IBREST Trial: Novel Formulation of Peppermint Oil Improves Symptoms of IBS

Written by Jaye Summers

Peppermint oil has been considered a remedy for bothersome gastrointestinal symptoms for centuries. While a recent meta-analysis suggested that peppermint oil was a safe and effective short-term treatment of irritable bowel syndrome (IBS) [Khanna R et al. *J Clin Gastroenterol.* 2014], oral ingestion of single-unit, liquid-filled enteric-coated peppermint oil can be associated with adverse effects such as heartburn, dyspepsia, or anal burning. These adverse effects likely occur due to the unpredictability of peppermint oil release in the gastrointestinal tract with these older formulations. [Epstein MS et al. DDW 2015 (poster 314)].

A novel, targeted-release formulation of peppermint oil appeared to significantly reduce 4 self-reported symptoms of severe abdominal symptoms associated with IBS, according to research presented in a poster by Brooks D. Cash, MD, University of South Alabama, Mobile, Alabama, USA.

The IBREST trial was a randomized, placebo-controlled, double-blinded study to compare the safety and efficacy of a proprietary, targeted-release formulation of peppermint oil compared with an identical placebo in a US population. This formulation consists of ultra-purified, solid-state microspheres triple-coated to facilitate oral ingestion and rapid delivery of the peppermint oil directly to the small intestine.

Inclusion criteria were the Rome III criteria for IBS with mixed symptoms or diarrhea, Total IBS Symptom Score (TISS) > 2 on a scale of 0 to 4, and persistent levels of abdominal pain ≥ 4 on a scale of 0 to 10. Patients were excluded if they had any other type of IBS, if they had organic gastrointestinal disease, or if they were unwilling to stop any restricted medications prior to enrolling in the study.

Three weeks before enrollment, patients were required to undergo laboratory testing and washout of all prohibited medicines; rescue medications were not allowed. Patients were also instructed to keep a 2-week baseline system diary. Patients were then randomized to either 2 capsules (each containing 90 mg) of peppermint oil TID (treatment group; n = 35) or to 2 identical placebo capsules TID (placebo; n = 37). The majority of patients were white and were women, with a mean age of 40.7 years (Table 1).

The primary outcomes were self-reported differences after 4 weeks of therapy between the 2 groups on the TISS and the frequency and intensity of the 8 symptoms that customarily constitute IBS: abdominal discomfort, bloating or distention, diarrhea, constipation, feeling of incomplete evacuation, urgency, pain on evacuation, and gas or mucus.

Table 1. Patient Characteristics

	Targeted-Released Peppermint Oil (n = 35)	Placebo (n = 37)
Mean age, y	40.2	41.1
IBS subtype		
IBS-M	16 (45.7)	18 (48.6)
IBS-D	19 (54.3)	19 (51.4)
Sex		
Women	28 (80.0)	26 (70.3)
Men	7 (20.0)	11 (29.7)
Race		
Caucasian	29 (82.9)	27 (73.0)
Black	6 (17.1)	8 (21.6)
Asian	0	1 (2.7)
Other	0	1 (2.7)
Patient completion		
Completed	34 (97.1)	36 (97.3)
Withdrawn	1 (2.9)	1 (2.7)

Data presented in n (%) unless otherwise indicated.

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with mixed symptoms.

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At baseline, there was no significant difference between the placebo and treatment groups with regard to the TISS or any of its 8 individual components. At week 4, patients in the treatment group achieved a significant reduction in the TISS ($P = .0246$), as well as in 4 of the 8 individual components—abdominal discomfort, abdominal bloating, pain at evacuation, and urgency of bowel movement ($P < .05$, Table 2).

There were 6 treatment-emergent adverse events (TEAEs): 2 in the treatment group and 4 in the placebo group. One TEAE above grade 1 was reported, and no serious TEAEs or deaths were reported. No patients dropped out of the study because of a TEAE.

In conclusion, patients with nonconstipated IBS randomized to a novel formulation of peppermint oil designed to release in the small intestine showed improvement in the TISS, a global IBS symptom score, as well as many of the common individual IBS symptoms,

Table 2. Percent Reduction From Baseline in Individual Irritable Bowel Syndrome Symptoms at 4 Weeks

Symptom	Treatment Group	Placebo Group
Abdominal pain or discomfort	−42.4*	−22.6
Abdominal bloating or distension	−34.1*	−19.2
Pain at evacuation	−48.1*	−25.4
Urgency of bowel movement	−41.3*	−26.1
Constipation	−43	−26.2
Diarrhea	−44.2	−36.1
Gas or mucus	−32.2	−23.9
Incomplete evacuation	−35.6	−23.9

Data presented in percentages.

*$P < .05$ vs placebo.

after 4 weeks of therapy compared with placebo. This formulation of peppermint oil was well tolerated and no safety signals were noted.

Simeprevir + Sofosbuvir Effective in Patients With Moderate to Severe Cirrhosis

Written by Jaye Summers

In December 2013, the FDA approved both simeprevir (SMV) and sofosbuvir (SOF) as oral treatments for chronic hepatitis C virus (HCV), providing clinicians with off-label access to an all oral-regimen for HCV genotype 1. Subgroup data from the phase 2 COSMOS study [Lawitz E et al. *Lancet*. 2014] showed that the combination of SMV + SOF with or without ribavirin (RBV) produced a 93% cure rate among people with Child-Pugh class A cirrhosis. However, the efficacy and safety of this drug combination with or without RBV among patients with worsening cirrhosis (Child-Pugh class B/C) remained unknown.

Varun Saxena, MD, University of California San Francisco School of Medicine, San Francisco, California, USA, presented data assessing the safety and efficacy of a 12-week combination of SMV + SOF with or without RBV in patients with cirrhosis Child-Pugh class B/C. These patients were compared with matched treated and untreated controls. The treated controls had been treated with telaprevir or boceprevir plus interferon and RBV, which was the standard of care at the time that they were treated.

Fifty-five adults with HCV genotype 1 (cases) received the drug combination; RBV was included at the discretion of the physician. Each of the 55 cases was matched with up to 3 treated and untreated controls based on age, treatment center, model for end-stage liver disease (MELD), and Child-Pugh class. At baseline, cases had a median age of 61 years. About half of patients were women; 35% had diabetes; 58% had HCV genotype 1a; 62% had previous HCV treatment; and 89% had cirrhosis Child-Pugh class B.

At baseline, patients had a median MELD score of 12; 64% had ascites; 49% had any hepatic encephalopathy; 35% had varices; and 35% had been exposed to RBV, highlighting their high morbidity. The study's 2 primary outcomes were the percentage of patients who achieved a sustained virologic response at week 12 (SVR12) and a number of safety outcomes:

- early treatment discontinuation,
- adverse events (AEs) requiring hospitalization,
- infections requiring antibiotics,
- hepatic decompensating events, and
- death.

A total of 73% of the cases achieved SVR12. Of the 27% who did not, 3 patients had detectable HCV RNA at the end of treatment, and 12 patients relapsed after the end of treatment. Multivariate analysis revealed that the absence of hepatic encephalopathy and platelets $\geq 100\,000/mm^3$ significantly predicted those patients likely to achieve SVR12 (OR, 3.37; 95% CI, 1.00 to 11.8; $P = .05$; OR, 4.29; 95% CI, 1.14 to 16.1; $P = .02$, respectively). Regarding safety, 11% of the cases discontinued treatment, and 11% discontinued treatment (of which 9% discontinued because of AEs); 22% were hospitalized due to AEs; 20% required antibiotics for infections; and 20% experienced hepatic decompensation. One patient died as the result of worsening liver and kidney function.

Table 1 compares the rates of HCV cure, early discontinuation, AEs, infections, and decompensation between the cases and the treated controls.

Table 1. SMV + SOF Cases vs Treated Historical Controls

Outcomes	SMV + SOF ± RBV (n = 55)	Telaprevir or Boceprevir With Peginterferon, RBV (n = 127)	*P* Value
HCV cure	73	38	< .01
Early discontinuation	11	75	< .01
Hospitalization due to adverse events	22	50	< .01
Infections	20	26	.37
Decompensation	20	36	.03

Values presented as percentage of cohort.

HCV, hepatitis C virus; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.