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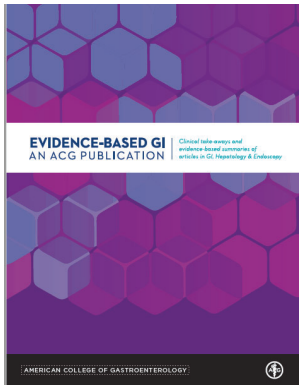

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TABLE OF CONTENTS

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INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

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

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx

IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

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

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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The Edge of a New Frontier: Anti-TL1A Monoclonal Antibodies for Ulcerative Colitis

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Guest Contributor

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Associate Editor

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IBD

This summary reviews Sands BE, Feagan BG, Biroulet LP, et al. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. N Engl J Med 2024; 391: 1119-29.

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

Keywords: Ulcerative colitis; tulisokibart; anti-TL1A monoclonal antibody

STRUCTURED ABSTRACT

Question: What is the efficacy and safety of tulisokibart, a tumor necrosis factor–like cytokine 1A monoclonal antibody (anti-TL1A) in patients with moderate to severe active ulcerative colitis (UC)?

Design: A phase 2, multicenter, double-blind, placebo-controlled trial (ARTEMIS-UC trial).

Setting: The trial was conducted in 14 countries, with enrollment from North America, Western Europe, Eastern Europe, and Australia.

Patients: Adults diagnosed with moderately to severely active colitis (defined by modified Mayo score of 4-9, an endoscopic subscore of ≥2, and rectal-bleeding

subscore of ≥ 1) with glucocorticoid dependence or treatment failure or intolerance to one or more conventional or advanced therapies approved for the treatment of UC. Notable exclusion criteria included UC limited to < 15 cm from the anal verge, fulminant colitis, surgical resection within 3 months of screening, concomitant primary sclerosing cholangitis, unresected low grade or high-grade dysplasia, severe disease affecting other organs (kidneys, liver, blood, lungs, heart, neurologic, ophthalmologic or cerebral), history of cancer within 5 years, risk for tuberculosis reactivation, active infections, or bacterial infections within 3 months.

Interventions: The study was conducted in 2 cohorts. Cohort 1 was agnostic to testing for drug response. Cohort 2 was limited to people who had a genetic-based diagnostic test to identify people with an increased likelihood of response to the anti-TL1A antibody. In both cohorts, patients were randomly assigned in a 1:1 ratio to receive intravenous tulisokibart at a dose of 1,000 mg on day 1, followed by 500 mg at weeks 2, 6, and 10, or placebo at the same time points.

Outcomes: The primary efficacy end point was clinical remission at week 12 in cohort 1, defined as a modified Mayo endoscopic subscore of 0-1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0-1 and not greater than the baseline value. Secondary end points assessed at week 12 were endoscopic improvement, clinical response, symptomatic remission, histologic improvement, histologic–endoscopic mucosal improvement, mucosal healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) response. The partial Mayo score (comprising the stool-frequency subscore, rectal-bleeding subscore, and physician's global assessment subscore) was an exploratory end point; each subscore has a range of 0-3, with higher scores indicating greater severity. Antibodies to tulisokibart were measured with the use of a high-sensitivity, drug-tolerant assay. Inflammatory activity was assessed by high-sensitivity C-reactve protein (CRP) and fecal calprotectin. Safety was assessed through monitoring of adverse events, physical examination, measurement of vital signs, electrocardiography, and laboratory evaluations.

Data analysis: The primary analysis, performed in cohort 1, assessed clinical remission at week 12. In addition, patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified sub-group analyses to assess the efficacy of tulisokibart.

The efficacy analysis followed a modified intention-to-treat principle, including all randomized patients who received at least 1 dose of tulisokibart or placebo. The

primary endpoint was tested between trial groups at a 2-sided significance level of 0.05 using the Cochran–Mantel–Haenszel test, with stratification by prior advanced therapy exposure and status of the test for likelihood of response. Treatment difference was estimated. Changes in IBDQ scores, fecal calprotectin, and CRP were summarized with descriptive statistics.

Funding: The trial was funded by Prometheus Biosciences, a subsidiary of Merck, the manufacturer of tulisokibart.

Results: Patients in all trial arms had similar baseline characteristics. Among 135 patients randomized in cohort 1 and 75 patients randomized in cohort 2, mean age varied from 37-42 years old, mean duration of disease, 6-8 years, mean modified Mayo score 7, and 48%-53% had prior biologic therapy. In cohort 1, a significantly higher percentage of patients receiving tulisokibart achieved clinical remission vs placebo at 12 weeks: 26% vs 1%, respectively; difference, 25 percentage points; 95% confidence interval [CI], 14 to 37; $P < 0.001$ (**Figure 1**). Additionally, tulisokibart-treated patients were more likely than placebo-treated patients to achieve endoscopic improvement, clinical response, and other secondary endpoints (Figure 1), as well as greater decreases CRP, fecal calprotectin, and change from baseline in the total IBDQ score. Subgroup analyses for clinical remission and endoscopic improvement showed a consistent benefit of tulisokibart as compared with placebo in patients receiving concurrent glucocorticoids and immunosuppressants.

A supplemental analysis combined patients with a positive test for likelihood of response from cohorts 1 (n=32) and cohort 2 (n = 43). In this patient group, tulisokibart-treated patients were more likely to achieve clinical remission at week 12 vs placebo-treated patients: 32% vs 11%, respectively; difference, 21 percentage points; 95% CI, 2 to 38; $P = 0.02$). However, tulisokibart-treated patients in this combined cohort trended toward endoscopic improvement vs placebo-treated patients, but did not quite attain statistical significance: 37% vs 19%, respectively; difference, 18 percentage points; 95% CI: -2 to 36; $P = 0.06$.

Among all the enrolled patients (cohorts 1 and 2), the percentage of patients reporting an adverse event was similar in the 2 trial groups (46% in the tulisokibart group and 43% in the placebo group). Most adverse events were mild to moderate in severity. Infections were the most common adverse event with 18% in both the drug arm and placebo arm experiencing an infection. Worsening UC was also assessed as an adverse event and occurred in 10% of patients in the placebo arm and 1% of patients in the drug arm.

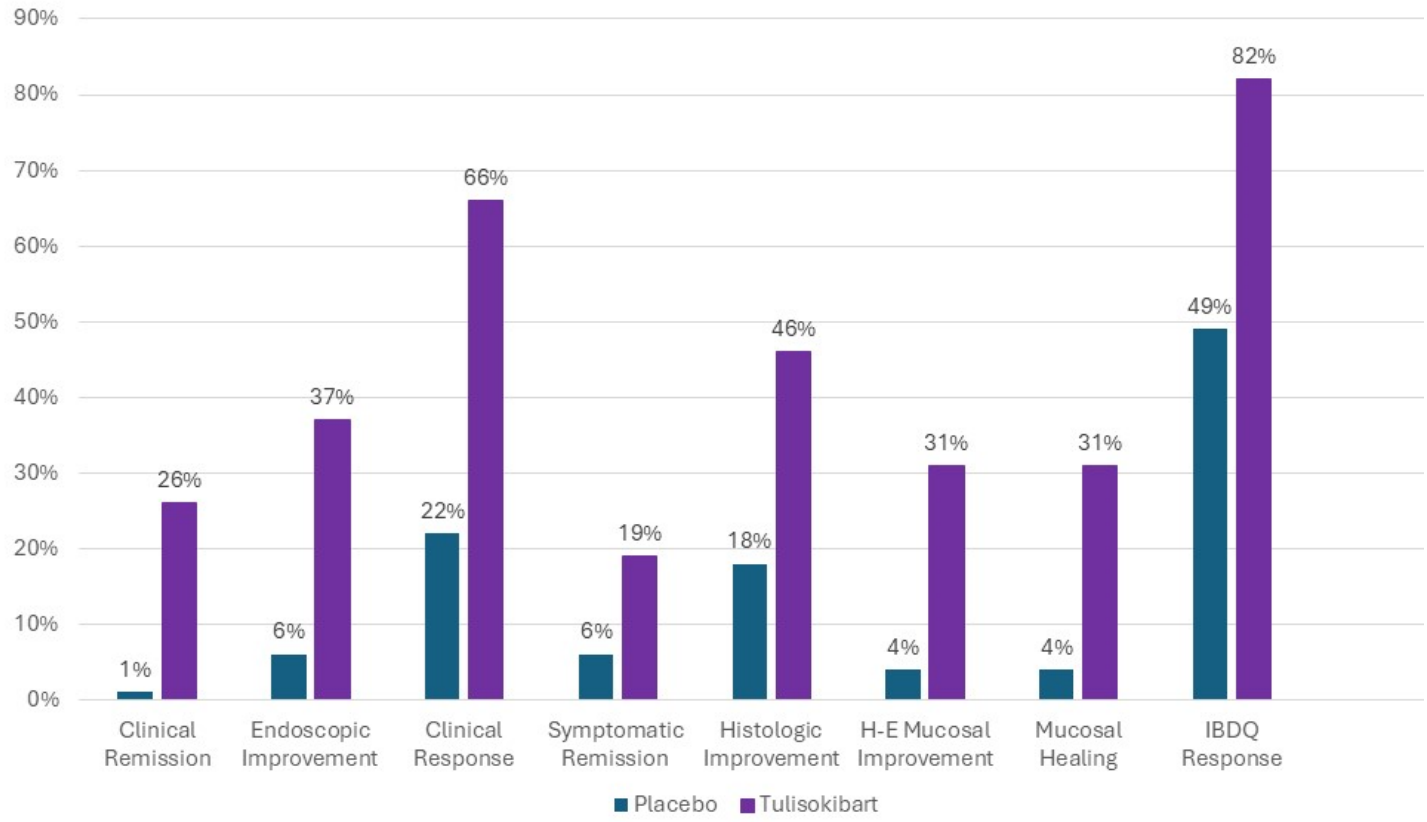

Figure 1. Percentage of patients reaching primary and secondary endpoint results in Cohort 1 (n=135). Primary endpoint was clinical remission. H-E, histologic-endoscopic.

COMMENTARY

Why Is This Study Important?

The therapeutic armamentarium for the treatment of moderate-to-severe UC has expanded rapidly over the past decade. However, it has been 5 years since the approval of a new biologic mechanism for the treatment of ulcerative colitis: Ustekinumab, an IL-23 targeted monoclonal antibody introduced in 2019. (Ozanimod, an oral sphingosine-1-phosphate modulator/small molecule was approved in 2021.) Therefore, tulisokibart offers the potential for a new treatment for UC patients that failed other biologic agents. It's a humanized IgG1-kappa monoclonal antibody that binds to TL1A with high affinity and specificity, preventing the interaction of TL1A and DR3. This suppresses type 1 and type 17 helper T-cell responses, enhances regulatory T-cell activity, and reduces pro-fibrotic pathways.[1] Ultimately, there are 2 exciting possibilities with this class of agents based on prior research. First, it may disrupt the fibrostenotic process that occurs as part of the inflammatory cascade in IBD patients. Second, genetic polymorphisms may identify patients that are more and less likely to respond to anti-TL1A monoclonal antibodies. Thus, there is the potential to provide IBD patients with precision-medicine approach

where treatment is selected based on a predictive biomarker.

While the proportion of patients who met the primary end point (clinical remission) in this trial is low (26%), that only 1% of patients in the placebo arm met this end point suggests that this was a highly treatment refractory population with nearly half the patients in the trial not demonstrating sustained response to an advanced therapy.[2] This is much more reflective of real-life practice. Also, higher proportions of patients demonstrated clinical response (66% vs 22%) and improvement in quality of life (82% vs 49%). These are promising numbers especially given that the endpoints were only assessed at 12 weeks.

Another novel aspect of this trial is the use of a genetic-based diagnostic test to predict response to the drug and stratify cohorts based upon this. While the test itself was only discussed briefly in the main article, data from the appendix reveals that a PCR-based assay was developed by the study sponsor which then evaluated polymorphisms in the genotypes related to TL1A biology. Testing was conducted by buccal swabs, and a machine-learning based approach to identify genotypes associated with therapeutic response was utilized. While this test has not been studied for clinical use and is not commercially available, this test and future iterations of the biomarker test represent hope for being able to better tailor medications to our patients.

Key Study Findings

Tulisokibart, a monoclonal antibody directed against TL1A, was more effective than placebo for induction of clinical remission at week 12 in patients with moderately to severely active ulcerative colitis.

Adverse events were similar in both drug and placebo arms: the overall adverse event rate was 46% in the drug arm and 43% in the placebo arm, however, only 1% of were serious adverse events in the drug arm and 8% in the placebo arm. Tulisokibart is a promising drug to study in a large Phase III clinical trial setting for the treatment of moderate to severe ulcerative colitis, even in those patients who have not been able to tolerate or have not had adequate response to other advanced therapies.

Caution

This study is only a Phase 2 trial, with a small number of people (90 in the drug arm and 88 in the placebo arm). Furthermore, the published data are only for induction and assess outcomes at 12 weeks, whereas the more meaningful outcomes are longer term. Phase 3 trials with larger cohorts and a longer duration to assess the impact of maintenance therapy is necessary to confirm the efficacy and safety of tulisokibart for treating moderate to severe ulcerative colitis. Additionally, the analysis of patients with a positive test for likelihood of response was constrained by a small sam-

ple size, as these patients were pooled from cohorts 1 and 2. Dedicated studies of the predictive value of this proprietary diagnostic assay are needed.

My Practice

Presently, this trial has not changed my clinical practice. However, it does offer hope for patients who have only had a good response to anti-TNF agents, without a response to small molecules or other biologic mechanisms. The recently published living UC guidelines and accompanying evidence synthesis highlight that while there are multiple approved highly efficacious treatments for UC for advanced therapy naïve patients: anti-TNF monoclonal antibodies, anti-integrin monoclonal antibodies, anti-IL 23 monoclonal antibodies, sphingosine-1-phosphate modulators, and JAK1 inhibitors. However, only JAK1 inhibitors and ustekinumab, an anti-IL23 monoclonal antibody are recommended for UC patients that previously tried and failed other advanced therapies.[3, 4] Unfortunately, ustekinumab tends to be a slower acting medication. Therefore, if tulisokibart continues to perform well in Phase 3 trials, then it may be a preferred biologic agent for advanced therapy experienced patients in light of the early response seen in this induction trial, at least for patients where JAK1 inhibitors are contraindicated.

Ultimately, it takes many years to bring a drug to the market, so it is not yet time to start speaking to our patients about this novel mechanism being a therapeutic option. Nevertheless, it's quite exciting to have a potentially new biologic agent with a unique mechanism of action which also has the potential to use a biomarker to identify patients most likely to be responders.

For Future Research

A Phase 2 trial to test the efficacy of tulisokibart for the treatment of Crohn's disease has been completed as well and both the UC and CD programs have moved to Phase 3 trials, which is promising. This drug is also being studied in much earlier stages for systemic sclerosis associated interstitial lung disease. It's possible that understanding the response to the anti-TL1A pathway in immune-mediated inflammatory disorders can help disentangle the complex relationship between inflammation and fibrosis. Additionally, this trial was novel in using a diagnostic test to predict response and not having chronologic age limits for exclusion. However, it is time to move beyond the placebo controlled new drug trial, which in this therapeutic era, I would argue is not just impractical from a recruitment standpoint, but also unethical.

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Cold vs Hot Snare Resection of Large Polyps: A Cooler, Safer Approach for Large Colorectal Polyps

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This summary reviews Steinbrück I, Ebigbo A, Kuellmer A, et al. Cold versus hot snare endoscopic resection of large nonpedunculated colorectal polyps: Randomized controlled German CHRONICLE trial. Gastroenterology. 2024 Sep;167(4):764-777.

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Keywords: Colorectal adenoma; colorectal neoplasia; endoscopic polypectomy; endoscopic procedures; therapeutic endoscopy

STRUCTURED ABSTRACT

Question: Does cold snare endoscopic mucosal resection (EMR) offer a safer and equally effective alternative to hot snare EMR for large (≥2 cm), nonpedunculated colorectal polyps (LNPCPs)?

Design: Randomized controlled multicenter trial comparing cold snare EMR with hot snare EMR, using a 1:1 randomization ratio with concealment of allocation and blinding of patients to treatment group.

Setting: Conducted at 19 tertiary referral centers in Germany between 2021 and 2023.

Patients: A total of 363 patients with 396 large, nonpedunculated colorectal polyps (≥2 cm) were included. Exclusion criteria included pedunculated polyps, residual/recurrent polyps, suspected malignancies, polyps with large nodules (>1-1.5 cm), antiplatelet/anticoagulant use that could not be held, or contraindications to treatment.

Intervention: Patients were randomly assigned to either cold snare EMR or hot snare EMR. Both groups adhered to standard procedural guidelines using piecemeal resection. Cold snare EMR avoided thermal injury by using mechanical-only resection. Normal saline, with or without staining liquids (e.g., indigo carmine) and/or diluted 1:10,000 adrenaline, was used for EMR.

Outcomes: Primary outcome was major adverse events (AEs), including perforation and postprocedural bleeding. Secondary outcomes were intraprocedural bleeding, residual/recurrent adenoma rates at follow-up, postpolypectomy syndrome, resection speed, and technical success rates. A standardized telephone interview was conducted 4 weeks after the procedure to assess for AEs and repeat colonoscopy to assess for residual adenoma after piecemeal resection was performed 4 (+/-2) months after index polypectomy.

Data Analysis: Statistical comparisons were made using intention-to-treat (ITT) and per-protocol (PP) analyses. ITT included all randomized patients. PP excluded cases in which allocated intervention was not carried out as planned (conversion of resection technique or other protocol violation).

Funding: Supported by the Gastroenterology Foundation, Küsnacht, Switzerland. The funder had no role in study design, data collection, analysis, or manuscript preparation.

Results: Among the 363 study patients, mean age was 66, male-52%, and histology determined that 46% adenomas with low-grade dysplasia and 35% were sessile serrated lesions (SSLs) or hyperplastic polyps. Cold resection was converted to hot in 14 cases. Cold EMR showed a slightly lower success rate than hot EMR (92.2% vs 97.5%; $P = 0.022$). En bloc resection was higher in the hot EMR group (2.1% vs 8.4%; $P < 0.001$). However, polyps were resected in more than 5 pieces at a higher rate in cold EMR (68.9% vs 45.8%; $P < 0.001$). There was no significant difference in resection speed.

Cold snare EMR had significantly fewer major AEs (1.0% vs 7.9%; $P = 0.001$). (Figure 1) No perforations occurred in the cold group, compared to 3.9% in the hot group. Postprocedural bleeding rate was also lower in the cold EMR group (1.0% vs 4.4%; $P = 0.04$). The only predictor for major AEs was polyp diameter ≥4 cm (odds ratio [OR], 3.37). Higher rates of residual/recurrent adenoma in cold EMR (23.7% vs 13.8%; $P = 0.020$). (Figure 1) Predictors of residual/recurrent adenoma were large lesions ≥4 cm (OR, 2.47; 95% confidence intervals [CI]: 1.25-9.09) and high-grade dysplasia/carcinoma (OR, 2.92; 95% CI: 1.22-7.00). Post-hoc analysis showed similar rates of residual neoplasia for SSL in the cold vs hot group (8.3% vs 4.8%; $P = 0.681$) and for laterally spreading tumors, while only the nodular-mixed type had significantly different rate of residual adenoma (40.5% vs 14.3%; $P = 0.011$).

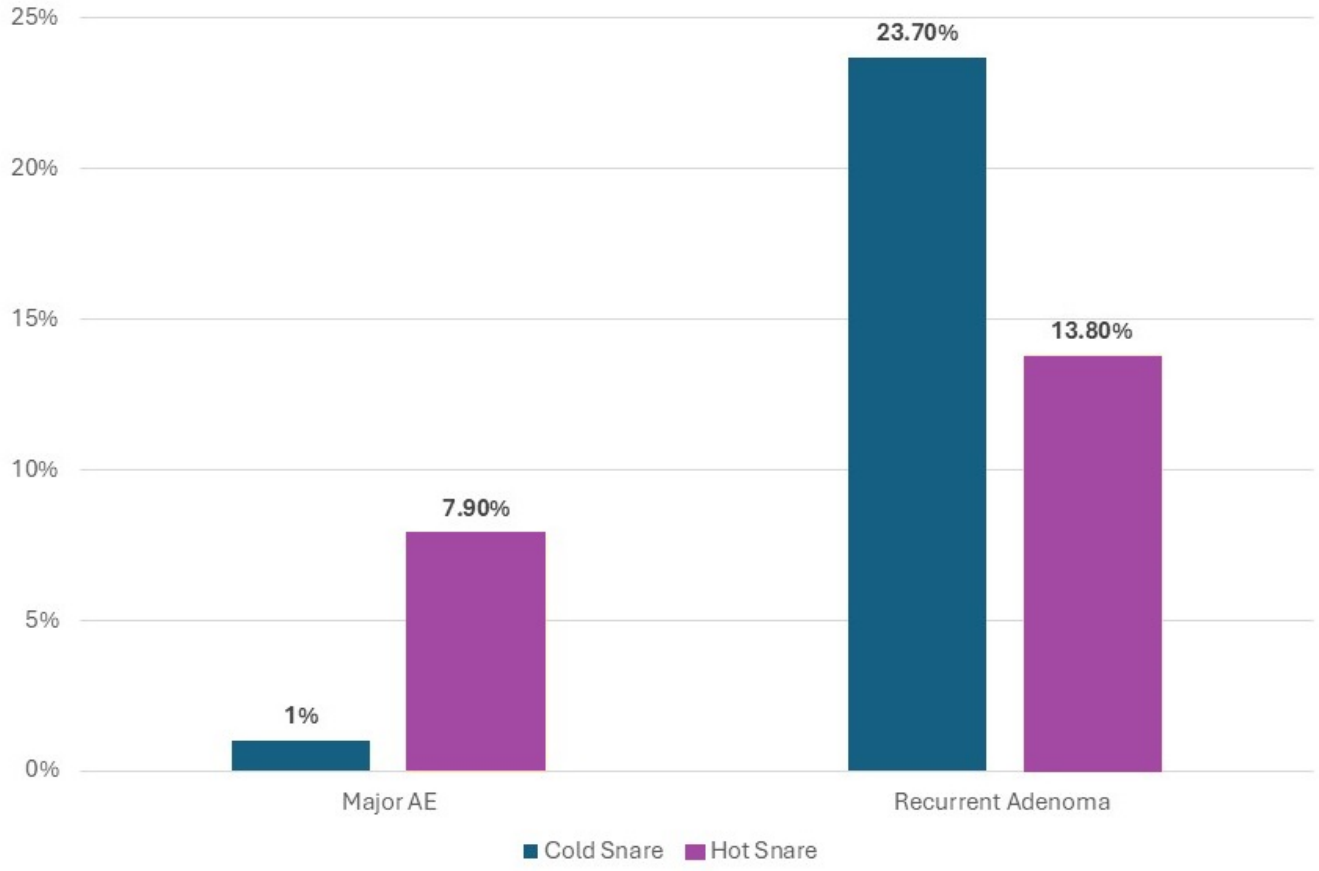

Figure 1. Rates of major adverse events (AE) and residual/recurrent adenoma in cold snare vs hot snare endoscopic mucosal resection groups.

COMMENTARY

Why Is This Important?

EMR is considered safe and effective for resecting LNPCPs ≥ 20 mm. However, there is limited evidence from prospective trials comparing safety and recurrence with cold snare EMR vs hot snare EMR. This is the first RCT comparing cold and hot snare EMR of LNPCPs ≥ 20 mm. Albeit, since publishing in Sept 2024 an RCT was published in Oct 2024 by O'Sullivan et al comparing cold vs hot snare EMR for flat NPCP ≥ 15 mm with similar results.[1] Given the frequency at which LNPCPs are encountered during colonoscopy more evidence is crucial to allow for appropriate decision making upon encountering such lesions.

Key Study Findings

Cold snare EMR is significantly safer than hot snare EMR for large (≥ 2cm) non-pedunculated polyps with a reduction of major AEs by >85% (7.9% to 1.0%).

No perforations were reported in cold resection compared to 8 cases in hot resection (0% vs 3.9%) and post-polypectomy bleeding was also significantly less frequent (1.0% vs 4.4%). The differences are both statistically significant and clinically relevant, especially when considering associated sequalae of such AEs including additional interventions and often patient admission with long hospital stays. Unfortunately, the substantial reduction in AEs by cold resection is accompanied by a higher rate of residual/recurrent adenoma (23.7% vs. 13.8%). This study did not include systematic margin coagulation of polypectomy site which have been shown to reduce residual/recurrence to <5%-10%.[2] Fortunately, residual adenoma at follow up is usually small in size and easy to treat but does expose patients to the risk of repeated colonoscopies.

Caution

Although endoscopists could not be blinded to treatment assignment (cold snare vs hot snare), patients were definitely blinded, and it appears that adjudicators of adverse events and endoscopists performing follow-up colonoscopy were blinded. There may be some variability in the performance of polypectomy among endoscopists that could not be fully captured by the reported data. Although there is no significant difference in residual/recurrence in SSLs, this may reflect an overall low number of SSLs and there was a strong numerical trend for higher rates of residual SSL when cold snare was performed.

My Practice

This study supports my practice of largely performing cold snare EMR for LNPCPs ≥20 mm considering the safety profile of the resection and ability to deal with residual/recurrence on follow up colonoscopies. Per my prior commentary[3], piecemeal cold snare of LNPCPs can be technically difficult, so

optimizing procedure volume may help minimize recurrence. Since my schedule includes extended endoscopy slots for complex EMR, my colleagues frequently refer patients with LNPCPs. Before I do any injection, I carefully identify the margins of the polyp using zoom focus, high-definition white light, and NBI. This is crucial to facilitate identification of residual tissue both centrally and at polyp margins after beginning resection. I mix epinephrine with a colloid injection fluid to lift LNPCPs, which is important to minimize bleeding when doing piecemeal cold snare, and I also routinely use soft-tip coagulation for thermal ablation of polyp margins to minimize recurrence.

Since my colleagues are referring patients with LNPCPs to me for complex EMR, I also ask them to inject dye 2 folds distal (i.e. closer to the rectum) from the lesion to facilitate polyp location on repeat colonoscopy and to avoid doing anything more than obtaining a pinch biopsy. This is preferable to initiating EMR, but failing to complete it, since incomplete EMR may produce sub-mucosal fibrosis that makes future EMR technically difficult.

For Future Research

Future work focused on technical developments to reduce recurrence and improve outcomes is vital. Studies comparing cold vs hot resection of different lesion morphologies and pathology can further advance our technique to allow for combining the safety of cold snare resection with lower residual/recurrence of hot snare EMR.

Conflict of Interest

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

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Combination Therapy as Primary Prophylaxis for High-Risk Esophageal Varices

HEPATOLOGY

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This summary reviews Tevethia HV, Pande A, Vijayaraghavan R, et al. Combination of carvedilol with variceal band ligation in prevention of first variceal bleed in Child-Turcotte-Pugh B and C cirrhosis with high-risk oesophageal varices: The 'CAVARLY Trial.' Gut 2024; 73: 1844-53.

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Keywords: Esophageal varices, carvedilol, variceal band ligation

STRUCTURED ABSTRACT

Question: Is combination therapy with non-selective beta blockers plus variceal band ligation (VBL) superior to monotherapy with either treatment for preventing first variceal bleed in patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C cirrhosis) and high-risk esophageal varices?

Design: Single center, unblinded, randomized controlled trial (RCT) with block randomization scheme.

Setting: Institute of Liver and Biliary Sciences, New Delhi, India from January 2017 through December 2018.

Patients: Inclusion criteria included: (a) individuals 18-75 years old; (b) cirrhosis based on liver biopsy or imaging; (c) Child-Turcotte-Pugh (CTP) score of 7-13; (d) endoscopically confirmed large (> 5 mm) esophageal varices or small

(< 5 mm) esophageal varices with red color signs (aka “red wale” signs) of red streaks or patches on top of varices; and, (e) no prior history of variceal bleeding. Exclusion criteria included hepatocellular carcinoma, known contraindication to non-selective beta blockers, portal vein thrombosis, platelet count < 30,000 per ml, concurrent anticoagulant use, and prior history of transhepatic intrajugular porto-systemic shunt (TIPS).

Interventions/Exposure: Patients randomized to non-selective beta blocker monotherapy received carvedilol 3.125 mg twice daily and increased their dose by 3.125mg weekly up to maximum dose of 12.5 mg twice daily. Patients randomized to VBL monotherapy underwent upper endoscopy with Cook’s multiband (6-shooter) ligator every 3 weeks until eradication of varices. Patients randomized to combination therapy received the same protocol for both carvedilol therapy and VBL. Endoscopists were blinded about whether patients were in combination therapy vs VBL monotherapy groups. Clinic visits were conducted within 1 week of study initiation and again at 3, 6, 9, and 12 months with additional visits if adverse events occurred. Hepatic venous pressure gradient (HVPG) was measured at baseline and 12 months.

Outcome: The primary outcome was incidence of first variceal bleed after 12 months of follow-up. Secondary outcomes included, but were not limited to, reduction in hepatic venous pressure gradient, survival at 12 months, incidence of post-VBL ulcer bleeding, and incidence of spontaneous bacterial peritonitis (SBP) and acute kidney injury (AKI). Per investigators, definition of variceal bleeding was consistent with Baveno IV criteria.

Data Analysis: Intention-to-treat (ITT) analysis was performed with censoring of patients who were lost to follow-up if they had not developed any outcome after the last clinic visit. Time-to-event analysis was performed using Cox proportional hazards regression method and Kaplan-Meier method.

Funding: None declared.

Results: Between January 2017 and December 2018, 463 patients were screened and 330 patients with decompensated cirrhosis were enrolled (n=110 per group) with mean age 51 years old, 85% male, mean CTP score-8.9, and etiology of cirrhosis was primarily non-alcoholic fatty liver disease (47%) or alcoholic liver disease (28%). Mean baseline HVPG was 16.6-17.4 mm HG across treatment groups. Although no statistically significant differences were identified in baseline de-

mographics, non-selective beta blocker monotherapy and VBL monotherapy groups had 54% of patients with Grade 2 varices with red color signs and 46% with Grade 3-4 large varices, while the combination therapy group had the reverse trend with 46% with Grade 2 varices with red color signs and 54% with Grade 3-4 varices. Mean carvedilol dose achieved in monotherapy group was 10.6 mg and was 9.8 mg in the combination therapy group.

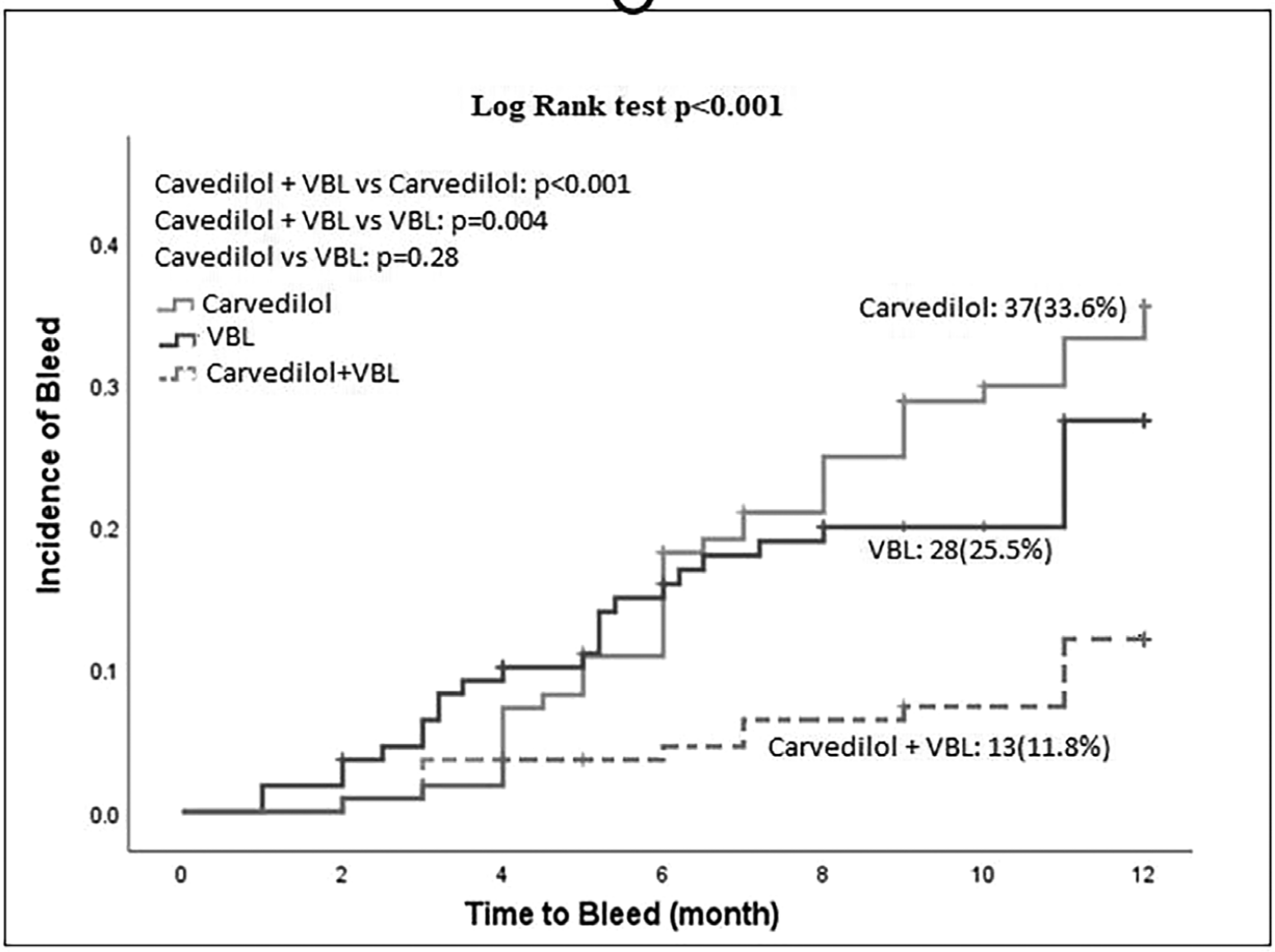
In the ITT analysis, the overall incidence of first variceal bleed was significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 11.8% vs 33.6% vs 25.5%, respectively, $P < 0.002$ (Figure 1). Per Cox proportional hazard regression, combination therapy reduced the incidence of first variceal bleed by 69% (hazard ratio [HR] = 0.31; 95% confidence intervals [CI]: 0.16-0.58) vs carvedilol and by 63% (HR = 0.37; 95% CI: 0.19-0.72) vs VBL. All-cause mortality at 1 year was also significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 6.3% vs 20% vs 14.5%, respectively, P=0.012.

Paired hepatic venous pressure gradients at baseline and 12 months were obtained in 223 patients and demonstrated significant reductions in HVPG of 21%-25% in the carvedilol monotherapy and combination therapy groups, but no significant reduction in the VBL monotherapy group. Post-VBL ulcer-related bleeding occurred in 10.9% of patients. Transient dysphagia occurred in 20% of post-VBL patients. Fatigue (19.1%) was the most common adverse event reported in carvedilol-treated patients.

COMMENTARY

Why Is This Important?

The 2024 guidelines[1] from the American Association for the Study of Liver Diseases (AASLD) recommend "if high-risk varices are detected, non-selective beta blockers or endoscopic band ligation are recommended; preference is given to non-selective beta blockers (including carvedilol) because of benefits beyond prevention of variceal hemorrhage." The guidelines emphasize that VBL should be performed as primary prophylaxis if the patient has a contraindication to non-selective beta blockers or cannot tolerate non-selective beta blockers. Per the guidelines, this recommendation for primary prophylaxis applies whether the patient has compensated cirrhosis with clinically significant portal hypertension or decompensated cirrhosis. Comparative RCTs of non-selective beta blockers and VBL for primary prophylaxis have produced mixed results, with some studies demonstrating non-inferiority



	Time	0	2	4	6	8	10	12
Carvedilol	At Risk	110	109	104	96	84	75	69
	Events	0	1	6	14	24	32	37
VBL	At Risk	110	101	89	81	76	75	64
	Events	0	5	11	16	20	21	28
Carvedilol+ VBL	At Risk	110	109	107	103	102	101	96
	Events	0	1	3	7	8	9	13

Figure 1. Kaplan-Meier curves of overall incidence of first variceal bleed over 12 months. Reproduced with permission from Tevethia et al. Gut 2024;73:1844–1853.

and others suggesting superiority for VBL, although there is an increased risk of major adverse events with VBL. However, there do not appear to be RCTs that compare combination therapy with non-selective beta blocker monotherapy or VBL monotherapy, especially in patients with decompensated cirrhosis and high-risk esophageal varices. Therefore, the study by Tevethia et al is a welcome addition.

Key Study Findings

The overall incidence of first variceal bleed was significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 11.8% vs 33.6% vs 25.5%, respectively, $P < 0.002$ (Figure 1). Also, all-cause mortality at 1 year was significantly lower in the combination therapy group vs non-selective beta -blocker monotherapy or VBL monotherapy: 6.3% vs 20% vs 14.5%, respectively, $P = 0.012$.

Caution

The lack of blinding may have biased results toward combination therapy in unknown ways. Future studies would benefit from using placebo tablets along with carvedilol and using blinded adjudicators to review endoscopy reports and hospitalization records to determine if incident variceal bleeding occurred. Since this study was conducted at a single institution in New Delhi, India, similar studies in more diverse settings would be helpful before generalizing these results.

My Practice

In my VA practice, I'll frequently initiate carvedilol therapy in patients with compensated cirrhosis and clinically significant hepatic venous pressure gradient (i.e., HVPG > 10mm Hg) based on non-invasive testing. If the patient doesn't have hypertension, then I'll start at 3.125 mg twice daily with a goal of increasing to 6.25 mg twice daily. This is because carvedilol demonstrates a trend for better tolerance than other non-selective beta blockers along with a possibility of decreasing incidence of ascites and providing a survival advantage.[1] The 2024 AASLD guidelines also now recommend this approach. Therefore, many of my patients with cirrhosis have already been started on carvedilol before decompensation occurs.

Consistent with AASLD guidelines,[1] I focus on using non-selective beta blockers in patients with compensated and decompensated cirrhosis as primary prophylaxis against variceal bleeding since VBL is associated with more severe adverse events. However, I do rely on VBL if the patient cannot tolerate non-selective beta blockers due to fatigue or hypotension (i.e., systolic blood pressure < 90 mm Hg). In the past, I occasionally individualized care and provided combination therapy if patients had particularly large esophageal varices or smaller varices with red wale signs during endoscopic screening/surveillance, but did not utilize a systematic approach to combination therapy. Given the results of the current

study, I expect to change my practice and routinely provide combination therapy for patients with decompensated cirrhosis and high-risk esophageal varices.

For Future Research

While the authors are to be commended for performing the first RCT to compare monotherapy with a non-selective beta blocker or VBL vs combination therapy in patients with decompensated cirrhosis, additional RCTs with blinding and in more diverse settings would be helpful to facilitate broadly generalizing these practices and to further quantify the benefits of combination therapy.

Conflict of Interest

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

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Long Term Efficacy and Safety of Dupilumab for Eosinophilic Esophagitis

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This summary reviews: Rothenberg ME, Dellon ES, Collins MH, et al. Efficacy and safety of dupilumab up to 52 weeks in adults and adolescents with eosinophilic oesophagitis (LIBERTY EoE TREET study): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2023; 8: 990–1004.

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Keywords: Eosinophilic esophagitis; dupilumab; RCT

STRUCTURED ABSTRACT

Question: Does weekly or every 2-week dosing dupilumab maintain its efficacy and safety for eosinophilic esophagitis (EoE) over 52 weeks in adolescents and adults?

Design: Phase 3, multicenter, double-blind, randomized, placebo-controlled trial of participants enrolled in 24-week Part B of LIBERTY EoE TREET study who continued to 28-week part C (part B–C) extended active treatment.

Setting: Sixty-five centers across 10 countries (Australia, Canada, Europe, and the US), including tertiary and private care clinics.

Patients: The study included 227 patients (median age: 24 years, range 12–65; 33% adolescents, 64% male; 91% White) with EoE confirmed by ≥15 eosinophils per

high-power field (eos/hpf) despite 8 weeks of high-dose proton-pump inhibitor (PPI) therapy and moderate dysphagia (Dysphagia Symptom Questionnaire [DSQ] score ≥ 10). Patients were excluded if severe adverse events occurred during initial treatment or if they could not continue treatment with study drug for alternate reasons.

Exposure: Weekly or biweekly subcutaneous dupilumab 300 mg vs placebo during Part B. Patients on placebo during Part B transitioned to active treatment during Part C, either weekly or biweekly. Those on active treatment during Part B, continued on the same regimen for additional 28 weeks.

Outcome: There were no primary efficacy end points for part B-C. Instead, Part B's co-primary, key secondary, and efficacy endpoints were assessed at week 52 as secondary endpoints for Part C, the extended active treatment period. The previous primary endpoints were: (a) histological Remission: proportion of patients achieving a peak eosinophil count of ≤ 6 eos/hpf at Week 52; (b) symptom Improvement: absolute change from baseline in DSQ scores at Week 52. Previous secondary outcomes utilized here included**:** reduction in peak eosinophil counts to ≤ 1 eos/hpf and ≤ 15 eos/hpf. Change in Histology Scoring System, EREFS scores, health related quality of life (HRQol) measured by EoE Impact questionnaire (EoE-IQ), severity and frequency of symptoms measured by EoE symptom questionnaire (EoE-SQ), and EoE diagnostic panel (EDP) transcriptome signature from Part B baseline to week 52.

Data Analysis: Efficacy assessed via histological remission (≤ 6 eos/hpf), change in DSQ scores, and endoscopic and histological grading. Intention-to-treat analysis applied.

Funding: Sanofi and Regeneron Pharmaceuticals.

Results: Overall, 168 (74%) patients had previously used swallowed topical corticosteroids (tCs) for EoE and 112 (49%) patients had inadequate response, intolerance, or contraindication to tCs. Eighty (35%) had history of prior dilations. Those on weekly dupilumab with disease improvement after 24 weeks of treatment maintained or continued to improve with an additional 28 weeks of treatment with weekly dosing. All 65 (100%) patients on weekly dupilumab achieved peak ≤15 eos/hpf after 52 weeks of treatment. Weekly dupilumab significantly reduced dysphagia symptoms, with a mean DSQ score improvement of –30.3 points, and decreased peak eosinophil counts by over 95%. Biweekly dupilumab improved histological, endoscopic, and transcriptomic outcomes to a similar extent as weekly dupilumab did over a 52-week period, but was less effective in symptom relief. Overall safety was consistent with the known dupilumab safety profile. Dupilumab

was well-tolerated, with injection-site reactions being the most common adverse event with 14% in the weekly and 11% in the placebo/weekly group.

COMMENTARY

Why Is This Important?

EoE is a chronic, immune-mediated condition characterized by symptoms such as dysphagia, food impaction, and histological inflammation of the esophagus. Current treatment options, including proton pump inhibitors (PPIs), elimination diets, and topical corticosteroids, often fail to achieve sustained remission or are not well-tolerated. Dupilumab, a monoclonal antibody targeting IL-4 and IL-13 pathways, represents a promising option that directly addresses the underlying type 2 inflammation driving EoE.[1-3]

Despite dupilumab's approval based on short-term efficacy data from the first 2 phases of the LIBERTY EoE TREET study at 24 weeks compared to palcebo, the question regarding it's longer term efficacy and safety was unclear. Long-term management options for EoE have remained a significant unmet need in the field. This study bridges that gap by demonstrating that weekly 300 mg dupilumab is well tolerated and maintains its efficacy for up to 52 weeks, providing sustained histological, symptomatic, endoscopic, and molecular profile improvements that was achieved at 24 weeks with a favorable safety profile.

Key Study Findings

This study highlights the sustained efficacy of weekly dupilumab in managing EoE over 52 weeks. A significant proportion of patients (85%) receiving weekly dupilumab achieved histological remission (≤6 eos/hpf), compared to only 5% of placebo-treated patients at 24 weeks. Over 52 weeks, weekly dosing outperformed biweekly regimens, especially in symptom relief, emphasizing the importance of higher dosing frequency for optimal outcomes.

Improvements were also evident in symptoms, with a mean reduction of –30.3 points in the DSQ scores in the weekly dupilumab group, reflecting meaningful relief from swallowing difficulties. These benefits extended across endoscopic and molecular parameters, with significant reductions in eosinophil counts and improvements in EREFS. The safety profile was favorable, with injection-site reactions being the most common adverse event and no new safety concerns emerging over the 52-week treatment period. These findings position weekly dupilumab as a highly effective and well-tolerated long-term treatment for EoE.

Caution

The study population was predominantly White (91%), limiting the generalizability of findings to more diverse racial and ethnic groups. Additionally, the trial was conducted primarily in tertiary care settings, where patients may present with more severe disease and have greater access to specialized care than those in community settings. Furthermore, the safety data were reassuring, but the study was limited to 52 weeks.

My Practice

Dupilumab has become a cornerstone in my approach to managing EoE, especially in patients who fail standard treatments like PPIs, dietary treatment, and topical corticosteroids. For patients with moderate to severe disease—defined by persistent dysphagia, significant histological activity, or severe fibrostenotic disease characterized by recurrent food impactions and/or need for frequent dilation therapy—I would recommend weekly dupilumab based on this study's findings. The histological and symptomatic improvements achieved with weekly dosing in this study support this regimen. For patients who demonstrate partial response after 24 weeks, I emphasize the potential for continued improvement over time, as seen in the extended 52-week data.

However, for patients with less severe disease, I may consider biweekly dosing, as it still provides substantial benefits, albeit to a lesser degree. When initiating dupilumab, I counsel patients on expected outcomes, highlighting its ability to reduce inflammation, improve swallowing function, and potentially eliminate the need for frequent endoscopies. I also discuss the most common side effect, injection-site reactions, and reassure patients about the therapy's overall safety profile over 52-weeks. Ultimately, with the complexity of managing chronic therapies for a lifelong disease, individualized decision-making should be emphasized when considering dupilumab for EoE.

For Future Research

Future studies should focus on addressing several key gaps to optimize the use of dupilumab in EoE. Research is needed to explore its cost-effectiveness in real-world settings. Additionally, trials that include more racially and ethnically diverse populations are essential to confirm the generalizability of these findings. Long-term safety and efficacy data beyond one year would provide crucial insights into its suitability as a chronic therapy. Studies that investigate biomarkers or clinical predictors of response could help identify which patients derive the most benefit, enabling more personalized treatment approaches. Finally, comparisons between dupilumab and other emerging therapies for EoE could further refine treatment algorithms, ensuring the best outcomes for patients.

Conflict of Interest

Dr Eluri has no reported conflicts of interest related to this summary.

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