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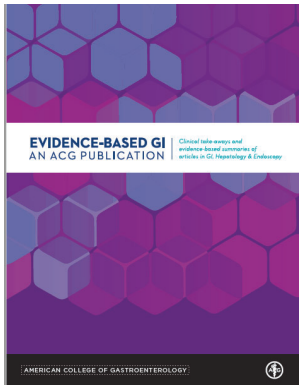

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IBSRELA®
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INDICATION

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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Risankizumab Is Superior to Ustekinumab for Induction and Maintenance of Crohn's Disease: The SEQUENCE Trial

Dr Sara Ghoneim
Guest Contributor

Dr Bharati Kochar
Associate Editor

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IBD

This summary reviews Peyrin-Biroulet L, Chapman JC, Colombel JF, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease. N Engl J Med 2024;391:213-223 .

Correspondence to Bharati Kochar, MD, MS. Associate Editor. Email: EBGI@gi.org

Keywords: Crohn's disease, risankizumab, Ustekinumab, RCT

STRUCTURED ABSTRACT

Question: Is risankizumab (Skyrizi, AbbVie Pharmaceuticals, San Francisco, CA), a p19 subunit-specific interleukin (IL)-23 monoclonal antibody, as efficacious and safe as ustekinumab (Stelara; Janssen Pharmaceuticals, Beerse, Belgium), a dual IL-12/23 inhibitor, in the treatment of patients with moderate-to-severe Crohn's disease who previously had unacceptable side effects or an inadequate response to at least one anti-tumor necrosis factor (TNF) therapy?

Design: Phase 3b, multicenter, open label, randomized comparator trial for 48 weeks.

Setting: Patients were recruited from 187 sites in 28 countries between September 2020-July 2023.

Patients: Inclusion criteria included: age 18-80 years; moderate-to-severe Crohn's

disease, based upon Crohn's disease activity index (CDAI) score of 220-450 with average daily stool frequency of ≥4 and/or an average abdominal pain score ≥2; endoscopic evidence of mucosal inflammation based upon simple endoscopic score for Crohn's disease (SES-CD) score ≥ 6 for ileocolonic or colonic disease or SES-CD ≥ 4 for isolated ileal disease; and history of unacceptable side effects or an inadequate response to at least one anti-tumor necrosis factor (TNF) therapy.

Multiple exclusion criteria included, but were not limited to: presence of ostomy or ileoanal pouch; short bowel syndrome; surgical bowel resection within 3 months of enrollment; and prior use of small molecules or biologics other than anti-TNFs.

Intervention: Patients were randomly assigned in 1:1 ratio to receive risankizumab or ustekinumab. In the risankizumab group, patients received 600 mg intravenous (IV) induction dose at week 0, 4, 8 followed by 360 mg subcutaneous (SQ) maintenance dose every 8 weeks from week 12 to 48. Patients in the ustekinumab group received the approved single weight-based induction IV dose followed by 90 mg SQ maintenance dose every 8 weeks until week 48. All enrolled patients also underwent a mandatory steroid taper starting at week 2.

Outcome: The 2 primary endpoints of this study were: (1) clinical remission at week 24 (defined as CDAI score ≤ 150) and (2) endoscopic remission at week 48 (defined as SES-CD of ≤ 4, and at least 2-point reduction from baseline and no subscore > 1 in any individual variable).

Secondary endpoints were tested hierarchically for superiority of risankuzimab to ustekinumab in the following order: clinical remission at 48 weeks (defined as reduction in SES-CD ≥50% from baseline, or at least 2-point reduction from baseline for patients with isolated ileal disease); endoscopic response at week 24; steroid-free endoscopic remission at week 48; and, steroid-free clinical remission at week 48. Safety events were assessed among all patients who received at least one dose of risankizumab or ustekinumab.

Data Analysis: Intention-to-treat analyses were performed. Since risankizumab was not approved for use when the trial was designed, noninferiority of risankizumab to ustekinumab in achieving clinical remission at week 24 was the primary analysis and was established with the 95% confidence interval (CI) for the risk difference between risankizumab and ustekinumab group set at greater than 10 percentage points. Superiority of risankuzimab compared to ustekinumab was evaluated using a 2-sided significance level of 0.05. Categorical variables were analyzed using the Cochran-Mantel-Haenszel test to assess common risk difference, stratified by the number of previous anti-TNF therapies that failed (1 or >1), and by

steroid use at baseline.

Funding: AbbVie Pharmaceuticals, manufacturer of risankuzimab.

Results: Among 520 patients randomized to risankuzimab (n =255) and ustekinumab (n= 265), demographic data included mean age 38-years-old; 49% female; 74% White, 20% Asian, 10% Hispanic; ileocolonic disease 43%, ileal disease only 17%, colonic disease only 40%; median duration of disease was 7.3 years; and, mean CDAI score was 307. Overall, 90.2% of patients in the risankuzimab group (230/255) and 72.8% of patients in the ustekinumab group (193/265) completed all the assigned treatment.

Risankuzimab was noninferior to ustekinumab with regards to clinical remission at week 24 (58.6% vs 39.5%; -18.4% [95% CI, 6.6-30.3]). Risankuzimab was superior to ustekinumab with regards to endoscopic remission at week 48 (31.8% vs 16.2%; -15.6% [95% CI, 8.4-22.9; P<0.001]; Figure 1).

Risankuzimab demonstrated superior efficacy to ustekinumab across all secondary endpoints (Table 1). Furthermore, the incidence of hospitalization related to Crohn's disease, or any other cause was significantly lower in the risankizumab group compared to the ustekinumab group (4% vs 13%, -8.45% [95% CI, 3.31-13.60]; 11% vs 19%, -7.13% [95% CI, 0.25-14.01]).

Adverse events were similar in the 2 groups. The incidence of serious adverse events was lower in the risankizumab compared to the ustekinumab group (10.3% vs 17.4%). Infection rates were similar in the 2 groups. One case of skin squamous -cell carcinoma (in the risankizumab group) and one case of anal squamous cell carcinoma (in the ustekinumab group) was reported.

	Risankizumab (n=255)	Ustekinumab (n=265)
Clinical Remission-Week 48	60.8%	40.8%
Glucocorticoid-Free Remission-Week 48	60.8%	40.4%
Endoscopic Response-Week 48	45.1%	21.9%

Table 1: Secondary trial endpoints.

$P < 0.001$ for all secondary endpoints

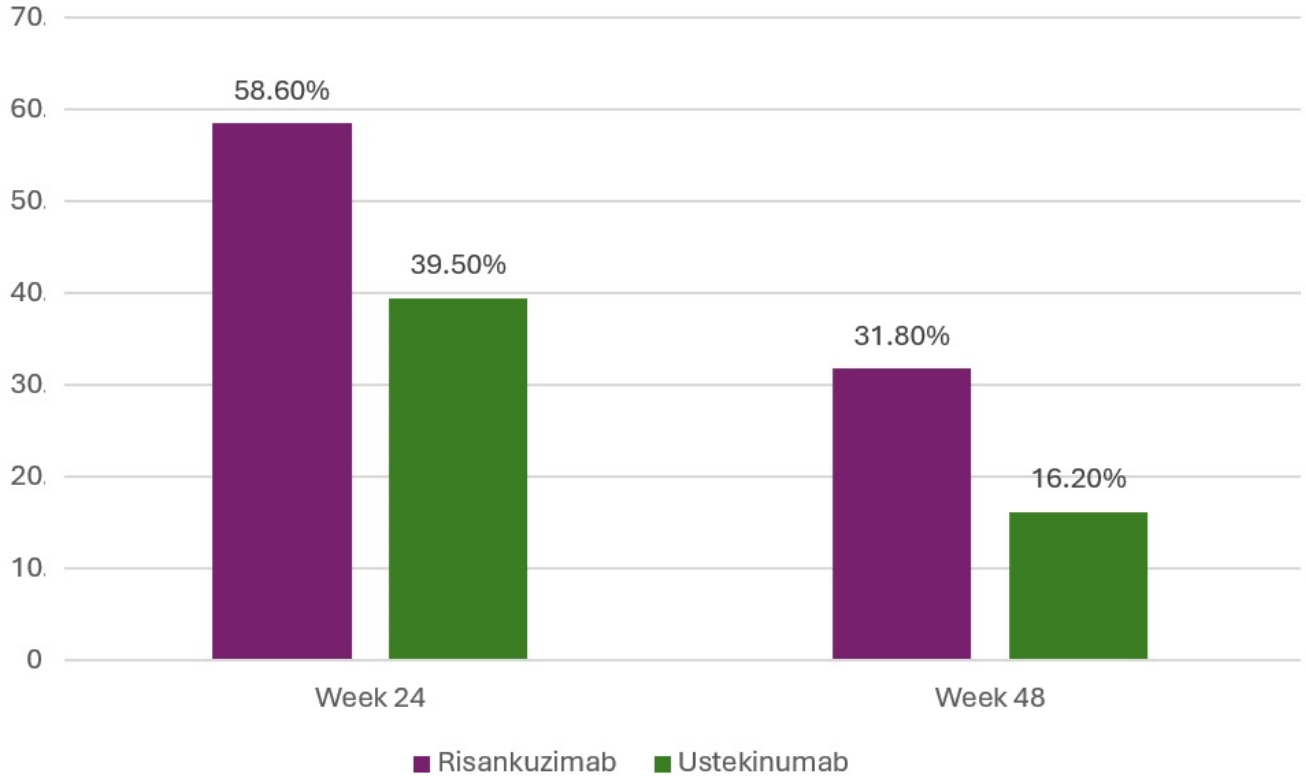

Figure 1. Co-Primary Endpoints: Clinical remission at week 24 and endoscopic remission at week 48.

COMMENTARY

Why Is This Important?

Head-to-head trials, comparing treatment options for IBD, are arguably the most practice changing studies. Yet to date we have very few published head-to-trial trials in IBD: SONIC, NORSWITCH, SEAVUE[1], and VARSITY[2] are the prominent ones since 2000. Head-to-head clinical trials are the most clinically pertinent to patients, providers and insurers. These trials answer the every day question of which medication should we use to treat this disease in this patient and what are the risks and benefits of each choice compared with the other choice, the true counterfactual, instead of compared with placebo, which is not a realistic counterfactual for patients who need to start advanced therapies. Unlike VARSITY and SEAVUE, which are trials to investigate the most efficacious first line advanced therapy in ulcerative colitis and Crohn's disease respectively, SEQUENCE helps position second line agents for Crohn's disease.

Key Study Findings

Risankizumab is non-inferior to ustekinumab in achieving clinical remission at 24 weeks in patients who have already been treated with an anti-TNF agent.

Importantly, risankizumab was superior to ustekinumab for clinical remission at 48 weeks (60.8% vs 40.8%, $P< 0.001$) and for endoscopic remission (31.8% vs 16.2%, $P< 0.001$).

There was no significant difference in adverse events between the study drugs and rates of opportunistic infections were less than 1% in both groups, reinforcing the relative safety of this class of biologic agents.

Caution

This was an open label study, so patients knew if they were receiving risankizumab and ustekinumab, which might impact their subjective assessment of abdominal discomfort and bowel habits. However, the reviewers were blinded to the treatment arm when assessing endoscopic healing. Also, risankizumab maintenance dosing was the higher 360 mg dose instead of the 180 mg maintenance dose, while dose escalation of ustekinumab to every 6 weeks or even every 4 weeks was not allowed. Finally, the drop-out rate was 28% in the ustekinumab arm versus 10% in the risankizumab arm, and this difference was primarily due to lack of efficacy in the ustekinumab arm, which may impact interpretation of results.

Whether the superior efficacy of risankizumab is due to binding on the p19 subunit or if there are specific properties of the drug itself that allow for better tissue penetration or another feature that result in greater endoscopic efficacy is unclear.[3] Finally, the superiority of risankizumab to ustekinumab in these moderate-severe Crohn's disease patients whose anti-TNF agents had failed to treat their condition is not generalizable to ulcerative colitis.

My Practice

These data are not surprising as the findings are parallel to what has been published in 2017 for the treatment of moderate to severe plaque psoriasis.[4] However, head-to-head trials like this must influence clinical practice. While ustekinumab may be a great first line biologic for Crohn's disease as the SEAVUE trial demonstrated, SEQUENCE shows us that when used as a second line agent after failure with an anti- TNF agent, risankizumab should be preferred for the greater efficacy for the stringent endpoint of endoscopic remission. It's not clear whether this increased efficacy can be extrapolated to the use of an anti-interleukin agent as a first line agent.

While SEQUENCE clarifies the positioning of risankizumab, ustekinumab will continue to have a large role in IBD treatment. There is likely to be a ustekinumab biosimilar available in the US by 2025 which should make ustekinumab more affordable. Furthermore, starting in 2024, ustekinumab has been covered by Medicare prescription drug plans as part of the Inflation Reduction Act of 2022 covering high cost medications. Since the financial burdens of biologic therapy are an important consideration and ustekinumab is an efficacious anti-IL 23 agent, it would be short sighted to overlook ustekinumab in the treatment of Crohn's disease.

Nevertheless, especially if I am starting an anti-IL 23 agent after failure of other advanced therapy for CD, it is worth appealing for risankizumab, citing this

paper if it is denied with the initial request.

Future Research

The number of head-to-head clinical trials are increasing, which is very useful for the IBD community. Two such trials, VIVID-1 and GALAXI-2/3, have presented preliminary data, although we're awaiting full publications. VIVID-1 compared mirikizumab, another anti-IL targeting the p19 subunit of IL-23, vs ustekinumab for the treatment of Crohn's disease in patients who have been previously treated with an anti-TNF agent. GALAXI-2/3 compared guselkumab, another anti-IL 23 monoclonal antibody, vs ustekinumab in patients with Crohn's disease who were both biologic naïve and exposed.

This trial was quite traditional in its inclusion and exclusion criteria, excluding patients with abnormal anatomy, advanced age, etc. Future investigation should also focus on novel clinical trial analytics and methodology to allow for these important sub-groups of patients who are the most challenging in the clinical practice to be assessed in a rigorous prospective manner.

Conflict of Interest

Dr. Ghoneim notes no conflicts of interest. Dr Kochar has received consulting fees from Pfizer, Inc and Bristol Meyers Squibb.

REFERENCES

1. Kochar B. SEAVUE: A Sea Change in Biologic Positioning for Crohn's Disease. Evidence-Based GI April. 2023; 1-6
2. Dalal RS, Allegretti J. ICYMI: Vedolizumab is Superior to Adalimumab for Clinical Remission and Endoscopic Improvement of Ulceraativ Colitis. Evidence-Based GI April 2023; 7-10.
3. Abraham C. Interleukin-23 p19 and Interleukin-12 p40, Head-to-Head, against Gut Inflammation. N Engl J Med 2024;391:275-277.
4. Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. New England Journal of Medicine 2017;376:1551-1560.

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Vonoprazan is Efficacious for Non-Erosive Reflux Disease (NERD): An Alternative for PPI-Resistant NERD Patients?

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This summary reviews Laine L, Spechler S, Yadlapati R et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: A randomized trial. Clin Gastroenterol Hepatol 2024; In Press. doi: 10.1016/j.cgh.2024.05.004.

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

STRUCTURED ABSTRACT

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

Design: Multicenter, double-blind, placebo-controlled randomized trial.

Setting: Ninety-one ambulatory sites throughout the United States.

Patients: Adult patients with a diagnosis of symptomatic gastroesophageal reflux disease (GERD) with heartburn as their predominant symptom with onset greater than 6 months, with heartburn at least 4 days during any consecutive 7-day period during screening and no esophagitis on upper endoscopy.

Key exclusion criteria included erosive esophagitis on endoscopy, *Helicobacter pylori* infection, antibiotic exposure within 4-weeks and use of other acid suppressing medications (histamine 2-receptor antagonists [H2Bs] and proton pump inhibitors [PPIs]) within 2-weeks. Presence of esophageal intestinal

metaplasia (Barrett's esophagus) would also result in exclusion.

Interventions/Exposure: Eligible subjects were randomly assigned with concealed allocation via a central randomization sequence generator. They were randomized in a 1:1:1 ratio in the 4-week placebo-controlled period to vonoprazan 10 mg, vonoprazan 20 mg, or placebo taken once-daily. During an 20-week extension period, those randomized to placebo initially were re-randomized in 1:1 fashion to either 10 mg or 20 mg dosing. Rescue antacid (Gelusil; Wellspring Consumer Healthcare, Sarasota, FL) was provided. After completing the 20-week extension period, an additional 4-week follow-up of selected subjects was performed.

Outcome: Subjects completed an electronic diary for heartburn and use of rescue antacids twice daily: every morning upon waking to record the previous night's maximum heartburn severity, and every night before bedtime to record that day's maximum heartburn severity. Heartburn severity was graded on a scale of 0 (no heartburn) to 4 (very severe heartburn).

The primary outcome was the percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days) over the 4-week treatment period. Secondary outcomes included percentage of days without antacid rescue usage and mean severity of heartburn.

Data Analysis: Intention-to-treat (ITT) analysis was performed. Sample size was calculated assuming an efficacy of 50% for vonoprazan dosing in the percentage of days without daytime or nighttime heartburn over the 4-week placebo-controlled study (as well as to detect a 20% difference between vonoprazan and placebo dosing with a standard deviation of 35%). These targets were established in line with prior placebo-controlled studies in the United States for vonoprazan. This resulted in a suggested sample size of 250 individuals.

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

Results: Between February 2022 and October 2022, 776 subjects were randomized in the placebo-controlled phase, with 739 individuals completing this phase and 728 participants randomized into the extension phase. Non-compliance was broadly similar among each of the 3 arms (ranging from 3.1 to 4.7%). Vonoprazan 10 mg and vonoprazan 20 mg daily dosing increased the percentage of 24-hour symptom-free days in comparison to placebo (placebo: 27.7%; 10 mg: 44.8%; 20 mg: 44.4%). The effect was rapid, with approximately 10% of the difference between vonoprazan and placebo occurring with the administration of 1 dose, and

20% with the second dose. In those subjects followed over 6 months, this increase in symptom-free days persisted and gradually increased to 60%-70% of days. There was no difference in efficacy between 10 mg and 20 mg daily vonoprazan dosing. As expected physiologically, gastrin levels increased in recipients receiving vonoprazan.

COMMENTARY

Why Is This Important?

Gastroesophageal reflux disease (GERD) is a highly prevalent family of conditions ranging from functional heartburn to erosive esophagitis for which no significant pharmacologic therapy innovation has occurred since the 1980s until potassium competitive acid blockers (PCABs) like vonoprazan were approved. Pre-PCABs, prescribed therapy was limited to histamine 2-receptor antagonists (subject to tachyphylaxis) and proton pump inhibitors (subject to cumbersome pre-prandial dosing and taking the medication with regularity). Previous data has shown that PCABs significantly improve healing of erosive esophagitis compared to PPIs. By showing that vonoprazan also improves nonerosive reflux disease (NERD) symptoms, this study expands the populations potentially benefiting from PCAB therapy and led the FDA to approve vonoprazan 10 mg daily for NERD.

The American College of Gastroenterology's 2022 guidelines on the diagnosis and management of gastroesophageal reflux disease (GERD)[1] recommend an 8-week trial of empiric PPIs and to discontinuation of PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs. Vonoprazan upends these guidelines as this administration recommendation can likely be shortened if PCABs are used increasingly in lieu of PPIs given how quickly patients can respond to PCABs. In addition, while 2022 guidelines recommend a conceptual rationale for a trial of switching PPIs to patients who have not responded to 1 PPI and that more than 1 switch to another PPI cannot be supported, it may become common to switch directly to a PCAB if 1 PPI taken correctly fails to control symptoms.

Additionally, the pharmacology of PCABs is more amenable to as-needed dosing. As opposed to PPIs, which are a pro-drug and need to be swallowed into an acidic empty stomach and then followed by eating food 30 minutes later to activate acid pumps, PCABs can be swallowed with or without food and do not require eating food 30 minutes after ingestion to turn on acid pumps and optimize efficacy. This could provide advantages for NERD patients given the lack of mucosal injury. In patients who do not wish to be burdened by pre-prandial timing or are concerned about daily PPI administration, it will likely be more difficult to convince them to do so in the vonoprazan era. As vonoprazan

acts via on-demand mechanisms compared to PPIs, gastroenterologists will have to update communication scripts and shared decision-making models for NERD management, which is not as clearcut as erosive esophagitis management.

Key Study Findings

Vonoprazan 10 mg and vonoprazan 20 mg daily dosing increased the percentage of 24-hour symptom-free days in comparison to placebo (placebo: 27.7%; 10 mg: 44.8%; 20 mg: 44.4%). The effect was rapid, with approximately 10% of the difference between vonoprazan and placebo occurring with the administration of 1 dose, and 20% with the second dose.

Caution

The major limitation is that patients were defined as having non-erosive reflux disease without ambulatory reflux monitoring, which would differentiate NERD symptoms due to an elevation in the acid exposure time and/or number of acidic reflux episodes versus other disorders. Thus, this NERD cohort included similar GERD-spectrum conditions like reflux hypersensitivity and functional heartburn which are more related to disordered gut-brain interaction (DGBI) and less to pathologic acid-related mucosal injury (which PCABs treat).

While the authors correctly state that switching to PCAB therapy without reflux testing would be closer to what is done in clinical practice, readers should not surmise that switching to vonoprazan is a panacea to refractory GERD symptoms. Ambulatory reflux monitoring should still be considered according to the Lyon 2.0 consensus[2], to identify reflux hypersensitivity and functional heartburn for whom other treatment modalities may be appropriate (including neuromodulators).

My Practice

Based on this RCT, in patients who are hesitant to undergo wireless or catheter-based ambulatory reflux testing, I would consider switching to vonoprazan with refractory NERD symptoms. This would be subject to prior authorization/formulary considerations. As management of reflux hypersensitivity and functional heartburn bear more similarity to DGBI-spectrum conditions, I recommend ambulatory testing in PPI refractory cases. However, I practice in a tertiary academic medical center with ready access to reflux monitoring which I can interpret personally; most practicing gastroenterologists do not have that luxury.

For Future Research

Future trials involving vonoprazan for NERD should study optimal parameters for recommending on-demand administration for NERD. In erosive esophagitis, due to mucosal injury, standing dosing is reasonable to heal or further prevent further erosive disease. Daily administration in NERD is of less clear necessity. In addition, the as-needed pharmacology of vonoprazan is attractive for patients who are hesitant to use a once- or twice-daily acid suppression regime such as those recommended for

PPIs (and has already been shown to be effective from a symptom perspective[3]). It would be helpful for such future PCAB studies to consider the use of ambulatory reflux monitoring to clarify why participants do not respond to PCABs when they suffer from NERD. If patients can be reliably identified as having functional heartburn or reflux hypersensitivity if they fail to respond to PCAB therapy, this would be a useful addition to the literature which could inform updated parameters for referral to ambulatory reflux monitoring.

Conflict of Interest

Dr. Vélez has received research funding from Ironwood Pharmaceuticals.

REFERENCES

1. Katz P, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol 2022; 117(1):27-56.
2. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. Gut 2024; 5;73(2):361-371.
3. Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: Efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. Aliment Pharmacol Ther 2023;58(10):1016-1027.

EVIDENCE-BASED GI
AN ACG PUBLICATION

ERCP with Extracorporeal Shock-Wave Lithotripsy For Chronic Pancreatitis: Is It A "Sham" for Improving Pain?

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This summary reviews Talukdar R, Olesen SS, Unnisa M et al. Extracorporeal Shock-Wave Lithotripsy and Endoscopy for the Treatment of Pain in Chronic Pancreatitis : A Sham-Controlled, Randomized Trial. Ann Intern Med. 2024 Jun;177(6):749-758.

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Keywords: chronic pancreatitis, ERCP, ESWL

STRUCTURED ABSTRACT

Question: Is combined extracorporeal shock-wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic duct (PD) decompression superior to a sham procedure in alleviating pain in patients with chronic pancreatitis and intraductal stones?

Design: Single-center, parallel-group, sham-controlled, randomized controlled superiority trial with masking of patients and outcome assessors to intervention. Patients were enrolled from February 2021 to July 2022.

Setting: Pancreas Clinic of the Asian Institute of Gastroenterology (Hyderabad, India), a tertiary care referral center serving patients in India and neighboring countries. ESWL procedures were performed by 2 physicians, and ERCP by 4 advanced

endoscopists with a minimum of 10 years of experience.

Patients: Patients ages ≥18 years diagnosed with chronic pancreatitis, based on criteria including presence of pancreatic calcifications, Cambridge III/IV pancreatic duct abnormalities, or histologic confirmation of chronic pancreatitis, were included. Patients were required to have chronic abdominal pain consistent with chronic pancreatitis that occurred ≥3 days per week for ≥3 months, with a pain intensity >3 on a 0 to 10 visual analog scale (VAS). In addition, patients had PD obstruction due to intraductal stones with upstream PD dilation, determined using either magnetic resonance cholangiopancreatography (MRCP) or abdominal computed tomography. Notable exclusion criteria included prior pancreatic surgery, ESWL, or endoscopic therapy of the PD.

Interventions: Patients were randomly assigned in a 1:1 ratio to receive combined ESWL/ERCP vs. sham treatment. ESWL was performed under epidural anesthesia, with additional sessions if complete stone fragmentation was not achieved during the initial session. ERCP was then performed the day after lithotripsy to achieve PD clearance, defined as >90% reduction in the initial stone volume. A single plastic pancreatic stent was inserted in all patients in the ESWL/ERCP group. In comparison, the sham intervention consisted of a superficial pinprick sensation with a needle and the lithotripsy machine was then activated without making contact with the patient's body. To ensure masking of the patients, the patient's eyes were covered during both the ESWL and sham procedures. In the sham group, patients underwent a sham ERCP, where an endoscope was used to intubate the duodenum without any intervention.

Outcomes: Primary outcome was the mean change in pain score as assessed by the VAS at 12 weeks. This was assessed using a patient pain diary which recorded average and maximal daily pain intensity scores. There were multiple secondary outcomes assessed at 12- and 24-week follow-up, including change in pain score at 24 weeks, partial pain relief (30% improvement in VAS score compared to baseline), number of pain-free days, number of days using opioids, and hospitalization. Safety end points included post-procedure acute pancreatitis, perforation, bleeding, and infections.

Data Analysis: Intention-to-treat analysis was reported. For the primary outcome, a repeated measures, linear, mixed-effect model was used. An interim analysis was performed which showed no statistically significant difference between groups.

Two-sided p-value <0.049 was used as the threshold for statistical significance for the primary end point to account for the interim analysis.

Funding: Asian Institute of Gastroenterology and Aalborg University Hospital.

Results: Among 106 patients, 52 were randomized to the ESWL/ERCP group and 54 to the sham group. Mean age was 38 years, 72% of patients were male, 21% were current smokers, and 49% of patients were on strong opiates. Pancreatitis was attributed to alcohol in 35% of patients and idiopathic in 57%, and the mean diameter of the PD calculi was 10.2 mm. The mean baseline VAS pain score was 5.9 in the ESWL/ERCP group and 5.7 in the sham group. PD clearance was achieved in 46 (88%) patients in the ESWL/ERCP group.

Primary outcome: At 12 weeks, the mean change from baseline in VAS pain score was -5.0 (95% CI: -5.4 to -4.5) in the ESWL/ERCP group and -4.3 (95% CI: -4.7 to -3.8) in the sham group, resulting in a statistically significant mean difference in change in VAS of -0.7 (95% CI: -1.3 to 0; p=0.039). (Figure 1) However, at 24 week follow-up, there was no significant difference in VAS pain score between ESWL/ERCP group vs sham group: -5.3 (95% CI: -5.8 to -4.7) vs -4.5 (95% CI: -5.1 to -3.8), respectively, producing mean difference in change in VAS of -0.8 (95% CI: -1.6 to 0.1). (Figure 1) Also, there was no significant difference between groups for percentage of patients that achieved at least 30% pain relief from baseline at either 12 or 24 weeks.

There were numerical improvements in other secondary outcomes in the ESWL/ERCP vs. sham groups at 12 weeks, including partial pain relief (98% vs. 91%, risk difference: 7% [95 CI: 1% to 16%]), median number of pain-free days (58.2 vs. 42.0, median difference: 16.2 days [95% CI: 3.9 to 28.5]), number of days using opioids (4.6 vs. 10.0, median difference: 5.4 [95% CI: 9.9 to 0.9]), prevalence of depression (17% vs. 35%, risk difference: 18% [CI: 34% to 2%]), and self-report of improved health status (71% vs. 46%, risk difference: 25% [95% CI: 7% to 43%]). Post-procedure acute pancreatitis was numerically higher in ESWL/ERCP group vs sham group: 6% vs 2%, respectively.

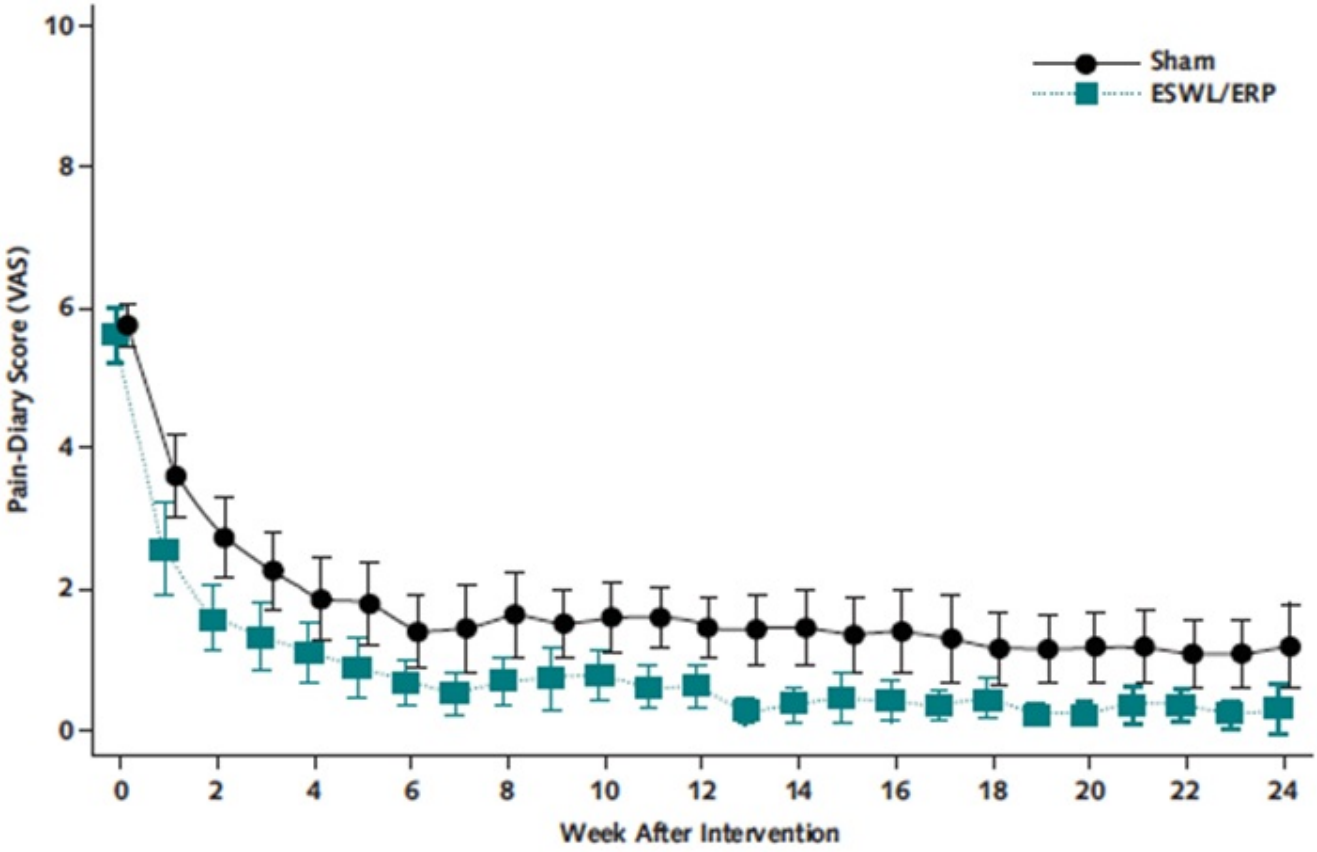

Figure 1. Visual analog scores for abdominal pain.

From *Annals of Internal Medicine*, Talukdar R, Olesen SS, Unnisa M. et al. Extracorporeal Shock-Wave Lithotripsy and Endoscopy for the Treatment of Pain in Chronic Pancreatitis : A Sham-Controlled, Randomized Trial. Ann Intern Med. 2024 Jun;177(6):749-758.

COMMENTARY

Why Is This Important?

Abdominal pain significantly impacts quality of life and morbidity in patients with chronic pancreatitis, and up to 30% of patients will have PD obstruction.[1,2] Current guidelines support treatment of obstructive PD stones in patients with abdominal pain due to chronic pancreatitis, as PD obstruction may exacerbate pain. Most recently, the 2022 American Gastroenterological Association Clinical Practice Update supported use of ESWL and/or pancreatoscopy with intraductal lithotripsy for PD stones >5 mm and use of ERCP for clearance of ≤5 mm MPD stones.[3] Similarly, the 2018 ESGE Guidelines recommend ESWL for the clearance of radiopaque obstructive main PD stones ≥5 mm and ERCP for main PD stones that are radiolucent or <5 mm.[4]

Evidence to support these statements has relied mostly on small or observational studies, which have suggested

that combined ESWL/ERCP is effective in treating pain from chronic pancreatitis with obstructing PD stones.[5-7] A 2016 meta-analysis of 27 studies examining the use of ESWL (predominantly in combination with ERCP) in chronic pancreatitis with PD stones >5 mm reported complete ductal clearance in 71% of patients, absence of pain in 53% of patients at 2-year follow-up, and improved quality of life in 88% of patients, further supporting the potential efficacy of this therapy.[8] However, is the improvement in abdominal pain truly due to the efficacy of the procedure or is it due to the placebo response from an invasive intervention for chronic pain?

Invasive interventions for chronic pain frequently demonstrate efficacy in observational studies, but fail when compared to sham procedures.[9] Among advanced endoscopists, one of the best known examples is the EPISOD randomized controlled trial (RCT).[10] Prior to its publication in 2014, it was common to perform ERCP with sphincterotomy among post-cholecystectomy patients with persistent abdominal pain, which was thought to be due to Sphincter of Oddi (SOD) dysfunction. This approach was also supported by data from unblinded. observational retrospective studies. However, the blinded EPISOD RCT compared this intervention to ERCP without sphincterotomy. (Note: PD stent placement was performed in all patients to reduce post-ERCP pancreatitis when SOD manometry was performed.) Patients in both groups experienced major reductions or resolution of abdominal pain, but sphincterotomy provided no additional benefit. The excellent RCT by Talukdar and colleagues also produces similar outcomes.

Their study, entitled the SCHOKE RCT, is the first sham-controlled randomized trial investigating the use of ESWL/ERCP with PD decompression for the treatment of pain in chronic pancreatitis with obstructive PD stone(s). The use of a sham control group here is particularly impactful, as prior studies have suggested a strong placebo effect in patients with chronic pancreatitis, with reports of remission of abdominal pain in up to 20% of chronic pancreatitis patients treated with placebo tablets.[11] This study (SCHOKE RCT) also found large reductions in abdominal pain in both groups. (Figure 1) However, there was only a modest improvement in VAS pain scores at 12 weeks with ESWL/ERCP compared to sham. This met the threshold for statistical significance, but did not meet the pre-specified and generally accepted threshold for minimal clinically important difference. Furthermore, this effect did not persist at 24 weeks. Multiple secondary outcomes were assessed which suggested a numerical improvement or trend in rates of partial pain relief, pain-free days, days using opiates, as well as depression and self-reported quality of life scores.

Key Study Findings

Among patients with chronic abdominal pain due to chronic pancreatitis with obstructive PD stone(s), reduction in the

VAS pain score (on a scale from 0 to 10) was significantly greater in patients who underwent combined ESWL/ERCP vs. sham procedure: -5.0 vs. -4.3; mean difference -0.7 (95% CI: -1.3 to 0). Although this was a statistically significant difference, it did not meet criteria for a pre-specified and generally accepted threshold for minimal clinically important difference in pain reduction, and no significant improvement was demonstrated at 24 weeks, although both groups had large reductions in abdominal pain (Figure 1).

Caution

This was a single-center study performed at a specialized center with significant experience treating patients with chronic pancreatitis. Follow-up time for the primary outcome was only 12 weeks, and improvement in abdominal pain was seen in a high proportion of the sham-control group. It may be helpful to conduct further studies with larger study populations and longer term follow-up to assess the durability of outcomes of ESWL/ERCP. Lastly, ESWL for pancreatic lithiasis is not widely available in the US, where ERCP with electrohydraulic lithotripsy may be more common. Therefore, generalizability to US practices may be limited.

My Practice

Currently, we will continue to consider endoscopic therapy in selected patients with pain related to chronic pancreatitis and evidence of PD obstruction amenable to endoscopic intervention (PD stone or stricture in the head, neck or proximal body). To avoid causing duct injury or pancreatitis in healthy pancreas, we may avoid endoscopic intervention if the downstream duct is not affected by chronic pancreatitis changes. For stones >5 mm that are amenable to ERCP with pancreatoscopy, we perform electrohydraulic lithotripsy. If this is not possible, we then consider ESWL followed by ERCP for stone extraction.

Importantly, if the patient does not benefit from endoscopic PD decompression, we may recommend referral for surgical evaluation, as several studies, including RCTs, have suggested that long-term outcomes with respect to pain control may be better after surgical vs endoscopic intervention.[12,13]

For Future Research

Long-term follow-up with larger study populations after ESWL/ERCP vs placebo/sham will be helpful to understand if there are any lasting benefits to PD decompression to treat pain in chronic pancreatitis. In addition, investigating optimal approaches to PD decompression (such as comparing ESWL/ERCP vs ERCP with pancreatoscopy-directed lithotripsy for large PD stones) may further inform clinical practice.

Conflicts of Interest

Dr. Zhou and Dr. Eldika report no financial conflicts of interest.

REFERENCES

1. Machicado JD, Amann ST, Anderson MA, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co -Morbidities. Am J Gastroenterol. 2017;112(4):633-642.
2. Olesen SS, Phillips AE, Faghih M, et al. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing and psychological distress on patient-reported outcomes in chronic pancreatitis. Gut 2022;71 (12):2518-2525.
3. Strand DS, Law RJ, Yang D, Elmunzer BJ. AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review. Gastroenterology 2022;163(4):1107-1114.
4. 4. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018. Endoscopy 2019;51(2):179-193.
5. Tandan M, Nageshwar Reddy D, Talukdar R, et al. ESWL for large pancreatic calculi: Report of over 5000 patients. Pancreatology 2019;19 (7):916-921.
6. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut. Apr 2007;56(4):545-52.
7. Vaysse T, Boytchev I, Antoni G, et al. Efficacy and safety of extracorporeal shock wave lithotripsy for chronic pancreatitis. Scand J Gastroenterol 2016;51(11):1380-5.
8. Moole H, Jaeger A, Bechtold ML, Forcione D, Taneja D, Puli SR. Success of Extracorporeal Shock Wave Lithotripsy in Chronic Calcific Pancreatitis Management: A Meta-Analysis and Systematic Review. Pancreas. 2016;45(5):651-8.
9. Cotton PB. Why Did Sham. Episod Patients Do So Well-Important Lessons for Research and Practice. Gastointest Endosc 2019; 89: 1054-55.
10. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of Endoscopic Sphincterotomy for Suspected Sphincter of Oddi Dysfunction on Pain-Related Disabillity Followng Cholecystectomy: The EPISOD RCT. JAMA 2014; 311: 2101-09.
11. Capurso G, Cocomello L, Benedetto U, Cammà C, Delle Fave G. Meta-analysis: the placebo rate of abdominal pain remission in clinical trials of chronic pancreatitis. Pancreas 2012;41(7):1125-31.
12. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis: The ESCAPE Randomized Clinical Trial. JAMA 2020;323(3):237-247.
13. Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology 2011;141(5):1690-5.

EVIDENCE-BASED GI
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In Case You Missed It
2022 ACG Clinical Guideline-Gastroparesis: Limited Evidence-Based Options

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MOTILITY

This summary reviews Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. Am J Gastroenterol 2022;117(8):1197-1220.

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Keywords: gastroparesis; metoclopramide; gastric emptying study; prucalopride

STRUCTURED ABSTRACT

Question: What are appropriate tests to diagnose gastroparesis? Which pharmacologic and non-pharmacologic therapies are superior to placebo to improve gastroparesis symptoms and improve gastric emptying?

Design: The Patient Intervention Comparison and Outcomes (PICO) format was used to develop key questions of clinical relevance to be addressed in the guideline. Two health services librarians performed literature searches of Pubmed (MEDLINE), EMBASE, and the Cochrane Library for English language publications up to 2021 in human populations using search terms consistent with key questions.

GRADE methodology was used to assess benefits and risks of therapies and diagnostic tests. When evidence was inadequate, an expert consensus was used to

make recommendations.

Patients: Adult patients, with or without diabetes, with one or more of the following cardinal symptoms of chronic nausea, vomiting, early satiety, postprandial fullness, bloating or upper abdominal discomfort in the absence of mechanical obstruction.

Interventions/Exposure:
Diagnostic testing: Scintigraphic gastric emptying (SGE), radiopaque markers, wireless motility capsule, stable isotope (^{13}C-spirulina) breath test and pyloric EndoFLIP evaluation.
Management: dietary recommendations, dopamine receptor agonists (metoclopramide, domperidone), 5-HT4 agonists (prucalopride, clebopride, revexepride, velusetrag, felcisetrag), ghrelin agonists (relamorelin), motilin agonists (erythromycin, azithromycin), dopamine D2 antagonist (haloperidol), antiemetics and central neuromodulators (aprepitant, tradipitant, nortriptyline), herbal therapies (Rikkunshito, STW5/Iberogast), acupuncture, gastric electric stimulation, intrapyloric injection of botulinum toxin and pyloromyotomy (G-POEM).

Outcomes: Diagnosis of gastroparesis (detection of delayed gastric emptying of solids), patient reported outcomes/symptoms and improvement in gastric emptying (pharmacologic and non-pharmacologic interventions).

Data analysis: The GRADE process was used to formulate the quality of evidence and the strength of recommendation for each question, based on study design, efficacy, and risks vs benefits. When the evidence was not appropriate for the GRADE process, an expert consensus approach was used to formulate key concepts statement.

The GRADE process[1,2] uses 2 types of guideline recommendations:

Strong Recommendation: Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by High or Moderate Level of Evidence from well-designed randomized controlled trials (RCTs) or RCTs with mild methodologic limitations.

Conditional Recommendation/Suggestion*:* Many providers might suggest this therapy or diagnostic test, while other providers would not suggest this intervention in similar patients. Conditional recommendations/suggestions are usually accompanied by Low quality or Very Low quality of evidence from studies without a comparator arm or placebo for comparison.

Funding: American College of Gastroenterology, through the Practice Parameters Committee.

Results: Selected guideline recommendations are listed in Table 1. Scintigraphic gastric emptying of a solid meal with a duration of at least 3 hours is recommended for diagnosis of gastroparesis (Strong Recommendation, Moderate Quality of Evidence). Shorter studies, especially gastric emptying studies which are only 90 minutes long, should not be used because they may produce false negative results.

Notably, the only strong treatment recommendations focus on therapies NOT supported for use. Neuromodulators, ghrelin agonists, and intrapyloric botox injections are not supported for use (Strong Recommendation, Moderate Quality Evidence). Small-particle diets, metoclopramide, domperidone, antiemetic agents, and 5HT4 agonists are suggested for symptom control or improvement in gastric emptying.

COMMENTARY

Why Is This Important?

In honor of Gastroparesis Awareness Month in August 2024, we're utilizing our "In Case You Missed It" (ICYMI) series to summarize a seminal guideline from 2022 that deserves further focus. This guideline demonstrates that there is a huge unmet medical need for effective treatments based on high-quality randomized controlled trials (RCTs).

Gastroparesis is commonly caused by diabetes. Idiopathic cases are also common and may occur as a post-viral syndrome. Of course, medications may also slow gastric motility. Among patients with gastroparesis, severity of delayed gastric emptying does not correlate with symptom severity. Management is further complicated by a significant overlap with functional dyspepsia. (i.e., functional dyspepsia patients report gastroparesis-type symptoms, yet have normal gastric emptying results.)

For an easily readable and concise summary of the guideline, the ACG's *Guide to the Guidelines*[3] by Brennan Spiegel and Hetal Karsan provides outstanding commentary about interpretation and application of the recommendations.

Key Study Findings

Gastroparesis is best diagnosed with a scintigraphic solid food gastric emptying study of at least 3-4 hours duration, but patients must stop pro-motility agents, antiemetics, opiods, marijuana, and neuromodulators (e.g., nortriptyline) for 48 hours before the exam and control glucose levels in order to produce accurate results.

	Strength of Recommendation[#]	Certainty of Evidence[t]
After exclusion of mechanical obstruction, scintigraphic gastric emptying of a solid meal over a duration of 3hrs or greater remains the standard test to diagnose gastroparesis.	Strong	Moderate
Dietary management should include a small-particle diet.	Conditional	Low
Metoclopramide is suggested over no treatment for management of refractory symptoms.	Conditional	Low
Where approved for use, domperidone is suggested for symptom management.	Conditional	Low
5HT4 agonists are suggested over no treatment to improve gastric emptying.	Conditional	Low
Antiemetic agents are suggested for symptom control, but do not improve gastric emptying.	Conditional	Low
Gastric electrical stimulation may be considered for control of gastroparesis symptoms as a humanitarian use device.	Conditional	Low

Table 1. Selected guideline recommendations for management of gastroparesis.

[#]Strong Recommendation: Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by High or Moderate Level of Evidence from well-designed randomized controlled trials (RCTs), or RCTs with mild methodologic limitations.

[t]Conditional Recommendation: Many providers might suggest this therapy, while other providers would consider alternative management. This variability reflects the low quality or very low quality of evidence from studies without a comparator arm or placebo for comparison.

Initial treatment may focus on a small-particle diet[4], which essentially focuses on foods that are less than 2 mm in diameter after chewing and/or are the consistency of mashed potatoes. Metoclopramide is the only US Food and Drug Administration (FDA)-approved medication for gastroparesis and has demonstrated improvement of nausea and other symptoms as well as accelerating gastric motility in small RCTs with methodologic limitations. The risk of tardive dyskinesia with metoclopramide is frequently overestimated, and is actually about 0.1% per 1,000 person-years of use.

Caution

The major limitation is that there are so few double-blind, placebo-controlled

RCTs of potential gastroparesis treatments to identify effective treatments.

My Practice

My approach is consistent with the ACG Guideline recommendations and the commentary found in the ACG's *Guide to the Guidelines* by Spiegel and Karsan. Specifically, when I suspect gastroparesis, I get a 4-hour scintigraphic solid-food gastric emptying study with patient off opiods, marijuana, promotility agents, antiemetics and neuromodulators for 48-72 hours before the test and try to insure that glucose levels have been controlled in my diabetic patients, since hyperglycemia could impact results.

For treatment, I start with a small-particle diet and use publicly available guides from the University of Virginia.[4] If the patient has constipation, which is quite common in gastroparesis, then I'll prescribe prucalopride 2 mg twice daily, which is FDA-approved for chronic idiopathic constipation. This is the only 5-HT4 agonist that is readily available in the US. If this is inadequate and the patient is willing to try metoclopramide, then I'll discuss the risks and benefits, document that discussion, and gradually increase the dose to 10 mg 3 times daily. Officially, the FDA only approves use for up to 12 weeks, but if the patient has failed multiple interventions and is doing much better with metoclopramide, then I'll again review risks/benefits with the patient, document the discussion, and continue the medication long-term.

Domperidone 10 mg 3 times daily, which has pro-motility and anti-emetic properties, may be the most effective and safest gastroparesis treatment based on RCTs and my own clinical experience. Although it's approved for use in virtually every country in the world, it's only available in the US through an FDA-monitored extended access Investigational New Drug program[5,6], which requires a lot of paperwork. In Eastern Michigan, my patients can easily drive into Windsor, Canada, see a physician there, and fill a domperidone prescription. Your patients may want to do their own investigations about how to legally obtain domperidone.

I avoid ondansetron as an antiemetic, since it may slow intestinal motility, and frequently use cyproheptadine, which is an antihistamine, 4 mg every 8 hours as needed. Finally, if my patients are taking opiods (especially if they are using them for abdominal pain due to gastroparesis), I bluntly educate them to taper off of them or expect to live with chronic gastroparesis symptoms. Although I will see gastroparesis patients on opiods, I'm candid that their symptoms are unlikely to resolve as long as they continue opiod use. My approach is similar if the patient chronically uses cannabis. Although symptoms of cannabinoid hyperemesis syndrome may improve within 10 days of stopping marijuana use, it may take up to 2 months to see symptom improvement. So, if your patient says that they stopped marijuana for a couple of days and their nausea and abdominal discomfort did not improve, that does not eliminate cannabinoid hyperemesis syndrome as an un-

derlying cause.

For Future Research

The absence of FDA-approved therapeutics represents a huge unmet medical need for patients. This is partly due to the lack of a FDA-approved patient-reported outcome for use in RCTs.

Conflict of Interest

Drs. Al Kazzi and Schoenfeld report no relevant conflicts of interest.

REFERENCES

1. AGREE Next Steps Consortium (2017). The AGREE II Instrument [Electronic version]. https://www.agreetrust.org/resource-centre/agree-ii/. Accessed July 12, 2024.
2. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010;182:E839-842.
3. Spiegel B, Karsan H. Guide to the Guidelines, Volume 1. Bethesda, MD: American College of Gastroenterology; 2023: 67-77.
4. University of Virginia Health System Nutrition. Diet Interventions for Gastroparesis. https://med.virginia.edu>sites>2023/12>gastroparesis-long-version-2023. Accessed August 6, 2024.
5. United States Food and Drug Administration. How to Request Domperidone for Expanded Access Use. Published online February 2, 2021. https://www.fda.gov/drugs/investigational-new-drug-ind-application/how-request-domperidone-expanded-access-use. Accessed August 15, 2024.
6. United States Food and Drug Administration. Information About Domperidone. https://www.fda.gov/drugs/information-drug-class/information-about-domperidone. Accessed August 15, 2024.