CLINICAL UPDATE

Advances in Irritable Bowel Syndrome From Digestive Disease Week 2015

Novel Peppermint Oil Formulation for Dietary Management of Irritable Bowel Syndrome

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Based on a Presentation From Digestive Disease Week 2015

G&H How common is irritable bowel syndrome in the United States?

BC Irritable bowel syndrome (IBS) is a prevalent condition that has been estimated to affect up to 15% to 20% of the US adult population. Approximately 12% of primary care visits and up to 25% of gastrointestinal (GI) specialist visits are attributed to IBS. Women are twice as likely as men to develop IBS, and younger adults are disproportionately affected.

G&H What symptoms are associated with IBS?

BC A general definition of IBS is abdominal pain associated with a change in the form and/or frequency of bowel movements in the absence of an alternative organic explanation. Patients with IBS often report improvement in their abdominal pain with a bowel movement and also frequently report other symptoms such as bloating. IBS is categorized into subtypes using the Rome III criteria based on the predominant stool form. Estimates of the relative prevalence of the different subtypes vary. According to a 2009 report by Drossman and colleagues, the most common subtype is mixed-presentation IBS (IBS-M), which affects 61% of patients, followed by diarrhea-predominant IBS (IBS-D), which affects 30% of patients, and constipation-predominant IBS (IBS-C), which affects 10% of patients. Other estimates have divided the subtypes more evenly. It is important to recognize that the subtype affecting a particular patient can change over time.

Patients with IBS are chronically bothered by their symptoms and often have a high level of frustration—in part because of the difficulty and uncertainty of the diagnosis, and perhaps owing to unfounded fears, but also because of the limited treatment options available. Periodic exacerbations can be severe, limiting health-related quality of life and productivity. Approximately 25% of patients describe their symptoms as severe; these patients report up to 13 physician visits per year, a frequency much higher than in individuals without IBS.

Based on information gathered over the past several decades, IBS is now considered a syndrome of symptoms with numerous heterogeneous etiologies rather than a single disease state. The 8 primary symptoms of IBS include abdominal pain or discomfort, bloating or distention, diarrhea, constipation, feeling of incomplete evacuation, urgency, pain at evacuation, and passage of gas or mucus. These symptoms can be incorporated into the Total IBS Symptom Score (TISS), which has been used as an endpoint in several IBS clinical trials. The TISS is generated by adding the intensity and frequency score for each of the 8 IBS symptoms and dividing by 8.

G&H What is the role of dietary modification in the management of IBS?

BC Dietary modification is a common first approach that patients and clinicians use for IBS. However, dietary measures can be problematic, as exclusionary diets such as a diet low in fermentable oligo-, di-, and monosaccharides and polyols or a gluten-free diet can be difficult to maintain and can incur increased expense related to the purchase of substitute products.

G&H How effective are the available treatments for IBS?

BC IBS presents a challenge with unmet needs. There are no therapies approved for IBS-M, and until recently, the only therapy approved for use in IBS-D—alosetron (Lotronex, Prometheus)—was available for use only with restrictions in a monitoring program. Two additional medications were recently approved for the treatment of IBS-D, rifaximin (Xifaxan, Salix) and eluxadoline (Viberzi, Actavis). Due to their recent approval status, it is too early to reach any conclusions regarding their effectiveness in the routine management of patients with IBS-D, but the clinical trial data with these 2 agents are promising. However, all of these agents require prescriptions, and many patients with IBS prefer to manage their symptoms with nonprescription agents, often on an as-needed basis.

For centuries, people have been using peppermint oil as part of their diet to manage digestive issues, and there are abundant data suggesting that this agent helps normalize digestive processes that are thought to be disrupted in IBS. Peppermint oil is comprised largely of monoterpenes, and the primary active ingredient is L-menthol, which makes up approximately 50% of its content. Peppermint oil is known to provide smooth muscle calcium channel antagonism, to contribute to normalization of orocecal transit time, and to exert carminative effects, kappa opioid agonism, anti-infective and anti-inflammatory effects, and serotonergic antagonism.

Over the past 5 decades, multiple clinical trials have evaluated the use of peppermint oil as a medical therapy for IBS. Many of these studies have been conducted in Europe and have used different formulations. In recent reviews, peppermint oil has demonstrated a number-needed-to-treat for IBS between 2 and 3, which is on par with other IBS therapies in the literature.

Recently, a new peppermint oil formulation (IBgard, IM HealthScience, LLC) was developed, which consists of a capsule containing sustained-release microspheres of ultra-purified peppermint oil. The efficacy and safety of this new formulation were evaluated in IBSREST (Irritable Bowel Syndrome Reduction Evaluation and Safety Trial). My colleagues and I designed this trial based on a high-quality, randomized, controlled trial of peppermint oil in IBS published by Cappello and colleagues in 2007. Their study recruited patients via the Rome II criteria, which are similar to the Rome III criteria used in our trial. While their trial used a mixed population of patients with IBS-D and IBS-C, our trial was comprised of patients with IBS-D and IBS-M. We randomly assigned patients to receive either peppermint oil or placebo twice daily for 4 weeks. Endpoints were based on the European Medicines Agency's 2003 *Evaluation of Medicines for Human Use* guidance for IBS and used binary endpoints for abdominal pain/discomfort and global symptoms.

G&H What were the efficacy outcomes in your trial?

BC Peppermint oil was significantly more effective than placebo at multiple points. Twenty-four hours after the first dose, patients in the peppermint oil arm reported an 18.8% reduction in the TISS from baseline, compared with a 9.8% reduction reported by patients in the placebo arm—a statistically significant difference of nearly twice the rate of global symptom improvement (P=.0092).

Looking at individual symptoms at 24 hours, there was a trend toward a greater improvement with peppermint oil vs placebo in all 8 of the primary IBS symptoms that are measured by the TISS. This difference reached statistical significance in the category of abdominal pain or discomfort, with patients reporting a 21% reduction from baseline vs a 10% reduction with placebo (P<.05). Patients in the peppermint oil arm also had a significantly greater reduction in the intensity of bowel movement urgency at 24 hours compared with patients in the placebo arm (25% vs 6%; P=.0374).

At 4 weeks, there was a greater separation in the reduction of individual IBS symptoms between peppermint oil and placebo, and several of these differences were statistically significant. The primary endpoint of the study, reduction in the TISS at 4 weeks, was significantly greater with peppermint oil vs placebo (40% vs 25%; P=.0246). These findings suggest that the difference between peppermint oil and placebo increased from approximately 10% at 24 hours to approximately 15% at 4 weeks. It should also be noted that the 25% response rate observed with placebo in this study is typical of response rates reported with placebo in other functional GI studies.

G&H Is peppermint oil effective in patients with severe symptoms?

BC My colleagues and I designed our study to try to recruit patients with more bothersome or severe symptoms, given the relative lack of effective therapies for these

patients. In order to enroll, patients had to have a baseline abdominal pain score of at least 4. (The current US Food and Drug Administration [FDA] recommendation for this score is at least 3, which would reflect more moderate or mild IBS.) Patients in our study also had to have a TISS of at least 2 on a scale of 0 to 4.

High-intensity and higher-frequency symptoms are obviously the most bothersome. My colleagues and I hypothesized that the new peppermint oil formulation could help manage severe symptoms by delivering L-menthol and the other components to the small intestine. Therefore, in our trial, we looked at reductions in the number of severe or unbearable IBS symptoms, rated as an average symptom score of 3 or higher (on a 0-4 scale).

Overall, the formulation seemed to have a more striking effect in patients with more severe or unbearable symptoms. In terms of the frequency of IBS symptoms, it was associated with a 30% reduction in severe or unbearable symptoms at 24 hours, whereas the reduction with placebo was 21%. The difference between arms was not statistically significant at this point. However, at 4 weeks, this difference reached statistical significance, with peppermint oil demonstrating a significantly greater reduction in the number of severe or unbearable symptoms vs placebo, at 66% and 42%, respectively (P=.0212).

As for the intensity of IBS symptoms, patients in the peppermint oil arm reported a 40% reduction in severe or unbearable abdominal pain intensity after 24 hours, compared with a 30% reduction with placebo. This numerical trend did not reach statistical significance. However, after 4 weeks, the reduction in unbearable abdominal pain intensity was 79% with peppermint oil, compared with 40% with placebo, and this difference was statistically significant.

Looking at individual IBS symptoms, peppermint oil was associated with a favorable trend over 4 weeks of use across all 8 unbearable or severe symptoms, with continued improvements observed over time. For most symptoms, the response rate approximately doubled from the 24-hour point to the 4-week time point.

G&H What was the safety profile of this formulation?

BC This is a very well-tolerated formulation of peppermint oil. The incidence of treatment-emergent adverse events was 5.7% in the peppermint oil arm compared with 10.8% in the placebo arm. Specific adverse events reported in the peppermint oil arm included 1 episode of dyspepsia (2.9%) and 1 upper respiratory tract infection (2.9%) that was likely not associated with the therapy. In the placebo arm, adverse events included flatulence, gastroesophageal reflux disease symptoms, viral gastroenteritis, upper respiratory tract infection, and back pain, reported in 1 patient each (2.7%). There were no discontinuations due to treatment-emergent adverse events in either arm, and no serious treatment-emergent adverse events or deaths occurred during the study.

G&H Is peppermint oil considered a drug?

BC As mentioned earlier, L-menthol makes up approximately half of the content of peppermint oil. The remaining 50% includes more than 90 components, of which only 40 have been characterized. Because the components have not been completely identified, peppermint oil is considered a medical food rather than a drug. Defined by the FDA in the 1986 Orphan Drug Act, medical foods are intended for the specific dietary management of a disease or condition. Although they do not require a prescription, they are given under medical supervision. To be a medical food, a product must comply with FDA labeling requirements, be comprised of ingredients that are generally recognized as safe and comply with FDA regulations, and be specifically formulated and processed (as opposed to naturally occurring). In my opinion, it is appropriate for this formulation, which recently became available over-the-counter in several pharmacies, to be considered a medical food.

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Dr Cash has served as a consultant to IM HealthScience, LLC.

Suggested Reading

Cappello G, Spezzaferro M, Grossi L, Manzoli L, Marzio L. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. *Dig Liver Dis*. 2007;39(6):530-536.

Cash BD, Epstein MS, Shah SM. IBgard, a novel targeted delivery system of peppermint oil, results in significant improvement in the Total IBS Symptom Score and individual IBS symptoms. Results from the U.S.-based, 4-week, randomized, placebo-controlled, multi-centered IBSREST trial. Presented at Digestive Disease Week; May 16-19, 2015; Washington, DC. Abstract Mo1290.

Cash BD, Epstein MS, Shah SM. 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. Presented at Digestive Disease Week; May 16-19, 2015; Washington, DC. Abstract Su1373.

Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *J Clin Gastroenterol*. 2009;43(6):541-550.

Epstein MS, Cash BD, Shah SM. 24-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. Presented at Digestive Disease Week; May 16-19, 2015; Washington, DC. Abstract 314.