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.

Current guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America do not recommend the use of SMV and SOF in patients with Child-Pugh B/C cirrhosis because of safety concerns [www.hcvguidelines.org. Accessed May 29, 2015]. However, Dr Saxena conjectured that these difficult patients (mostly those with Child-Pugh B cirrhosis) can be successfully treated and that data from this study may help inform future treatment recommendations.

DIRECT Trial Shows Surgery Better Than Conservative Treatment for Diverticulitis

Written by Brian Hoyle

The multicenter, randomized, controlled DIRECT trial [NTR1478] comparing surgical vs conservative treatment of diverticulitis in 109 patients revealed a significant benefit of surgery at 6 months.

According to Marguerite Stam, MD, Meander Medical Center, Amersfoort, The Netherlands, first cases of diverticulitis overwhelmingly (90% of cases) are mild. In the aftermath, 30% to 40% of patients will report no complaints, 30% will be persistently symptomatic, and 30% will experience recurrences.

For those with symptoms and recurrence, the decision of whether to operate or not is controversial. Little evidence for decision making is available, with only 1 small prospective study [Forgione A et al. *Ann Surg.* 2009] and 1 retrospective study [Pasternak I et al. *Int J Colorectal Dis.* 2012] published. The DIRECT trial sought to provide further clarification.

From mid-2010 to mid-2014, patients from 27 centers in The Netherlands were randomized to conservative or operative treatment of their diverticulitis. The primary end point was quality of life measured by the Gastrointestinal Quality of Life Index (GIQLI), SF-36 Healthy Survey Update (SF-36), EuroQOL 5-dimension questionnaire (EQ-5D), and a visual analog scale ranking of pain. Secondary outcomes included mortality and morbidity at 6 months.

Inclusion criteria included patients aged 18-75 years, persistent abdominal complaints (continuing lower left abdominal pain, altered bowel habits, and persistence of symptoms for >3 months), frequent recurrence of diverticulitis, signs of inflammation, and American Society of Anesthesiology ranking I, II, or III. Exclusion criteria were prior sigmoidectomy, stenosis, perforation, fistula, malignancy, and inability to complete questionnaires.

The target number of patients in the intention-to-treat analysis was 214. However, accrual was slow and challenging because of preferences for surgery or conventional treatment. As a result, and considering the clinical relevance of the study, enrollment was ended early.

The 109 enrolled patients were randomized to surgery (n=53), with 47 patients ultimately receiving surgery and 6 electing to receive conservative treatment, or conservative treatment (n=56), with 43 patients choosing this option and 13 opting instead for surgery. At baseline, the surgery and conservative treatment groups were comparable for age, body mass index, sex, number of recurrences, and duration of ongoing symptoms.

Most of the surgical treatments were laparoscopy involving primary anastomosis. Complications in the surgery group included anastomotic leakage (13%), stenosis (4%), surgical site infection (9%), ileus >7 days after surgery (8%), and cardiovascular/pulmonary events (4%). Among the 13 patients randomized to conservative treatment who elected surgery, recurrences occurred in 5.

At 6 months, the primary end points of GIQLI, active physical health component of SF-36, EQ-5D, and pain favored surgery ($P=.0001$, $P=.0106$, $P=.0013$, and $P<.0001$, respectively). In the aforementioned 13 patients, the outcomes with surgery were not significantly different from baseline rankings.

Recurrence of symptoms in all patients receiving surgery comprised 8 cases, all occurring prior to surgery.

The DIRECT trial revealed significant quality of life benefit of elective resection over conventional treatment for patients with diverticulitis. The results are important in the counseling of patients concerning treatment.