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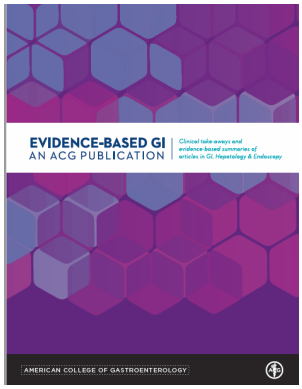

The American College of Gastroenterology (ACG) is an international organization with more than 14,000 physician members representing some 85 countries. The College's vision is to be the pre-eminent professional organization that champions the evolving needs of clinicians in the delivery of high-quality, evidence-based and compassionate health care to advance world-class care for patients with gastrointestinal disorders through excellence, innovation, and advocacy in the areas of scientific investigation, education, prevention, and treatment. *Evidence-Based GI* is a member publication of the American College of Gastroenterology.

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SER-109, an Oral Microbiome Therapy, Decreases Recurrent Clostridioides difficile Infection

Jessica R. Allegretti, MD, MPH

Associate Director, Crohn's and Colitis Center, Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Jessica R. Allegretti, MD, MPH
Associate Editor

This summary reviews Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an Oral Microbiome Therapy for Recurrent Clostridioides difficile Infection. N Engl J Med 2022; 386(3): 220-229. PMID: 35045228. https://pubmed.ncbi.nlm.nih.gov/35045228/

Correspondence to Jessica R. Allegretti, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Will spore-forming bacteria, which may compete metabolically with *Clostridioides difficile* spores for essential nutrients and modulate bile-acid profiles to re-establish resistance to colonization, reduce recurrent *C. difficile* infection (CDI) after successful antibiotic therapy?

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Fifty-six US and Canadian Sites from July 2017 through September 2020.

Patients: The trial included adults with 3 or more confirmed episodes of CDI within 12 months, which was defined as 3 or more unformed bowel movements over 2 consecutive days, positive *C. difficile* toxin test, and resolution of symptoms while receiving 10-21 days of antibiotic therapy. Patients were required to test positive for *C. difficile* toxin by enzyme immunoassay. A total of 281 patients were screened and 182 underwent randomization. Mean age was 65.5 years; 59.9% female; 93% White; 73.1% previously treated with vancomycin, and 26.9% previously treated with fidaxomicin before randomization.

Exposure: Patients were randomized 1:1 to receive SER-109, an investigational microbiome therapeutic composed of live purified Firmicutes bacterial spores with approximately 3×10^7 spore colony-forming units or 4 placebo

capsules, daily, for 3 consecutive days. All patients were given 10 ounces of magnesium citrate the night before treatment to minimize persistent active antibiotic in the colon.

Outcome: Sustained clinical response defined as no recurrence of CDI up to 8 weeks after dosing (the primary efficacy end point).

Data Analysis: Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomization. Patients who were lost to follow-up, discontinued participation in the trial prematurely, or died without a recurrence of CDI before 8 weeks after treatment were defined as having a CDI recurrence. Cochran–Mantel–Haenszel test was used to calculate the relative risk of recurrent CDI with SER-109 vs placebo, stratified according to age (<65 years or ≥65 years) and previous antibiotic regimen for the qualifying episode (vancomycin or fidaxomicin).

Results: The percentage of patients with a CDI recurrence was lower in the SER-109 group compared to placebo (12% vs 40%, respectively; RR = 0.32; 95% CI: 0.18-0.58). Most recurrences (75%) occurred within 2 weeks after treatment administration. No serious adverse events were assessed as being related to SER-109. The common adverse events were mild GI disorders.

Funding: Seres Therapeutics, manufacturer of Ser-109.

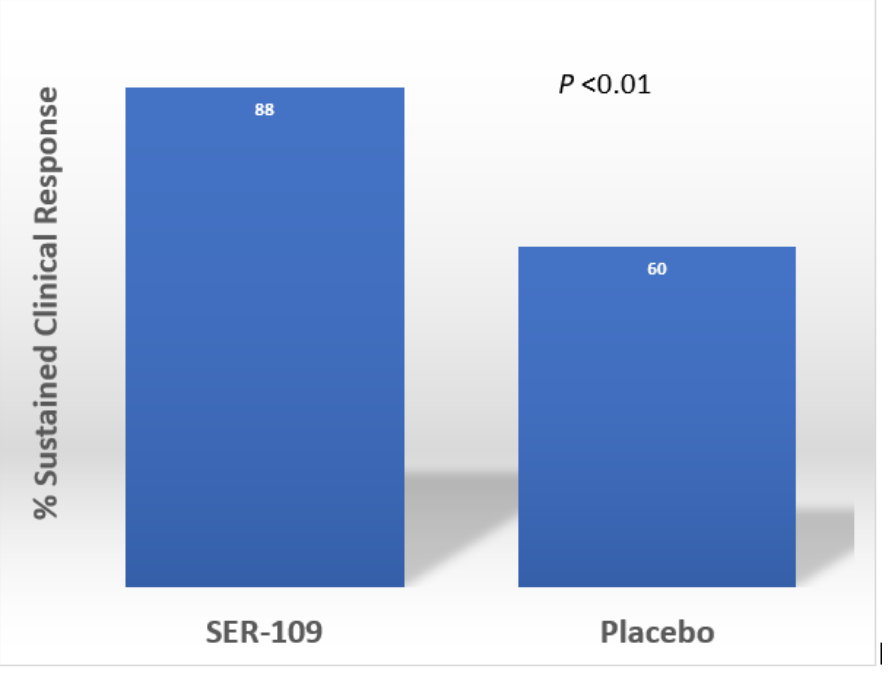

Figure 1. Primary efficacy outcome

COMMENTARY

Why Is This Important?

Recurrent CDI remains a huge public health issue with cases continuing to rise. While fecal microbiota transplantation (FMT) has been shown to be effective for the prevention of recurrent CDI, there are currently no effective FDA-approved therapies[1]. In addition, restrictions brought on by the pandemic have limited access to FMT[2]. Therefore, new treatments to minimize CDI are sorely needed.

An FDA application for approval to use SER-109 will likely be submitted in 2022. The current study demonstrates the efficacy of starting treatment for recurrent CDI with antibiotics followed by a microbiome therapeutic to assist with microbiome repair to minimize recurrent infection.

Key Study Findings

Patients treated with SER-109 had much lower risk of recurrent CDI compared to placebo (12% vs 40%, respectively; RR = 0.32; 95% CI: 0.18-0.58) after a course of standard of care antibiotics. There were no serious adverse events found to be related to SER-109 observed through week 8.

Caution

While the study did show superiority of SER-109 over placebo, the trial design may not be representative of clinical practice. Notably, the protocol requires 10 ounces of magnesium citrate on the evening before initiating SER-109 to improve efficacy by ensuring adequate antibiotic wash out. However, it's unclear how failure to do this bowel prep will impact efficacy. This protocol also mandated enzyme immunoassay toxin positivity as entry criteria and most centers around the country are still using PCR testing.

My Practice

I am currently still off "traditional" FMT under the FDA policy of enforcement discretion for those with 3 or more confirmed episode of CDI. Instead, our regional Center of Excellence for FMT gets properly screened and frozen stool from OpenBiome's biobank. However, OpenBiome has limited supply and is only providing material to these Centers of Excellence.

Therefore, if your patient has recurrent CDI, then I suggest referral to a regional Center of Excellence (OpenBiome's website provides a list of these sites) or academic medical centers with FMT programs. You can also check clinicaltrials.gov for active trials of investigational microbiome agents.

SER-109 is currently under review by the FDA for approval. The FDA will probably rescind their current policy allowing FMT when we have FDA-approved microbiome therapeutics, and I certainly intend to use them. The biggest challenge, as with many things in medicine, will be insurance coverage and cost to the patient.

For Future Research

Several microbiome-based therapeutics are currently under investigation. We are likely to have several options for the prevention of recurrent CDI in the near future. Future research on microbiome-based therapeutics, both full spectrum and defined consortia, in other chronic diseases are definitely needed, too. Some studies are already underway with inflammatory bowel disease[3].

Conflicts of Interest

Dr. Allegretti reports serving as a consultant for Seres Therapeutics, Finch Therapeutics, and is a scientific advisor for Openbiome.

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EVIDENCE-BASED GI
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When is Routine Prophylactic Clipping Indicated Post-Polypectomy?

Jeffrey Lee, MD, MPH
Associate Editor

Jeffrey Lee, MD, MPH

Research Scientist and Attending Gastroenterologist, Department of Gastroenterology, Kaiser Permanente San Francisco Medical Center, California.

This article reviews: Gupta S, Sidhu M, Shahidi N, et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. Lancet Gastroenterol Hepatol 2022; 7(2):152-160. PMID: 34801133 https://pubmed.ncbi.nlm.nih.gov/34801133/

Correspondence to Jeffrey Lee, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does routine prophylactic clipping prevent clinically significant post-endoscopic mucosal resection (EMR) bleeding within the right colon for polyps > 20 mm?

Design: Randomized controlled trial.

Setting: Single tertiary medical center in Australia (Westmead Hospital, Sydney, New South Wales, Australia).

Patients: Two hundred and thirty one patients who underwent an EMR with electrocautery of non-pedunculated colorectal polyps > 20 mm were included in this trial conducted from February 2016 to December 2020; 118 were assigned to the clip group and 113 to the no clip group (control). Among the clip and control groups, the mean age of the study participants was 70 and 71 years, 41% and 50% were women, 25% and 29% were on antithrombotic agents, and mean lesion size was 35.7 mm and 37.2 mm, respectively. Antithrombotic agents were held for appropriate periods prior to colonoscopy and then re-started 48 hours after the procedure.

EMR was performed with electrocautery (ERBE ENDO CUT Q, Effect 3) after injection of succinylated gelatin (Gelofusine) mixed with 0.4% indigo carmine and 1:100,000 epinephrine. Cold avulsion and snare-tip soft coagulation were also implemented during the trial as appropriate. If deep mural injury types II-V occurred during EMR, then mechanical clip closure

was performed. After EMR was completed, the endoscopist was informed about patient allocation to prophylactic clip or no clip group.
Exposure: Prophylactic clipping (intervention) of the EMR defect vs no clipping (control). In the clip group, hemostatic clips were deployed less than 5 mm apart to close the EMR defect.
Outcome: Primary outcome was clinically significant post-EMR bleeding, defined as hematochezia necessitating emergency department presentation, hospitalization, or re-intervention within 14 days post-EMR.
Results: In the intention-to-treat analysis, clinically significant post-EMR bleeding occurred less frequently in the clip group than in the control group (4 of 118 patients [3.4%] vs 12 of 113 [10.6%]; *P*=0.031; absolute risk reduction 7.2% [95% CI 0.7-13.8]; number needed to treat: 13.9) (**Figure 1**). Clinically significant post-EMR bleeding remained lower in the clip grip versus the control group in the per-protocol analysis (1.1% vs 9.4%; *P*=0.019; absolute risk reduction 8.2%; number needed to treat: 12.1). There were no differences between groups in adverse events, including delayed perforation and post-EMR pain.
Funding: None

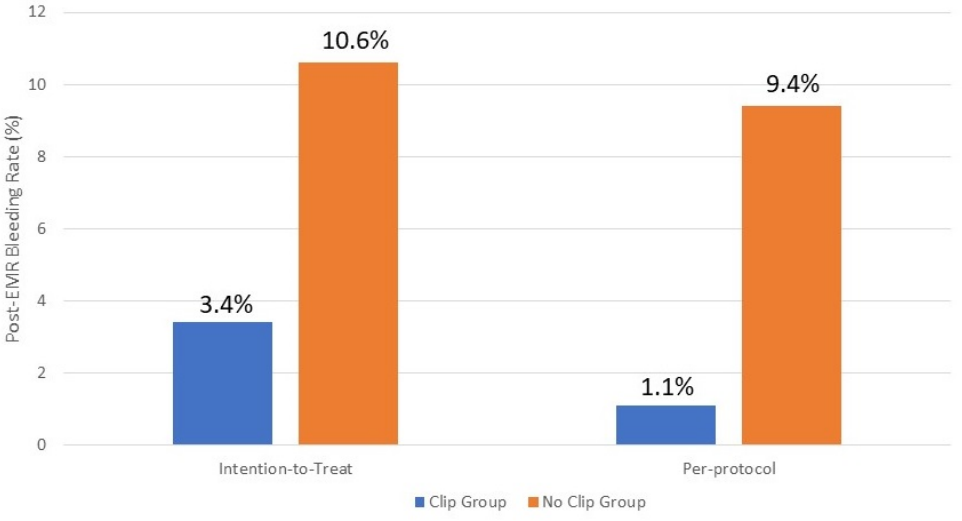

Figure 1. Post-EMR Bleeding Rates

COMMENTARY

Why Is This Important?

Despite recent advances in endoscopic resection of complex colorectal polyps, post-resection bleeding remains a problem. Clinically significant post-EMR

bleeding occurs in 4%-10% of cases and is frequently seen in the right colon[1-3]. Management of post-EMR bleeding can be costly and resource intensive, often requiring hospitalizations and a repeat colonoscopy. Randomized trials evaluating prophylactic clipping for prevention of post-EMR bleeding are limited and have shown discordant results in the right colon[4-6]. Given the conflicting evidence on this topic, this study fills an important gap by using a well-designed, randomized controlled trial to assess the impact of prophylactic clipping for the prevention of post-EMR bleeding in the right colon.

Key Study Findings

In an intention-to-treat analysis, clinically significant post-EMR bleeding in the right colon decreased from 10.6% to 3.4% with prophylactic clipping of the defect (P=0.031). In the per-protocol analysis, clinically significant post-EMR bleeding in the right colon was reduced from 9.4% to 1.1% with prophylactic clipping (P=0.019) (**Figure 1**). The median number of clips used was 5 across both groups. In the control group, bleeding risk was highest in the cecum (19%) compared with the risk of bleeding occurring within the rest of the right colon (3%). The benefit of clip closure was greatest for EMR defects that were 20 mm-39 mm in size and among defects located within cecum. There were no differences between groups in rates of adverse events, including perforation (<1% in each group), and in post-EMR pain (clip group, 3%; no-clip group, 5%).

Caution

The findings from this study may not be replicated in other health care settings given that this trial was conducted at a tertiary referral center with expertise in EMR. Specifically, the study endoscopists were gastroenterologists with advanced training and an established tertiary referral practice in complicated EMR.

My Practice

My general approach for placing prophylactic clips to prevent post-EMR bleeding depends on the size and location of the EMR defect, and whether the patient will need to be placed back on anticoagulants (e.g., warfarin, direct oral anticoagulants) or antiplatelet agents (e.g., clopidogrel). For lesions less than 2 cm in size, I typically do not place prophylactic clips due to the lack of benefit and low bleeding risk, particularly if I used a cold snare polypectomy technique. In a recent systematic review and meta-analysis, Spadaccini et al

showed there was no difference in post-polypectomy bleeding rates with or without prophylactic clip placement after resection of lesions less than 2 cm in size[7]. For lesions 2 cm in size or greater in the right colon, I routinely place prophylactic clips (e.g., Boston Scientific Resolution 360 Clip, MicroTech SureClip, Cook Instinct Endoscopic Clip) for prevention of post-EMR bleeding because of its thinner walls and higher bleeding risk[2]. However, as seen in this study and others, very large lesions (i.e., > 4 cm) may not be amenable to complete closure with prophylactic clips[3-6]. In these instances, I will coagulate all visible vessels with a coagulation grasper or with snare tip soft coagulation depending on the vessel size, and place clips at sites of potential deep mural injuries. Lastly, for patients with conditions that require prompt resumption of anticoagulation or antiplatelet agents, I routinely place prophylactic clips to decrease the risk of post-EMR bleeding, which has been shown to be cost-effective[8].

For Future Research

More research is needed on effective closure methods for lesions greater than 4 cm, and lesions in the left colon removed by electrocautery.

Conflicts of Interest

Dr. Lee reports no conflicts of interest related to this study.

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When to Use Prophylactic Antibiotics for Management of Acute-on-Chronic Liver Failure?

Sonali Paul, MD, MS

Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, University of Chicago Medicine, Center for Liver Disease, Chicago, Illinois

Sonali Paul, MD, MS
Associate Editor

Kulkarni AV, Tirumalle S, Premkumar M, et al. Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial. Am J Gastroenterol. 2022; 117(4):607-616. PMID: 35041634 https://doi.org/10.14309/ajg.0000000000001611
Correspondence to Sonali Paul, MD, MS, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does prophylactic norfloxacin prevent bacterial infections and improve transplant-free survival in patients with acute on chronic liver failure (ACLF)?

Study Design: Double-blind, placebo-controlled trial of 143 patients with ACLF randomized to norfloxacin 400mg daily or placebo for 30 days. Patients were contacted by telephone every 7 days for the first month, and then every 2 weeks for the next 2 months, and asked about infectious symptoms.

Setting: Department of Hepatology, Asian Institute of Gastroenterology in Hyderabad India from October 2019 to May 2021.

Patients: One hundred forty-three patients with ACLF seen in the outpatient setting (within at least 5 days of discharge if recently hospitalized) aged 18 to 75 years old (mean 43.5 years) with a mean Model for End Stage Liver Disease (MELD) of 28 were included in this study. Alcohol was the most common cause of ACLF for both groups. ACLF was defined using the Asian Pacific Association for the Study of the Liver (APASL) criteria defined as an acute hepatic injury resulting in jaundice (total bilirubin 5 mg/dL), coagulopathy (interquartile range [international

ratio] ≥1.5), complicated within 4 weeks by ascites or hepatic encephalopathy in a patient with chronic liver disease or cirrhosis[1]. Exclusion criteria included those with a history of spontaneous bacterial peritonitis, current bacterial infections, renal failure, malignancy, GI bleeding within 7 days, antibiotic exposure within 5 days, hepatic encephalopathy, those receiving prophylactic rifaximin, those who received fluoroquinolones in the last month, and those receiving omega 3 fatty acid lipid emulsions for ACLF. **Exposure**: Participants were randomized to norfloxacin 400 mg daily or placebo for 30 days in addition to standard medical therapy (diuretics, steroids for alcohol-associated or autoimmune hepatitis, hepatitis B/C treatments, beta blockers, lactulose, and nutritional support). **Outcome**: The primary outcome was bacterial infections at days 30 and 90. Transplant-free survival at 30 and 90 days were the secondary outcomes.

Data Analysis: Kaplan-Meier survival analysis used to assess incidence of infections and transplant-free survival at 30 and 90 days. A sub-group analysis of patients with alcohol associated hepatitis receiving steroid therapy was also analyzed.

Results: The incidence of bacterial infections at 30 days was significantly lower in the norfloxacin group at 18% (95% confidence interval [CI] 10-29) compared to the placebo group 34% (95% CI 23-46; *P*=0.03). Similarly, the incidence of infections at 90 days was 46% (95% CI 34-58) and 62% (95% CI 50-73; *P*=0.02) respectively. There were trends towards increased transplant-free survival at both 30 and 90 days in the norfloxacin group compared to placebo, but this did not reach statistical significance. Thirty-day survival was 78% (95% CI 66-87) vs 65% (95% CI 52-76; *P*=0.084), and 90-day survival was 58% (95% CI 46-70) vs 44% (95% CI 32-56; *P*=0.058), respectively.

Patients in the norfloxacin group also had lower incidences of hepatic encephalopathy (32% vs 52% in placebo; *P*=0.01), acute kidney injury (24% vs 37% in placebo, *P*=0.09), and ACLF grade progression (21% vs 42% in placebo; *P*=0.006; Figure 1). Of those receiving steroid therapy for alcohol associated hepatitis, bacterial infections were lower in those receiving norfloxacin at 30 days compared to placebo (10% vs 39%, *P*=0.06) and 90 days (30% vs 69% respectively; *P*=0.03). There were no significant differences in mortality, encephalopathy, or acute kidney injury. Notably, 25% in the norfloxacin group developed urinary Candida compared to only 3% in the placebo group.

Funding: Cipla India Ltd. provided the drugs and placebo but did not fund the trial and was not involved in treatment allocation, data collection, or interpretation.

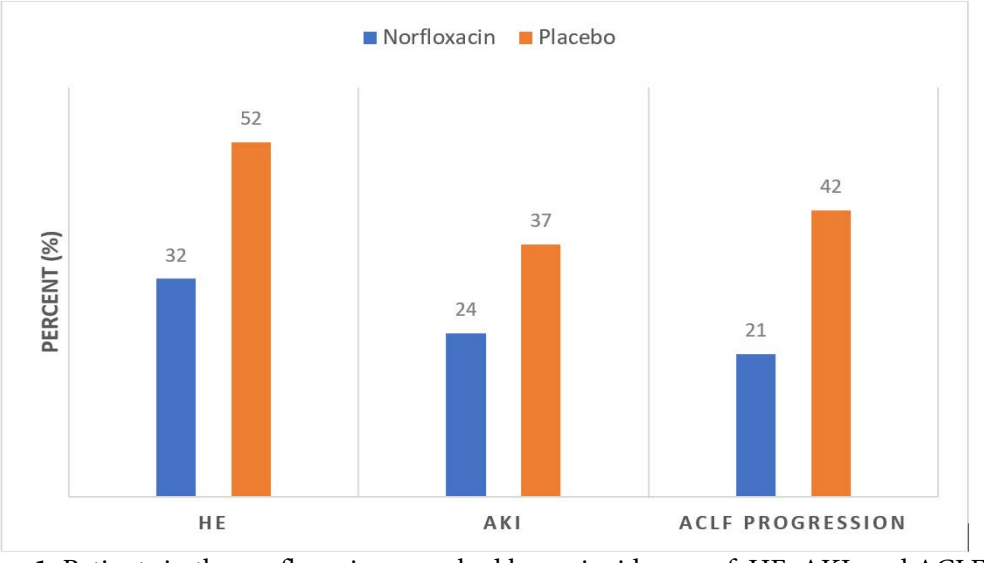

Figure 1. Patients in the norfloxacin group had lower incidences of HE, AKI, and ACLF progression compared to placebo.
ACLF, acute on chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy.

COMMENTARY

Why is this important?

ACLF is a relatively recent described entity in patients with chronic liver disease and portends poor prognosis. ACLF definitions vary (**Figure 2**) but is

Organ	APASL ACLF Research Consortium	EASL CLIF-C ACLF	NACSELD
Liver	Total Bilirubin PT/INR	Total bilirubin PT/INR	--
Kidney	Creatinine	Creatinine/Dialysis	Dialysis
Brain	HE grade	HE grade	HE grade III/IV
Circulatory	Lactate	MAP, vasopressors	MAP, vasopressors
Respiratory	--	PaO_2 or SpO_2 / FiO_2	Mechanical ventilation
Major Organ failure Category	**Predominantly Hepatic failure variables**	**Combination of hepatic and extrahepatic organ failure variables**	**Predominantly extrahepatic organ failure variables**

Figure 2. Definitions of Acute on Chronic Liver Failure[2]

diagnosed with a combination of both hepatic and extrahepatic organ failures. The most recent American College of Gastroenterology Guidelines (ACG) on the Management of ACLF define it as a condition in patients with chronic liver disease (with or without cirrhosis) who have elevated bilirubin and prolonged international normalized ratio. It is associated with the potential for multiple organ failure (kidney, lung, cardiovascular, neurological)_and portends high 3-month mortality without treatment of underlying disease, liver support, or transplantation[2]. The guideline is an invaluable tool that summarizes the current data and management strategies on ACLF and addresses important aspects both from a hepatic and extrahepatic organ perspective.

Infection is a leading cause of mortality in patients with cirrhosis, including those with acute on chronic liver failure. About 40% of patients with ACLF develop bacterial infections which predicts mortality[3]. Therefore, strategies for infection prevention are needed for optimal management of patients with acute on chronic liver failure. The ACG guideline does not recommend routine prophylactic antibiotics for patients with ACLF, although prophylactic antibiotics for primary and secondary spontaneous bacterial peritonitis prophylaxis are recommended without recommending any specific antibiotic regimen.

Key Study Findings

Norfloxacin prophylaxis was found to be safe in preventing bacterial infections at 30 and 90 days and trended toward improved transplant-free survival compared to placebo in patients with ACLF but did not quite reach statistical significance: 30-day survival of 78% vs 65%, P=0.084 and 90-day survival of 58% vs 44%, P=0.058, respectively. Patients receiving norfloxacin also had decreased incidences of hepatic encephalopathy, acute kidney injury, and ACLF progression but did have higher incidence of Candida urinary tract infections. In those receiving steroids for alcohol-associated hepatitis, norfloxacin significantly decreased the risk of bacterial infections at days 30 and 90, but did not have any significant effect on mortality.

Caution

While novel and significant findings, this study has several limitations. First, the study population was very restrictive with only patients with ACLF defined by APASL criteria. Other ACLF criteria exist, such as those by European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) and North American Consortium for the Study of End-Stage Liver Disease (NACSELD) (**Figure 2**), and results may not be applicable when these definitions are applied. The patients studied also predominantly had alcohol-related liver disease, so findings may not relate to other disease states such as nonalcoholic fatty liver disease or viral hepatitis. Those with recent infections, hospitalizations, recent antibiotics, and current hepatic encephalopathy were also excluded which severely limits generalizability to many patients with ACLF.

My Practice

As mentioned previously, infection remains a top concern in patients with ACLF. In my hepatology practice, I follow the current American Association for the Study of Liver Diseases (AASLD) practice guidelines which recommend prophylactic antibiotics (indefinitely) in those with cirrhosis and low ascitic fluid protein (<1.5 g/dL) and evidence of renal dysfunction (creatinine > 1.2 mg/DL, blood urea nitrogen level > 25 mg/dL) or serum sodium level < 130 mEq/L or Child-Turcotte-Pugh score > 9 with bilirubin > 3mg/dL[4]. I also give antibiotic prophylaxis in patients receiving steroids for alcohol-associated hepatitis. My preferred regimen is ciprofloxacin 500 mg daily. While the current data show a benefit of norfloxacin prophylaxis in patients with ACLF, given the restrictive inclusion criteria, it may be difficult to apply this to my patient population.

For Future Research

Use of norfloxacin in addition to other antibiotics that are commonly used in primary prophylaxis such as ciprofloxacin and Bactrim (sulfamethoxazole-trimethoprim) should also be assessed in future studies. Additionally, patients with other types of liver diseases, not just alcohol, should be included in future studies with the use of other ACLF definitions.

Conflicts of Interest

Dr. Paul reports no conflicts of interest.

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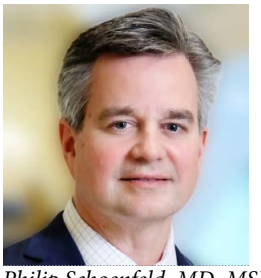
Tenapanor (IBSRELA) for Treatment of IBS-C: Effective Over 26 Weeks



Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus)-Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI

Philip Schoenfeld, MD, MSEd, MSc (Epi)
Editor-in-Chief

This article reviews Chey WD, Lembo A, Yang Y, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome with Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2). Am J Gastroenterol 2021; 116: 1294-1303. https://doi.org/10.14309/ajg.0000000000001056

Correspondence to Philip Schoenfeld, MD, MSEd, MSc (Epi), Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is tenapanor (IBSRELA), a first-in-class, small-molecule inhibitor of the GI sodium/hydrogen exchanger isoform 3 (NHE3) superior to placebo in patients with inflammatory bowel syndrome with constipation (IBS-C) for improving global IBS-C symptoms, abdominal discomfort, and complete spontaneous bowel movements (CSBM) based on FDA-defined responder endpoints?

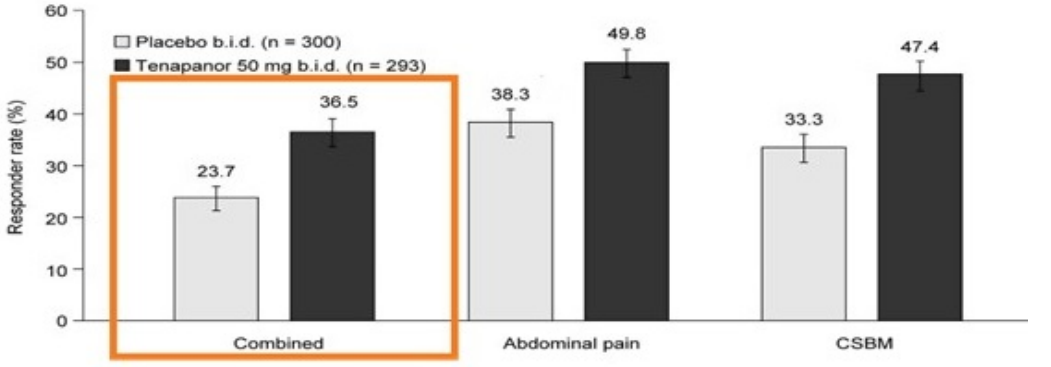
Design: Multicenter, double-blind, placebo-controlled randomized controlled trial.

Setting: Nintey-two United States centers conducted from December 2015 through August 2017.

Patients: Five hundred nintey-three outpatients meeting Rome III IBS-C criteria.

Interventions/Exposure: Tenapanor 50mg b.i.d. vs placebo b.i.d. for 26 weeks.

Outcome: The primary endpoint was the proportion of patients meeting the FDA-defined endpoint: > 6 of first 12 weeks as combined responders for abdominal pain improvement and complete spontaneous bowel movements (CSBMs) in the same week. Per FDA requirements, patients used a touch-tone phone and an interactive voice response phone system to record symptoms daily. An abdominal pain responder was defined as > 30% improvement in average weekly worst abdominal pain from baseline, and a CSBM responder had



Risk difference versus placebo, % (95% CI)	12.9 (5.5, 20.2)	11.5 (3.6, 19.4)	14.1 (6.3, 21.9)
P value	<0.001	0.004	<0.001

Figure 1. ≥ 6/12 week responders for FDA-combined endpoint, abdominal pain endpoint, and CSBM endpoint.

an increase of >1 weekly CSBM from baseline. Key secondary endpoints included 6/12 week responders for abdominal pain, 6/12 week responders for CSBM, 9/12 week combined responders, and 13/26 week combined responders.

Data Analysis: Intention-to-treat analyses were performed. For responder rates or proportions, Cochran-Mantel-Haenszel tests with pooled investigator site as a stratification (adjustment) variable were used. For degrees of relief of IBS symptoms and treatment satisfaction, analysis of variance models with terms for pooled investigator site and treatments as covariates were used.

Results: In all, 593 IBS-C patients were randomized and included in the intention-to-treat (ITT) analysis (mean age: 45.4 years old; 82.1% female; 63.6% White; Baseline Symptoms: Abdominal Score = 6.3 on 0-10 scale; 0.1 CSBMs/week; 1.6 SBMs/week). Approximately, 81.1% from the ITT analysis completed entire 26 weeks of treatment. Tenapanor-treated patients were more likely to be ≥ 6/12 week combined responders compared to placebo-treated patients: 36.5% vs 23.7% (aRR = 1.55, 95% CI: 1.20-1.99, $P< 0.0001$) (**Figure 1**) as well as ≥ 6/12 week abdominal pain responders and CSBM responders per FDA criteria (**Figure 1**). Significantly more tenapanor patients were 9/12 week responders: 18.4% vs 5.3% (aRR = 3.47, 95% CI: 2.03-5.94, $P<0.0001$). Mean improvement in CSBM and mean decrease in abdominal pain was maintained through 26 weeks (**Figure 2**). Diarrhea was more commonly reported by tenapanor-treated patients versus placebo-treated patients (16.0% vs 3.7%), although discontinuation of study medication due to diarrhea only occurred in 6.5% of tenapanor-treated patients.

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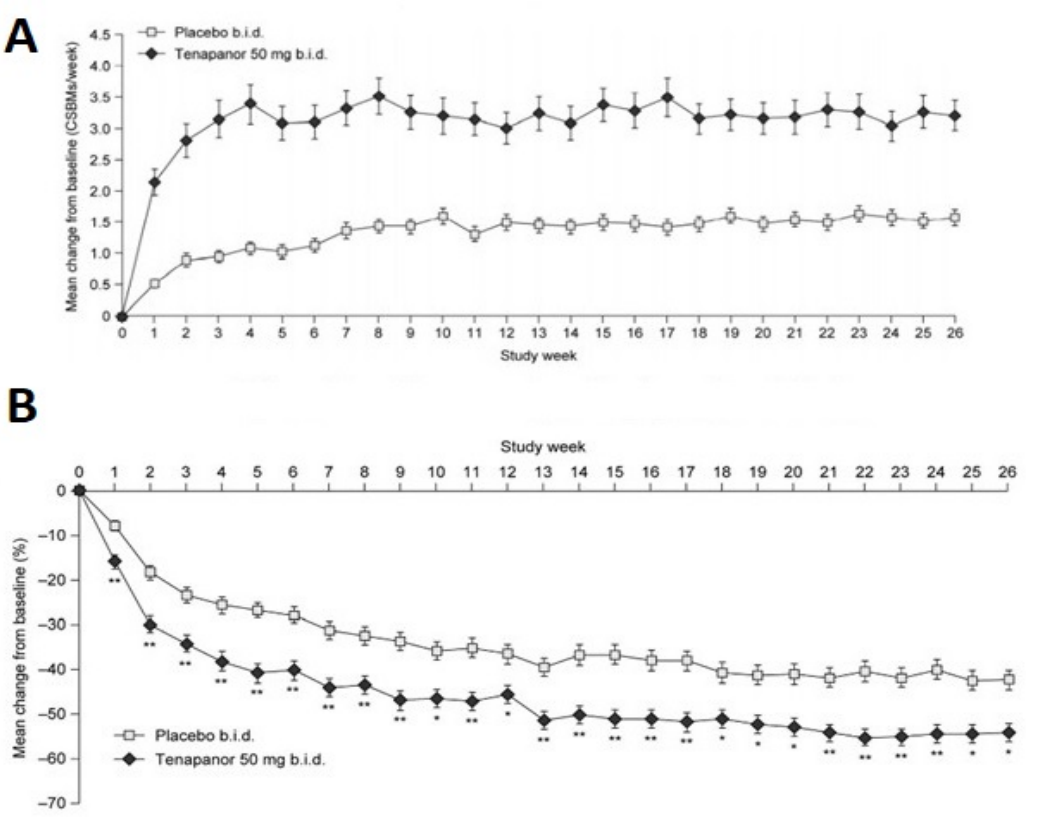

Figure 2. Weekly change in CSBMs (A) and abdominal pain (B).

COMMENTARY

Why Is This Important?

Although IBS is commonly characterized by altered intestinal motility and visceral hypersensitivity, the underlying pathophysiology is complex and may involve defective brain-gut interactions, alterations in gut flora, genetic predispositions, and defects in enteric nervous system functioning, among others. Thus, it's unsurprising that even the most effective IBS treatments rarely demonstrate efficacy in more than 50% of patients[1]. Therefore, it's heartening that we're getting more treatment options for IBS-C.

Tenapanor (IBSRELA) is the first sodium/hydrogen exchanger 3 (NHE3) inhibitor approved for use. NHE3 is expressed on the surface of the intestine, and tenapanor inhibits dietary sodium absorption by inhibiting NHE3[2]. Animal studies demonstrate that it also decreases intestinal permeability and visceral

hypersensitivity, although the mechanism for these actions is unclear since the pharmacologic action primarily blocks sodium absorption[2].

Key Study Findings

Tenapanor is clearly superior to placebo for improvement in abdominal discomfort, stool frequency and stool consistency.

Based on the FDA-required, > 6/12 week combined response endpoint, tenapanor-treated patients were more likely to improve compared to placebo-treated patients: 36.5% vs 23.7% (aRR = 1.55, 95% CI: 1.20-1.99, $P< 0.0001$). Tenapanor-treated patients were also more likely to be 9/12 week responders: 18.4% vs 5.3% (aRR = 3.47, 95% CI: 2.03-5.94, $P < 0.0001$).

Some practitioners might be disappointed that only 36.5% of patients were "responders," but the complicated patient-reported outcomes required by the FDA are a high threshold for "success" and don't necessarily translate well to clinical care. It's notable that tenapanor-treated patients improved from mean of 0.1 CSBMs/week to more than 3 CSBMs/week, which was consistent through 26 weeks as well as achieving approximately 50% reduction in abdominal pain from baseline (**Figure 2**).

Caution

With respect to study design, this is an excellent clinical trial that meets all FDA-requirements for a Phase III RCT. Based on baseline characteristics (e.g., average of 0.1 CSBMs/week), study patients had fairly severe IBS-C symptoms, which might impact generalizability of study results. Since tenapanor works at the surface of the colonic mucosa, it's considered "minimally absorbed". This is consistent with finding no drug-drug interactions and no difference in adverse events between tenapanor- and placebo-treated patients with the exception of diarrhea.[2] As seen with most effective treatments for IBS-C, a minority of patients will experience diarrhea. Diarrhea was more commonly reported by tenapanor-treated patients vs placebo-treated patients (16.0% vs 3.7%), although discontinuation of study medication due to diarrhea only occurred in 6.5% of tenapanor-treated patients.

My Practice

Per the ACG Guideline on Management of IBS[1], guanylate cyclase-C agonists (i.e., linaclotide and plecanatide) are the only treatments that receive a strong recommendation based on high quality RCT evidence and they are the cornerstone of my treatment for IBS-C. Although I recognize that many practitioners may prefer to start IBS-C treatment with an osmotic laxative, it's worth remembering that the ACG Guideline suggests against using polyethylene-glycol products (e.g., MiraLax) to relieve global IBS symptoms in IBS-C since RCTs report no significant differences versus placebo for improvement in abdominal discomfort symptoms. Regardless, when patients are referred to me, they have invariably already tried osmotic laxatives, and most patients will have tried and failed these over-the-counter medications prior to seeing a gastroenterologist for IBS-C[1]. For patients who don't get adequate relief with linaclotide or plecanatide, I'll try tenapanor. Since tenapanor has a unique mechanism of action, I won't wait for patients to fail trials of linaclotide AND plecanatide. I'll simply switch to tenapanor after a patient fails their initial course of a guanylate cyclase-C agonist.

Consistent with the study findings, I'll emphasize to patients that it may take 8-12 weeks to achieve optimal decrease in abdominal discomfort symptoms and encourage patients to continue treatment even if there is only mild improvement in the first 1-2 weeks. I'll also proactively educate my patients that loose stools may occur in the first week of treatment, since this is when tenapanor-associated diarrhea is most likely to occur.

Since I treat more severe IBS-C patients, I frequently combine therapies. I doubt that I'd combine tenapanor with a guanylate cyclase-C agonist, but I will combine it with peppermint oil capsules as an on-demand or daily anti-spasmodic treatment or a neuromodulator, such as duloxetine (Cymbalta) at 30-60mg daily, and/or referral to our dietitician for instruction in low-FODMAP diets.

For Future Research

Comparative statements about the efficacy of tenapanor (IBSRELA) compared to other IBS-C treatments can't be made in the absence of head-

to-head trials. It would be optimal, albeit unlikely, to see these types of trials in the future. Also, RCT data about the efficacy of combination therapy (e.g., tenapanor plus neuromodulator) would be helpful. Based on my clinical experience, many patients will experiment by only using tenapanor 50 mg daily or even as a prn medication. Real-world data about this would be instructive.

Conflict of Interest

Dr. Schoenfeld reports that he sits on advisory boards and speakers bureaus, and is a consultant for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Salix Pharmaceuticals. He also serves as an advisory board member for Takeda Pharmaceuticals, Ardelyx Pharmaceuticals, and Phathom Pharmaceuticals.

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