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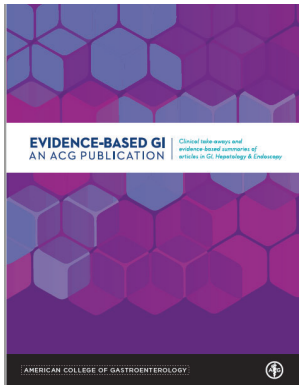

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EBGI **Volume 4, Issue 5**

May 2024

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IBSRELA®
(tenapanor) tablets
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DISCOVER FIRST-IN-CLASS IBSRELA

A Therapy With a Different Mechanism of Action for Adults With IBS-C

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INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.

CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

Reference: IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.; 2022.

Please see Brief Summary of full Prescribing Information on the following page.

ardelyx

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IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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In Case You Missed It

Budesonide Oral Suspension Improves Outcomes in Eosinophilic Esophagitis

ESOPHAGUS

Dr Swathi Eluri
Associate Editor

Swathi Eluri, MD, MSCR

Senior Associate Consultant, Mayo Clinic Florida, Jacksonville, FL; and Adjunct Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

This summary reviews Hirano I, Collins MH, Katzka DA, et al. Budesonide oral suspension improves outcomes in patients with eosinophilic esophagitis: results from a phase 3 trial. Clin Gastroenterol Hepatol 2022;20(3):525-534.e10

Correspondence to Swathi Eluri, MD, MSCR, Associate Editor. Email: EBGI@gi.org

Keywords: eosinophilic esophagitis, topical corticosteroid, budesonide

STRUCTURED ABSTRACT

Question: What is the efficacy and safety of budesonide oral suspension (BOS) 2.0 mg twice daily compared with placebo in adolescents and adults with eosinophilic esophagitis (EoE) over a 12-week period?

Design: This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted between 2015 and 2019. Eligible patients were randomized in a 2:1 manner to receive BOS 2.0 mg twice daily (10 mL at a concentration of 0.2 mg/mL) or placebo for 12 weeks

Setting: Sixty-six centers in the United States.

Patients: Patients were 11–55 years of age with histologic evidence of EoE, defined as having ≥15 eosinophils/high-power field [eos/hpf] from at least 2 levels of the esophagus during screening. To be included, patients also need to

have dysphagia on at least 4 days in any 2 consecutive weeks during screening and in the 2 weeks before randomization measured using the Dysphagia Symptom Questionnaire (DSQ).

Intervention: BOS 2.0 mg twice daily vs placebo for 12 weeks. BOS is an immediate release topical steroid, and the viscous formulation allows for longer contact time of the drug to the esophageal mucosa and thereby optimizing delivery.

Outcomes: Co-Primary Efficacy Endpoints were: (a) proportion of stringent histologic responders, defined as ≤6 eos/hpf across all available esophageal levels (proximal, middle, or distal); and (b) proportion of patients experiencing a significant improvement in dysphagia symptoms, defined as ≥30% reduction in their DSQ score from baseline.

Key secondary efficacy endpoint was change in DSQ Score from baseline to week 12 of treatment, providing insight into the overall improvement in dysphagia symptoms over the study period. Additional secondary efficacy endpoints included proportion of full responders, defined as patients achieving both a stringent histologic response (≤6 eos/hpf) and a dysphagia symptom response (≥30% reduction in DSQ score), mean change in EoE Endoscopic Reference Score (EREFS), proportion of patients achieving deep histologic response (≤1 eos/hpf) or histologic response (<15 eos/hpf), and mean change in EoE Histology Scoring System (EoEHSS) Total Score Ratios from baseline to week 12 of therapy.

In addition to monitoring adverse events, including esophageal and oral candidiasis, at every study visit, safety assessments included dual x-ray absorptiometry for bone mineral density (for patients 11–17 years of age), and routine clinical laboratory and adrenocorticotropic hormone (ACTH) stimulation tests.

Data Analysis: Modified intention-to-treat analysis and per-protocol analysis were performed. Co-primary efficacy endpoints were compared using the Cochran–Mantel–Haenszel (CMH) test, stratified for several factors including age and dietary therapy. An analysis of covariance model was generated for the key secondary efficacy endpoints, with treatment and age group as factors and the baseline DSQ score as a continuous covariate.

Funding: Shire ViroPharma, Inc., a member of the Takeda group of companies, manufacturer of budesonide oral suspension.

Results: Three hundred and eighteen patients (BOS, n = 213; placebo, n = 105)

were randomized and received ≥1 dose of study treatment. Mean age was 34 years old with 13% <18 years old; 60% male; mean peak eosinophil count was 75 eos/hpf; 10% currently on diet restriction and 84% were concurrently using proton pump inhibitors (PPIs).

Patients treated with BOS were more likely to be responders vs placebo-treated patients for both co-primary endpoints. For strict histologic response, responder rate was 53.5% vs 1.0%, respectively; Δ53% [95% confidence interval (CI), 43.8%–59.5%]; P <.001. For ≥30% reduction in dysphagia symptom questionnaire score, responder rate was 52.6% vs 39.1%, respectively; Δ13% [95% CI, 1.6%–24.3%]; P =.024. **(Figure 1)**. Results were similar for the per-protocol set. Full response, defined as achieving both stringent histologic response and ≥ 30% reduction in dysphagia symptom questionnaire score, occurred more frequently with budesonide oral suspension: 30% vs 0%, respectively, P <0.001.

BOS-treated patients also had greater improvements in least-squares mean DSQ scores and EREFS over 12 weeks than placebo-treated patients: DSQ, –13.0 (SEM 1.2) vs –9.1 (SEM 1.5) (Δ–3.9 [95% CI, –7.1 to –0.8]; P =.015); EREFS, –4.0 (SEM 0.3) vs –2.2 (SEM 0.4) (Δ–1.8 [95% CI, –2.6 to –1.1]; P <.001).

BOS was well tolerated with mild to moderate treatment-emergent adverse events (TEAEs), which were comparable in BOS (61%) and placebo (61%) groups after 12 weeks.

COMMENTARY

Why Is This Important?

EoE is a chronic, immune-mediated, inflammatory disease of the esophagus that can lead to esophageal dysfunction including symptoms of dysphagia, esophageal strictures, and food impactions.[1] Management typically involves PPIs and elimination diets.[2] Off-label use of topical corticosteroids from inhalers, originally formulated for asthma, is also common. However, these inhaled formulations aren't optimized for esophageal delivery by swallowing an inhaled dose. This potentially leads to inadequate treatment response and associated risks of uncontrolled disease activity such as food impaction and reduced responsiveness to dilation. Although some compounding pharmacies will create an oral suspension, obtaining insurance coverage for off-label medications can be challenging to obtain.

Therefore, Food and Drug Administration (FDA)-approval of a budesonide oral suspension, which was partly based on this study, addresses a significant unmet medical need for more effective EoE

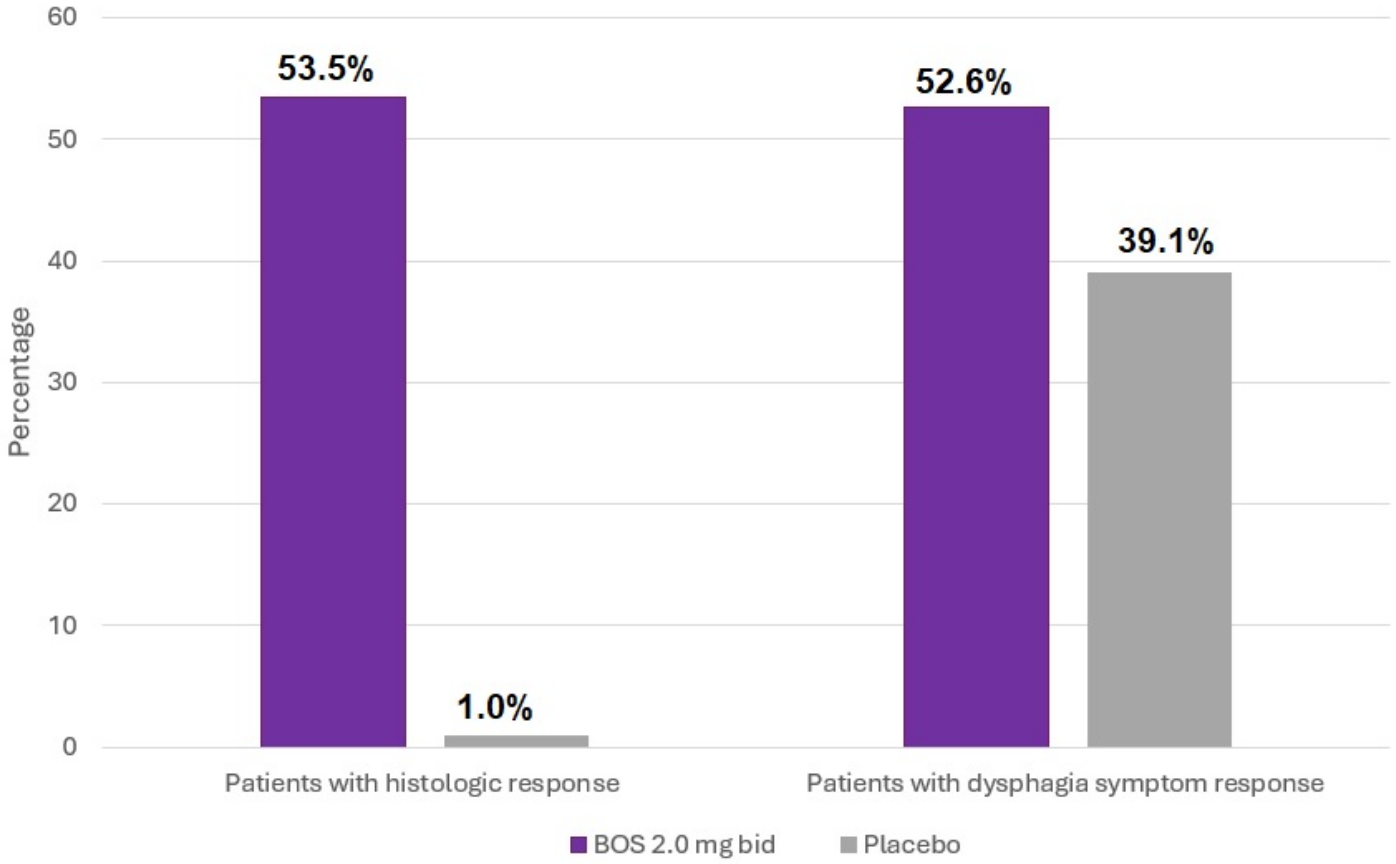

Figure 1. Co-primary endpoints.

treatments. It is the first US phase 3 trial of a corticosteroid therapy for EoE and the largest clinical trial for EoE at time of publication.

Key Study Findings

BOS-treated patients were more likely than placebo-treated patients to achieve strict histologic response (53.5% vs 1.0%) and ≥30% reduction in dysphagia symptom questionnaire score (52.6% vs 39.1%).

Key secondary efficacy endpoints, such as deep histologic response (≤1 eos/hpf), histologic response (≤15 eos/hpf), reduction in EREFS score, and maximum peak eosinophil count, also favored BOS over placebo. Additionally, BOS-treated patients showed greater reductions EoEHSS scores compared to placebo.

Caution

The study population is heterogeneous in terms of being on prior or concomitant medical or dietary therapies for EoE. The group also comprised of those with more severe disease so there might be a component of selection bias as it is unclear if the results can be generalizable to those with milder disease forms of EoE. Additionally, it is important to recognize that patients were only followed for the predetermined endpoint of 12 weeks, so we do not have longer term data regarding side effects and possible complications with maintenance therapy for BOS.

My Practice

Topical steroids are recommended as one of the treatment options in the management of EoE per societal guidelines. However, there have been limitations with the lack of availability of budesonide oral suspension other than in select specialty pharmacies which are not accessible to everyone. Alternate corticosteroid formulations designed for used in other conditions, such as asthma, typically are unsuccessful in achieving optimal esophageal mucosal delivery, which can affect treatment outcomes. Having BOS approved by the FDA based on the results of this study leads to easier access for EoE patients for a viable steroid therapy.

In most cases, I will initiate high dose PPI therapy for patients with EoE as the first step with a repeat endoscopic exam with biopsies after 8-12 weeks of therapy. This is important because improvement in dysphagia symptoms may not correlate with histologic remission. Achieving histologic remission is believed to be important to minimize the development of esophageal strictures that could require dilation. I include dietary therapy and/or topical corticosteroids as second line treatment depending on patient choice. When using elimination diets, I'll frequently start with elimination of dairy and then may also eliminate wheat products before having patients start a more restrictive 6-food elimination diets. I'll usually have these patients work with a dietitian to improve compliance. Finally, I usually reserve dupilumab, an FDA-approved monoclonal antibody injected subcutaneously weekly, for more severe and refractory cases of EoE.

For Future Research

Future studies with long term follow-up data could help assess the sustained efficacy and long-term safety outcomes of BOS in management of EoE. Additional assessments in the pediatric population only can help provide insights regarding dosing and side effects. Comparative effectiveness studies evaluating BOS to other treatments for EoE such as PPIs and dupilumab can help identify the most appropriate treatment option for differing patient population or phenotypes of EoE. Finally, the new American College of Gastroenterology guidelines on the management of EoE are forthcoming and may further direct optimal management.

Conflict of Interest

None to report

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CRC SCREENING

Multi-Target Stool DNA Test for CRC Screening: How Accurate is the New Version?

Dr Philip Schoenfeld
Editor-in-Chief

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

This summary reviews Imperiale T, Porter K, Zella J, et al. Next-generation multitarget stool DNA test for colorectal cancer screening. N Engl J Med 2024; 390: 984-93.

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

Keywords: colorectal cancer screening, stool test, fecal immunochemical test

STRUCTURED ABSTRACT

Question: What is the sensitivity and specificity of a new version of a multi-target stool DNA test (mt-sDNA) for colorectal cancer (CRC) screening for detection of stage I, II, and III CRC and advanced precancerous lesions in average -risk individuals aged ≥40 years old?

Design: The BLUE-C study is a prospective, observational diagnostic test study using colonoscopy as the gold standard for detection of CRC and precancerous lesions.

Setting: One-hundred eighty-six sites in the United States.

Patients: Asymptomatic individuals ≥40 years old scheduled for CRC screening colonoscopy. Key exclusion criteria included: (a) history of inflammatory bowel disease; (b) prior history of advanced adenomatous polyps or CRC; (c) medical or family history of inherited polyposis syndromes; and (d) currently up to date with CRC screening (e.g., had a normal screening colonoscopy ≤9 years or negative fecal immunochemical test (FIT) within previous 6

months). Individuals with family history of CRC in first-degree relatives were also included.

Interventions/Exposure: Stool specimens for next-generation mt-sDNA test and FIT were obtained prior to colonoscopy bowel preparation and mailed for processing. The next-generation mt-sDNA test analyzes DNA abnormalities in colonic mucosal cells sloughed from the colon wall into stool. The new molecular panel encompasses additional methylated DNA markers compared to the current version of mt-sDNA test while continuing to test for fecal hemoglobin. Separate FIT was considered positive based on threshold of 100ng/ml of hemoglobin.

Outcome: Primary outcome was sensitivity for CRC and specificity for advanced neoplasia, defined as CRC plus advanced precancerous lesions, which were defined as adenomas ≥10mm, adenoma with villous histology or high grade dysplasia, carcinoma in situ, or serrated lesion ≥10mm. Secondary outcome was sensitivity for advanced precancerous lesions and comparison of sensitivity of FIT and next-generation mt-sDNA test for CRC and advanced precancerous lesions.

Data Analysis: Sensitivity (percentage of individuals with the disease who have a positive test) and specificity (percentage of individuals without the disease who have a negative test) with corresponding 95% confidence intervals (CIs) were calculated with standard formulas. For previous FDA-approved CRC screening tests, a test was considered acceptable if the lower boundary of the 95% CI for CRC sensitivity was >65% and if the lower boundary of 95% CI for specificity of advanced precancerous lesions was >85%.

Funding: Exact Sciences, manufacturer of Cologuard and next generation Cologuard/Cologuard 2.0.

Results: Between November 2019 and January 2023, 20,176 individuals had full data from colonoscopy and stool tests completed. Overall, mean age was 63 years old, 53% were female, 60% were White, 5.2% with family history of CRC in a first-degree relative, and 13.4% had positive next-generation mt-sDNA test. Among the individuals with full data, 0.5% (98/20,176) had CRC and 10.6% (2,144/20,176) had advanced precancerous lesions. Among individuals with CRC, 84% (82/98) had stage I-III CRC.

For CRC stages I-III, 92.7% (76/82) had a positive next generation mt-sDNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas or adenomas with high-grade dysplasia or carcinoma in situ), 43.4% (931/2,144) had a positive next generation mt-sDNA test and

sensitivity rose to 74.6% when limited to lesions with high-grade dysplasia (85/114) (**Table 1**). Approximately 7% of participants had a false positive test, defined as positive stool DNA test but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Since FIT had only 64.6% sensitivity for stages I-III CRC and 23.3% sensitivity for advanced precancerous lesions (Table 1), the mt-sDNA test was significantly better for both comparisons. The stool DNA test was positive for 79% (23/29) of stage I-III CRC where FIT was negative, and stool DNA was positive for 34% (555/1644) of advanced precancerous lesions where FIT was negative. However, only 4.3% of participants had a false positive FIT, which was defined as positive FIT but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Disease	Sensitivity of stool DNA	Sensitivity of FIT
Stage I-III CRC	92.7% (95% CI: 85-97)	64.6% (95% CI: 53-75)
Advanced precancerous lesions	43.4% (95% 41-45)	23.3% (95% CI: 22-25)
High-grade dysplasia lesions	74.6% (95% 66-82)	47.4% (95% CI: 38-57)

Table 1. Sensitivity of next generation multi-target stool DNA test and fecal immunochemical test

COMMENTARY

Why Is This Important?

As discussed in prior commentaries,[1] only about 59% of the eligible US population is up to date with CRC screening, equating to more than 40 million unscreened individuals. Therefore, new interventions to improve screening are sorely needed.[2] Given the desire of some patients to avoid colonoscopy with the associated bowel preparation, sedation, and time missed from work, stool-based tests for CRC screening are a viable option. Although annual FIT is inexpensive for healthcare systems, the sensitivity for Stage I-III CRC is 65% (i.e., approximately 35% of individuals with Stage I-III CRC will have a negative test). The limited sensitivity of FIT could be overcome by performing it annually, but multiple studies demonstrate that adherence to FIT is at best 75% and then decreases to approximately 30%-35% in subsequent years.[2-4] Therefore, stool-based tools with improved sensitivity and higher adherence would be beneficial.

In the study by Imperiale et al, the next generation mt-sDNA test demonstrates superiority to FIT for sensitivity of stage I-III CRC (92.7% vs 64.6%) as well as for advanced precancerous lesions (43.4% vs 23.3%) while improving specificity to 92.7% for non-neoplastic or negative colonoscopy. Compared to the currently available mt-sDNA test,[5] the sensitivity remains the same, but the specificity is improved, leading to fewer false-positive tests requiring colonoscopy. Finally, based partly on quality control processes developed by Exact Sciences, adherence to completing mt-sDNA tests may be twice as high compared with standard FIT (85% vs 43%).[6]

Key Study Findings

For CRC Stage I-III, sensitivity was 92.7% (76/82) since 92.7% of individuals with stage I-III CRC had a positive next generation mt-sDNA test. Sensitivity was 43.4% (931/2144) for advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas or adenomas with high-grade dysplasia or carcinoma in situ. Approximately 7% of participants had a false positive test, defined as positive mt-sDNA test, but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Caution

The next-generation mt-sDNA test was not directly compared to the current version, limiting assessment of how the new DNA biomarker panel improves diagnostic test characteristics for stage I-III CRC and advanced precancerous lesions.

My Practice

As per prior commentaries,[1] colonoscopy is my primary tool for CRC screening since it's also a CRC prevention tool. Nevertheless, I do see average-risk individuals who are fearful of colonoscopy, sedation, or simply doing the bowel preparation and want a non-invasive alternative. What's the best option for these individuals? At my VA institution, we're limited to offering annual FITs as a stool-based screening test, and this is certainly an appropriate cancer detection tool. However, mt-sDNA tests clearly produce higher sensitivity than FIT for stage I-III CRC and advanced precancerous lesions. This limitation may be overcome if patients get FIT annually, but adherence to annual FIT may be less than 40% in repeated years and adherence to mt-sDNA is considerably better.

Of course, mt-sDNA tests are significantly more expensive than FIT as a CRC screening test, but this cost is borne by insurers instead of individual patients, since mt-sDNA tests are covered under the Affordable Care Act as an approved CRC screening test. Therefore, the out-of-pocket cost for a vast majority of CRC screen-eligible individuals will be zero.

For Future Research

Future efforts to improve specificity (i.e., minimizing frequency of false positive tests, which drives use of colonos-

copy) while preserving high sensitivity for CRC will be beneficial. Since mt-sDNA tests are recommended for use every 3 years, additional longitudinal data will also be helpful.

Conflict of Interest

Dr. Schoenfeld previously served as a speaker for Exact Sciences and has discontinued that relationship.

Note: The authors of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Linaclotide Effective for Functional Constipation in 6-17 Year Olds: First FDA-Approved Constipation Treatment for Children

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This summary reviews Di Lorenzo C, Khlevner J, Rodriguez-Araujo G, et al. Efficacy and safety of linaclotide in treating functional constipation in paediatric patients: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Gastroenterol Hepatol 2024;9(3):238-250.

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Keywords: constipation, diarrhea, double-blind method, RCT, treatment outcome.

STRUCTURED ABSTRACT

Question: Is linaclotide, a guanylate cyclase C receptor agonist approved for treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation (IBS-C) in adults, effective, safe, and well-tolerated for treatment of bothersome functional constipation symptoms in pediatric patients (ages 6-17 years)?

Design: Randomized, double-blinded, placebo-controlled multicenter, parallel-group, 12-week, phase 3 trial.

Setting: Sixty-four clinic or hospital sites in 7 countries, including United States, Canada, Israel, Italy, and the Netherlands.

Patients: Study patients must have had ≤2 unassisted defecations per week for ≥2 months before the screening visit and meet a modified Rome III criteria for

pediatric functional constipation **(Table 1).** Patients with IBS were excluded from this study.

Intervention: linaclotide 72 μg oral once daily taken 30 minutes before a meal at the same time each day vs identical placebo for 12 weeks.

Outcomes: Primary efficacy endpoint was change from baseline (CFB) in spontaneous bowel movements (SBM) frequency rate (SBMs per week) over the study period. SBM was defined as a bowel movement that occurred in the absence of a rescue medication (e.g., laxative, enema, etc.) the day of or before the movement. The secondary efficacy endpoint was CFB in stool consistency using the pediatric Bristol Stool Form Scale. Additional endpoints were CFB in 12-week frequency rate of complete SBM, straining with bowel movements, overall responder (defined as ≥2 SBM/week increase from baseline), and abdominal bloating among others.

Data Analysis: Modified intention-to-treat analysis, including all patients who received at least 1 dose of the study intervention, using ANCOVA analysis to identify differences in primary and secondary endpoints between linaclotide and placebo. Change from baseline (CFB) reported as least-squares mean (LSM). Prespecified analyses also stratified results by age group: 6-11 years old and 12-17 years old.

Funding: Ironwood Pharmaceuticals and AbbVie Pharmaceuticals, manufacturer of linaclotide. The funders of the study participated in the study design, research, data collection, data analysis, data interpretation, writing of the article, and approval of submission for publication.

Results: Among 1,002 patients screened and 330 met inclusion criteria and were randomly assigned between October 2019 and March 2022. Overall, median age was 11.0 years, 55% were female, and 70% were White. Baseline SBMs per week were 1.3 per week in the placebo group and 1.2 per week in the linaclotide group.

Compared to the placebo group, linaclotide-treated patients had significantly greater improvements in SBM per week. Specifically, linaclotide-treated patients increased from 1.2 SBM per week to 3.4 SBM per week while placebo-treated patients only increased from 1.3 SBM per week to 2.3 SBM per week **(Figure 1)**. Based on LSM change from baseline, linaclotide-treated patients also demonstrated significant improvements in stool consistency, straining, and frequency of

complete SBM per week. Linaclotide-treated patients were also more likely to be overall responders with an increase of ≥ 2 SBM per week: 43% vs 23%, $P = 0.0001$. Improvement in SBM per week was numerically higher in the linaclotide-treated 6-11 year old group vs the linaclotide-treated 12-17 year old group, although this increase did not achieve statistical significance.

Modified Rome III Criteria (≥2 months of ≤2 unassisted defecations per week) plus at least 1 of the following once per week:
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel movements
History of large diameter stools that might obstruct the toilet
Presence of a large fecal mass in the rectum
At least 1 episode of fecal incontinence

Table 1. Modified Rome III criteria for pediatric functional constipation.

COMMENTARY

Why Is This Important?

Constipation is one of the most common functional gastrointestinal disorders in pediatric patients, affecting approximately 1 in 7 of children worldwide, with significant impact on quality of life.[1] It's also one of the most common referrals for our pediatric gastroenterology colleagues. Nonpharmacologic therapies, including parental education, behavioral modifications (e.g., regular toileting for 5-10 minutes after meals), and diet modification with fiber supplementation or addition of kiwifruit, prunes, or prune juice, are the first line of treatment. Although glycerin and bisacodyl suppositories are approved for use in children ≥6 years old with constipation, no other over-the-counter treatments appear to be officially Food and Drug Administration (FDA)-approved for pediatric constipation. Nevertheless, polyethylene glycol (MiraLax; Bayer US, Whippany, NJ) is frequently recommended for pediatric constipation[2] based on randomized controlled trial data, although constipation persists in more than 20% of patients necessitating other interventions. Unfortunately, among prescriptions treatments for adult chronic idiopathic constipation, neither prucalopride nor lubiprostone have been shown to be superior to placebo in children.[3-4] Given the lack of proven constipation treatments for pediatric patients and the frequency of this complaint, new treatments are needed.[5]

Linaclotide is a guanylate cyclase C agonist approved for treatment of chronic idiopathic constipation (72ucg or 145ucg) and IBS-C (290ucg) in adults. Results from this study led to FDA approval of linaclotide as the first

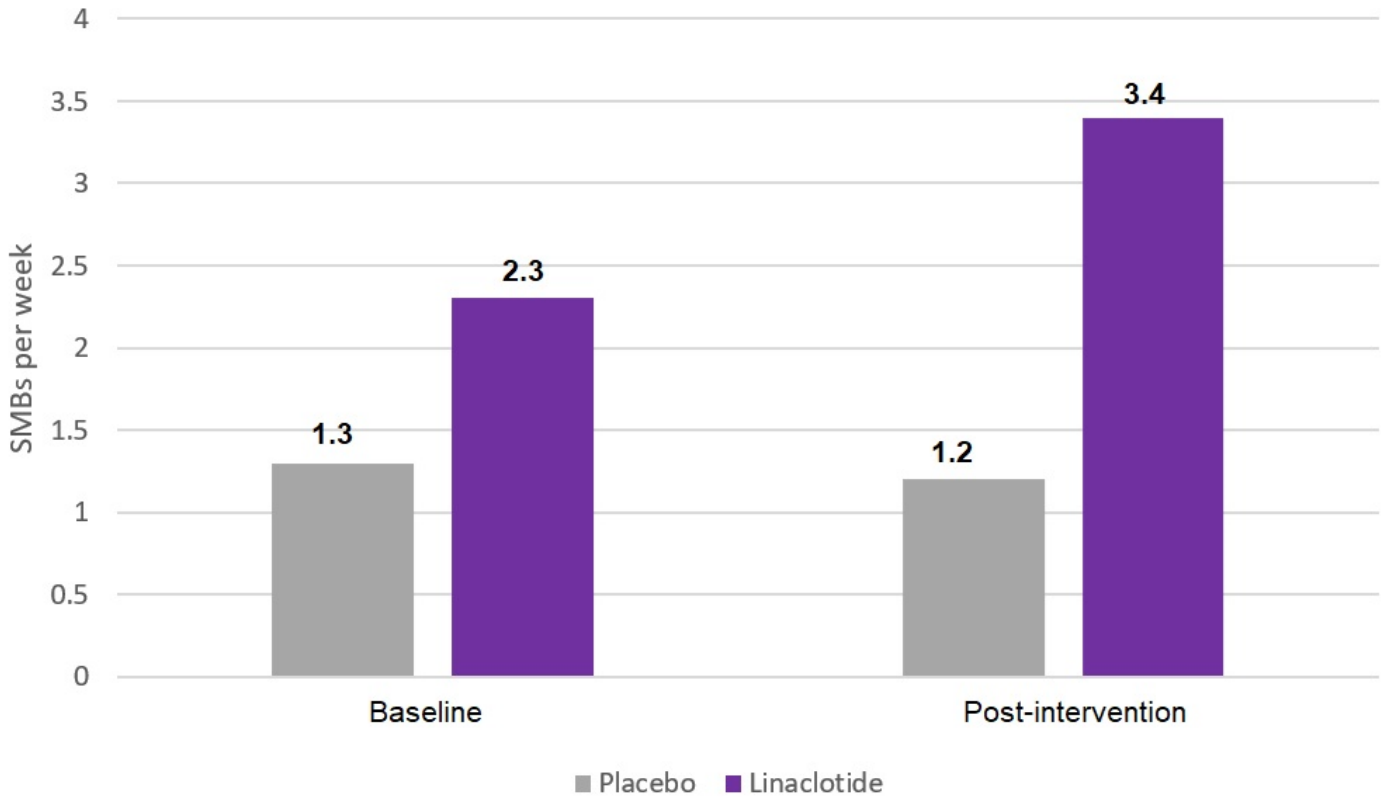

Figure 1. Primary endpoint results in increase in spontaneous bowel movements (SBM) per week.

approved prescription treatment for pediatric (ages 6-17 years) patients with functional constipation.

Key Study Finding

In this double-blinded, randomized, placebo-controlled trial linaclotide improved SBMs per week over baseline significantly. Specifically, linaclotide-treated patients increased from 1.2 SBM per week to 3.4 SBM per week.

Patients also had a relatively rapid benefit from linaclotide with 57% of patients having an SBM within 48 hours of treatment.

Caution

This study only followed patients for 12 weeks, which is a relatively brief period given the chronicity of functional constipation and as such long-term effects cannot be analyzed. In addition, rescue medications were used frequently by placebo-treated patients (60%) and linaclotide-treated patients (52%).

My Practice

Based on consultation with pediatric gastroenterology colleagues, linaclotide will be incorporated into their management of pediatric functional constipation, but will be reserved for patients that first fail non-pharmacologic interventions and polyethylene glycol. While the 72ucg dose will be used for 6 -11 year olds, the 145ucg dose may be used in older adolescents, especially if they don't get an adequate response to the 72ucg dose.

For Future Research

Long-term real-world data will be helpful in confirming safety and efficacy of linaclotide in children. Further subgroup analysis based on gender, type of previous failed treatments, and age will be beneficial.

Conflict of Interest

Dr. Abu-Heija reports no potential conflicts of interest for this summary.

Note: The authors of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

PROFILE: Can Molecular Biomarkers Predict Outcomes to Crohn's Disease Treatment?

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IBD

This summary reviews Noor NM, Lee JC, Bond S, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol 2024; 9: 415-27.

Keywords: Crohn's disease, biomarkers, biologics

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STRUCTURED ABSTRACT

Question: Can a prognostic molecular biomarker, derived from T-cell transcriptional signatures, help determine who will benefit from an early top-down versus accelerated step-up treatment strategy for adults with newly diagnosed Crohn's disease (CD)?

Design: The PROFILE (predicting outcomes for CD using a molecular biomarker) study is a multi-centered, open-label, biomarker-stratified randomized controlled trial (RCT).

Setting: Patient were screened from 40 hospitals in the United Kingdom. The study enrolled from December 2017 to January 2022.

Patients: This study included patients aged 16–80 years old with symptomatically active (Harvey-Bradshaw Index [HBI] $\geq$ 7) CD diagnosed within 6 months of screening. To be eligible, subjects had to have biochemical evidence of active in-

flammation, defined as a C-reactive protein above the upper limit of normal and/or a fecal calprotectin >200 ug/g. Additionally, subjects were required to have endoscopically active disease, defined as Simple Endoscopic Score for CD ≥4, and be naïve to immunosuppressive therapies. Patients with "clinically significant" obstructive or perianal disease were excluded.

Interventions/Exposure: PredictSURE-IBD (PredictImmune Ltd, Cambridge, UK) is a T-cell transcriptional signature that was intended to help determine which patients with CD may benefit from upfront biologic therapy. Based on results of this blood-based test, patients were identified as high risk of inflammatory bowel disease (IBD) treatment escalation (IBDhi) versus those who were at low risk for IBD treatment escalation (IBDlo).

Using stratified block randomization based on biomarker group (IBDhi vs IBDlo), disease location (colonic vs other) and mucosal inflammation (mild vs moderate vs severe), eligible participants were then randomized 1:1 to a top-down or accelerated step-up treatment (**Figure 1**).

Outcomes: The primary endpoint was the incidence of sustained steroid-free and surgery-free remission from the completion of the initial steroid induction to week 48. Objective evidence of disease, such as elevated inflammatory markers, were required to determine failure. There were 5 secondary end points, which are as follows: (1) endoscopic remission by week 48, (2) quality of life measured by the IBD-Q, (3) number of flares requiring treatment escalation, (4) cumulative steroid exposure and (5) number of Crohn's-related hospitalizations and surgeries.

Data Analysis: The primary analysis was to determine the interaction between the intervention (PredictSURE-IBD) and treatment to determine if the primary outcome can be achieved. The sample size was determined for 92% power with a 2-sided 5% *P*-value. The primary analysis was an intention to treat analysis, but a secondary per-protocol analysis was also conducted.

Funding: Funding for this trial was provided by Wellcome and PredictImmune Ltd, which are the commercial entities with stake in the biomarker studied.

Results: Among 386 newly diagnosed CD patients enrolled in the trial, mean age was 33-34 years old, female sex was 46%-47%, White ethnicity was 87%-89%, ileal disease alone was 33%-34%, colonic disease was 26%-28%, and remainder was ileocolonic disease. Disease behavior was classified as inflammatory in 85%-

88%, stricturing in 11%-14%, and penetrating in 1%. Biomarker status (IBDhi vs IBDlo) was evenly split at 50% in step-up arm and top-down treatment arm.

Sustained steroid-free and surgery-free remission was more frequent in the top-down treatment arm than the accelerated step-up arm: 79% vs 15%, $P< 0.0001$ (**Figure 2**). However, there was no significant biomarker-treatment interaction, meaning that the biomarker was not useful for guiding therapy for CD. Additionally, all secondary outcomes were better in the top-down group than the step-up ground, but again the biomarker did not exert an influence on the outcome. Endoscopic remission, defined as absence of ulceration at week 48, was also significantly higher in the top-down treatment arm: 67% vs 44%, $P< 0.0001$. They reported 11 urgent abdominal surgeries in the trial period (2 in the top-down group and 9 in the step-up group).

Trial visit	Accelerated step-up	Top-down
Week –2 (screening)	Start steroid induction for active Crohn's disease	Start steroid induction for active Crohn's disease
Week 0 (randomisation)	Following randomisation, continue steroid taper	Following randomisation, start infliximab and immunomodulator, and continue steroid taper
Week 4, 16, 32, 48 (after randomisation)	If in remission, continue on current step of treatment If flare 1, start steroids and immunomodulator If flare 2, start infliximab alongside immunomodulator	If in remission, continue infliximab and immunomodulator If flare 1, additional course of steroid medication If flare 2, consider non-response and trial withdrawal

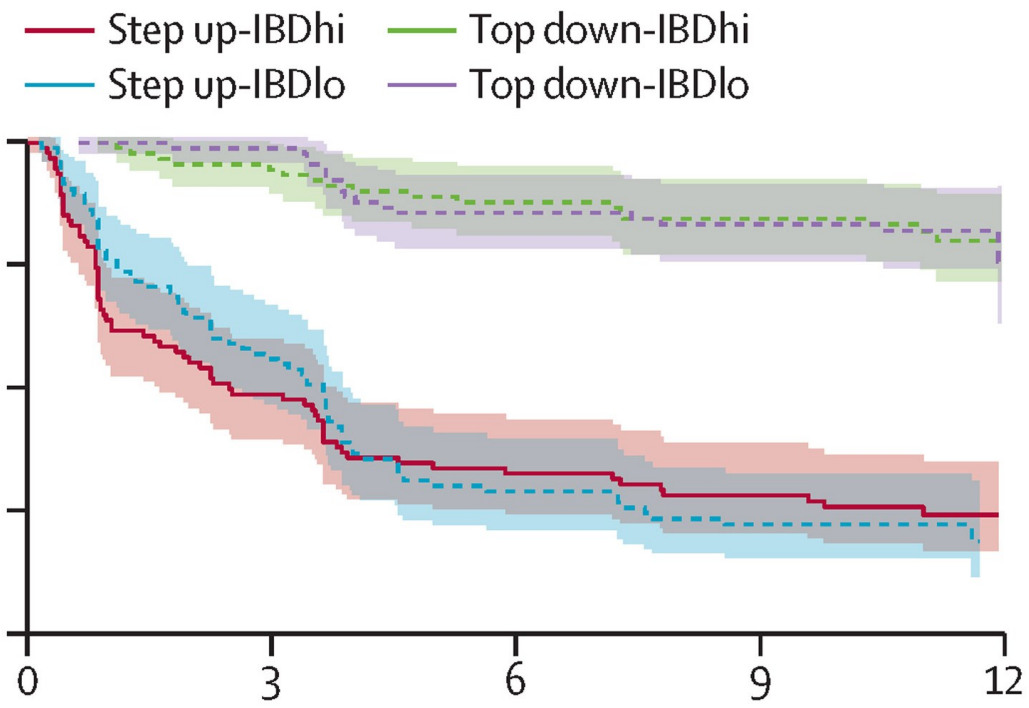
Figure 1. Trial visits and escalation summary.

COMMENTARY

Why Is This Important?

This was a negative study because the PredictSURE-IBD biomarker did not predict which patients would benefit from step-up vs top-down therapy for CD. However, it is an important study because it provides strong evidence that early (<6 months of diagnosis) initiation of top-down treatment with biologic therapy for CD is critical. The clinical response for CD patients treated early with infliximab and an immunomodulator was 79% with endoscopic remission of 67%, which is much higher than many CD trials.

The first trial to study this concept was the REACT trial, an open-labeled cluster randomized trial in Belgium and Canada.[1] They randomized centers to "conventional management" which during the study period (2010-2013) was step-up treatment or early combined immunosuppression and assessed steroid-free remission based on a HBI at 12 months. As a secondary analysis, they



Top down-IBDlo	92 (0)	89 (1)	76 (1)	71 (3)	7 (62)
Step up-IBDlo	95 (0)	52 (0)	25 (2)	18 (1)	3 (14)
Top down-IBDhi	94 (0)	86 (3)	78 (1)	73 (2)	7 (63)
Step up-IBDhi	95 (0)	44 (2)	28 (1)	23 (1)	3 (17)

Figure 2. Kaplan-Meier analysis of time to flare, surgery, or both. Time to first event by biomarker–treatment group with data censored at 12 months.

determined major adverse events (surgery, hospitalizations, other disease-related complications) at 24 months. The primary outcome in this trial was also negative, but they demonstrated a lower rate of major adverse events in the early combined immunosuppression arm. The REACT trial enrolled patients with a median CD duration between 12-13 years, which is much later in the disease course than patients in the PROFILE study. A recent meta-analysis of 25 trials testing biological agents for the treatment of IBD demonstrated that induction of remission was more successful in CD when the drug was started in patients with ≤18 months disease duration compared with those with disease duration >18 months, while this stratification by disease duration was not noted for patients with ulcerative colitis.[2] The difference in disease duration of patients enrolled in the REACT and PROFILE trials may be a leading explanation for the difference noted. Additionally, patients in the PROFILE study had a higher mean HBI score (9-10) compared with patients in the REACT trial (4). Another possible explanation may be that PROFILE used objective

evidence of remission in addition to a symptomatic measure.

CD is often a transmural disease. Delays in effectively treating CD may lead to disease complications such as medically refractory disease, stricturing or penetrating complications. The robust inflammation that characterizes CD requires early and up-front biologic therapy. Ultimately, this emphasizes the importance of avoiding recurrent courses of steroids for patients with CD and willingness to start some type of biologic therapy earlier in disease course.

The importance of biomarkers in assessing IBD is increasingly recognized. The CALM study randomized patients with CD naïve to immunomodulators to monitoring with clinical symptoms alone or symptoms and biomarkers to monitor disease activity with this monitoring guiding treatment decision making.[3] They concluded that a significantly higher proportion of patients in the tight control group achieved the primary endpoint of mucosal healing at week 48. Trials like CALM and PROFILE highlight the importance of studying treatment strategies for IBD. Although the PredictSURE-IBD panel was not a predictive biomarker, a recent clinical practice guideline highlights the appropriate role of biomarkers for the management of CD.[4]

Key Study Findings

There was no significant biomarker-treatment interaction with PredictSURE-IBD, meaning that the biomarker was not useful for guiding step-up vs top-down therapy for CD within 6 months of diagnosis.

Sustained steroid-free and surgery-free remission was more common in the top-down treatment arm where CD patients were treated early with infliximab and an immunomodulator vs step-up treatment arm (79% vs 15%, respectively, $P > 0.0001$) as well as for endoscopic remission (67% vs 44%, respectively, $P < 0.0001$).

Caution

A major limitation of the PROFILE trial is that treating physicians were blinded to the intervention (biomarker result), but not to the treatment (step up versus top down) which may lead to an over estimation of the treatment effect in the top-down treatment group. Also, about one third of patients did not have an end of trial colonoscopy due to COVID-19 related shutdowns.

My Practice

While my use of biomarkers is not changed based on the PROFILE trial, this trial provides robust data to support upfront biologic therapy for Crohn's disease with numbers to cite to patients for likelihood of success when a biologic is started within 6 months of diagnosis. Despite guideline recommendations that biologic agents are first line therapy for Crohn's disease, there is a tremendous amount of hesitation from patients and sometimes providers to begin biologics early in the course of disease. Although caution about starting a longitudinal medication is understand-

able, this study provides reassurance that the best chance of success for controlling Crohn's disease comes with early initiation of biologic therapy.

For Future Research

Unfortunately, in tertiary care practice, it is increasingly rare to see patients within 6 months of a new diagnosis of IBD. In the US, the next steps should be implementation research to facilitate early initiation of biologic therapy in appropriate patients and obtain a better understanding of obstacles both from a patient's perspective as well as a provider's perspective.

Conflict of Interest

Dr Kochar received consulting fees from Pfizer and Bristol Meyers Squibb.

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