**MEETING HIGHLIGHTS**

**Digestive Disease Week**

**Walter Alexander**

Digestive Disease Week is supported by the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the American Society for Gastrointestinal Endoscopy, and the Society for Surgery of the Alimentary Tract. The 2015 meeting, held from May 17 to 19 in Washington, D.C., was attended by 14,521 physicians, allied health professionals, and exhibitors. Key sessions on pharmacological treatment included several on irritable bowel syndrome and others on pancreatitis and *Helicobacter pylori* infection.

**Effects of Rifaximin on Urgency, Bloating, and Abdominal Pain in Patients With IBS-D: A Randomized, Controlled, Repeat Treatment Study**

- William D. Chey, MD, Professor of Internal Medicine, University of Michigan, Ann Arbor, Michigan

“Repeat treatment with rifaximin led to significantly greater likelihood of improvement in IBS-related symptoms than placebo for abdominal pain and stool consistency, bloating, and urgency,” Dr. Chey concluded in his oral presentation of TARGET 3 results. This randomized, double-blind trial tested rifaximin in 636 irritable bowel syndrome (IBS-D) patients who had responded to an initial course of rifaximin but had a recurrence within 18 weeks. Repeat treatment consisted of two courses of rifaximin 550 mg three times a day for 14 days or placebo.

IBS is characterized by chronically recurring symptoms that typically include abdominal pain, bloating, urgency, and altered bowel patterns. IBS affects 44 million Americans annually, Dr. Chey said. Among the symptoms of the type of IBS marked by chronic or recurrent diarrhea (IBS-D), abdominal pain, bloating, and urgency are considered to be the most bothersome. The study examined the effect of subsequent courses of rifaximin on core symptoms in rifaximin responders. Subjects were considered weekly responders if in a given month they had positive bloating responses (0 or 1 on a scale of 0 to 6 in half or more days of a given week, or 0 to 2 every day in a given week) or positive urgency responses (30% or greater improvement from baseline in the percentage of days with urgency) during two or more weeks.

The primary endpoint, assessed after the first repeat treatment during the four-week follow-up period, was the proportion of responders. The rifaximin group included 328 subjects (mean age, 47.9 years; 68% female; mean body mass index [BMI], 29.9) and the placebo group had 308 (mean age, 45.6 years; 71% female; mean BMI, 29.7). The proportion of responders for IBS-related abdominal pain and stool consistency in the first repeat-treatment phase was 32.6% for rifaximin and 25.0% for placebo ($P = 0.0232$) in a worst-case analysis and 35.4% versus 25.6% in a last observation carried forward (LOCF) ($P = 0.0051$). With second repeat treatment, LOCF differences were similar at 36.9% for rifaximin and 29.3% for placebo ($P = 0.0375$).

**Impact of Simvastatin on Risk of Recurrent Acute Pancreatitis**

- Bechwien U. Wu, MD, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California

Episodes of recurrent pancreatitis were reduced in patients who initiated simvastatin after their initial event in a retrospective study from an integrated care setting.

Dr. Wu said interest in studying the relationship between statin use and pancreatitis was stimulated by case reports arousing suspicion that statins—simvastatin in particular—were causing pancreatitis in patients who were having recurrent episodes of this inflammation. Dr. Wu’s initial study, however, found the incidence of acute pancreatitis was lower among patients receiving simvastatin. The current study, conducted to further explore a possible relationship between statin use and recurrent pancreatitis, included 712 patients hospitalized for an initial episode of acute pancreatitis between January 2006 and December 2012 who started treatment with simvastatin after an initial episode of acute pancreatitis had a significantly lower incidence of recurrent acute pancreatitis (1.59 episodes per 1,000 person-years among new simvastatin users versus 4.46 episodes per 1,000 person-years among non-simvastatin users). The adjusted incidence-rate ratio for recurrent pancreatitis with simvastatin use compared with nonuse was 0.34 (95% confidence interval [CI], 0.26–0.45, $P < 0.0001$).

Dr. Wu concluded, “Our message is that simvastatin is not a causative agent, and based on its cardioprotective effects, its use should be continued.” He added that the mechanism of benefit with respect to recurrent acute pancreatitis does not appear to be lipid-lowering. “We have some preliminary data suggesting that it is really acting by a totally separate pleiotropic mechanism,” he said. Further research will be needed to determine if statin use may be a valuable means to reduce recurrent acute pancreatitis events.

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Assessment of all parameters revealed significant benefits for rifaximin over placebo (IBS-related abdominal pain, $P = 0.0212$; stool consistency, $P = 0.0241$; IBS-related bloating, $P = 0.0345$; and urgency, $P = 0.0251$). Rates of adverse events (AEs) were 42.7% for rifaximin and 45.5% for placebo, with low serious AE rates (1.2% for rifaximin and 1.3% for placebo).

Dr. Chey concluded, “With repeat two-week courses of therapy, rifaximin produced significant improvements in core symptoms of IBS-D.”
Effect of Ramosetron in Female Patients With Irritable Bowel Syndrome With Diarrhea: A Randomized, Placebo-Controlled Phase III Trial

• Shin Fukudo, MD, Professor, Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Ramosetron, a serotonin 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist that has previously been shown useful for treating IBS-D in men, is also effective for treating women with IBS-D, according to results of a phase 3, randomized, placebo-controlled trial.

In Dr. Fukudo’s earlier research,¹ the monthly responder rate for ramosetron among men was 50.3% compared with 19.6% for placebo (P < 0.001) at month 1. Other research had suggested that serotonin 5-HT₃ receptor antagonists might have a gender-specific effect in patients with IBS-D. Alosetron has been approved only for women and ramosetron only for men.

To test ramosetron’s efficacy in female IBS-D patients, Dr. Fukudo’s current study enrolled 576 female outpatients (ages 20–64 years) with IBS-D diagnosed with Rome III criteria at 70 centers in Japan. They were orally administered 2.5 mcg of ramosetron (n = 292) or placebo (n = 284) once daily before breakfast for 12 weeks after a one-week baseline period. The coprimary endpoints included monthly responder rates in global improvement of IBS symptoms based on weekly responders (scores of 0 [completely relieved] or 1 [considerably relieved] on a scale of 0–4), monthly responders for improvements in stool consistency, and weekly responders on the Bristol Stool Form Scale.

Among the trial participants, the mean age was about 41 years, with mean disease duration of about 159 months. The severity of abdominal pain or discomfort on the 0–4 scale was about 1.76, and stool frequency per day was about 2.2.

Dr. Fukudo reported that responder rates favoring ramosetron were significant by the second week. Monthly responder rates for global improvement were significantly higher for ramosetron than for placebo (one month, 31.5% versus 19.4%; P = 0.001), increasing over the course of the trial (last point, 50.7% versus 32.0%; P < 0.001).

Stool-consistency monthly responder rates increasingly favored ramosetron throughout the study, starting with the first week (month 1, 33.2% versus 17.6%; P < 0.001; last point, 40.8% versus 24.3%; P < 0.001). Daily average scores for the Bristol Stool Form Scale favored ramosetron significantly by the second day (P = 0.018). The favorable change in stool frequency was also greater for ramosetron than for placebo (approximately 0.5) by the second day (P < 0.001). Similarly, monthly responders with improved abdominal pain or discomfort were at 51.4% versus 37.7% for placebo (P = 0.001) at the last point, and improved abnormal bowel habit responders were at 50.3% versus 31.0% (P < 0.001) at the last point.

Dr. Fukudo noted that while gastrointestinal AEs were more common with ramosetron than with placebo, they were clinically manageable. The ischemic colitis rate of 0.001% with ramosetron, he underscored, is lower than the U.S. incidence (0.0126%). He concluded that ramosetron at 2.5 mcg is effective in women with IBS-D. Why this dose—half of that given to men—is sufficient in women is not precisely understood, he said.

Twenty-Four-Hour Results From a Placebo-Controlled Trial to Evaluate a Novel Peppermint Oil Delivery System, Targeting Release in the Small Intestine. Results From the U.S.-Based, 4-Week, Randomized, Placebo-Controlled, Multi-Centered IBSREST Trial

• Michael S. Epstein, MD, Chief Medical Officer, IM HealthScience LLC, Boca Raton, Florida

For IBS patients, current formulations of mint oil may cause heartburn, nausea, and anal burning because they tend to “dose-dump” in the stomach or pass all the way through the colon. However, a novel delivery system (IBgard, IM HealthScience LLC) allows solid beads of highly purified L-menthol to pass through the pylorus to the small intestine, where they are fully absorbed.

Twenty-four-hour results of the Irritable Bowel Syndrome Reduction Evaluation and Safety Trial (IBSREST) revealed a significantly greater reduction in the Total IBS Symptom Score (TSS) for IBgard than for placebo, according to Dr. Epstein.

The IBgard system’s triple coating restrains L-menthol release until pH exceeds 5.0, which in small-intestine simulation models allows 80% release in four hours. “Once it reaches the mucosa there, its antispasmodic, anti-inflammatory, 5-HT₃ agonist and antibacterial effects occur locally,” Dr. Epstein said in an interview after the oral session where he described results of the IBSREST trial.

The objective of IBSREST was to evaluate IBgard’s effectiveness and safety for the management of patients with IBS-D (diarrhea) and IBS-M (mixed diarrhea and constipation). IBSREST included men and women meeting Rome III IBS criteria (IBS-D or IBS-M) with average daily IBS-related abdominal pain of 4.0 or greater on a scale of 0–10 each week of a two-week baseline period. They also had scores of 2.0 or greater on the TISS scale of 0–4. The TISS is based on the intensity and frequency of eight IBS symptoms (abdominal pain or discomfort, bloating or distention, pain at evacuation, urgency, constipation, diarrhea, mucus or gas, and sense of incomplete evacuation).

IBSREST included 72 patients, divided roughly evenly between IBS-M and IBS-D. Their mean age was 40.6 years. Thirty-five patients were randomized to IBgard 180 mg three time daily, 30 to 90 minutes before meals, and 37 patients to placebo.

The first IBSREST endpoint was 24-hour reduction in TISS. The TISS reduction for IBgard was significantly greater than that for placebo (–18.8% for IBgard versus –9.8% for placebo, P = 0.0092). While reductions were greater for IBgard than placebo for each of the TISS components, reductions reached statistical significance only for abdominal pain or discomfort (–21% versus –10% for placebo; P < 0.05). For the subcategory of intensity of bowel movement urgency at 24 hours, the reduction with IBgard was also significantly greater (–25.2% versus –5.7%, P = 0.0374). “This is pretty powerful stuff,” Dr. Epstein commented. “It is not your mother’s peppermint oil.”

“The results are promising for on-demand application for IBS-M/D symptom relief,” Dr. Epstein noted. He emphasized that IBgard is a medical food product, not a drug or dietary supplement. A medical food is defined by section 5(b)(3) of the Orphan Drug Act as “a food which is formulated to be consumed or administered internally under the supervision of a physician and
which is intended for the specific dietary management of a disease or condition for which distinct nutritional requirements, based on scientific principles, are established by medical evaluation.”

IBgard was well tolerated with no treatment-emergent AEs in the first 24 hours.

**IBgard, a Novel Small Intestine Targeted Delivery System of Peppermint Oil, Results in Significant Improvement in Severe and Unbearable IBS Symptom Intensity. Results From a U.S.-Based, 4-Week, Randomized, Placebo-Controlled, Multi-Center IBSREST Trial**

- Brooks D. Cash, MD, Professor of Medicine, University of South Alabama, Fairhope, Alabama

In IBSREST, the number of IBS symptoms rated as severe or unbearable over four weeks was significantly reduced with IBgard. Among treatments for the three IBS subtypes (M, mixed/alternating; D, diarrhea; and C, constipation), approved products are lacking for IBS-M and options for IBS-D are limited, Dr. Cash said.

Derangements in gut immunity, microbiota, sensation, motility, secretion, and digestion have all been proposed as possible etiologies of IBS. L-menthol, the main constituent of peppermint oil, has antispasmodic, anticaarminative, topical analgesic, anti-infective and 5-HT3 receptor antagonism properties. IBSREST evaluated the efficacy and tolerability of IBgard in a population with severe/unbearable symptoms. High symptom severity reflects higher intensity and frequency of individual symptoms, leading in IBS patients to lower quality of life, work disruptions, and frequent physician visits (more than one per month).

“Our study was selective for patients with severe symptoms because that is where the unmet need is,” Dr. Cash said. He pointed out that in studies of other treatments, patients with more severe IBS tend to respond less well. The targeted delivery of mint oil in solid microspheres to the small intestine with IBgard was expected to address the unmet need.

The randomized, placebo-controlled trial included 72 patients (mean age, approximately 41 years) who met Rome III criteria for IBS-D or IBS-M, had average daily IBS-related abdominal pain of at least 4 on a scale of 0–10, and had a Total IBS Symptom Score (TISS) of at least 2 on a scale of 0–4. After a three-week period for assessment of symptom severity and washout of prohibited medication, subjects were randomly assigned to receive IBgard 180 mg three times a day or placebo for four weeks.

After 28 days, the reduction from baseline in the number of severe and unbearable symptoms (average of frequency and intensity, 3 or more) was –66% for IBgard compared with –42% for placebo ($P = 0.0212$). The reduction in patient-reported severe or unbearable abdominal pain intensity at 28 days was –79.4% for IBgard and –40.5% for placebo ($P < 0.0001$). Trends in percentage reduction in severe or unbearable individual intensity scores were favorable for IBgard across all eight severe/unbearable parameters (from 71% to 90%), more than at 24-hour assessment (30% to 47%). Among individual severe or unbearable intensity scores, the greater improvement from baseline for IBgard compared with placebo was significant for abdominal pain or discomfort ($P = 0.0015$), abdominal bloating or distension ($P = 0.0036$), and sense of incomplete evacuation ($P = 0.0038$), with strong trends for passage of gas or mucus ($P = 0.0543$) and bowel-movement urgency ($P = 0.0603$).

IBgard was well tolerated and safe. No patients withdrew from the study because of treatment-emergent AEs. “Severe-symptom patients responded as well as those with less severe symptoms. That’s very reassuring,” Dr. Cash said.

“Over four weeks, IBgard was effective at improving the composite IBS symptom score and the individual IBS symptom components, including severe or unbearable abdominal pain intensity at four weeks,” Dr. Cash concluded.

**Third-Line Rescue Therapy With Moxifloxacin Or Levofloxacin-Based Triple Regimen for Helicobacter pylori Infection in Area With High Quinolone Resistance**

- Ae-Ra Lee, MD, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

Treatment of *Helicobacter pylori* with quinolone-based regimens did not produce satisfactory eradication rates in a region with high levels of antibiotic resistance, according to a poster presentation of research from South Korea.

While moxifloxacin- or levofloxacin-based regimens have often been used at his institution, Dr. Lee said, increasing levels of antibiotic resistance in South Korea have become a significant limitation. In *H. pylori* isolates, primary and secondary resistance rates to these two fluoroquinolones increased from 5.7% to 34.6% from 2003 to 2012 at Dr. Lee’s hospital.

Dr. Lee’s retrospective analysis of efficacy and tolerability from April 2003 to December 2013 looked at moxifloxacin- or levofloxacin-based third-line rescue therapy for *H. pylori* with a standard triple regimen consisting of a proton pump inhibitor (standard twice-daily dose), amoxicillin (1,000 mg twice daily) plus either moxifloxacin (400 mg daily, n = 49) or levofloxacin (500 mg twice daily, n = 46). All patients had experienced two prior consecutive eradication failures and were similar with respect to their first-line (standard triple regimen) or second-line treatment (bismuth-based quadruple regimen), previous ulcer history, smoking, alcohol, and general endoscopic findings.

The $^{13}$C-urea breath test, histology, or rapid urease test were used to evaluate *H. pylori* eradication. Dr. Lee’s intent-to-treat analysis found eradication rates of 38.8% (19 of 49) in the moxifloxacin group and 43.5% (20 of 46) in the levofloxacin group ($P = 0.802$). A per-protocol analysis placed the eradication rates at 42.1% and 43.9%, respectively ($P = 1$). Compliance was somewhat higher in the levofloxacin group (89.3% versus 77.6%). Minor AE rates were significantly higher for moxifloxacin than levofloxacin (28.9% versus 12.2%; $P = 0.017$).

In view of the unsatisfactory eradication rates, Dr. Lee recommended continued research to identify novel rescue regimens for *H. pylori* other than quinolone-based regimens.

**REFERENCE**