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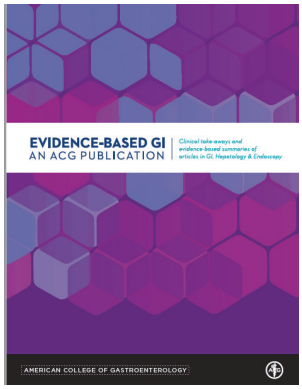

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EBGI Volume 4, Issue 6

June 2024

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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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Tirzepatide Produces NASH Resolution and Decreases Fibrosis: Results from the SYNERGY-NASH Trial

Dr Nicole Rich
Associate Editor

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LIVER

This article reviews Loomba R, Hartman ML, Lawitz EJ. et al. Tirzepatide for metabolic-dysfunction associated steatohepatitis with liver fibrosis. NEJM 2024 Jun 8. Online ahead of print.

Correspondence to Nicole Rich, MD, MSCS. Associate Editor. Email: EBGI@gi.org

Keywords: MASH, MAFLD, fibrosis, tirzepatide

STRUCTURED ABSTRACT

Question: Does tirzepatide, a once weekly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonist, decrease fibrosis in and resolve metabolic-dysfunction associated steatohepatitis (MASH)?

Design: Phase 2 multicenter, dose-finding, double-blind, placebo-controlled, randomized controlled trial (RCT).

Setting: One hundred and thirty sites across 10 countries (Belgium, France, Israel, Italy, Japan, Mexico, Poland, Spain, United Kingdom, United States) between January 2020 and January 2023.

Patients: Adults aged 18 to 80 years, with or without type 2 diabetes, body

mass index (BMI) between 27 and 50 kg/m^2 and biopsy-confirmed MASH. All participants had biopsies at time of screening or no more than 6 months prior to screening and were required to have nonalcoholic fatty liver disease activity score (NAS) $\geq$ 4 and fibrosis stage of F2 or F3. Exclusion criteria included: 1) alcohol consumption $\geq$14 standard drinks weekly for women and $\geq$21 standard drinks weekly for men; 2) HgbA1c > 9.5%; 3) concomitant use of GLP-1 receptor agonists or other medications to promote weight loss; and 4) fibrosis stage F0 (no fibrosis), F1 and F4 (cirrhosis).

Interventions: Participants randomized 1:1:1:1 to 1 of 4 study arms: 1) tirzepatide 5 mg once weekly; 2) tirzepatide 10 mg once weekly; 3) tirzepatide 15 mg once weekly; or 4) placebo once weekly, all administered subcutaneously for 52 weeks. Tirzepatide starting dose was 2.5 mg once weekly and increased by 2.5 mg every 4 weeks until target dose attained (based on assigned study arm).

Outcomes: Primary endpoint was resolution of MASH without worsening of fibrosis (defined as no increase in fibrosis stage) at week 52. MASH resolution was defined as no steatosis (steatosis score of 0) or simple steatosis (steatosis score of 1, 2, or 3) without steatohepatitis and lobular inflammation score of 0 or 1 and ballooning score of 0. Outcomes were assessed by central, independent review by 2 pathologists. Key secondary endpoints included: 1) decrease of at least 1 fibrosis stage without worsening of MASH (i.e., no increase in NAFLD activity score); 2) decrease in NAFLD activity score by at least 2 points with reduction of at least 1 point in each of 2 NAFLD activity score components (steatosis, lobular inflammation, hepatocyte ballooning); 3) changes in liver fat content assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF); and 4) changes in body weight.

Data Analysis: Intention-to-treat analysis, with missing values imputed assuming they would follow the pattern of results in the placebo group.

Funding: Eli Lilly, manufacturer of tirzepatide.

Results: Among 190 participants randomized (mean age 54.4 years, 86% White, 12% Asian, 36% Hispanic ethnicity), 165 completed the trial and 157 had end-of-treatment biopsies that could be evaluated at week 52. Mean body mass index was 36.1, 52% had type 2 diabetes, mean NAFLD activity score was 5.3, and fibrosis stage was F2 in 43% and F3 in 57% at enrollment.

Target tirzepatide dose was achieved with dose escalation among 96%, 96% and 85% in the 5-mg, 10-mg, and 15-mg groups, respectively. Dose reduction was later required in 0%, 20%, and 3% in the 5 mg, 10 mg, and 15 mg groups, respectively.

At week 52, MASH resolution without worsening fibrosis was achieved in 44% of participants in the tirzepatide 5 mg arm, 56% in the tirzepatide 10 mg arm and 62% in the tirzepatide 15 mg arm compared to 10% in the placebo arm ($P < 0.001$ for all comparisons).

Regarding the secondary endpoint of improvement by at least 1 fibrosis stage without worsening of MASH, this occurred in 55%, 51% and 51% of participants in the tirzepatide 5 mg, 10 mg, and 15 mg arms, respectively, compared to 30% in the placebo arm.

At week 52, mean percentage change in body weight compared to baseline was -10.7%, -13.3%, and -15.6% in the 5 mg, 10 mg, and 15 mg tirzepatide arms compared to -0.8% in the placebo arm. Larger decreases in aminotransferases (AST, ALT) and noninvasive assessments of liver fat, inflammation, and fibrosis were also observed in the tirzepatide arms at week 52 compared to placebo.

Adverse events (AEs) were common in both the tirzepatide (92%) and placebo (83%) arms. In the tirzepatide arms, the most common AEs were gastrointestinal events (nausea, diarrhea, decreased appetite, with 96% being mild to moderate in severity). Serious AEs occurred in 6% of participants in the tirzepatide arms and 6% in the placebo arm. Ultimately, AEs led to trial discontinuation in 4% of participants in the tirzepatide arms and 4% in the placebo arm.

COMMENTARY

Why Is This Important?

GLP-1 receptor agonists (GLP-1 RAs) have revolutionized the management of patients with obesity and type 2 diabetes, with beneficial effects beyond weight reduction and improved glycemic control, including better control of hypertension, improvements in metabolic profile, improved outcomes in patients with obstructive sleep apnea, and overall reduction in cardiovascular risk.[1-4] Weight loss (by lifestyle changes, diet modification, and bariatric surgery) has well-documented benefits in MASH, and until recently,[5] no drugs had been proven effective in phase 3 trials to improve MASH. Early placebo-controlled randomized controlled trials (RCTs) of GLP-1RAs conducted in patients with obesity and type 2 diabetes

suggested beneficial effects on the liver, including improvements in liver biochemistries suggesting reduction in inflammation. Further, the addition of GIP receptor agonism to GLP-1 receptor agonism, as in tirzepatide, has direct effects on white adipose tissue (beyond weight loss alone) also believed to be beneficial in MASH. The SYNERGY-NASH trial included additional histologic assessments to demonstrate the efficacy of tirzepatide for MASH improvement without worsening of fibrosis compared to placebo, an endpoint endorsed by the Food and Drug Administration.

Key Study Findings

Among patients with biopsy-proven MASH and liver fibrosis (F2 or F3), all three doses of tirzepatide (5 mg, 10 mg, and 15 mg doses administered once weekly) were superior to placebo with regard to MASH resolution without worsening of fibrosis.

Tirzepatide use was also associated with improvements in body weight, liver biochemistries, and noninvasive assessments of liver fat, inflammation and fibrosis. Overall, tirzepatide appears to be safe and well-tolerated, with the most common adverse events being gastrointestinal; serious events and adverse events leading to trial discontinuation were similar across the 4 study arms, including the placebo arm.

Caution

It is hypothesized that MASH resolution may result in regression of fibrosis, which is the most important predictor of major adverse liver outcomes (MALO),[6] defined as the development of hepatic decompensation (ascites, overt hepatic encephalopathy, variceal bleeding), liver transplantation or liver-related death.[7] One limitation of the SYNERGY-NASH trial (as well as other recently published phase 2-3 RCTs in MASH[5, 8]), is the trial duration was not long enough to assess the effect of tirzepatide on MALO. Further, given the study's relatively small sample size (N=190), there was insufficient power to detect differences in fibrosis improvement with tirzepatide compared to placebo. The authors of the trial acknowledge that fibrosis improvement will likely require more than 52 weeks of therapy. Further, it is unknown whether there is a "celling" of fibrosis regression that can be achieved with GLP-1RAs (or weight loss alone). Lastly, the study excluded patients that have progressed to cirrhosis (F4) and those that have yet to develop fibrosis (F0) or have earlier stages of fibrosis (F1). Thus, it remains unclear whether tirzepatide will benefit this broader population.

My Practice

Since I'm not an obesity specialist, I'm relying on commentary from one of *Evidence-Based GI's* former Associate Editors, Sonali Paul, MD, who is certified in obesity medicine as well as being a hepatologist who specializes in treating MASH and uses tirzepatide in her practice.[9] Dr. Paul has noted that the results of these studies are helpful to quote when educating her patients about the potential benefits of tirzepatide for

MASH/MAFLD, although she primarily uses tirzepatide in patients with concurrent obesity or Type II DM. Dr. Paul previously noted that insurance coverage for GLP-1 RAs can be an issue, but this has been improving.

Again, per prior commentaries in Evidence-Based GI,[9] gastroenterologists should be prepared to get referrals for patients experiencing GI side effects on GLP-1 receptor agonists. Per Dr. Paul, a common problem is increasing the dose of GLP-1 RAs too quickly. When she prescribes agents like tirzepatide, she usually increases the dose gradually in 2.5 mg increments every 4 weeks based on tolerability. Therefore, if clinically important nausea develops, then revert to a lower dose as opposed to starting an anti-nausea agent or simply discontinuing the medication totally. Remember-continued treatment will be required to maintain weight loss in most patients since obesity is a chronic disease. If patients develop mild constipation, then treatment with an osmotic laxative without lowering the dose is acceptable.

For Future Research

Studies with longer duration and larger sample sizes are needed to further clarify the efficacy of tirzepatide (and other agents under investigation for MASLD) on fibrosis regression and risk reduction of major adverse liver outcomes (MALO). Additionally, future studies will be needed to assess efficacy and safety of tirzepatide in patients that have already developed cirrhosis. Given high prevalence of MASLD in the US, ongoing efforts to screen and define the at-risk population for MALO and identify those most likely to benefit from long-term MASH therapy remains of critical importance.

Conflict of Interest

Dr. Rich has served as consultant or on advisory boards for AstraZeneca, Eisai, Exelixis and Genentech, unrelated to the present work.

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

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Rohit Loomba, MD

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Oral Vonoprazan for Prevention of High-Risk Peptic Ulcer Rebleeding: A Better Alternative Than IV PPIs?

Dr Philip Schoenfeld
Editor-in-Chief

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This summary reviews Geeratragool T, Kaosombatwattana U, Boonchote A, et al. Comparison of vonoprazan vs intravenous proton pump inhibitor for prevention of high-risk peptic ulcers rebleeding after successful endoscopic hemostasis: a multicenter randomized noninferiority trial. Gastroenterology 2024; In Press. https://doi.org/10.1053/j.gastro.2024.03.036

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Keywords: vonoprazan, pantoprazole, peptic ulcer bleeding

STRUCTURED ABSTRACT

Question: Is vonoprazan 20 mg oral twice per day (bid) non-inferior to intravenous (IV) pantoprazole 8 mg per hour to reduce recurrent peptic ulcer bleeding in high-risk patients after achieving endoscopic hemostasis?

Design: A multicenter, unblinded, non-inferiority, randomized trial.

Setting: Three university teaching hospitals and 3 community hospitals in Thailand.

Patients: Adult patients presenting with nonvariceal upper gastrointestinal (GI) bleeding were screened and recruited. All patients were initially treated with IV bolus of 80 mg pantoprazole followed by continuous infusion of IV pantopra-

zole 8 mg per hour prior to upper endoscopy. Patients found to have pulsatile ulcer bleeding (Forrest Ia), oozing from a visible vessel in ulcer (Forrest Ib) or a non-bleeding visible vessel in ulcer (Forrest IIa) underwent endoscopic hemostasis with combinations of hemoclipping, thermal therapy with bipolar probe coaptation or argon plasma coagulation with or without injections of adrenaline at the discretion of the endoscopist. Individuals with adherent clot over peptic ulcer (Forrest IIb) had the clot vigorously irrigated or removed with forceps or cold snare and then reclassified prior to endoscopic hemostasis. If clot could not be removed, then patient remained in the study.

Exclusion criteria included in-hospital upper GI bleeding, advanced malignant disease, pregnancy, history of upper GI bleed in past month, or concurrent source of upper GI bleeding (e.g., Mallory-Weiss tear).

Interventions/Exposure: After endoscopic hemostasis was achieved, patients were randomized to receive oral vonoprazan 20 mg bid for 3 days and then continued for 28 days at 20 mg vonoprazan daily vs continued IV pantoprazole at 8 mg per hour for 72 hours, and then converted to oral omeprazole 20 mg bid for 28 days.

Randomization performed based on computer-generated 1:1 block of 4 randomization without stratification. Concealment of allocation maintained by using sealed, opaque, consecutively numbered envelopes with treatment assignment. Study was unblinded.

Outcome: The primary outcome was the 30-day re-bleeding rate while 3-day re-bleeding rate and 7-day re-bleeding rate were secondary outcomes. Confirmation of re-bleeding first required presence of fresh hematemesis > 200 ml or fresh hematochezia/melena after stool color had normalized plus hypotension (systolic blood pressure < 90 mm Hg) or tachycardia (heart rate > 100 beats per minute) with melena or decrease in hemoglobin by > 2 gm/dl with melena. If these findings were present, then a repeat upper endoscopy was required to confirm re-bleeding with endoscopic findings of active bleeding from Forrest Ia or Forrest Ib peptic ulcer or Forrest IIb peptic ulcer with blood or blood clots in the stomach or duodenum.

Data Analysis: Intention-to-treat (ITT) analysis and per protocol analysis was performed. ITT analysis also used to calculate Kaplan-Meier curves for time-to-event

analysis. Sample size was calculated assuming that the re-bleeding rate during first 3 days of IV pantoprazole use would be 7.7% and would be 6.4% during remaining days of oral omeprazole use and that rates of re-bleeding would be similar among the oral vonoprazan group and the oral omeprazole group. A margin within 10% via the Farrington and Manning Test would confirm non-inferiority.

Funding: Siriraj Research and Development Fund, Faculty of Medicine Siriraj Hospital, Mahidol University, and the Gastroenterological Association of Thailand.

Results: Between September 2021 and March 2023, over 1,600 individuals with acute upper GI bleeding were screened, and 214 had lesions at high-risk for peptic ulcer re-bleeding (Forrest Ia, Ib, IIa, IIb). Twenty of these patients were excluded due to inability to achieve endoscopic hemostasis, multiple organ failure, or concomitant upper GI bleeding from another cause. Among the 194 study patients that were randomized and included for analysis (vonoprazan group = 98 and IV pantoprazole group = 96), mean age was 66, male 70%, and endoscopic finding of Forrest 1a (splurting bleeding) =2%-4%, Forrest 1b (oozing bleeding) = 10%-12.5%, Forrest IIa (non-bleeding visible vessel) = 85%-78%, and Forrest IIb (adherent clot) = 3%-5%. Most common interventions for endoscopic hemostasis were adrenaline injection with bipolar gold probe coaptation (74%) and adrenaline injection plus hemoclip (17%).

The 3-day, 7-day, and 30-day re-bleeding rates with oral vonoprazan were numerically lower and non-inferior to IV pantoprazole (**Table 1**). In sub-group analysis, the 30-day re-bleeding rates were not found to be significantly different when classified by Forrest classification, aspirin use, study site, or Charlson comorbidity index. Among peptic ulcers that re-bled in both groups, most were large Forrest IIa (non-bleeding visible vessel) ulcers located in the duodenal bulb. In the Kaplan-Meier analysis, time to re-bleeding event was numerically lower with oral vonoprazan vs IV pantoprazole, although this was not statistically significant:

Re-bleeding rates	Vonoprazan oral	Intravenous pantoprazole
Day 3	3.1% (3/98)	6.3% (6/96)
Day 7	5.1% (5/98)	8.3% (8/96)
Day 30	7.1% (7/98)	10.4% (10/96)

Table 1. Re-bleeding rates at day 3, 7, and 30.

COMMENTARY

Why Is This Important?

Current standard of care for patients with upper GI bleeding is to provide high-dose proton pump inhibitors (PPIs), usually as an IV bolus of 80 mg IV pantoprazole followed by a continuous infusion of 8 mg per hour pantoprazole. This is largely because in vitro studies demonstrated that clot-lysis by pepsin could be minimized if the gastric pH >4. Furthermore, in vitro studies demonstrate that platelet aggregation is enhanced when gastric pH approaches 7.[1-3] This laboratory finding led to the use of oral and IV PPIs to reduce recurrent peptic ulcer bleeding by stabilizing clots, especially after endoscopic hemostasis of high-risk ulcers,[1-2] and multiple double-blind, placebo-controlled randomized controlled trials (RCTs) confirmed the benefit of PPIs. However, guideline recommendations provide some nuances about dosing and administration of PPIs for this indication.

Current ACG guidelines[1] recommend high-dose PPI therapy be given continuously or intermittently for 3 days after successful endoscopic hemostatic therapy of a bleeding ulcer (Strong Recommendation, Moderate to High-Quality Evidence) but the authors note that there is not a recommendation for or against for pre-endoscopic PPI therapy for patients with upper GI bleeding. In other words, there is insufficient RCT data to demonstrate benefits of starting PPI therapy when a patient initially presents upper GI bleeding. This is understandable because this initial treatment would only benefit Forrest IIb ulcers (ulcer with adherent clot). Also, although increasing gastric pH with PPIs is beneficial AFTER endoscopic hemostasis (probably by maintaining clot integrity over the ulcer) based on RCT data, the ACG guideline does not clearly recommend IV vs oral administration of PPIs or IV continuous vs intermittent dosing. That's because different RCTs have used different dosing and administration protocols, laboratory studies produce varying results about how high gastric pH can be raised by different oral and IV regimens of PPIs, and also because we're not sure if it's crucial to raise gastric pH to 7, which facilitates platelet aggregation and clot integrity or if we simply need to raise gastric pH >4 to minimize clot lysis by pepsin.[1,3]

Vonoprazan, a potassium-competitive acid blocker which was marketed for erosive esophagitis and *Helicobacter pylori* infection in 2024, may offer an alternative to PPIs for reducing recurrent peptic ulcer bleeding. In randomized crossover studies of 20 mg vonoprazan daily vs 30 mg lansoprazole daily,[4] vonoprazan demonstrated significantly longer half-life (7.9 hours vs 1.5 hours), increased time with gastric pH >4 on day 1 (62.4% vs 22.6%), improvement in gastric acid suppression within 2.5 hours, and was over 100x more potent at acid suppression than

lansoprazole with a mean gastric pH = 5.9 by day 7. Thus, it seems likely that vonoprazan bid would be non-inferior or even superior to IV pantoprazole in high-risk peptic ulcer patients.

Key Study Findings

The 3-day (3.1% vs 6.3%), 7-day (5.1% vs 8.3%), and 30-day re-bleeding rates (7.1% vs 10.4%) with oral vonoprazan were numerically lower and non-inferior to IV pantoprazole (**Table 1**).

Caution

Since the study was unblinded, investigators could be biased in their interpretation of subjective outcomes (e.g., hematemesis or residual blood in stomach). Also, this was designed as a non-inferiority trial, so the sample size is inadequate to determine if oral vonoprazan could be superior to IV pantoprazole. Finally, since much of this study was conducted during the COVID-19 pandemic, median time to endoscopy after initial presentation was longer than originally anticipated: 27 hours (interquartile range: 18-49). This probably led to fewer ulcers being classified as Forrest Ia or Ib and more being classified as Forrest IIa (non-bleeding visible vessel).

My Practice

Based on this RCT, data about the impact of vonoprazan vs proton pump inhibitors on gastric pH[4], and the reduced cost associated with using oral vonoprazan bid vs a continuous intravenous infusion of pantoprazole, I am planning to start using vonoprazan for patients with bleeding peptic ulcers after endoscopic hemostasis.

Based on our current hospital protocols, we initially treat patients with upper GI bleeding with an IV bolus of 80 mg pantoprazole followed by a continuous infusion of 8 mg per hour. This study does not address whether oral vonoprazan could be substituted here, so I may wait for additional data before making further changes.

For Future Research

Larger comparative RCTs with appropriate blinding are needed to determine if oral vonoprazan is superior to IV pantoprazole for reducing recurrent peptic ulcer bleeding after endoscopic hemostasis. Smaller randomized crossover trials that compare gastric pH when patients are treated with vonoprazan 20 mg bid vs intravenous pantoprazole would also be helpful.

Conflict of Interest

Dr. Schoenfeld reports serving as an advisory board member and speaker bureau member for Phathom Pharmaceuticals, manufacturer of vonoprazan.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Long-Term Efficacy and Safety of Ustekinumab for Ulcerative Colitis: 4-Year Data from the UNIFI Long-Term Maintenance Study

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IBD

This summary reviews Afif W, Arasaradnam RP, Abreu MT, et al. Efficacy and safety of ustekinumab for ulcerative colitis through 4 years: final results of the UNIFI long-term maintenance study. Am J Gastroenterol 2024;119(5):910-921.

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Keywords: Ustekinumab, ulcerative colitis

STRUCTURED ABSTRACT

Question: What is the long-term (4-year) efficacy and safety of ustekinumab for ulcerative colitis (UC)?

Design: This was a long-term extension of the UNIFI randomized controlled trial comparing ustekinumab to placebo for induction of remission and maintenance of remission of ulcerative colitis. Those who responded to ustekinumab induction and completed 44 weeks of ustekinumab maintenance therapy were eligible for the long-term extension. Patients were followed through week 200, at which time endoscopic assessment was performed.

Setting: The original UNIFI trial enrolled patients from 24 countries.[1]

Patients: Three hundred and forty-eight UC patients were randomized to ustekinumab, 90mg subcutaneous (subq) every 8 weeks (q8wks) or 90mg subq every 12

weeks (q12wks), during the UNIFI maintenance of remission stage and completed 44 weeks of maintenance therapy were included.

Interventions: Ustekinumab 90 mg subq q12wks (n=172) or 90 mg subq q8wks (n=176). Beginning at week 56 (after 12 week of induction therapy and 44 weeks of maintenance of remission therapy), patients in the q12wks group could undergo dose optimization to receive ustekinumab 90 mg q8wks.

Outcomes: Multiple outcomes were assessed including symptomatic remission (Mayo stool frequency score 0 or 1 and rectal bleeding score of 0), corticosteroid-free symptomatic remission, full Mayo clinical remission (Mayo score $\leq$2), full Mayo clinical response (decrease in score by $\geq$30% or $\geq$3 points), modified Mayo score response (no physician global assessment subscore), and endoscopic improvement, among others. Adverse events and immunogenicity were also assessed.

Data Analysis: Symptomatic remission was evaluated using non-responder imputation for missing data and treatment failure, observed cases analysis, and modified observed case analysis. Safety events were evaluated using event rates per 100 person-years.

Funding: The study was funded by Janssen Research & Development, LLC.

Results: Of 348 study patients, 55.2% achieved symptomatic remission at week 200. Among these, 96.4% were in corticosteroid-free symptomatic remission. Of 171 patients who completed endoscopic evaluations at week 200, approximately 70% in both groups had clinical remission and approximately 80% in both groups had endoscopic improvement (**Figure 1**). The full Mayo score outcomes at week 200 are presented in Figure 1.

The most frequently observed adverse events included nasopharyngitis, worsening of ulcerative colitis, and upper respiratory tract infections. No deaths, major cardiovascular events, or tuberculosis infection were observed. Four patients did develop opportunistic infections with cytomegalovirus (n=2), oral herpes, (n=1) and *Listeria monocytogenes* (n = 1). Approximately 5.5% of patients developed anti-drug antibodies, but this did not appear to affect treatment efficacy.

COMMENTARY

Why Is This Important?

Ustekinumab, which is directed at the p40 subunit shared by interleukin (IL)-12 and IL-23, was the first IL-23 monoclonal antibody approved for the treatment of UC in the US, and is also approved for treatment of adults and pediatric patients with psoriatic arthritis and plaque psoriasis. Data about the long-term durability, efficacy, and safety of this drug class in the UC population was limited, and performance of endoscopy

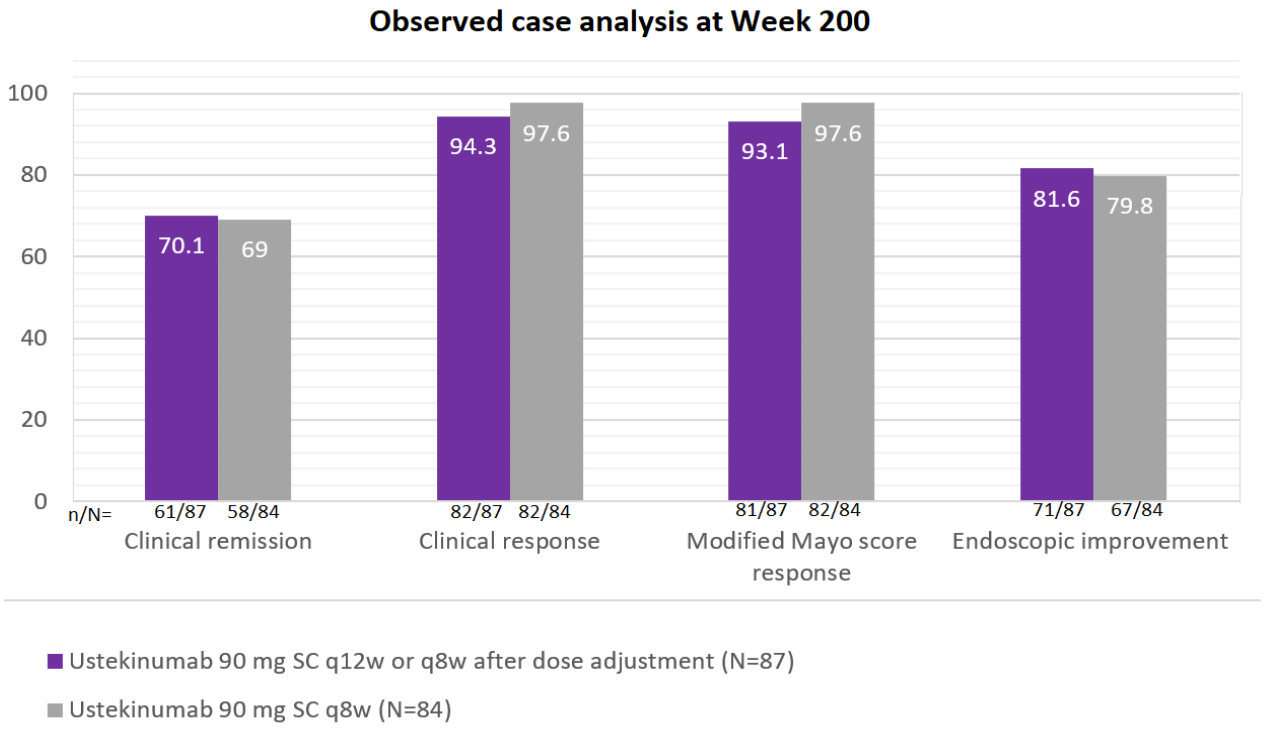

Figure 1. Full Mayo score outcomes at week 200. q8wks, every 8 weeks q12wks; every 12 weeks; SC, subcutaneous.

at week 200 enhanced the assessment of efficacy. The UNIFI long-term extension study confirms that ustekinumab is effective in maintaining both steroid-free clinical remission as well as endoscopic response through 4 years of treatment in UC patients.

Importantly, adverse event data over 4 years in the UC population were similar to long-term safety data in the psoriatic arthritis and plaque psoriasis populations. Specifically, minimal opportunistic infections with CMV were observed with no cases of tuberculosis, no major cardiovascular events, and no increase in nonmelanoma skin carcinomas compared to UC patients treated with placebo. Finally, immunogenicity/ development of antibodies to ustekinumab was uncommon (5.5%) and reportedly did not impact treatment efficacy.

Key Study Findings

Among UC patients who achieved induction of remission and maintenance of remission after 52 weeks of therapy, ustekinumab remained effective in maintaining symptomatic remission (55%), full Mayo clinical remission (70%), and endoscopic improvement (81%) at week 200.

Outcomes were overall similar between q8wks and q12wks dosing. Long-term safety events were consistent with the known safety profile of ustekinumab in other disease states and immunogenicity was overall uncommon (5%) and inconsequential.

Caution

After 1 year, patients were unblinded and placebo was discontinued. There-

fore, the observations of this study do not reflect a comparison to a control group. Additionally, endoscopic assessments were not available for all patients and were not centrally read, so these assessments may suffer from inter-reader variability. The study is also not adequately powered to compare q8w vs q12w dosing regimens, and further dose optimized regimens (every 4 weeks or every 6 weeks) were not assessed.

My Practice

In my practice, I commonly prescribe ustekinumab to both bio-naïve and bio-experienced patients with moderate-to-severe UC. The long-term data presented in this study demonstrate that those who respond to ustekinumab IV induction often maintain clinical remission through 4 years of treatment. These findings allow me to provide reassurance when counseling my patients regarding the efficacy, safety, and durability of this treatment option, particularly for individuals who are hesitant to initiate a biologic therapy. I also commonly dose optimize ustekinumab empirically to every 4 weeks or every 6 weeks after loss of clinical response to q8w dosing, as this has been shown in real-world studies to be effective in recapturing response.[2-3]

For Future Research

Long-term studies are needed to investigate the efficacy and safety of further dose-optimized regimens of ustekinumab, including every 4 weeks and every 6 weeks regimens. Randomized trials comparing the efficacy of ustekinumab to other advanced therapies for UC are also needed.

Conflict of Interest

Dr. Dalal has research grant support from Janssen and Pfizer and has served as a consultant for Janssen, Takeda, and Centaur Labs.

Note: The authors of this AJG 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

Do Not Extend Interval Between CRC Screening Colonoscopies from 10 to 15 Years: Perils of Administrative Databases

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This summary reviews Liang Q, Mukama T, Sundquist K, et al. Longer interval between first colonoscopy with negative findings for colorectal cancer and repeat colonoscopy. JAMA Oncol 2024 May 2:e240827.

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Keywords: colonoscopy; colon cancer; case-control study

STRUCTURED ABSTRACT

Question: After a negative colonoscopy, is the risk of colorectal cancer (CRC) reduced for longer than 10 years compared to controls who don't get colonoscopy?

Design: Retrospective case-control study using nationwide health and administrative databases.

Setting: Sweden.

Patients: Cases were individuals aged 45-69 years old who underwent their first colonoscopy for any indication between 1990-2016 and had no adenomas found during colonoscopy. For each case, up to 18 controls matched for sex, birth year, and baseline age (i.e., follow-up starting at same age when matched case underwent colonoscopy) were identified from Swedish healthcare registries and followed from 1990-2018. Exclusion criteria included family history of CRC and presence of inflammatory bowel disease.

Interventions/Exposure: Colonoscopy with no adenomas or CRC found (i.e.,

negative colonoscopy). Initial indication for colonoscopy was not recorded. Since there was only limited CRC screening with biennial fecal occult blood tests in Sweden starting in 2008, most colonoscopies were likely performed for diagnostic purposes. Data on quality of colonoscopy, including quality of bowel preparation, cecal intubation, and adenoma detection rates (ADR), were not available.

Outcome: CRC incidence and CRC-specific mortality.

Data Analysis: Standardized incidence ratios and standardized mortality ratios after adjustment for multiple potential confounders, including birth year, sex, baseline age at time of colonoscopy, geographic location, and socio-economic status.

Funding: Publication states that funding was obtained by co-investigators Q Liang, K Sundquist, J Sundquist, and M Fallah, but does not state source of funding. Q Liang received grant support from the China Scholarship Council.

Results: The study cohort included 110,074 individuals with negative colonoscopy and 1,981,332 matched controls who did not have colonoscopy recorded in Swedish health databases. Study population was 59% female with median age interquartile range (IQR) of 59 years old (52-64). During up to 29 years of follow-up, CRC occurred in 0.44% of individuals with negative colonoscopy and in 1.1% of individuals without colonoscopy. For CRC-specific mortality, rates were 0.10% and 0.28%, respectively.

At year 15 after negative colonoscopy, the standardized incidence ratio for CRC was 0.72 (95% confidence interval [CI] 0.54-0.94) and standardized mortality ratio for CRC-specific mortality was 0.55 (95% CI 0.29-0.94). At Year 15, the 10-year cumulative risks of CRC and CRC–specific death in the exposed group (negative colonoscopy) were 72% and 55% of the 10-year cumulative risks in the control group, respectively.

Furthermore, the difference in 5-year cumulative incidence rates of CRC between individuals who had a second screening at year 10 negative for CRC (2.9/1,000 individuals) and those who did not have a second screening (5.3/1,000 individuals), showed that 2.4 CRC cases per 1,000 individuals could be missed by extending the screening to 15 years.

COMMENTARY

Why Is This Important?

We're summarizing this study because it was publicized extensively in gastroenterology news services and the lay media. The media emphasized the authors' provocative conclusion that the interval between colonoscopies could be extended to 15 years. This conclusion seems

overly optimistic given study design limitations (see ***Caution*** section). As discussed in prior summaries,[1-2] the methodology of these epidemiologic reports is frequently flawed and usually does not produce conclusions that should change patient care. Instead, these studies are most helpful as hypothesis-generating exercises and may serve as the foundation for design of prospective studies. Unfortunately, it can be confusing for patients and physicians when this type of study is publicized.

Nevertheless, there is growing data that the intervals after negative screening colonoscopies could be extended beyond 10 years.[3-4] Prospectively collected data from Germany indicates that only 5%-6% of individuals have advanced adenomas found on repeat screening colonoscopy performed 10 years after a negative screening colonoscopy and that the incidence remains low for several more years.[3] A recent Canadian population-based cohort study[4] found individuals with a negative colonoscopy were less likely to develop CRC compared to similar controls who didn't get colonoscopy, even if the colonoscopy was performed more than 15 years ago. These findings most likely reflect that individuals with no adenomas found on screening colonoscopy are less than average-risk for developing CRC. Whether due to genetic or environmental factors, individuals with negative colonoscopies seem less likely to develop adenomas than the average individual.

Key Study Findings

At Year 15, the 10-year cumulative risks of CRC and CRC–specific death in the exposed group (negative colonoscopy) were 72% and 55% of the 10-year cumulative risks in the control group, respectively.

Caution

The indication for colonoscopy was not recorded and most individuals probably underwent colonoscopy as a diagnostic test instead of for average-risk CRC screening. More importantly, it's likely that the quality of colonoscopy was sub-optimal. Although no data was recorded about key colonoscopy quality indicators, including cecal intubation rates, frequency of adequate bowel preparation, or adenoma detection rates, data from the NordiCC randomized controlled trial[5] reported an ADR of only 14.4% among Swedish endoscopists in the context of a clinical trial from 2009-2014. Therefore, it's likely that the ADR was poor among the "negative colonoscopy" patients in this study, and the protective effect of colonoscopy would be minimized. In fact, when looking at the unadjusted rates of CRC in the cases and controls, colonoscopy appears to have reduced the risk of CRC by only about 60%.

My Practice

For the reasons outlined above, these data won't change my current practice. After a normal screening colonoscopy, I'll continue to recommend repeat

screening colonoscopy in 10 years, which is consistent with current US clinical practice guidelines. It's worth remembering that the 10-year interval after a negative screening colonoscopy is based largely on our understanding of the adenoma-carcinoma sequence. This stepwise progression of accumulating multiple genetic mutations in the colon is quite slow and estimated to take at least 10 years.[6] If individuals with a negative screening colonoscopy are truly less than average risk for developing adenomas, then we may be able to extend the interval between colonoscopies. However, we need more and better data first. Until we have that data and until guideline recommendations change, I'll continue to educate my patients to come back in 10 years after a negative screening colonoscopy.

For Future Research

Ongoing prospective studies will clarify the risk of extending the interval after normal screening colonoscopies from 10 to 15 years.

Conflict of Interest

Dr. Schoenfeld reports no relevant conflicts of interest.

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