM-SST was used in addition to any FD medications usually used (as defined previously), and patients were placed into PDS or EPS subgroups based upon their symptoms.

At 24 hours, FD patients in the overall population who received COLM-SST plus usual medication experienced a statistically significant (P=.0393) decrease in their PDS symptoms as well as an improvement of their EPS symptoms (P=.0764). As for patients within the PDS subgroup, at 24 hours, those who received COLM-SST had a statistically significant decrease in terms of PDS (P=.0225) and EPS symptoms (P=.0121). In addition, at 24 hours, patients in the EPS subgroup who received COLM-SST had a statistically significant decrease in EPS (P=.0028) and PDS symptoms (P=.0186).

Lacy BE, Chey WD, Cash BD, Epstein M, Shah SM. A caraway oil/L-menthol combination improves functional dyspepsia (FD) symptoms within the first 24 hours: results of a randomized controlled trial, which allowed usual FD treatments. Presented at: Digestive Disease Week; May 6-9, 2017; Chicago, IL. Poster Sa1620.

Once-Daily Mosapride Is Not Inferior to Conventional Mosapride in Patients With Functional Dyspepsia

Once-daily mosapride (UI05MSP015CT, Korea United Pharm) did not show inferiority to conventional mosapride in terms of efficacy and safety for the treatment of FD, according to results of a multicenter, randomized, active-controlled, double-blind, phase 3 clinical trial. These findings were presented in a poster by Dr Hyuk Yoon and colleagues at DDW 2017.

FD patients were randomly assigned to once-daily mosapride (15 mg once daily before breakfast) or conventional mosapride (5 mg 3 times daily before each meal) and corresponding placebo for 4 weeks. The primary endpoint consisted of change in gastrointestinal symptom score (GSS) from enrollment to 4 weeks, and secondary endpoints were change in quality of life according to Nepean Dyspepsia Index-Korean version (NDI-K), general symptom improvement, and adverse event rate.

In total, 138 FD patients (once-daily mosapride, 70; conventional mosapride, 68) were enrolled in university tertiary care centers in South Korea (intention-to-treat [ITT] analysis set: female, 71.3%; mean age, 44.0 ± 15.4 years). Per-protocol (PP) analysis consisted of 59 patients in the once-daily mosapride group and 58 patients in the conventional mosapride group. No significant differences were seen in baseline characteristics, including drug compliance between the once-daily and conventional mosapride groups (ITT/PP 95.5%/96.9% vs 96.3%/97.1%; P=.375/.087). GSS change for ITT/PP analysis was -9.69 ± 6.44/-9.80 ± 6.00 and -10.01 ± 5.92/-10.03 ± 5.53 in the once-daily and conventional mosapride groups, respectively. The mean difference in GSS change between the 2 groups was 0.33 (95% CI, -1.75 to 2.41) and 0.24 (95% CI, -1.88 to 2.35) for ITT/PP analysis, which demonstrated noninferiority of

once-daily mosapride (*P*=.755/.824). General symptom improvement for ITT/PP analysis did not differ between the once-daily and conventional mosapride groups (ITT/PP 37.1%/39.0% vs 55.9%/56.9%; *P*=.0274/.351). In addition, there was no difference in NDI-K score change between the once-daily and conventional mosapride groups (ITT/PP 13.8/14.3 vs 16.7/16.9; *P*=.204/.263). Finally, the rates of adverse events did not differ between the once-daily and conventional mosapride groups (13.24% vs 4.29%; *P*=.062).

Yoon H, Ho Lee D, Lee Y-H, et al. Multi-center, randomized, active-controlled, double-blind, non-inferiority, phase 3 clinical trial to evaluate the efficacy and safety of UI05MSP015CT in functional dyspepsia (MARS study). Presented at: Digestive Disease Week; May 6-9, 2017; Chicago, IL. Poster Tu1674.

Upper Gastrointestinal Symptoms Improved and Gastric Emptying Changed by Gluten-Free Diet in Patients With Irritable Bowel Syndrome and Functional Dyspepsia

A 1-month gluten-free diet improved upper gastrointestinal symptoms and caused gastric emptying changes in patients with concomitant irritable bowel syndrome and FD, according to the results of a nonrandomized, controlled clinical trial. These findings, which were reported in a poster by Dr María Inés Pinto Sanchez and colleagues at DDW 2017, suggest that a gluten-free diet may be a therapeutic option for FD, although further research is needed.

The trial, which was conducted from 2012 to 2016, examined adult patients who fulfilled the Rome III criteria for irritable bowel syndrome as well as healthy volunteers, who composed the control group. At baseline and following 1 month of treatment with a gluten-free diet, the study participants underwent a gastric emptying test via videofluoroscopy and assessment of gastrointestinal symptoms (via the Gastrointestinal Symptoms Rating Scale). A specialized dietitian evaluated compliance of the diet.

In total, the trial consisted of 45 patients with irritable bowel syndrome and 24 healthy volunteers. Among the irritable bowel syndrome patients, 22 (47.2%) met the Rome III criteria for FD. In 6 (34.5%), the chief complaint was early satiety. Overall in the irritable bowel syndrome arm, there were no changes in gastric emptying from baseline to after 1 month of gluten-free diet (remaining gastric content, 13.6% vs 13.17%; *P*=.3) However, a significant gastric emptying change was seen in patients with FD and early satiety (25.4% vs 7.12%; *P*=.03), according to a subgroup analysis. In addition, there was an improvement in upper gastrointestinal symptoms from baseline to 1 month of gluten-free diet in all patients with irritable bowel syndrome (24.5 vs 17.5; *P*<.001) and in those who had concomitant dyspeptic symptoms (24.5 vs 18.5; *P*=.02).

Pinto Sanchez MI, Causada Calo N, Nardelli A, et al. Gluten-free diet improves upper GI symptoms and promotes changes in gastric emptying in IBS patients with functional dyspepsia. Presented at: Digestive Disease Week; May 6-9, 2017; Chicago, IL. Poster Tu1683.