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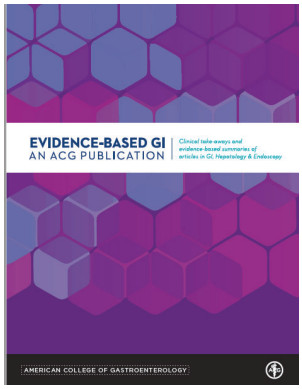

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INDICATION

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

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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Subcutaneous Infliximab for Maintenance of IBD Remission: Added Convenience With Potential for Improved Efficacy?

Dr Elie Al Kazzi
Associate Editor

Elie S. Al Kazzi, MD, MPH

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IBD

This summary reviews Hanauer SB, Sands BE, Schreiber S et al. Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for inflammatory bowel disease: Two randomized Phase 3 trials (LIBERTY). *Gastroenterology*. 2024;167:919–933.

Correspondence to Elie S. Al Kazzi, MD, MPH, Associate Editor Email: EBGI@gi.org

Keywords: Crohn's Disease, Ulcerative colitis, infliximab, maintenance, subcutaneous, biosimilar

STRUCTURED ABSTRACT

Question: Is the subcutaneous (subq) CT-P13 infliximab (IFX) biosimilar efficacious as maintenance therapy for patients with moderate-to-severe Crohn's disease (CD) or ulcerative colitis (UC)?

Design: Two randomized, placebo-controlled, multicenter and international clinical trials (LIBERT-CD AND LIBERTY-UC).

Setting: There were 148 clinical sites in 26 countries for the CD study, and 104 clinical sites in 14 countries for the UC study.

Patients: Adult patients with moderate-to-severe CD or UC who are IFX naïve

and have never had any intolerance or inadequate response to any other anti-TNF biologic.

Intervention: During the induction phase, all patients received the intravenous (IV) formulation of CT-P13 IFX at 5 mg/kg at 0, 2 and 6 weeks. At week 10, clinical responders were randomized into the maintenance phase to receive either the subq formulation of CT-P13 IFX at 120 mg every 2 weeks or a placebo until week 54. At week 22, dose escalation of subq CT-P13 IFX to 240 mg was permitted for patients who initially responded and subsequently lost response. Concomitant use of stable doses of immunomodulators and 5-ASA agents was also permitted.

Outcomes: A primary efficacy outcome at week 54 was clinical remission: absolute Crohn's Disease Activity Index (CDAI) score of <150 points for CD patients and stool frequency and endoscopic subscores of 0–1 points and rectal bleeding subscore of 0 points for UC patients. A co-primary outcome for the CD study was endoscopic response (50% decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] from baseline). Secondary outcomes included endoscopic remission, corticosteroids-free remission, pharmacokinetics, immunogenicity and safety evaluations by monitoring treatment-emergent adverse events.

Data analysis: Intention-to-treat analysis. A Cochran–Mantel–Haenszel chi-square test was used for the outcomes.

Funding: Celltrion, Inc, a global pharmaceutical company based in South Korea who manufactures CT-P13 IFX biosimilar

Results: Among the 343 patients who were randomized for the CD study, 58% were male, median age was 36 years, 91% White, mean diagnosis duration was 4.3 years, mean CDAI was 312, and mean SES-CD was 11.5, with 43% receiving corticosteroids at week 0 and 75% of them achieved clinical remission at week 10. Study completion rate was 85% of randomized patients in treatment arm. Among the 438 patients who were randomized for the UC study, 55% were male, median age was 37 years, 98% White, mean diagnosis duration was 6.1 years, mean total Mayo was 8.8, and mean modified Mayo was 6.6, with 41% receiving corticosteroids at week 0 and 49% of them achieved clinical remission at week 10. Study completion rate was 82% of randomized patients in treatment arm.

Subq CT-P13 IFX showed superior efficacy over placebo for all primary and secondary outcomes for both studies (Table 1). These results remained valid for patients requiring dose escalation at week 22. The mean pre-dose serum concentration maintained a consistent and therapeutic level up to week 54 in both studies for patients receiving CT-P13 SC. In the CD study, 65.1% of patients receiving subq CT-P13 IFX had positive conversion in anti-drug antibodies, while 76.2% in the placebo group. In the UC study, these numbers were 63.8% in the treatment group vs 91.8% in the placebo group.

Adverse events were similar in both arms of both studies, and most were considered not related to the study drug.

	For the CD Study		For the UC Study	
	Subq CT-P13 (n=231)	Placebo (n=112)	Subq CT-P13 (n=294)	Placebo (n=144)
Clinical remission	62.3%	32.1%	43.2%	20.8%
Endoscopic response	51.1%	17.9%	-	-
Clinical response	65.8%	38.4%	53.7%	31.3%
Endoscopic remission	34.6%	10.7%	35.7%	16.7%
Corticosteroid-free remission	40.4%	22.7%	36.7%	18.0%

Table 1. Primary and secondary outcomes for both studies at week 54.
CD, Crohn's disease; Subq, subcutaneous; UC, ulcerative colitis.

COMMENTARY

Why Is This Important?

One of the main strengths of this study is that it provides updated outcomes for an established medication. Unlike the original IFX studies that were used to approve IFX for moderate to severe inflammatory bowel disease (IBD) patients,[1,2] this trial uses not only clinical remission but also endoscopic remission and endoscopic response, which are the current and updated standards of practice in evaluating therapy options for IBD patients. Nonetheless, when it comes to patient-oriented outcomes, the results of this study are rather comparable to the early pivotal studies.

The benefit of subq formulations of IFX biosimilars is increased convenience for patients who no longer need to plan

their schedule around timing of intravenous administration of infliximab. Furthermore, subq formulation of IFX is associated with fewer sub-therapeutic serum trough levels of IFX versus IV administration. It's possible that subq administration would produce more consistent therapeutic serologic concentrations of IFX, which could translate to increased efficacy compared to maintenance of IBD remission with IV administration of IFX.

Key Study Findings

These trials demonstrated superiority of subq CT-P13 IFX biosimilar vs placebo for maintenance of remission in both moderately to severely active CD and moderately to severely active UC.

Both studies met their (co-) primary end points and key secondary end points at week 54, and improvements were also seen in additional efficacy and biomarker results. Biweekly dosing of CT-P13 SC was well tolerated, with no new safety signals, and provided consistent serum IFX concentrations.

Caution

This is a placebo-controlled trial, not a head-to-head trial comparing maintenance of IV and subq formulation of the CT-P13 medication. However, the subq formulation has been on the market in Europe since 2020, and there is literature on comparing both formulations for specific outcomes.[3,4] Also, given the spectrum of effective and safe medications for IBD, placebo-controlled trials may be an undue hardship on IBD patients and an active control may be preferable whether the trial is designed as a superiority or non-inferiority trial.

My Practice

Anti-tumor necrosis factor (TNF) medications remain the first-line regimen for a good number of IBD patients. With this new subq formulation being FDA approved, insurers are now starting to cover it, and it will become more available to our patients. In my practice, whenever I am recommending an anti-TNF (when clinically indicated), I go over the different options available, including the subq formulation of new and established medications. The appeal of injectable medications for certain patients are flexibility, ability to travel or work remotely, not being tethered to an infusion center(which proved to increase safety and compliance during the COVID-19 pandemic[5]), among others.

Some potential barriers are inability to maneuver the injection in patients with limited fine motor skills, the need for stable housing to keep the medication refrigerated, and the lack of safety data in some special populations such as pregnant patients.[6,7] I will engage with my patient to help them get to a well-informed decision on their IBD care plan. This study ushers in a new era for one of the most established medications and its biosimilars, while we also have new oral medications competing with

infusions and injectables at various efficacies and safety profiles.

For Future Research

As we have increased the options of IBD medications to our patients with a new formulation of a well-known and well-studied drug, I look forward to additional real-world evidence to validate the efficacy in special populations such as pregnant patients, long-term safety and utilization patterns of this SC formulation from the United States and the world.

Conflict of Interest

Dr. Al Kazzi reports no conflicts of interest.

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

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On-Demand Vonoprazan for Non-Erosive Reflux Disease Symptoms: A New Option

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This summary reviews Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: Efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. *Aliment Pharmacol Ther*. 2023 Nov;58(10):1016-1027 .

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Keywords: vonoprazan, Gastro-esophageal Reflux Disease (GERD), Non-erosive Reflux Disease (NERD)

STRUCTURED ABSTRACT

Question: Is oral vonoprazan 10 mg daily, 20 mg, or 40 mg daily effective "on-demand" in the management of non-erosive reflux disease (NERD)?

Design: Multicenter, blinded, placebo-controlled randomized trial.

Setting: Fifty-four ambulatory sites throughout the United States.

Patients: Adult patients with non-erosive reflux disease with negative endoscopies participated in this study. A negative endoscopy consisted of an absence of reflux-related changes. This included an absence of any grade of erosive esophagitis by the Los Angeles grading system, Barrett's esophageal intestinal metaplasia, or other mucosal abnormalities. The Rome IV classification scheme for disordered gut-brain interaction was used to diagnose patients with functional

heartburn and functional dyspepsia for exclusion; there was no ambulatory reflux monitoring to distinguish between NERD and functional heartburn. Additional exclusion included those with eosinophilic esophagitis, esophageal varices, esophageal stricture, infectious esophagitis, and history of caustic or radiation-related trauma to the esophagus.

Interventions/Exposure: During a 4-week open-label run-in period, all patients were administered vonoprazan 20 mg daily. Afterwards, eligible patients were randomized in 1:1:1:1 fashion to receive vonoprazan 10 mg, 20 mg, 40 mg, or placebo in the 6-week on-demand study period. During the study period, the study agent was taken at the onset of symptoms, with only one dose being eligible for a 24-hour period. Rescue antacid was provided during pre-screening through the on-demand period and for 1-week subsequently during a "safety follow-up" period.

Outcome: The primary outcome was the percentage of heartburn episodes that were completely relieved within 3-hours and without further symptoms for 24-hours after use of study drug, including lack of a need to take rescue antacid. Secondary outcomes included: (1) relief of symptoms within 3-hours, with possible recurrence within 24-hours; (2) the mean number of rescue antacid tablets taken per day; (3) the percent of days that the study drug was taken during the on-demand period; and, (4) the percentage of 24-hour symptom-free days during the on-demand period among other secondary endpoints.

Data Analysis: Intention-to-treat (ITT) analysis was performed. Sample size was calculated assuming that each patient would have 4 evaluable heartburn episodes and that there would be a difference of 15% between each vonoprazan dose and placebo for the primary endpoint. It was assumed that 50 patients (with at least 4 episodes) in each arm would be necessary. A high rate of ineligibility (due to a lack of heartburn episodes) of 60% was posited, resulting in the target of 500 patients needing to be recruited for the run-in period, to achieve 200 subjects (50 participants in each arm). Secondary end point analyses were performed using either Fisher's exact text or a rank-sum test.

Funding: Phathom Pharmaceuticals, Buffalo Grove, IL, manufacturer of vonoprazan.

Results: A total of 1,115 patients were screened for the study, with 458 subjects

enrolled into the run-in period. The cohort was primarily female(64.8%). The majority of screen failures occurred due to not having filled out enough diary entries as well as having had heartburn episodes within the last 7 days of the run-in period. A total of 207 patients were randomized into the 6-week on-demand period, with roughly equal allocation in each of the 4 study arms (all groups with either 51 or 52 participants).

In all 3 doses of vonoprazan (10 mg, 20 mg, and 40 mg), there were significantly more heartburn episodes relieved completely within 3-hours with sustained relief for 24-hours compared to placebo: vonoprazan 10 mg: 56.0%; vonoprazan 20 mg: 60.6%; vonoprazan 40 mg: 70.0%; placebo: 27.3%, $P<0.0001$ (Figure 1). A similar trend was elicited when examining solely for relief within 3-hours (a secondary end point).

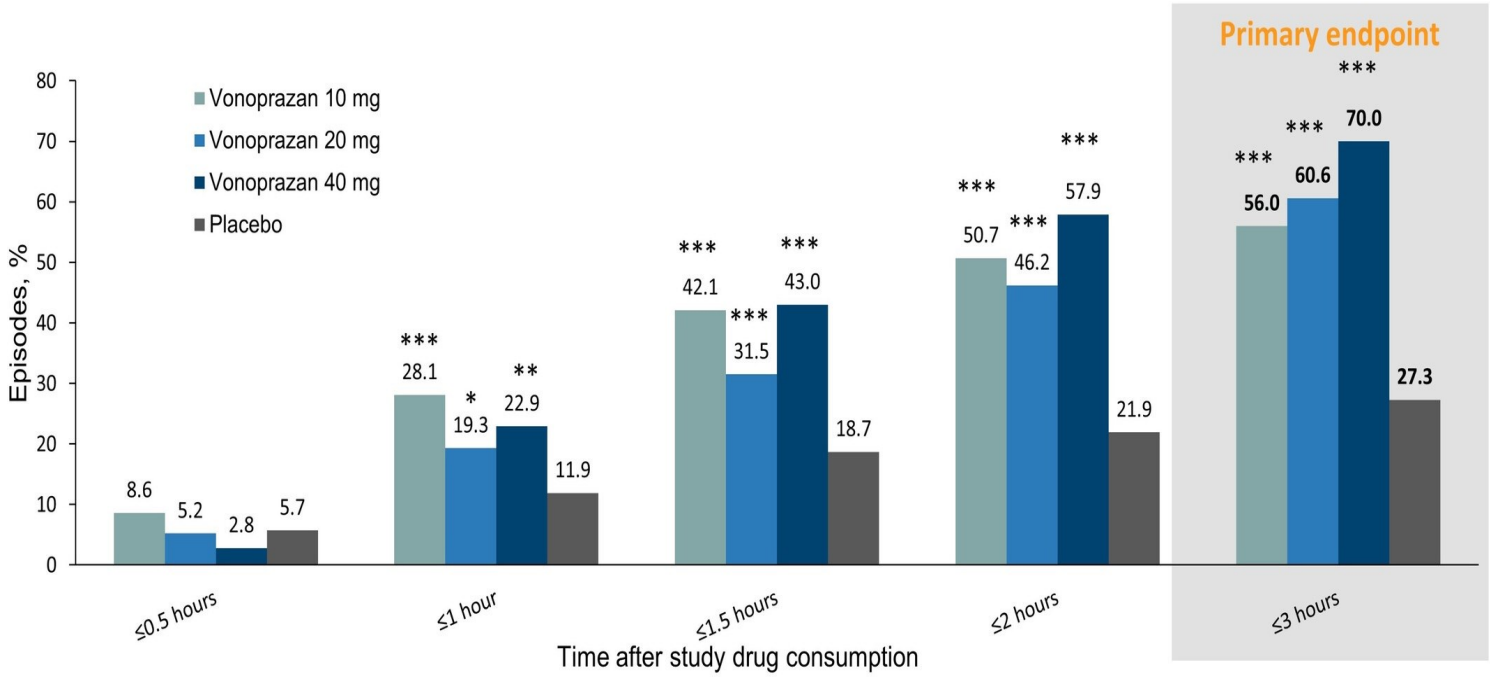

Figure 1. Proportion of heartburn episodes relieved within 3 hrs or less with no further heartburn symptoms in next 24 hours.

COMMENTARY

Why Is This Important?

The family of illnesses termed "gastroesophageal reflux disease" (GERD) includes a range of conditions from erosive esophagitis to non-erosive reflux disease (NERD) to reflux hypersensitivity and functional heartburn. The former 2 conditions are marked by acid-related changes to the esophagus, and the latter 2 disorders are thought to be more representative of a nerve hypersensitivity state, including potentially disordered gut-brain interaction. Recent literature is rich in describing the benefit of potassium competitive acid blockers (PCABs), like vonoprazan, for a variety of foregut conditions, especially since vonoprazan 20 mg has a more rapid onset of action (< 2 hours) and has a longer halflife than standard dose proton pump inhibitor (approximately 8 hours vs 1.5 hours, respectively) while also being approximately 100-fold more potent at acid suppression. Additionally, vonoprazan can be taken with or without food while proton pump inhibitors should be taken on an empty stomach and followed by eating food 30-60 minutes later for optimal efficacy. Therefore, this article expands that paradigm further—it queries for the benefit of on-demand vonoprazan usage for NERD. It demonstrates that such a benefit exists for PCABs.

Most recent acid suppression guidelines for the treatment of GERD- spectrum complaints center on the penultimately developed treatment class, proton pump inhibitors (PPIs). The American College of Gastroenterology's 2022 GERD guidelines[1] recommend an 8-week trial of empiric PPIs and to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs. Vonoprazan adjusts the NERD treatment landscape. For patients who may be hesitant to pursue daily administration of PPIs, it will become increasingly untenable to "force" them to take a daily medication for NERD-spectrum complaints when PCABs exist that are potent suppressors that can be taken as needed.

Key Study Findings

Vonoprazan 10 mg, vonoprazan 20 mg, and vonoprazan 40 mg on-demand dosing was more effective than placebo at improving NERD symptoms within 3-hours of administration as well as within 1 hour or within 2 hours (**Figure 1**).

It resulted in an improvement that was sustained over 24-hours as well. This builds on literature associating PCAB utilization with effective *Helicobacter pylori* treatment, healing of erosive esophagitis, and daily management of NERD.

Caution

As with other studies looking at the use of PCABs to treat GERD-spectrum complaints, the major limitation of this article is the lack of ambulatory reflux monitoring, which is the only modality that differentiates reliably NERD from

reflux hypersensitivity and functional heartburn. While the authors preemptively address this by stating that current diagnostic criteria for NERD do not require such monitoring, it remains an unknown in this study. I question how the authors were able to address functional heartburn in particular, as this was a condition that was excluded from enrollment. Namely, functional heartburn criteria include the presence of "no" symptom relief of heartburn symptoms despite optimal use of acid suppressing therapy. In my clinical practice at least, rarely does someone describe a total lack of symptom relief from acid suppression therapy, but rather a less-than-expected benefit. I suspect that there are a large number of people represented in this study who actually have functional heartburn (possibly those not responding well to vonoprazan administration). This methodologic limitation most likely minimized the documented efficacy of vonoprazan since patients with functional heartburn usually have minimal response to acid suppression medications.

Additionally, there is a discrepancy with evidence-based consensus as to the importance of Los Angeles Grade A esophagitis. The Los Angeles grading scheme has been well accepted for over 20 years[2]. In this study, LA Grade A patients were excluded; Lyon 2.0 consensus generally minimizes the importance of LA Grade A esophagitis in clinical decision making. Namely, Lyon considers only LA Grade B, C, or D esophagitis as evidence of acid-related damage secondary to GERD[3]. In view of the increased role of the Lyon protocol in the management of GERD, it could have been useful to include participants in this study with LA Grade A esophagitis as this would reflect more accurately clinical practice as it relates to reflux esophagitis severity.

My Practice

Based on this trial, I find that my hesitancy towards using vonoprazan centers on the bane of clinicians' existence: cost, formularies, and prior authorization. There is the potential for inequity as well in the use of vonoprazan, as those capable of out-of-pocket payment or with excellent coverage via commercial insurance may more frequently obtain PCAB prescription. That being said, I think the success of vonoprazan has changed permanently the GERD/NERD treatment landscape. With patients at times concerned with the consequences of frequent PPI usage, it will become increasingly untenable to recommend they take a daily medication in the absence of erosive esophagitis if on-demand PCABs are sufficient to control their symptoms. As a neuromotilist, I am prepared for vigorous debate in the foregut disease world, centered on use of the first new class of acid suppressing therapy since omeprazole was approved in the late 1980s.

For Future Research

The yawning gap that has existed in research studies of vonoprazan is the lack of ambulatory reflux monitoring to fur-

ther characterize research cohorts. Generally, study authors have correctly stated that the absence of reflux monitoring reflects normal clinical practice, where access to such technology is uneven. Yet, ambulatory reflux monitoring remains the gold standard that should be employed as it relates to defining the physiologic necessity for acid suppression. Clinically, it still benefits patients long term to receive reflux hypersensitivity or functional heartburn diagnoses (thus avoiding unnecessary pharmacologic treatment). Accurately defining who would benefit from PCABs can best occur through ambulatory reflux monitoring – this is the next best step for vonoprazan-related research.

Conflict of Interest

Dr. Vélez reports no potential conflict of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Suboptimal Adherence to Guidelines When Recommending Timing of Repeat Colonoscopy

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This summary reviews Shapiro JA, Holub JL, Dominitz JA R, et al. Colonoscopy quality measures and adherence to follow-up guidelines among endoscopists participating in a U.S. endoscopy registry. *Gastrointest Endosc*. 2024 Aug 5:S0016-5107(24)03404-7

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Keywords: CRC screening, colon polyp surveillance, colonoscopy

STRUCTURED ABSTRACT

Question: To what extent are endoscopists in the United States meeting performance targets for colonoscopy quality?

Design: Retrospective, cross-sectional study using a national registry database.

Setting: The United States.

Population: Outpatient screening colonoscopies between 2016-2019, in average-risk adults aged 50 to 75 years in the GI Quality Improvement Consortium (GIQuIC) database. Included colonoscopies were performed by an endoscopist with at least 100 colonoscopies in the GIQuIC dataset meeting the inclusion criteria. If a patient had multiple eligible colonoscopies during the study period, only

the first colonoscopy was included.

Interventions/Exposure: To estimate the proportion of patients who received follow-up recommendations consistent with guidelines, patient-level analyses were used. Endoscopist-level analyses were used to identify the proportion of endoscopists with at least 90% adherence to use of guideline-based surveillance intervals. Follow-up intervals issued by the US Multi-Society Task Force (USMSTF) on colorectal cancer (CRC) in 2012 were used to assess endoscopist adherence to recommended intervals.

Outcomes: Colonoscopy quality measures based on targets established by the American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) in 2015, including cecal intubation rate ($\geq$ 95% in CRC screening colonoscopies), adequacy of bowel preparation ($\geq$ 85% in CRC screening colonoscopies), adenoma detection rate (ADR) of $\geq$ 20% in women and $\geq$ 30% of men, and endoscopist's recommended follow-up interval to the next colonoscopy, which included recommending surveillance colonoscopy in 5 years after finding 1-2 small adenomas (as opposed to the 2020 guidance recommending interval of 7-10 years after finding 1-2 small adenomas).

Data Analysis: Descriptive statistics and 95% confidence intervals (CIs) were obtained for all included quality measures. Chi-square tests for heterogeneity were used to compare quality measures by endoscopist specialty, endoscopist sex, and region. Statistical significance was defined as P-value < 0.05. Both patient-level and endoscopist-level analyses of the recommended follow-up interval were performed. Analyses for the other quality measures were performed only at the endoscopist level.

Funding: The Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, provided financial support through a contract with GI Quality Improvement Consortium, Ltd.

Results: This study included 2,588,860 patients/colonoscopies performed by 3,735 endoscopists. Of the patient cohort, 54.7% were ages 50-59 years, 53.5% were female, and 58.6% were White. Most colonoscopies (79.9%) were performed in an ambulatory surgery/endoscopy center. Endoscopists were predominantly male (83.8%), gastroenterologists (88.5%), and located in the southern US (42.0%) or northeastern US (22.3%).

At least 90% of endoscopists met performance targets for cecal intubation rate, adequate bowel preparation, and ADR in male and female patients. ADR of at least 20% for female patients was achieved in 90% of endoscopists, and at least 30% for male patients achieved in 91.2% of endoscopists. ADR was higher among gastroenterologists vs non-gastroenterologists and among female endoscopists vs. male endoscopists.

Adherence to guideline-based surveillance recommendations varied based on colonoscopy/pathology finding. For colonoscopies without any findings, 64.7% (95% CI 62.8%-66.5%) of endoscopists met the target of at least 90% adherence to guideline recommendation, whereas only 14.5% (10.4%-19.8%) of endoscopists met the adherence target after a finding of an advanced adenoma and 14.7% (10.0%-21.0%) of endoscopists met the adherence target after a finding of a sessile serrated polyp <10 mm without dysplasia.

Follow-up intervals shorter than the interval based on guidelines were recommended in 30.7% of colonoscopies with small sessile serrated lesions without dysplasia, 22.9% of colonoscopies with advanced adenomas, and 16.2% of colonoscopies with advanced serrated lesions. For colonoscopies with no findings or colonoscopies with 1-2 small tubular adenomas, the recommended surveillance interval was shorter than the guideline-based recommendation in 12.0% and 13.5% of colonoscopies, respectively. On the other hand, some patients with higher risk findings received a follow-up interval recommendation longer than that recommended in guidelines, including 18.2% of patients with advanced serrated lesions and 6.3% of patients with advanced adenomas.

COMMENTARY

Why Is This Important?

Recently, the ACG/ASGE published new guidelines for quality indicators for colonoscopy, including a goal performance target of at least 90% adherence to appropriate screening/surveillance intervals. [3] This recommendation remains unchanged from the 2015 ACG/ASGE guidelines.[4] Whereas this and other studies have suggested overall good adherence to quality indicators such as ADR, bowel preparation, and cecal intubation rate, adherence to recommended surveillance intervals remains limited. A 2019 systematic review/meta-analysis found adherence to recommended surveillance intervals in 48.8% (95% CI 37.3%-60.4%) of colonoscopies, lower after detection of low-risk lesions (44.7%) compared to high-risk lesions (54.6%).[1]

Adherence to the revised 2020 USMSTF guidelines appears to be similarly limited. In a retrospective analysis of first-time average-risk colonoscopies performed at a tertiary care center from 2021-2022, Dong et al evaluated 532 colonoscopies, finding that overall adherence was 48.9% but varied widely with pathology: 8.3% for low-risk adenomas, 88.3% for high-risk adenomas, and 63.1% for sessile serrated polyps.[2] They did find that adherence to guidelines improved with increasing time from release of the guideline (i.e., later date of colonoscopy), which suggests that increased time for awareness/education about recommendations could potentially improve adherence.

This study by Shapiro et al. highlights the sub-optimal adherence to guideline-based colonoscopy surveillance intervals in the United States. Interestingly, in contrast to some prior studies, this study demonstrates worse adherence in patients with more advanced pathology. Most discordant follow-up intervals after a colonoscopy with advanced pathology were attributed to shorter than recommended follow-up intervals; however, longer than recommended intervals were also noted in these patients, particularly after a finding of an advanced sessile serrated lesion.

This study's strengths include utilization of a large national database from the GIQuIC registry, which represents about one-third of US gastroenterologists. It also included more comprehensive pathology compared to some prior studies, as it includes pathology for both adenomas and sessile serrated polyps.

Key Study Findings

Endoscopist adherence to guideline-based surveillance intervals after screening colonoscopy was low in this study using the GIQuIC database.

Only 15%-65% of endoscopists adhered to guideline-based intervals over 90% of the time depending on pathology results, with 12%-31% of recommendations being shorter than the recommended interval.

Caution

This study included endoscopists within the GIQuIC database. GIQuIC participation is at the discretion of endoscopy centers. Thus, generalizability of these findings to endoscopists not included in the database may be limited, as colonoscopies not captured in GIQuIC may potentially be of lower quality than those included in the database. Nevertheless, over 33% of US gastroenterologists engaged in clinical care actively participate in GIQuIc.

My Practice

At my institution, our recommendation regarding colonoscopy surveillance intervals is delivered using a standardized colonoscopy pathology letter which outlines the number of polyps removed, the pathology of the polyps removed,

and the recommended surveillance interval based on the findings, which includes auto-populated options based on intervals from the USMSTF guidelines. This letter is sent to the patient and his/her primary care doctor. I find this workflow facilitates adherence to guideline-based recommendations as it provides a structure to review pathology findings.

In the future, adherence to guideline-recommended intervals for surveillance colonoscopy may be calculated and reported back to individual endoscopists. This may facilitate improved adherence. Alternatively, artificial intelligence programs have demonstrated $\geq$ 95% adherence to guideline recommendations in pilot studies. If suboptimal adherence to guideline recommendations continue, then this option may get more attention.

For Future Research

Qualitative research to identify the reasons why physicians may vary their recommended surveillance intervals is needed to understand factors contributing to poor adherence to guideline recommendations. In addition, research to identify risk factors for worse adherence to recommended follow-up intervals will be needed to guide interventions to improve adherence to guidelines. Additional research may clarify the role of artificial intelligence programs to automate the process for notifying patients about pathology results and recommended timing of repeat colonoscopy.

Conflicts of Interest

Dr. Zhou reports no potential conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Reintroducing Foods After Completing Restrictive Low FODMAP Diet

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MOTILITY

This summary reviews Van den Houte K, Colomier E, Routhiaux K, et al. Efficacy and findings of a blinded randomized reintroduction phase for the low FODMAP diet in irritable bowel syndrome. *Gastroenterology* 2024; 167: 333-42.

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Keywords: FODMAPs, irritable bowel syndrome, diet

STRUCTURED ABSTRACT

Question: Does reintroduction of specific fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) trigger recurrent or worsening irritable bowel syndrome (IBS) symptoms after completing a 6-week restrictive low FODMAP diet?

Design: Single center, 9-week, blinded, randomized crossover trial.

Setting: Leuven University Hospital, Leuven, Belgium.

Patients: Consecutive adults with IBS based on Rome IV criteria to a specialized tertiary care clinic were eligible. Exclusion criteria included concurrent major organic or psychiatric disorders, antibiotic use in previous 12 weeks, history of substance or alcohol abuse in past 2 years, pregnant or lactating women,

and patients who previously tried low FODMAP diets. Drugs known to impact gastrointestinal symptoms were excluded from use during the trial.

Interventions/Exposure: After a 2-week run-in period to confirm active IBS symptoms, enrolled patients completed a 6-week restrictive low FODMAP diet using the Monash FODMAP calculator and under the direction of a dietician (i.e., elimination phase) and completed the IBS Symptom Severity Score (IBS-SSS) at week zero, 2, 4, and 6. Range of IBS-SSS is 0-500 with IBS-SSS of 75-174 = mild IBS; 175-299 = moderate IBS; and, 300-500 = severe IBS. If study patients experienced at least a 50-point reduction in IBS-SSS from baseline during the elimination phase, then they were considered responders and entered the 9-week, blinded randomized crossover trial with reintroduction of FODMAPs in powdered form.

During the blinded randomized crossover trial, patients continued a low FODMAP diet and also completed 7 separate cycles of reintroducing specific FODMAPs in powder form. Each cycle consisted of dissolving a specified powder in water and drinking it during meals 3x daily for 7 days and then completing their IBS-SSS on day 7. This was followed by a 2-day washout period where patients did not consume any study powder before starting the next cycle.

Patients were randomly assigned to dissolve 1 specific FODMAP powder, labeled A-G, during each 7-day reintroduction cycle. The specific FODMAP powders tested over the 9-week trial were daily doses of 20 grams fructans, 60 grams fructose, 12 grams B-Galacto-Oligosaccharides, 60 grams lactose, 15 grams mannitol, 15 grams sorbitol, or 30 grams glucose, which was considered the control powder.

Outcome: A rise of $\geq$ 50 points in IBS-SSS over the mean score in the elimination phase was defined as a specific FODMAP trigger.

Data Analysis: Wilcoxon Signed Rank Tests for within subject contrasts with data presented as mean +/- standard deviation. No allowance for multiple statistical inference was made.

Funding: Methusalem Grant from Leuven University

Results: Between November 2019 and July 2022, 117 IBS patients (mean age 36, 84% female, mean body mass index 24.5) were recruited with 12 dropping out

during baseline evaluation. Distribution based on IBS subtype was 37% IBS with diarrhea (IBS-D), 40% IBS-mixed (IBS-M), 22% IBS with constipation (IBS-C) with average baseline IBS-SSS of 301 +/- 97. The mean IBS-SSS score decreased significantly from baseline compared to 6 weeks of restrictive low FODMAP diet: 301 +/- 97 vs 150 +/- 116 with a responder rate (≥ 50-point reduction in IBS-SSS compared to baseline) of 80%. Although 94 responders entered the FODMAP re-introduction trial, 17 patients were lost to follow-up due to COVID (n = 4) or due to discontinuing intervention (n=13), leaving 77 patients to evaluate at the end of the 9-week trial.

Symptom recurrence, defined as a rise of ≥ 50 points in IBS-SSS, occurred in 85% of study patients. When assessing mean IBS-SSS scores for the entire group from the elimination phase vs FODMAP reintroduction cycles, mannitol (sugar found in multiple fruits and vegetables, including cauliflower, watermelon, kimchi, mushrooms) and fructans (carbohydrate found in wheat, garlic) powder produced significant increases of approximately 71-73 in mean IBS-SSS. However, during blinded reintroduction, an individualized pattern of symptom recurrence occurred with 2.5 +/- 2 different FODMAPs triggering significant increases in IBS-SSS scores. Again, mannitol and fructans were most likely powders to trigger recurrent symptoms among individual patients (54% and 56%, respectively). Rates of symptom recurrence with reintroduction of other FODMAPs were fructose 27%, B-Galacto-Oligosaccharides 35%, lactose 28%, sorbitol 23%, and control/glucose 26%.

COMMENTARY

Why Is This Important?

Current ACG guidelines[1] recommend a limited trial of a low FODMAP diet in patients with IBS to improve global symptoms. This is because foods high in FODMAPs lead to increased water retention in the colon and increased colonic fermentation by bacteria in the gut, producing increases in short-chain fatty acid production and gaseous colonic distention. Thus, a low FODMAP diet may be particularly helpful for IBS-D patients with predominant bloating symptoms, although it may be helpful for bloating symptoms in all types of IBS patients. Unfortunately, the ACG guideline recommendation on low FODMAP diets is a "Conditional Recommendation, Very Low-Quality Evidence," since there is very limited randomized controlled trial (RCT) data from small studies with inadequate blinding of patients. Furthermore, when recommending a low FODMAP diet, it's important to educate patients that this diet is fairly restrictive and should

only be followed for 4-6 weeks before FODMAP foods are reintroduced in small quantities in order to see which foods trigger symptoms. Randomized trial data on this reintroduction phase has been virtually non-existent prior to the current study by Van den Houte et al.

By using FODMAP powders to facilitate blinding, utilizing a randomized crossover trial design, and by individually testing multiple categories of FODMAPs in the reintroduction cycle, the authors have performed a rigorous study to assess this topic. They should be commended for this great effort, which confirms that IBS patients demonstrate an individualized pattern of FODMAPs triggering recurrent symptoms and identifies specific categories of FODMAPs that are most likely to trigger symptoms.

Key Study Findings

Mannitol, which is a sugar found in multiple fruits and vegetables and may be a food additive in ultra-processed foods, and fructans, a carbohydrate found in wheat, produced significant increases of approximately 71-73 in mean IBS-SSS and were most likely to trigger IBS symptoms among individual patients.

Nevertheless, an individualized pattern of symptom recurrence occurred with 2.5 +/- 2 different FODMAPs triggering significant increases in IBS-SSS scores. This indicates the importance of gradually reintroducing multiple different FODMAP foods to determine the multiple triggers to IBS symptoms after patients complete a restrictive low FODMAP diet.

Caution

This is a small (n = 77) study of patients with severe IBS seen at a single institution in Belgium. Therefore, similar studies in larger groups of patients in more diverse settings are needed before generalizing these results.

My Practice

In my practice, diet modification is a cornerstone of IBS management. Initially, I advise patients to complete a 4-week lactose-free diet, especially if they have IBS-D with predominant bloating symptoms. I also ask them to try and identify specific food triggers while recommending that they greatly reduce their intake of ultra-processed foods and to use a soluble fiber supplement (e.g., 1 tablespoon of psyllium in 8 ounces of water daily). Having said that, many of my IBS patients have already tried and failed these basic diet modifications.

Consistent with ACG guidelines[1], I recommend a trial of a low FODMAP diet for motivated IBS patients, especially if bloating is a predominant symptom, while also emphasizing that a restrictive low FODMAP diet should only be followed for 4-6 weeks. However, I do not simply provide a hand-out with a list of high and low FODMAP foods. Instead, I refer these patients to a dietician to

develop a meal plan for the initial restrictive low FODMAP diet phase, followed by additional dietary counseling to reintroduce small amounts of FODMAPS in order to identify specific food triggers, eventually followed by a final phase of dietary counseling where the patient establishes a long-term diet plan that does not deprive the patient of important nutrients. For patients that are comfortable using phone apps, I prefer the Monash University FODMAP app to facilitate diet planning, although multiple apps are available.

For Future Research

While the authors are to be commended for performing a blinded, crossover trial of reintroducing FODMAPs, RCTs of patients with moderate IBS in more diverse settings are needed. Qualitative research to identify optimal approaches to implementing restrictive low FODMAP diets and the FODMAP reintroduction phase would also be helpful.

Conflict of Interest

Dr. Schoenfeld reports no potential conflicts of interest for this summary.

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