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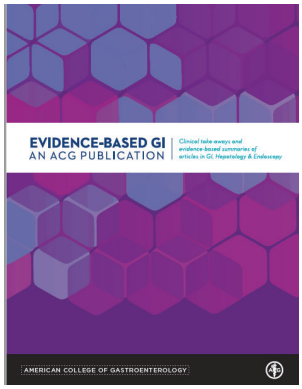

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TABLE OF CONTENTS

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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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Add Pancreatic Duct Stent to Indomethacin to Minimize Post-ERCP Pancreatitis in High-Risk Patients

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

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

PANCREAS

This summary reviews Elmunzer BJ, Foster LD, Serrano J et al. for the SVI Study Group. Indomethacin with or without prophylactic pancreatic stent placement to prevent pancreatitis after ERCP: a randomized trial. Lancet 2024;403: 450-58.

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

STRUCTURED ABSTRACT

Question: Is rectal indomethacin non-inferior to rectal indomethacin plus prophylactic pancreatic duct (PD) stent placement for minimizing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in high-risk patients?

Design: Multi-center, prospective, randomized, non-inferiority trial with masking of patients, treating clinicians, and outcome assessors to intervention. Patients enrolled from September 2015 through January 2023.

Setting: Twenty referral centers for complex ERCP in the US and Canada. Over 100 advanced endoscopists of varying experience participated.

Patients: Adults ≥18 years old who had no indication for PD stent placement except pancreatitis prevention and met 1 or more criteria for increased risk of

post-ERCP pancreatitis. Those criteria included: history of post-ERCP pancreatitis, difficult cannulation (defined as at least 6 cannulation attempts or ≥6-minute duration of cannulation), precut sphincterotomy, pancreatic sphincterotomy, short duration (≤1 min) balloon dilation of an intact biliary sphincter or clinical suspicion of sphincter of Oddi dysfunction. Patients could also be enrolled if they met ≥2 minor criteria: female sex and age <50 years old, history of recurrent pancreatitis, or ≥3 PD injections.

Interventions: Patients were randomly assigned (1:1 ratio) to receive two 50 mg indomethacin suppositories peri-procedurally vs two 50 mg indomethacin suppositories peri-procedurally plus prophylactic PD stent placement. All procedure-related interventions, including technical approach to PD stent placement, were at the discretion of the endoscopist. In order to ensure masking, personnel participating in ERCP were precluded from further study patient care for the first 48 hours after ERCP.

Outcomes: Primary outcome was post-ERCP pancreatitis, defined as new onset or increase of abdominal pain, elevation of pancreatic enzymes ≥3X upper limit of normal 24 hours after ERCP, and hospitalization for at least 2 nights. This validated definition was applied as a diagnostic framework by 3 experts at non-enrolling centers who were blinded to patient allocation, and which required agreement by 2 of 3 adjudicators. The secondary outcome was moderate or severe post-ERCP pancreatitis, which also included assessment of radiographic data.

Data Analysis: Intention-to-treat and per-protocol analyses were reported. Non-inferiority margin was defined as 5%. Hence, if there were <5% increased absolute risk of post-ERCP pancreatitis in the upper bound of the 2-sided 95% confidence interval (CI) for the rectal indomethacin alone group, then it would be considered non-inferior to rectal indomethacin plus prophylactic PD stent placement.

Funding: National Institutes of Health.

Results: Among 1950 randomized patients, 38.7% were male, mean age was 55.7 years, and 83.8% were White. Approximately 26%-27% had suspected sphincter of Oddi dysfunction, 82%-84% had difficult cannulation, and 10%-12% required precut sphincterotomy for access. Prophylactic PD stent placement could not be achieved in 19.3% of patients assigned to that group.

Post-ERCP pancreatitis occurred in significantly more patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 14.9% vs 11.3%; risk difference 3.6%, 95% CI: 0.6-6.6. Since the upper limit of 95% CI for absolute risk difference was greater than 5% (i.e., 6.6%), non-inferiority was not demonstrated. Relative risk difference was 1.32; 95% CI: 1.05-1.66, indicating that high-risk patients had > 30% increased risk of post-ERCP pancreatitis without PD stent placement. Per protocol analysis produced similar findings. Moderate or severe post-ERCP pancreatitis was numerically more frequent for patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 8.0% vs 6.0%; risk difference 2.1%, 95% CI: -0.2 – 4.3 and post-hoc analysis of pancreatitis-related death identified 3 deaths in the rectal indomethacin alone group vs 0 in the rectal indomethacin plus PD stent: risk difference 0.3%; 95% CI: 0.0-0.7.

COMMENTARY

Why Is This Important?

Post-ERCP pancreatitis is a dreaded complication, which occurs in up to 15% of high-risk patients,[1-2] and leads to hospitalization and even death. Pancreatic duct stent placement, which ensures adequate drainage of the pancreas despite possible edema in pancreatic tissue, minimizes post-ERCP pancreatitis. However, it's time consuming, technically difficult, expensive, and requires subsequent abdominal x-rays to ensure spontaneous passage of the stent. If the stent doesn't pass spontaneously, which occurs in up to 20% of patients, then an EGD is required to remove the stent.

In 2012, a landmark RCT demonstrated that rectal administration of NSAID suppositories decreased post-ERCP pancreatitis[3], and rectal indomethacin is now widely used with ERCP. However, this has also been associated with decreased use of prophylactic PD stent placement.[4-5] Nevertheless, the American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend rectal indomethacin PLUS prophylactic PD stent placement for high-risk patients, although Level 1 randomized controlled trial (RCT) evidence to support this was lacking.

With the publication of this seminal RCT, Level 1 evidence supporting this guideline recommendation is now available. This is a particularly elegant study. The investigators did not limit study endoscopists to expert biliary endoscopists at a few high-volume centers. Instead, over 100 advanced endoscopists with varying skill levels and years of experience participated, which enhances generalizability of study results. Masking was enforced by excluding ERCP team personnel from study patient care for 48 hours after ERCP and by having an outside panel of 3 expert endoscopists interpret clinical and laboratory data to determine if post-ERCP pancreatitis

occurred using a standardized definition. Almost 2000 patients were enrolled over 8 years to provide an adequate sample size to assess for non-inferiority. Ultimately, the study demonstrated that rectal indomethacin alone increased the risk of post-ERCP pancreatitis by more than 30% compared to rectal indomethacin plus prophylactic PD stent placement in high-risk patients.

Key Study Findings

Post-ERCP pancreatitis occurred in significantly more patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 14.9% vs 11.3%; risk difference 3.6%, 95% CI: 0.6-6.6.

Caution

PD stent placement procedures were not standardized, including selection of PD stent, and duration and number of attempts at PD stent placement. This is understandable since there is no standard of care to prophylactic PD stent placement. In fact, PD stent placement failed in approximately 20% of patients assigned to this group, but the per-protocol analysis was similar to the ITT analysis. This indicates that failure to successfully place prophylactic PD stents did not increase risk of post-ERCP pancreatitis. Also, approximately 500 study patients underwent ERCP for possible sphincter of Oddi dysfunction (SOD) and SOD manometry is high-risk for post-ERCP pancreatitis. However, the utility of diagnosing and then treating these patients with sphincterotomy is increasingly controversial.

My Practice

Since I am not an interventional endoscopist, I consulted with the lead author of the study, B. Joseph Elmunzer, MD, MSc, about his practices. He performs PD stent placement plus rectal indomethacin in all patients at high-risk for post-ERCP pancreatitis. He also boluses most patients with 2.5-3.0 liters of lactated ringer's (LR) solution intravenously (IV) during the peri-procedural period unless they are elderly and/or have cardio-vascular or pulmonary disease. As Dr. Elmunzer emphasized, this has not yet been demonstrated to minimize post-ERCP pancreatitis in well-designed RCTs.

He gives rectal indomethacin to virtually all ERCP patients to minimize post-ERCP pancreatitis, regardless of risk. However, since the cost of rectal indomethacin has risen precipitously, he may hold it in selected patients at very low risk, such as some patients with prior sphincterotomy who are getting uncomplicated bile duct stent changes.

For Future Research

Optimal approaches to PD stent placement, including type of stent, should be explored and additional preventive treatments, including bolus intravenous lactated Ringer's solution to minimize post-ERCP pancreatitis should be identified.

Conflicts of Interest

Dr. Schoenfeld reports no financial conflicts of interest.

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

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Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study

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This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. Non-erosive gastro-oesophageal reflux disease and incidence of oesophageal adenocarcinoma in three Nordic countries: population based cohort study. BMJ 2023;382:e076017.

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

STRUCTURED ABSTRACT

Question: Are patients with non-erosive gastroesophageal reflux disease (GERD) at an increased risk of developing esophageal adenocarcinoma?

Design: This is a population-based cohort study.

Setting: Hospitalized and specialized outpatient healthcare settings in Denmark, Finland, and Sweden.

Patients: Study included 486,556 adults (>18 years of age) with GERD who underwent upper endoscopy between January 1, 1987, to December 31, 2019. Of this group, 285,811 had non-erosive GERD and 200,745 in the validation cohort had erosive GERD. In the non-erosive GERD group, median interquartile range (IQR) age was 59 (44-70) years and 59% were women. In the erosive GERD group, median (IQR) age was 58 (45-69) years and 45% were women.
Exposure: Non-erosive GERD was defined by an absence of esophagitis and any other esophageal findings at endoscopy. Erosive GERD was defined by the

presence of esophagitis at endoscopy.

Outcome: The incidence rate of esophageal adenocarcinoma was assessed for up to 31 years of follow-up.

Data Analysis: Standardized incidence ratios (SIR) with 95% confidence intervals (CI) of esophageal adenocarcinoma were calculated in the non-erosive GERD, erosive GERD groups, and the general population. Changes in standardized incidence ratios were assessed across 5 periods of follow-up: <1 year, 1-4 years, 5-9 years, 10-14 years, and 15-31 years, and plotted using Poisson regression. Stratified analyses were performed based on age, sex, and calendar period.

Funding: Swedish Research Council (2019-00209), Swedish Cancer Society (180684), and Nordic Cancer Union (186058).

Results: Among 285,811 patients with non-erosive GERD, the incidence rate of esophageal adenocarcinoma was 11 out of 100,000 person-years and was similar to that of the general population (SIR = 1.04; 95% CI: 0.91-1.18) and did not increase with longer (15-31 years) follow-up time (SIR = 1.07; 95% CI: 0.65-1.65). Those with erosive GERD were found to have 2.3 times the expected number of cancers compared to the general population (SIR = 2.36; 95% CI: 2.17-2.57) with increasing risk of progression to esophageal adenocarcinoma with longer follow-up time (SIR = 2.73; 95% CI: 2.15-3.42) **(Figure 1).**

COMMENTARY

Why Is This Important?

GERD is a prevalent chronic condition, which when untreated can lead to complications such as erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma.[1] However, a significant portion of patients with GERD do not develop erosive disease and subsequent clinical sequelae. Prior studies[2] have investigated the risk of developing erosive esophagitis in GERD patients with a normal baseline endoscopy with reported prevalence ranging from 4%-5%. However, no prior study has been able to definitively estimate the incidence of esophageal adenocarcinoma in patients with non-erosive GERD and compare that with healthy controls. In other words, is there an increased risk of esophageal adenocarcinoma in patients with endoscopically-confirmed non-erosive GERD. If they aren't at increased risk, then that infers that additional surveillance EGD is not needed to look for Barrett's esophagus. The authors of this paper aimed to answer this

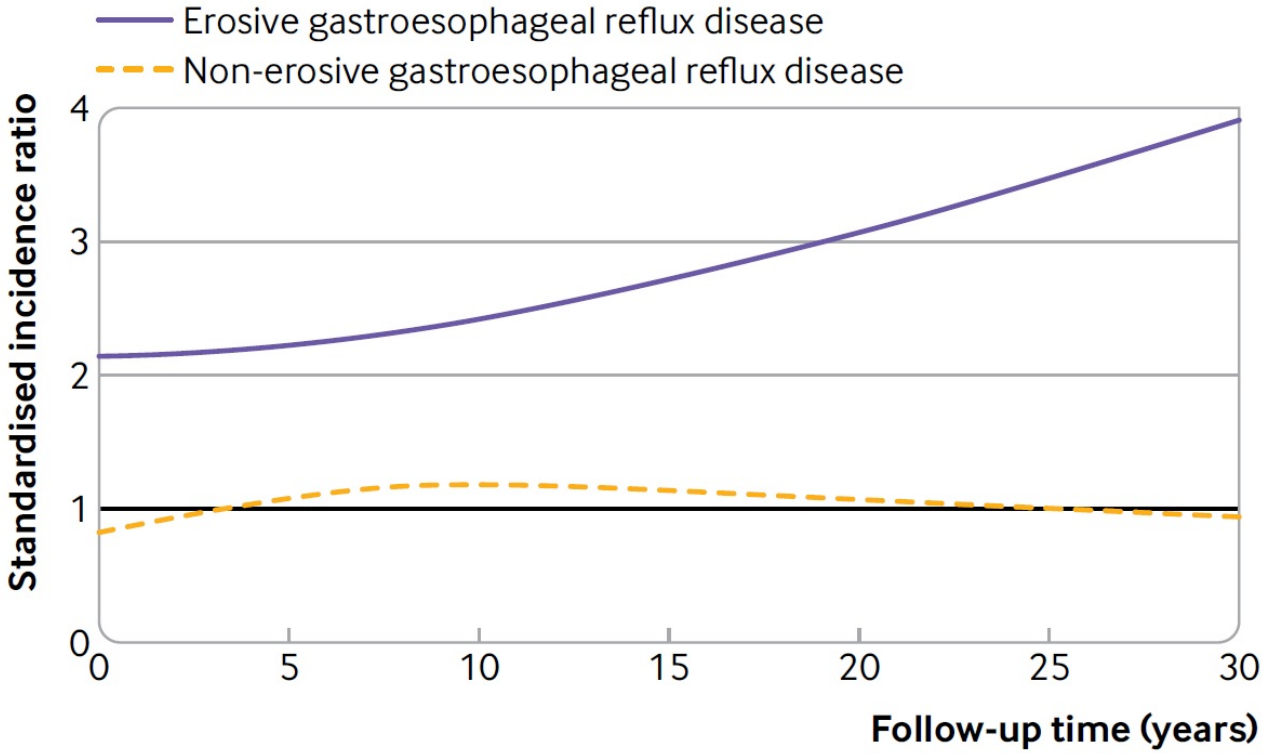

Figure 1. Standardized incidence ratios of oesophageal adenocarcinoma over follow-up time among patients with non-erosive (dashed line) and erosive (solid line) gastrooesophageal reflux disease compared with the general population of the same age, sex, and calendar period. Reproduced from article with permission from BMJ Publishing Group Ltd.

question though a Nordic population-based cohort study with a very large patient population followed for over 30 years.

Key Study Findings

Patients with non-erosive GERD are at similar risk to the general population of developing esophageal adenocarcinoma even after longer follow-up duration (SIR 1.07; 95% CI: 0.65-1.65). GERD patients with erosive disease on endoscopy, as expected, had an increased risk of development of esophageal adenocarcinoma during a comparable follow-up period (SIR 2.73; 95% CI: 2.15-3.42).

Caution

Although this is a well-designed, population-based cohort study in Nordic countries, there are significant methodologic limitations. Firstly, the diagnosis of GERD for the study population was made through a single *International Classification of Diseases* diagnostic code, which is neither sensitive nor specific. While it is likely that the patients in the erosive disease group had definitive pathologic GERD, it is highly plausible that a significant proportion in the non-erosive GERD group did not have pathologic acid reflux disease and likely could have had functional heartburn (i.e., patient complains of GERD symptoms, but does not have abnormal esophageal acid exposure or physiologic acid reflux that is correlated with GERD

symptoms). This is an important delineation as the risk for developing Barrett's esophagus and esophageal adenocarcinoma is not a concern in those with functional heartburn. Second, another major limitation is the lack of clarity regarding use of proton-pump inhibitor (PPI) therapy, especially in the erosive GERD group. Multiple studies[2,3] have shown that PPIs successfully treat erosive esophagitis. If the patients in the non-erosive group were maintained on PPI therapy, they are less likely to develop complications such as cancer. Similarly, if a disproportionate number of patients in the erosive group were not maintained on PPIs, they are more likely to develop complications. One way to address this would have been to adjust for the use of PPI therapy, which would have strengthened the methodology. Finally, there is concern for misclassification bias, with patients who initially had erosive disease that improved with PPI therapy labeled as non-erosive. While patients in the non-erosive group were advised to stop PPIs a few weeks before their EGD, adherence to this is unknown and it is also unclear whether the duration of stopping PPI was sufficient for the reactivation of erosive disease.

My Practice

This study addresses a gap in literature regarding the risk of developing esophageal adenocarcinoma in GERD patients without erosive disease. Ultimately, the results of this study support what we do clinically.[4,5] Specifically, ACG guidelines do not recommend repeat screening upper endoscopies in GERD patients with non-erosive GERD. It also re-affirms that EGD in GERD patients should be performed when they are off PPI for 2-4 weeks in order to assess for erosive esophagitis.

In my practice, I think that the nuanced interplay between true pathologic acid reflux, use of PPI therapy, recurrent symptoms, and disease complications such as Barrett's esophagus, and esophageal adenocarcinoma need to be considered when deciding on optimal management. In patients with suspected GERD and a normal endoscopy, reflux monitoring performed off PPI therapy is most effective to confirm a diagnosis of symptomatic acid reflux.[5] This facilitates adequately optimizing treatment of non-erosive GERD patients from an acid suppressive standpoint, which will help prevent the development of esophagitis and associated disease sequelae.

For Future Research

An optimal future study to answer this specific question would be a prospective cohort with baseline GERD confirmed by pH monitoring and use of standardized PPI therapy protocols.

Conflict of Interest

None to report.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Making Bowel Preparation Palatable: Efficacy of a Novel Sports Drink Flavor-Optimized PEG and Sulfate Bowel Preparation

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Dr Ahmad Abu-Heija
Associate Editor

This summary reviews Bhandari R, Goldstein M, Mishkin DS, et al. Comparison of a novel, flavor-optimized, polyethylene glycol and sulfate bowel preparation with oral sulfate solution in adults undergoing colonoscopy. J Clin Gastroenterol; 2023;57(9):920-927..

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STRUCTURED ABSTRACT

Question: In patients undergoing a colonoscopy, does a flavored polyethylene glycol (PEG) and sulfate solution (FPSS) that is optimized to taste like a sports drink (SUFLAVE; Braintree Laboratories, Braintree, MA) offer better tolerability with similar bowel cleansing to a well-established, US Food and Drug Administration (FDA)-approved, oral sulfate salt (OSS)-based bowel preparation (SUPREP; Braintree Laboratories)?

Design: Investigator-blinded, randomized, controlled, non-inferiority study in outpatients undergoing colonoscopy for routine indications.

Setting: Thirty-two United States study sites with subjects recruited from gastroenterology practices.

Patients: A total of 500 adult subjects were randomized and 450 subjects took the preparation and were included in analysis between July 2020 and February

2021. Mean age was 56.2 years, with 58.8% female, 84.4% White. Indications included screening, polyp surveillance, GI symptoms, and inflammatory bowel disease. Patients with routine endoscopy contraindications (e.g. ileus, GI obstruction), previous significant abdominal surgeries, as well as patients with baseline electrolyte abnormalities were excluded. In addition, patients on laxatives, diuretics, and antihypertensive agents as well as patients with a history of severe renal, liver, or cardiac insufficiency were also excluded.

Intervention: The sports drink flavor-optimized FPSS solution consisted of approximately 3 L administered in a split dose with 1 L consumed the night before the procedure and 1 L again in the morning, 5-8 hours before the procedure along with 16 oz of water with each dose. The comparator group were given the standard OSS bowel preparation in a split dose with total fluid consumed amounting to 2.8 L.

Outcomes: The primary efficacy endpoints included quality of bowel cleansing using a US FDA bowel prep scoring scale which also accounts for the work of endoscopist cleansing during the exam. Cleansing was evaluated globally and segmentally using a 4-point scale, as shown in **Table 1.**

The primary efficacy endpoint was global cleansing. Grades of “good” or “excellent” for global cleansing of the colon were considered successful, while grades of “poor” and “fair” were considered failures. Secondary efficacy endpoints included the number (percentage) of “excellent” preparations (global score), segmental cleansing success, adequacy of cleansing and need for repreparation, adenoma detection rate (ADR), duration of colonoscopy, the volume of intraprocedural water needed to irrigate the colon, and cecal intubation rate. In addition, procedures were recorded and underwent independent blinded central reading by GI reviewers.

Subject acceptance of the prep was evaluated using a questionnaire filled by the patients when they returned for their colonoscopy after finishing the prep. Questionnaire included questions pertaining to difficulty of prep consumption, overall experience with prep comparison of this prep to previous prep, whether or not they would take the same prep again, and their rating of the aftertaste of the prep.

Data Analysis: Intention-to-treat analysis.

Funding: Braintree Laboratories, a part of Sebela Pharmaceuticals.

Results: Both preparations achieved similar global cleansing scores with high rates of cleansing success, 94% for sports drink flavor-optimized FPSS and 94% for standard OSS. This result demonstrated noninferiority between bowel preparation. Both preparations were safe and well-tolerated in the study population with no significant difference in adverse events. As for subject satisfaction, the sports drink flavor-optimized solution of PEG and sulfate solution was rated more favorably than OSS -based prep on multiple measures, including ease of consumption, overall prep experience, as well as taste **(Table 2).** No clinically significant differences in electrolytes were identified from baseline to date of colonoscopy for either group.

Scale	Description
Excellent	• No more than small bits of feces/fluid which can be suctioned easily • Achieves clear visualization of the entire mucosa
Good	• Feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire mucosa
Fair	• Enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa
Poor	• Large amounts of fecal residue and additional bowel prep required

Table 1. Bowel prep scale.

COMMENTARY

Why Is This Important?

An adequate bowel preparation plays an essential role in our ability to provide patients with high-quality colonoscopy. Poor bowel preparation is associated with lower ADR, reduced cecal intubation rate, prolonged procedural time, and increased risks.[1,2] One of the commonly cited reasons for incomplete bowel preparation is the palatability of traditionally marketed bowel preps. Certainly, the classic 4 liter PEG-electrolyte lavage solution (ELS) (GoLytely, Braintree Laboratories, Braintree, MA) is not only large volume, but also has an unpleasant taste. This has led to widespread popularity of using 238 grams PEG-3350 (MiraLax; Bayer USA, Whippany, NJ) plus 64 ounces of a sports drink (Gatorade; Pepsico, Chicago, IL) + bisacodyl tablets. No prescription is required, and the retail cost is usually about $20-$25, while the sports drink flavoring makes it palatable. However, despite real world evidence[3] that this bowel preparation is effective, it is not FDA-approved, is hypo-osmolar, and has been associated with severe hyponatremia.[4]

Therefore, the introduction of an FDA-

	FPSS	OSS	*P*
Overall Success	93.8%	94.2%	<0.001 (non-inferiority)
Grade			
Excellent	46.9%	62.1%	
Good	46.9%	32.1%	
Fair/Poor/Missing	6.2%	5.8%	
Secondary Endpoints			
Cecal intubation rate	99.1%	98.2%	0.366
ADR	34.7%	39.2%	0.261
Procedure duration	15.5 min	15.2 min	0.552
Intraprocedural water	121.7 mL	122.8 mL	0.771
Preference Questionnaire			
Experience consuming prep			
Very Easy + Easy +Tolerable	86.8%	74.3%	0.009
Overall experience			
Excellent + good	74.0%	58.4%	<0.001
Would you request it again?			
Yes	80.2%	69.9%	0.015
Would you refuse?			
Yes	11%	17.7%	<0.001
Pleasant aftertaste of prep			
Very or quite unpleasant	20.7%	45.6%	<0.001
Tastes like a sports-drink			
Agree	57.3%	35.4%	<0.001

Table 2. Primary endpoint: local endoscopist cleansing ratings. Abbreviations: ADR, adenoma detection rate; FPSS, flavored polyethylene glycol and sulfate solution; OSS, oral sulfate salt bowel prep.

approved, effective FPSS bowel preparation that is flavor-optimized to mimic a sports drink is a welcome addition for patients. Ultimately, the best bowel preparation for the patient is one that they tolerate and will consume as instructed. Otherwise, the likelihood of getting a successful colon cleansing diminishes.

Key Study Findings

In this randomized, investigator blinded trial, the sports drink flavor-optimized formulation of FPSS achieved similar bowel cleansing rates, cecal intubation rates, ADR, and procedural time to the

Both treatment arms achieved approximately 94% successful bowel cleansing. This was done while appealing better to patients in terms of the overall experience and after-taste of the prep, with more patients noting that they would request it again as a bowel cleansing solution for future procedures.

Caution

The bowel preparation scale used in this study is different from the Boston Bowel Prep Scale, which assesses cleanliness of each bowel segment after endoscopist washing, suctioning, and cleansing of residual stool and liquid. Another limitation is the generalizability of the ADR as the studied population was a mix of screening and diagnostic procedures.

The most important limitation may be that only average-risk individuals were enrolled while most individuals at high-risk for poor bowel cleansing (e.g., prior abdominal surgery, frequent use of laxatives to treat constipation) were excluded. It's unclear if patients with a past history of poor bowel cleansing could be enrolled. Also, since these are not osmotically-balanced solutions, patients at higher risk of electrolyte abnormalities due to renal, cardiac, or liver dysfunction were not enrolled. This limits generalizability of results.

My Practice

I'm often asked, "Any changes in the bowel prep since my last colonoscopy?" The poor palatability of regularly prescribed bowel preps is one of my patients' most common concerns. This explains why some patients only agree to repeat colonoscopy if they can use the "MiraLax-Gatorade-bisacodyl" bowel prep. Therefore, I've begun to offer this PEG and OSS bowel preparation that is flavor-optimized to mimic a sports drink, especially since it's an FDA-approved alternative that is efficacious and with a known safety profile. Cost is an issue with bowel preparations, so my nurses have downloaded coupons which promise that the patient co-pay for commercially insured patients will be no more than $50 dollars, although this is still more expensive than the over-the-counter costs of the "MiraLax-Gatorade -bisacodyl" prep.

I would not offer this to patients with

multiple risk factors for colonic dysmotility (e.g., history of constipation with laxative use, diabetes mellitus, obesity, ongoing opioid use, etc.) or a history of poor bowel preparation despite adherence to bowel preparation. For these high-risk patients, I usually have patients take 6 liters of PEG-ELS as a split-prep with 4 liters on the day before the colonoscopy and 2 liters on the day of colonoscopy. If they use an osmotic laxative on a daily basis, then I may have them double the dose for 3-4 days before colonoscopy. However, I also note that combining 15 mg bisacodyl on the day before colonoscopy along with 4 liters PEG-ELS as a split-prep is the regimen with the best randomized controlled trial data supporting its efficacy in high-risk patients.[5]

For Future Research

Emphasis on tolerability of bowel preps is definitely a step in the right direction for achieving higher levels of bowel cleansing and as such improving outcomes. More work to evaluate the safety of this bowel preparation in patients with advanced kidney and heart disease would also provide physicians with more bowel prep options to utilize in these high-risk populations.

Conflict of Interest

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

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Continued Treatment With Tirzepatide Is Necessary to Maintain Weight Loss

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Editor-in-Chief

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OBESITY

This summary reviews Aronne LJ, Horn DB, Bays HE, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial. JAMA 2024; 3310: 38-48.

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STRUCTURED ABSTRACT

Question: Is continued treatment with tirzepatide (Zepbound; Eli Lilly, Indianapolis, IN), a glucose-dependent insulinotropic polypeptide (GIP) and glucagon -like peptide-1 (GLP-1) receptor agonist, necessary for maintenance of weight loss?

Design: Thirty-six week, open-label lead-in treatment with tirzepatide, followed by 52-week, randomized, double-blind, placebo-controlled withdrawal trial.

Setting: Seventy sites in Argentina, Brazil, Taiwan, and the United States.

Patients: Eligible patients were: (a) ≥18 years old; (b) obesity defined as body mass index (BMI) ≥30; or, (c) overweight defined as BMI ≥ 27 plus at least 1 weight-related complication (e.g., obstructive sleep apnea, hypertension, dyslipidemia, cardiovascular disease). Key exclusion criteria were diabetes and

prior surgery for obesity.

Intervention: During a 36-week, open-label, treatment lead-in period, study patients were started on tirzepatide 2.5mg subcutaneous (subq) weekly and had their dose increased every 4 weeks until a maximum tolerated dose of 10 mg or 15 mg weekly was achieved. Patients also received nutritional counseling to adhere to a healthy 500 kcal/day diet and lifestyle counseling to achieve ≥150 minutes (2.5 hours) of physical activity per week. Study patients who achieved maximum tolerated dose of 10 mg or 15 mg tirzepatide weekly by week 36 were then randomized 1:1 to continue tirzepatide or receive matching placebo subq injections for 52 weeks.

Outcome: Primary outcome was percent change in body weight from time of randomization (week 36) through end of study at week 88, (52 weeks after randomization). Key secondary endpoints included proportion of patients maintaining ≥80% of weight loss from week 36 to week 88.

Data Analysis: Intention-to-treat analysis using 2-sample t test for primary outcome.

Funding: Eli Lilly, manufacturer of tirzepatide, designed and oversaw the study including data collation and analysis.

Results: Of 783 individuals who started the 36 week, open-label, lead-in treatment period, approximately 7% (n = 53) withdrew due to side effects, while 670 achieved maximum tolerated dose of 15 mg subq weekly (93%) or 10 mg subq weekly (7%). Among the 670 study patients, mean age was 48 years old, 71% female, 80% White, and mean baseline weight was 107 kg/235 pounds with mean BMI of 38.4. During the 36-week, open-label treatment period, study patients achieved mean weight loss of 21%, or approximately 22.5kg/50 pounds.

During the 52-week, randomized withdrawal period (week 36 through week 88), study patients who continued on tirzepatide had an additional mean weight loss of 5.5%, or approximately 6kg/13 pounds. However, study patients randomized to placebo subq injections regained 14.0% of body weight, or approximately 15kg/33 pounds **(Figure 1).** At week 88, significantly more patients treated with tirzepatide maintained at least 80% of weight loss from initial open-label treatment period

compared to patients switched to placebo: 89.5% vs 16.6%, $P < 0.001$.

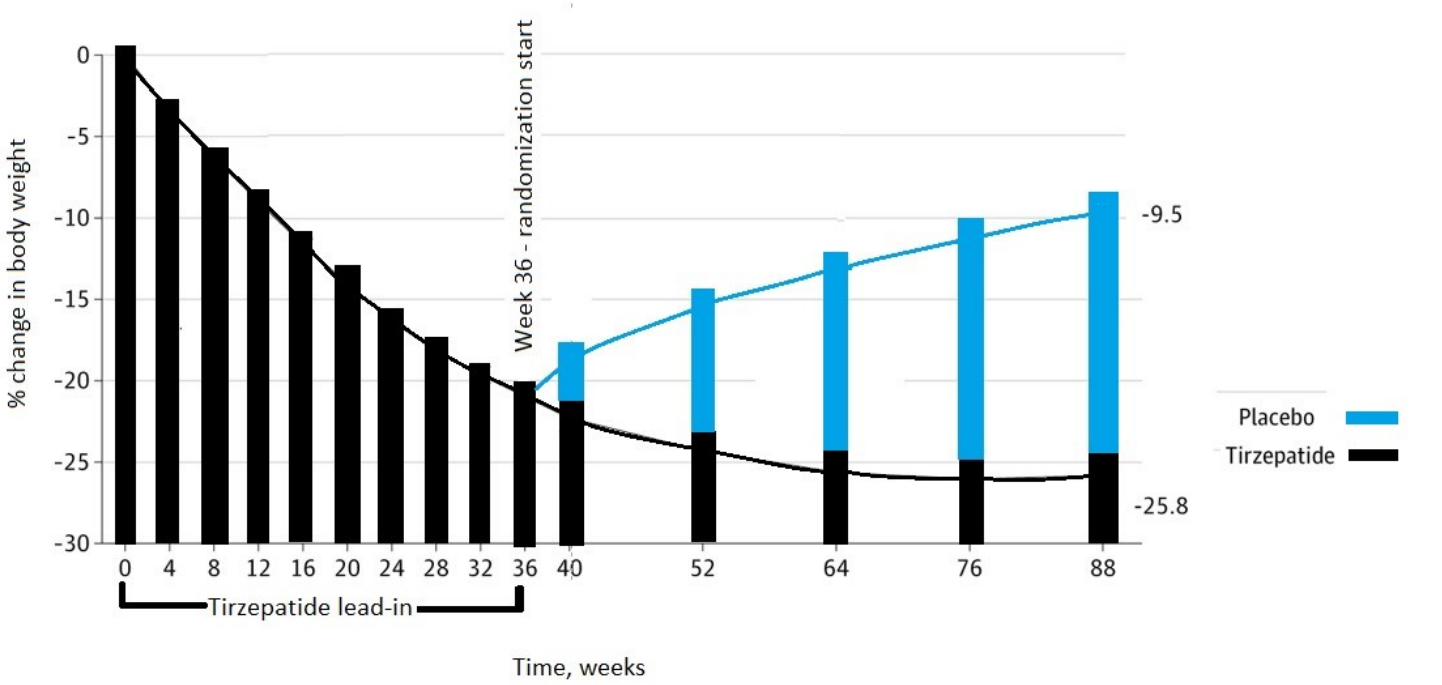

Figure 1. Tirzepatide vs placebo and body weight change. Patients were randomized at week 36.

COMMENTARY

Why Is This Important?

When patients initiate treatment with GLP-1 receptor agonists, like semaglutide, or GIP and GLP-1 receptor agonists, like tirzepatide, they frequently ask physicians if they will need to continue the medication indefinitely in order to maintain weight loss. These data clearly demonstrate that continued medication use is necessary for the vast majority of patients.

This shouldn't be surprising. Obesity is increasingly viewed as a chronic disease, and only bariatric surgery, endoscopic sleeve gastroplasty, and GLP-1 receptor agonist agents have demonstrated efficacy for sustained, clinically important weight loss.[1-3] Unfortunately, intensive lifestyle and nutritional interventions, including restricted eating schedules, have not demonstrated similar sustained benefits.[4]

Hepatologists are increasingly using these agents for metabolic dysfunction-associated steatohepatitis patients with obesity, and gastroenterologists frequently see patients with GI side effects, like nausea or constipation, after starting GLP-1 receptor agonists. Therefore, we need to understand the risks and benefits of these medications as well as understanding how to mitigate side effects.

Key Study Findings

During the 36-week, open label tirzepatide treatment period, mean weight loss was 21%, or approximately 22.5 kg/50 pounds.

During the 52-week, randomized withdrawal period, individuals who continued on tirzepatide had an additional mean weight loss of 5.5%, or approximately 6kg/13 pounds, while individuals randomized to placebo subq injections regained 14.0% of body weight, or approximately 15kg/33 pounds **(Figure 1)**.

Caution

GI side effect were common during the 36-week, open-label treatment period, and included nausea (35.5%), diarrhea (21.1%), constipation (20.7%), and vomiting (16.4%). Although tirzepatide was recently approved by the US Food and Drug Administration for obesity, lack of insurance coverage and high out -of-pocket costs remain potential barriers to maintenance use.

My Practice

Since I'm not an obesity specialist, I consulted with one of our former Associate Editors, Sonali Paul, MD, MS, who is certified in obesity medicine and has expertise in using these medications for management of obese metabolic dysfunction steatohepatitis patients. She noted the following pearls for management, which we have discussed in prior EBGI summaries.[1,4-5]

When prescribing GLP-1 receptor agonists, the dose should be gradually increased in 2.5 mg increments every 4 weeks based on tolerability. Treatment should be reverted to a lower dose if clinically important nausea develops. If patients develop mild constipation, treatment with an osmotic laxative without lowering the dose is acceptable. Continued treatment will be required for maintenance of weight loss in the majority of patients since obesity is a chronic disease, although the lowest effective dose should be used.

There does appear to be a small risk of developing pancreatitis based on all available data,[5] so do not use in patients with a history of pancreatitis. As discussed in a prior EBGI summary,[5] significant weight loss does increase the risk of gallstone development and also may increase the risk of cholecystitis and choledocholithiasis. Current data is insufficient to support a causal link between GLP-1 receptor agonists and gastroparesis or bowel obstruction.[5]

Finally, as discussed in a prior EBGI summary,[5] whether or not GLP-1 receptor agonists need to be discontinued prior to endoscopic procedures to minimize aspiration risk during monitored anesthesia care remains controversial. Although the American Society for Anesthesiology updated their preoperative fasting guidelines in 2023 and recommended that subq injections of

GLP-1 receptor agonists should be held for 1 week, there is insufficient research data to support this recommendation and position statements from our GI societies do not support this. Nevertheless, many endoscopists and patients will be required by their anesthesiology team to hold subq injections of GLP-1 receptor agonists for one week if deep sedation with propafol is used. In my own practice, I do not routinely hold GLP-1 receptor agonists when performing colonoscopy or even upper endoscopy with midazolam and fentanyl for sedation.

For Future Research

Ongoing research will investigate other potential long-term adverse events that could be associated with weight loss, including sarcopenia.

Conflict of Interest

Dr. Schoenfeld has no relevant conflicts of interest.

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

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