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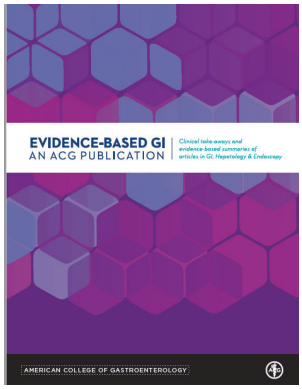

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EBGI **Volume 3, Issue 11**

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

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

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INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

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

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx

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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Etrasimod, a Sphingosine 1-Phosphate Receptor Modulator, for Moderate-Severe Ulcerative Colitis: New Options for Oral Therapy

Dr. Philip Schoenfeld
Editor-in-Chief

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Associate Editor

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IBD

This summary reviews Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): Two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet 2023; 401: 1159-71.

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

STRUCTURED ABSTRACT

Question: Is etrasimod (Velsipity; Pfizer, Rochester, MI), a sphingosine 1-phosphate (S1P) receptor modulator, superior to placebo for clinical remission at week 12 and week 52 in moderately to severely active ulcerative colitis (UC)?

Design: To assess induction of remission at 12 weeks, 2 multi-center, double-blind, placebo-controlled randomly controlled trials (RCTs; ELEVATE UC 12 and ELEVATE UC 52) were conducted with 2:1 randomization assignment. In ELEVATE UC 52, patients completed an additional 40-week maintenance period using a treat-through design—patients were not re-randomized to etrasimod or placebo based on clinical response/remission after 12 weeks. Patients continued with their assigned treatment, etrasimod or placebo, for the entire 52 weeks. Randomization was stratified based on prior exposure to biologics or janus kinase (JAK) inhibitors, baseline corticosteroid use, and baseline disease severity.

Setting: In ELEVATE UC 12, 354 patients were enrolled between September 2020 and August 2021 at 407 sites across 37 countries. In ELEVATE UC 52, 433

patients were enrolled between June 2019 and January 2021 at 315 sites across 40 countries.

Patients: Inclusion criteria included: (a) 16-80 years old; (b) moderate-severe UC based on a modified Mayo Score of 4-9 with endoscopic subscore of $\geq$ 2, rectal bleeding subscore $\geq$ 1; (c) inadequate response, loss of response, or intolerance of at least 1 approved UC therapy. [Note: the modified Mayo Score assesses rectal bleeding score (0-3), stool frequency score (0-3), endoscopy subscore (0-3), so the score range is 0-9 with 9 representing most severe UC.] Patients with isolated proctitis (<10 cm of rectal involvement) who met other inclusion criteria were also enrolled. Patients on stable doses of 5-aminosalicylates (5-ASA), corticosteroids or budesonide were also allowed to enroll.

Exclusion criteria included clinically significant cardiovascular condition (e.g., myocardial infarction, stroke, second or third degree atrio-ventricular block), history of opportunistic infections or macular edema, pregnancy or lactation, and prior history of failing to induce remission with $\geq$ 3 biologic agents or JAK1 inhibitors.

Interventions/Exposure: Etrasimod 2mg oral daily vs placebo.

Outcome: Primary endpoint was clinical remission after 12 weeks, defined as: rectal-bleeding sub score 0; stool-frequency sub score $\leq$1 with a decrease of at least 1 from baseline; and, an endoscopy sub score $\leq$ 1. For ELEVATE UC 52, a co-primary endpoint was clinical remission at week 52. Multiple secondary endpoints were assessed, including: (a) symptomatic response; (b) endoscopic improvement, defined as endoscopy sub score $\leq$ 1 without friability; (c) endoscopic improvement plus histologic remission and, (c) clinical response.

Data Analysis: Modified intention-to-treat (ITT) analysis defined as patients who were randomized and received at least 1 dose of study medication was performed for the primary endpoint using the Cochran-Mantel-Haenszel method. Safety analysis performed for any patient who received study medication in both induction and maintenance RCTs.

Funding: Pfizer, manufacturer of etrasimod.

Results: Patient characteristics across both RCTs included mean age 39-41, mean disease duration 6-7 years, mean modified Mayo Score at baseline 6.6, prior biologic or JAK1 inhibitor therapy (37%-38%), concomitant steroid use at start of trial (32%-33%). Extent of colitis was: pancolitis (32%-35%), left-sided colitis (54%-63%), isolated proctitis (4%-10%). Etrasimod 2 mg oral daily was superior to placebo for producing clinical remission at week 12 (27% vs 7%, P <0.001 in ELEVATE UC 52 and 25% vs 17%, P = 0.026 in ELEVATE UC 12) and at week 52 (32% vs 7%, P <0.001 in ELEVATE UC 52).

Etrasimod 2mg oral daily was superior to placebo for key secondary endpoints at week 12 and week 52, including endoscopic improvement, symptomatic remission, and endoscopic improvement + histologic remission. For the prespecified secondary endpoint of clinical response at week 12, etrasimod was also superior in ELEVATE UC 52 (62% vs 34%, $P < 0.001$) and ELEVATE UC 12 (62% vs 41%, $P = 0.0002$).

Adverse events of special interest, including opportunistic infections, herpes zoster, and macular edema, were low ($\leq$ 1%) and similar between groups. No malignancies were reported. Absolute lymphocyte count decreased by approximately 50% from baseline after 2 weeks in the etrasimod-treated patients. Among 527 etrasimod-treated patients, 9 bradycardia events were reported on days 1-2 with 2 being accompanied by mild-moderate dizziness, and 3 asymptomatic patients were identified with AV block, type 1 or 2.

***Note**: Although these trials used a classic double-blind, placebo-controlled, randomized study design with modified ITT analysis, study methodology and results are too detailed to summarize comprehensively. Readers are encouraged to review the full study publication.*

COMMENTARY

Why Is This Important?

As discussed in prior summaries[1], multiple UC treatments have become available in the past 5 years. In addition to commonly used anti-TNF antibody treatments like infliximab and adalimumab, anti-integrin antibody treatments like vedolizumab, anti-interleukin-12/23 antibodies such as ustekinumab and risankizumab, and JAK1 inhibitors like upadacitinib and tofacitinib are approved by the US Food and Drug Administration for use. Given this expanding menu of therapies, new algorithms are needed to help gastroenterologists choose preferred treatment for individual UC patients by accounting for the strengths and limitations of individual agents.[2]

Etrasimod is an oral sphingosine 1-phosphate (S1P) receptor modulator, which partially and reversibly blocks the trafficking of lymphocytes from lymphoid organs to the peripheral blood and appears to minimize lymphocyte mobilization to inflammatory sites. It's the second oral S1P receptor modulator to become available for treatment of UC after ozanimod (Zeposia; Bristol Myers Squibb, Princeton, NJ). Notably, a 7-day dose escalation is recommended with ozanimod to minimize bradycardia, while no dose escalation is recommended with etrasimod. The ELEVATE trials included isolated ulcerative proctitis patients, who are usually excluded from these types of studies and oral etrasimod may be an option if these patients fail to respond to oral and/or topical 5-ASA

treatment. As opposed to biologic agents, the risk of opportunistic infections may be lower with S1P receptor modulators based on mechanism of action, but comparative RCTs are lacking.

Also, since the prescribing information warns of the potential for cardiac arrythmias, opportunistic infections, liver injury and macular edema, patients should get complete blood count, electrocardiogram, liver function tests, and ophthalmic assessment before or near the start of treatment. In particular, the recommendation for ophthalmic assessment may delay initiation of treatment. Patients should get vaccination against varicella-zoster virus or demonstrate antibodies to the virus prior to initiating treatment.

Ultimately, Sandborn and colleagues should again be commended for designing a methodologically rigorous RCT. The use of the treat-thru approach in ELEVATE UC 52 is unique and may be particularly helpful since it more closely replicates clinical practice and provides estimates of delayed clinical response/ remission after 12 weeks.

Key Study Findings

Etrasimod 2 mg oral daily was superior to placebo for producing clinical remission at week 12 (27% vs 7% in ELEVATE UC 52 and 25% vs 17% in ELEVATE. UC 12) and at week 52 (32% vs 7% in ELEVATE UC 52).

Caution

A minority of study patients were previously treated with biologic agents, which may impact generalizability of results. Also, it's unclear why there were numerical differences in placebo rates of clinical remission between ELEVATE UC 52 and ELEVATE UC 12.

My Practice

Etrasimod may be ideal for UC patients with moderate disease activity who prefer an oral agent and who do not have a history of cardiovascular events as well as ulcerative proctitis patients resistant to standard oral therapies. We avoid it in patients that are pregnant or planning for pregnancy in the near future. If patients have severe snoring, which may represent undiagnosed sleep apnea, we may avoid it. Ultimately, we individualize our care by reviewing risks and benefits of different therapies with each patient and conduct shared decision making.

For Future Research

Future RCTs may define efficacy of etrasimod for Crohn's disease. Given the increasing number of available agents with different mechanisms of actions, comparative RCTs would be welcome to help establish positioning of therapies as well as longer-term safety data, including in pregnant women.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest. Dr. Dalal has received grant

support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs.

The authors of ELEVATE UC 12 and ELEVATE UC 52 are active on social media. Tag them to discuss their work and this EBGI summary:

@bruce_sands1 (Bruce Sands)

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EVIDENCE-BASED GI
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*P*ost-*E*ndoscopy *E*sophageal Adeno*C*arcinoma: Take a *PEEC* at Endoscopy Quality in Barrett's Esophagus

Jennifer M. Kolb
Associate Editor

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[1]*Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, and Parenteral Nutrition, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

This summary reviews Wani S, Holmberg D, Santonin G, et al. Magnitude and time-trends of post-endoscopy esophageal adenocarcinoma and post-endoscopy esophageal neoplasia in a population-based cohort study: The Nordic Barrett's Esophagus Study. Gastroenterology 2023; 165:909-19.
Correspondence to Jennifer M. Kolb, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Among a cohort of adults with newly diagnosed Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC), how many of these cancers are categorized as post-endoscopy esophageal adenocarcinoma (PEEC) and post-endoscopy high-grade dysplasia + EAC (PEEN)?

Design/Setting: The Nordic Barrett's Esophagus Study (NordBEST) was a population-based cohort study using national patient registries from 3 Nordic countries: Denmark, Finland, and Sweden (**Figure 1)**.

Patients: Adult patients aged >18 diagnosed with BE (with an accompanying endoscopy code) during the time period January 1, 2006, through December 31, 2020, were included in the cohort. Patients with prior esophageal or gastric sur-

gery or cancer were excluded. Participants were followed until a diagnosis of high-grade dysplasia (HGD) or EAC, death, or the end of the study period.

Study Definitions: PEEC were defined as EAC, and PEEN was defined as EAC or HGD diagnosed between 30-365 days from the index endoscopy where BE was identified. The purpose of the 30-day time lag was to allow for additional procedures required to appropriately diagnose or stage any neoplasia identified on the index exam as well as completion of the pathology report. Cancers that were diagnosed between 0-29 days of the index endoscopy/BE diagnosis were categorized as index EAC and those diagnosed beyond 1 year as incident EAC.

Outcomes/Analysis: The primary outcome was the rates of PEEC and PEEN reported as incidence rates (IRs) per 100,000 person-years for the entire study period and for 3 calendar periods: 2006-2010, 2011-2015, and 2016-2020. Incidence rate ratios (IRRs) of EAC were computed using Poisson regression to compare the incidence of PEEC vs incident EAC. For the outcome of PEEN, only data from Sweden could be used since this was the only country that reported on HGD.

Various sensitivity analyses were conducted to evaluate the impact of modifying the 30-365 day time interval for occurrence of PEEC/PEEN to a) 30 days – 3 years and b) 6 months to 3 years. In analysis a, changing the upper limit of the time window to 3 years was done given that most endoscopists would recommend a surveillance interval of 3 years for non-dysplastic BE. The 6 months (analysis b) was chosen to allow for the possibility of erosive esophagitis on index endoscopy requiring follow up endoscopy to document healing and evaluate for BE.

Funding: Swedish Research Council (2019-00209)

Results: Between 2006-2020, there were 20,588 patients with newly diagnosed BE (14.8% Denmark, 20.5% Finland, 64.6% Sweden) and 293 cases of EAC (0.01%). Of these cases, 69 (23.5%) were categorized as PEEC, 14.7% as index EAC, and 61.8% as incident EAC. The IRs for PEEC was 392/100,000 person-years (95%CI 309-496) and lower for incident EAC 208 (95%CI 180-241). Among 279 patients diagnosed with HGD/EAC (Sweden only), 17.2% were categorized as PEEN with an IR of 421/100,000 person-years (95% CI 309-496).

Time trend analysis using 5-year intervals demonstrated rising incidence of PEEC/PEEN (p=0.02) with no change in IRs of incident EAC. Predictors of PEEC were older age and male sex. Sensitivity analyses using different definitions/time windows to categorize PEEC demonstrated largely similar results, or an even higher proportion of these cases, as well as a consistent increase in incidence across time-trend analyses.

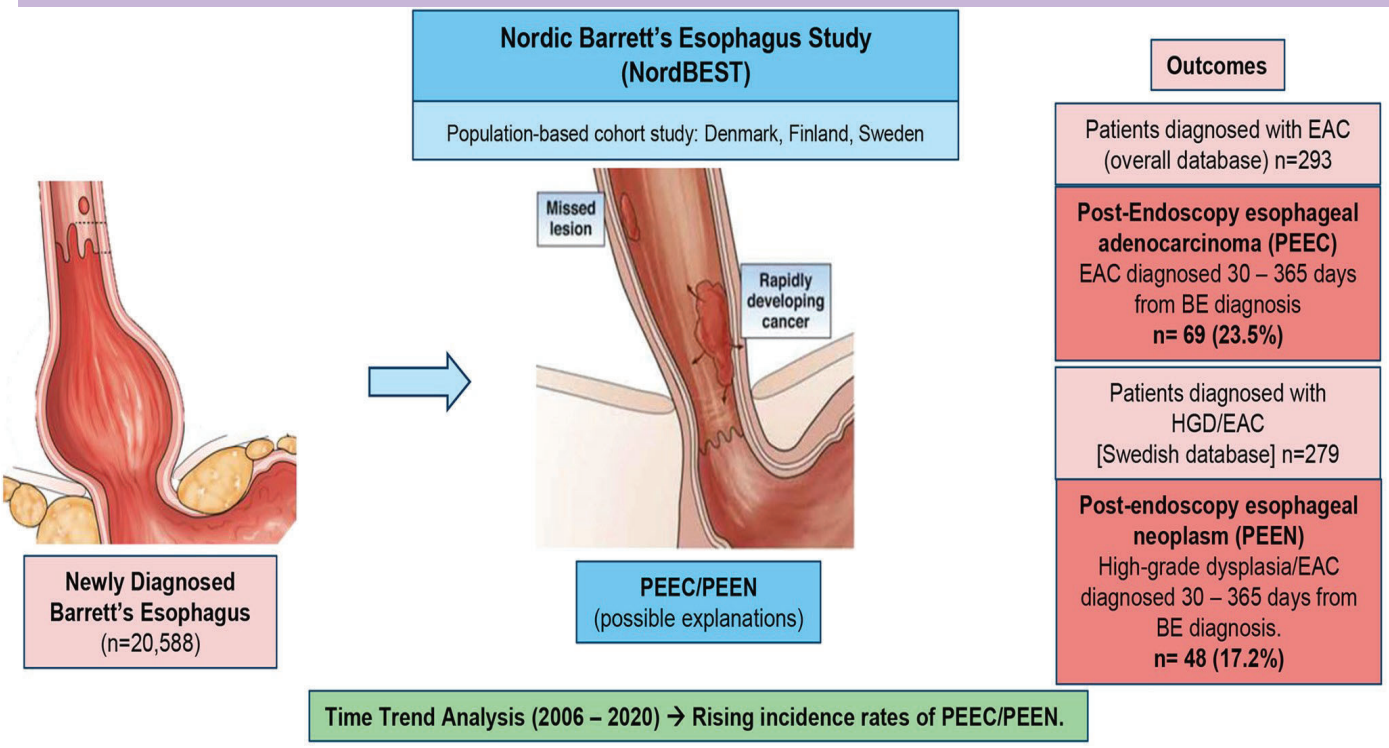

Figure 1. Study results and outcomes. Used with permission from Elsevier, copyright 2023.

COMMENTARY

Why Is This Important?

The majority of EAC cases present at a late stage associated with poor survival. Barrett's esophagus (BE) is the known precursor lesion to EAC and provides the opportunity to intervene through screening in at risk individuals and enrolling those with BE in surveillance or treatment programs. The goal of surveillance is to identify low-grade or high-grade dysplasia or early cancer at a treatable stage. However, current early cancer detection practices are ineffective. One potential explanation for these limitations is PEEC/PEEN, similar to the concept of post-colonoscopy colorectal cancer and related to endoscopy quality. These cancers are found in patients with BE within a short time frame after a negative upper endoscopy and it is thought that they might have been missed on the initial examination, or

perhaps have rapidly progressive biology.

The proportion of PEEC in EAC cases has been evaluated in several prior studies. An updated systematic review and meta-analysis of 52 studies with 145,726 patients demonstrated a PEEC rate of 21% (95% CI 13-31) and PEEN rate of 26% (95% CI 19-34) which were both lower among studies with only non-dysplastic BE (PEEC 17%, PEEN 14%).[1] The proportion of PEEC increased over time from 5% in studies prior to 2000 to 30% in studies after 2015. Most of this US data comes from heterogenous observational studies in diverse practice settings that used different definitions of PEEC/PEEN and varying endoscopic techniques. The present study is unique and important because it is the first population-based report on the magnitude of PEEC/PEEN.

Key Study Findings

Among this cohort of 20,588 newly diagnosed BE patients from 3 Nordic countries, nearly 1 in 4 EAC cases (23.5%) met the definition of PEEC. Using only data from Sweden, nearly 1 in 5 cases of HGD + EAC (17%) met the definition of PEEN. The incidence of PEEC/PEEN rates increased over time.

Caution

The study provided robust data from 3 countries on PEEC and is the only population-based report on this. However, the outcome of HGD was only reported in the Swedish database. There was no patient level, provider level, or center level data. It is still unclear why the rates of PEEC/PEEN are increasing despite stabilizing EAC incidence rates in these countries and endoscopist-level limitations in performance of EGD can't be identified. The authors provide some hypotheses- poor quality endoscopy due to training issues or high pressure for clinical volume, significant use of endoscopy in the first year after a new BE diagnosis- but these require validation in other datasets.

My Practice

At the present time, it is believed that most cases of PEEC/PEEN can be attributed to missed lesions (versus aggressive biology). Accordingly, an international expert panel suggested multiple strategies to reduce the rates of PEEC/PEEN which all emphasize the importance of a high-quality endoscopic examination. I follow a 10-step approach (Table 1) to a high quality endoscopic exam in a patient with known or suspected BE.[2-3] Some highlights of this exam include 1) use of standardized reporting systems to describe

Approach	Rationale
Identify esophageal landmarks, including the location of the diaphragmatic hiatus, gastroesophageal junction, and squamocolumnar junction	Critical for future examinations
Consider use of a distal attachment cap (especially in patients with prior diagnosis of dysplasia)	Facilitate visualization
Clean mucosa well using water jet channel and carefully suction the fluid	Remove any distracting mucus or debris and minimize mucosal trauma
Use insuffiation and desufflation	Fine adjustments to luminal insuffiation can help with detection of subtle abnormalities
Spend adequate time inspecting Barrett's segment and gastric cardia in retroflexion	Careful examination increases dysplasia detection
Examine the Barrett's segment using high-definition white light endoscopy	Standard of care
Examine the Barrett's segment using chromoendoscopy (including virtual chromoendoscopy)	Enhances mucosa pattern and surface vasculature
Use the Paris classification to describe the circumferential and maximal Barrett's segment length	Standardized reporting system
Use the Paris classification to describe superficial neoplasia	Standardized reporting system
Use the Seattle protocol (in conjunction with electronic chromoendoscopy) with a partially deflated esophagus to sample with Barrett's segment	Increases dysplasia detection

Table 1. Ten step approach to endoscopic examination of Barrett's esophagus[2]

anatomic landmarks, the Barrett's segment, and any visible lesions, 2)use of high definition white light endoscopy and chromoendoscopy, 3) spending adequate time inspecting the BE segment, 4) Seattle protocol sampling strategy (4 quadrant biopsies every 1-2cm along the BE segment) along with targeted biopsies, 5) adherence to guideline recommended surveillance intervals for

NDBE.

For Future Research

More data using a large, nationally representative sample is needed to describe the rates of PEEC/PEEN in the US population. Future studies should focus on the clinical and endoscopic characteristics of PEEC and try to elicit the contributing factors for these cases. Additionally, efforts to standardize how PEEC/PEEN rates are calculated in an automatic fashion can inform mechanisms for its use as a quality indicator with defined performance thresholds.

Conflict of Interest

Dr. Kolb reports no potential conflict of interest.

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

@LagergrenJesper

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Surveillance of Branch Duct IPMN – Enough is Enough, At Least in Older Adults and Small, Stable Lesions

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This article reviews Marchegiani G, Pollini T, Burelli A, et al. Surveillance for Presumed BD-IPMN of the Pancreas: Stability, Size, and Age Identify Targets for Discontinuation. Gastroenterology. 2023 Oct;165(4):1016-1024.e5.

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STRUCTURED ABSTRACT

Question: What patient groups with presumed branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) are at very low risk of malignant progression (where their likelihood of pancreatic cancer is no different from that of an age-matched general population)?

Design: Retrospective analysis of prospective collected data.

Setting: This was an international multicenter study, including centers in Europe, the United States, and Asia under the auspices of the Verona Evidence-Based Meeting on IPMN Consortium. Each institution prospectively collected data that included clinicopathologic data, including demographics, radiological and endoscopic characteristics of the cyst, surgical data, clinical data with comorbidities. IPMN-related features included CA19-9, cyst size, location, cyst wall, mural nodules, solid components, septae, and main pancreatic duct size. From the data, authors evaluated presumed BD-IPMN without worrisome features (WFs) or high-risk stigmata (HRS) at diagnosis who underwent surveillance. **Table 1** lists WFs and HRS that may indicate need for more intense

surveillance, interventional EUS, or surgery.

Patients: There were 3,844 adults with BD-IPMN, lacking any WF or HRS who were enrolled in surveillance programs. Median age was 66, and 60% were female. Initial BD-IPMN diameter was median 12mm (interquartile range [IQR] 9mm). BD-IPMN was a presumptive diagnosis based on the presence of 1 or more dilated branch ducts communicating with a nondilated main pancreatic duct (MPD) (5 mm or smaller) on high-resolution cross-sectional imaging or endoscopic ultrasound. Exclusion criteria included those who underwent surgery within 12 months of cyst detection, those with a prior history of pancreatic cancer or prior pancreatic surgery, and those with cysts suspicious for a diagnosis other than BD-IPMN.

After determining inclusion, clusters of individuals at risk for cancer development were defined according to cyst size and stability for at least 5 years, and age-matched controls were used for comparison using standardized incidence ratios (SIRs) for pancreatic cancer. The authors identified persons who had BD-IPMN that did not develop WF or HRS over 5 years (termed "Trivial BD-IPMN").

Outcomes: The primary endpoint was the development of pancreatic cancer, defined as either IPMN with associated invasive carcinoma or IPMN with concomitant pancreatic ductal adenocarcinoma (PDAC). Secondary endpoints were development of WFs and HRS during follow-up, along with risk factors for developing pancreatic cancer, like cyst size, growth rate, and survival.

Worrisome Features	High Risk Stigmata
Cyst size of ≥3 cm	Obstructive jaundice
Enhancing mural nodule <5 mm	Enhanced mural nodule ≥5 mm
Thickened enhanced cyst walls	Main PD size of ≥10 mm
Pain PD size of 5-9 mm	
Abrupt change in the main PD caliber with distal pancreatic atrophy	
Elevated serum level of carbohydrate antigen (CA)19-9	
Lymphadenopathy	
Rate of cyst growth >5 mm/2 years	

Table 1: Worrisome features and high-risk stigmata of IPMNs.

Statistical Analysis: Data were analyzed using Cox proportional hazard models to assess the association between WF/HRS development and overall survival. To calculate the SIR of pancreatic cancer of the cohort compared to the general population, the authors obtained sex-specific pancreatic cancer rates from the World Heath Organization's International Agency for Research on Cancer (IARC). Age-standardized incidence was assessed.

Funding: This study was supported by funding from the Italian Ministry of Health (Grant FIMP-CUP Q8 1142 J38D19000690001).

Results: Of 3,844 patients with presumed BD-IPMN, 775 (20.2%) developed WFs and 68 (1.8%) HRS after a median surveillance of 4.4 years. Another 164 (4.3%) underwent surgery. For the entire study cohort, 1,617 (42%) remained stable without developing WFs or HRS for at least 5 years with another 1220 (31.4%) remaining stable during less than 5 years surveillance.

Of the 775 who developed WF, 121 (15.6%) developed at least 1 other WF. Developing 2 of more WFs was associated with worse survival: hazard ratio (HR) 2.38 (95% confidence interval [CI] 1.47–3.86; $P< 0.001$) compared with the development of only 1 WF: HR 1.43 (95% CI 1.02–2.02; $P=0.036$). Developing HRS during surveillance was associated with the diagnosis of an invasive cancer at final pathological examination (26.9% vs 10.1%, $P=0.042$), whereas the development of a WF was not ($P >0.05$). No individual WF or HRS was associated the diagnosis of HGD, but an abrupt change in MPD caliber ($P=0.021$), a Ca19-9 $\geq$ 37 U/L ($P=0.001$) and the presence of jaundice ($P=0.021$) were associated with the diagnosis of an invasive cancer.

In patients with a Trivial BD-IPMN, the development of a WFs and/or HRS after the first 5 years of surveillance was associated with worse overall survival: WF : HR 2.79 (95% CI 1.46–5.32; $P=0.002$); HRS: HR 5.52 (95% CI 1.94–15.69; $P=0.001$).

SIR of developing pancreatic cancer

In patients 75+ years of age, the SIR of developing pancreatic cancer was 1.12 (95% CI 0.23-3.39), and in patients 65+ years with stable lesions smaller than 15 mm in diameter after 5 years, the SIR was 0.95 (95% CI 0.11-3.42). The disease-specific mortality for patients who did not develop WFs or HRS for at least 5 years was 0.3% (n = 5). Table 2 indicates SIR by subgroup.

Subgroup	SIR (95% CI)
All Patients	4.65 (3.32-6.33)
Non-trivial	9.23 (6.08-13.42)
Trivial	2.29 (0.10-3.36)
Trivial ≤15 mm	0.93 (0.10-3.36)
Trivial 16-29 mm	1.42 (0.38-3.64)
Cysts >30 mm with no development of additional WFs/HRS for at least 5 years	10.29 (4.12-21.21)
Trivial <65 y	7.02 (2.26-16.38)
Trivial 65-74	2.17 (0.70-5.07)
Trivial ≥75 y	1.12 (0.23-3.39)
Trivial ≥65 y and cycst ≤15 mm	0.95 (0.11-3.42)

Table 2: Standardized incidence ratio (SIR) by branch-duct intraductal papillary mucinous neoplasms subgroup.

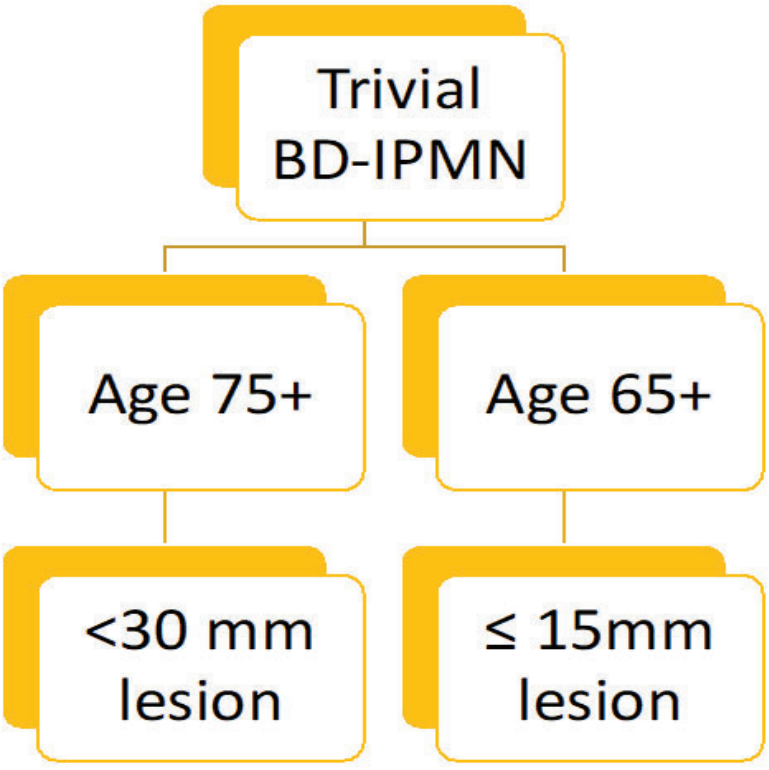

Figure 1. When to consider discontinuing surveillance if no worrisome features or high-risk stigmata.

COMMENTARY

Why Is This Important?

Incidentally detected pancreatic cysts are a burgeoning issue. With more frequent and higher quality cross-sectional imaging, the detection of pancreatic cysts has increased substantially over the last 2 decades – they are identified in at least ~10% of MRIs.[1,2] It is thought that some of these may harbor malignant potential – though it is not as clear-cut a transition as the adenoma to carcinoma pathway seen in colorectal cancer. But as pancreatic ductal adenocarcinoma (PDAC) remains among the deadliest cancers – with a has a 5-year survival of less than 10% – and a rising incidence (increasing by 0.5% to 1.0% per year), it is a worrying issue to clinicians and patients alike.[3,4]

In response, guidelines for surveillance were formed. Multiple guidelines exist, including the ACG's 2018 Clinical Guideline on the diagnosis and management of pancreatic Cysts.[5] BD-IPMNs represent one of the more common types of pancreatic cystic lesions, and their surveillance entails cross-sectional imaging and/or endoscopic ultrasound. Surveillance can be offered until a patient is no longer a surgical candidate, though apart from suggestions of considering lengthening intervals if lesions are stable, there is little guidance regarding when to stop surveillance. Given the healthcare burden and cost associated with surveillance, as well as the impact on patients, studies evaluating whether and in whom surveillance can be stopped are critical.

Key Study Findings

In this study of 3,844 adults with BD-IPMN lacking any WF or HFS at baseline who were enrolled in surveillance programs, the authors demonstrate that surveillance discontinuation is a feasible option in presumed BD-IPMN stable for at least 5 years in patients older than 75 years with cysts <30 mm or older than 65 years with cysts ≤15 mm.

They demonstrate that in these populations, the risk of developing pancreatic malignancy is not significantly higher than that of the general population.

Caution

The authors did an excellent job answering an important question in a clinically relevant way, but it is important to consider that the cohort consists of persons enrolled in surveillance programs at high-volume centers, portending bias. BD-IPMN was a presumptive (not confirmed) diagnosis, though that is reflective of real-world practice. The data was collected over 30 years, and there are variations in imaging (and particularly endoscopic ultrasound) that may introduce biases. And while surveillance was relatively short (median follow up just under 5 years), there were persons who developed WF or HRS after having stable findings for many years. Finally, while a multicenter international study, it would be important to know whether there are

practice or patient differences across locations.

My Practice

My practice in this area mirrors what the authors advocate. I recommend stopping surveillance in individuals greater than 75 years of age with small and stable lesions. I liken this to colon cancer screening cessation, particularly in persons with comorbidities or marked frailty. For persons above 65 years of age, my approach is more individualized – but the present study encourages me to consider cessation, or at least a marked lengthening of surveillance interval for persons above 65 with a lesion that is ≤15mm. In general, I find that shared-decision making is best, particularly given the concern that pancreatic pathology can invoke in patients.

For Future Research

Ideally in the future, we will have guidance and recommendations for other patients or cyst characteristics for which we can stop or lengthen surveillance. We should also have (with ongoing studies such as CAPS and PRECEDE) a more concrete understanding of the potential "benefits" and "harms" of screening/surveillance – essential to shared-decision making. The authors' study also highlights the need for diagnostic criteria and tools more nuanced and predictive than WF alone. Finally, we need further research on the carcinogenic pathway in pancreatic cancer, so we can better counsel patients on their risk.

Conflicts of Interest

Dr. Kumar reports no conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

GI Adverse Events with GLP-1 Receptor Agonists for Weight Loss: Understanding the Risks

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GENERAL GI

This summary reviews Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M. Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. JAMA Medicine 2023; In Press. doi:10.1001/jama.2023.19574.

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STRUCTURED ABSTRACT

Question: Are glucagon-like peptide 1 (GLP-1) receptor agonists associated with an increased risk of biliary disease, pancreatitis, and other gastrointestinal (GI) adverse events?

Design: Retrospective cohort study.

Setting: Random sample of 16 million patients (2006-2020) from the PharMetrics Plus database (IQVIA), which is a large health claims database of outpatient prescriptions and *International Classification of Diseases – 9th* and *10th Edition* (*ICD-9/ICD-10*) diagnoses.

Patients and Interventions/Exposure: New users of semaglutide (n= 613) and liraglutide (n=4,144), which are GLP-1 receptor agonists approved for diabetes, and users of buproprion-naltrexone (n= 654), an Federal Drug Administration (FDA)-approved weight loss agent, which served as active comparator.

Outcome: Patients were observed from first prescription of medication to diagnosis of defined GI adverse events, based on *ICD-9/ICD-10* codes or end of the study period in 2020. Biliary disease included cholecystitis, cholelithiasis, and choledocholithiasis. Other GI adverse events of interest were pancreatitis, bowel obstruction, or gastroparesis defined by *ICD-9/ICD-10* coding or use of promotility agent.

Data Analysis: Hazard ratios (HR) calculated using Cox proportional hazards model after adjusting for age, sex, smoking, hyperlipidemia, geographic location, and abdominal surgery in the previous 30 days.

Funding: No funding is reported.

Results: Incidence rates for pancreatitis (adjusted HR [aHR] 9.1, 95% confidence interval [CI] 1.25-66), bowel obstruction (aHR 4.2, 95% CI 1.02-17.4), and gastroparesis (aHR 3.7, 95% CI 1.2-11.9) were significantly higher among users of GLP-1 receptor agonists compared to bupropion-naltrexone users. Biliary disease was numerically higher, but did not achieve statistical significance in the primary analysis: aHR = 1.5; 95% CI: 0.9-2.5.

COMMENTARY

Why Is This Important?

We selected this study, which was published as a Research Letter in *JAMA Medicine*, because it was publicized extensively in the media. As discussed in prior summaries[1], the methodology of these epidemiologic reports is frequently flawed and does not confirm or even support a causal relationship between medicine and adverse event.

Nevertheless, given the popularity of GLP-1 receptor agonists for weight loss and their possible impact on delaying GI motility, gastroenterologists may frequently be asked about potential GI risks of these medications. Notably, although there was not a statistically significant increase in biliary disease among GLP-1 receptor agonist users in this study, the FDA[2] added warnings and precautions about acute cholecystitis and biliary disease to the label in late 2022 based on data from placebo-controlled RCTs as well as other observational data[3].

Key Study Findings

Incidence rates for pancreatitis (aHR 9.1, 95% CI 1.25-66), bowel obstruction (aHR 4.2, 95% CI 1.02-17.4), and gastroparesis (aHR 3.7, 95% CI 1.2-11.9) were significantly higher among users of GLP-1 agonists compared to bupropion-naltrexone users.

Biliary disease was numerically higher,

but did not achieve statistical significance in the primary analysis (aHR 1.5, 95% CI: 0.9-2.5).

Caution

This is a hypothesis-generating study and should not be considered a study that answers a question. Since semaglutide was not approved for weight-loss until 2021 and liraglutide is still only FDA-approved for diabetes, the vast majority of GLP-1 receptor agonist users in this study had diabetes, which may cause gastroparesis. Misclassification frequently occurs with *ICD-9/ICD-10* coding. Furthermore, data on duration and dose of GLP-1 agonist use was not considered.

My Practice

Gastroenterologists frequently see patients with GI symptoms after starting GLP-1 receptor agonists. Since one of us (S.P.) frequently prescribes GLP-1 receptor agonists for metabolic dysfunction-associated fatty liver disease (MAFLD) patients with obesity, a review of some pearls may be helpful.

If these patients have been successful with weight loss and glycemic control of their diabetes, then they may be hesitant to discontinue GLP-1 receptor agonists even if they are suffering from nausea, constipation, or abdominal discomfort—which are common given the medications possible mechanism of action on slowing GI motility. When I prescribe GLP-1 receptor agonists, I gradually increase the dose based on tolerability. Therefore, if a patient develops nausea, then I may revert to a lower dose. If patients develop constipation, then I usually treat with an osmotic laxative without lowering the dose.

I educate my patients that there does appear to be a small risk of developing pancreatitis based on all available data. Also, I explain that significant weight loss does increase the risk of gallstone development and may be associated with increased risk of cholecystitis and choledocholithiasis. This is most likely a result of GLP-1 receptor agonists producing the desired effect, weight loss, as opposed to a direct effect of GLP-1 receptor agonists on reduced gallbladder emptying or suppression of cholecystokinin, which has been hypothesized.[2] Current data is insufficient to support a causal link between GLP-1 receptor agonists and gastroparesis or bowel obstruction.[4-5] Ultimately, discontinuation of GLP-1 receptor agonists usually resolves nausea and vomiting. If the patient is subsequently diagnosed with gastroparesis, it is almost certainly due to underlying diabetes.

The current controversy is whether or not GLP-1 receptor agonists need to be discontinued prior to endoscopic procedures to minimize aspiration risk during monitored anesthesia care. The American Society for Anesthesiology updated their pre-operative fasting guidelines in 2023 and recommended that GLP-1 receptor agonists should be held for 1 week, despite lacking data.[6] Therefore, regardless of the position statements from our GI societies,[7-8] your anesthesiology team may refuse to provide

monitored anesthesia care unless the patient holds their GLP-1 receptor agonist. Since these medications are administered subcutaneous weekly, many patients may forget, leading to a last-minute cancellation of the procedure. In my own practice (P.S.), 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

Additional studies assessing the impact of GLP-1 receptor agonists on gastric emptying and their potential impact on fasting prior to endoscopic procedures are sorely needed.

Conflict of Interest

Dr. Schoenfeld and Dr. Paul have no relevant conflicts of interest.

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