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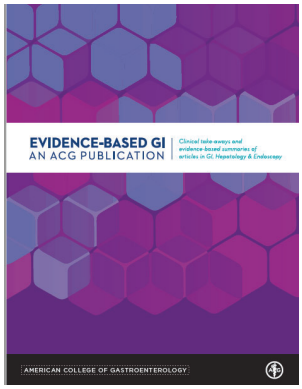

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INDICATION

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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Cell-free DNA Blood Test for CRC Screening: A Promising Development Won't "Eclipse" Current Tools

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

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This summary reviews Chung DC, Gray DM, Singh H, et al. A Cell-free DNA blood-based test for colorectal cancer screening. N Engl J Med 2024; 390: 973-83.

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Keywords: colorectal cancer, cell-free DNA, screening

STRUCTURED ABSTRACT

Question: What is the sensitivity and specificity of a cell-free DNA (cf DNA) blood test for colorectal cancer (CRC) screening (Shield; Guardant Health, Palo Alto, CA) for detection of Stage I, II, and III CRC and advanced precancerous lesions in average-risk individuals aged 45-84 years old?

Design: Prospective observational diagnostic test study using colonoscopy as the gold standard for detection of CRC and precancerous lesions: ECLIPSE (Evaluation of the ctDNA LUNAR Test in an Average Patient Screening Episode) study.

Setting: Two hundred sixty-five primary care and endoscopy centers in the United States.

Patients: Average-risk individuals aged 45-84 years old scheduled for CRC screening colonoscopy. Key exclusion criteria included: (a) history of inflammatory bowel disease; (b) family history of CRC in first-degree

relative; (c) prior history of adenomatous polyps; and (d) currently up-to-date with CRC screening (e.g., had a normal screening colonoscopy ≤ 9 years).

Interventions/Exposure: Whole blood samples (30-80 ml) were collected and shipped at ambient temperatures to central biorepository, processed to plasma, and then stored at -80°C until the assay was performed. The assay evaluates extracellular DNA molecules in the plasma that have been released from tissue into the bloodstream: aberrant DNA methylation status, aberrant DNA fragmentation patterns, and pathogenic variants in Kirsten rat sarcoma virus (KRAS) and adenomatous polyposis coli (APC) genes. Using these data and a logistic regression model, a binary outcome (abnormal signal detected or normal signal detected) is reported.

Outcome: Coprimary outcomes were sensitivity for CRC, including Stage I, II, and III, and specificity for advanced precancerous lesions, defined as adenomas ≥10 mm, adenoma with villous histology or high-grade dysplasia, carcinoma in situ, or serrated lesion ≥10 mm. The secondary outcome was sensitivity for advanced precancerous lesions.

Data Analysis: Sensitivity (percentage of individuals with the disease who have a positive test) and specificity (percentage of individuals without the disease who have a negative test) with corresponding 95% confidence intervals (CIs) were calculated with standard formulas. [Note: for previous US Food and Drug Administration (FDA)-approved CRC screening tests, a test was considered acceptable if the lower boundary of the 95% CI for CRC sensitivity was >65% and if the lower boundary of 95% CI for specificity of advanced precancerous lesions was >85%.

Funding: Guardant Health, manufacturer of Shield, cf DNA blood-based test.

Results: Between October 2019 and September 2022, 22,877 patients were enrolled, producing 65 individuals with CRC; 74% (48/65) had stage I, II, or III CRC). An additional 10,193 participants without CRC were randomly selected to complete clinical validation of cf DNA blood-based test. Among this group, 7,861 met all inclusion and exclusion criteria, had complete colonoscopies, and evaluable cf DNA blood-based tests. This final study cohort had mean age of 60 years old (range 45-84), 54% female, 79% White, and 11.4% had a positive cf-DNA blood-based test.

For CRC Stage I-III, 87.5% (42 of 48) had a positive cf-DNA blood-based test. This includes 100% sensitivity for Stage II CRC (14/14) and Stage III

CRC (17/17), but only 65% (11/17) for Stage I CRC (**Table 1**). For advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas or adenomas with high-grade dysplasia or carcinoma in situ), 13.2% (147 of 1,116) had a positive test. Approximately 10% of participants had a false positive test, defined as positive cf-DNA blood-based test, but no adenomas, advanced precancerous lesions or CRC found on colonoscopy.

Disease	Sensitivity (95% CI)	Specificity (95% CI)
Stage I-III CRC	87.5% (75-94)	
Stage I CRC	65% (41-83)	
Stage II CRC	100% (78-100)	
Stage III CRC	100% (82-100)	
Advanced precancerous lesion	13.2% (11-15)	89.6% (89-90)

Table 1. Diagnostic test characteristics. CI, confidence interval; CRC, colorectal cancer

COMMENTARY

Why Is This Important?

Only about 59% of the eligible US population is up-to-date with CRC screening, equating to more than 40 million unscreened individuals. Therefore, new interventions to improve screening are sorely needed.[1] Given the relative lack of adherence with annual fecal immunochemical tests (FIT) as well as the desire of some patients to avoid colonoscopy with the associated bowel preparation, sedation, and time missed from work, blood-based tests for CRC screening offer the potential for a convenient and easily accessible tool.

I commend the investigators for completing the ECLIPSE study and expanding the science of CRC screening. Currently, the cf-DNA blood-based test can be ordered by physicians, but it's not covered by Medicare. Given the relatively low sensitivity of cf-DNA blood-based tests for Stage I CRC, poor sensitivity for advanced adenomas, and uncertainty around insurance coverage, this test won't soon supplant other CRC screening tools. In contrast to this test, the newest version of multi-target stool DNA tests[2] demonstrates sensitivity of almost 44% for

advanced adenomas with sensitivity for Stage I-III CRC of 92.7% (95% CI 85-97) while also being covered by Medicare and commercial insurers.

Key Study Findings

For CRC Stage I-III, the sensitivity of the cf-DNA blood-based test was 87.5% (95% CI 75-94), consistent with 42 of 48 individuals with Stage I-III CRC having a positive cf-DNA blood-based test. However, the sensitivity for Stage I CRC was only 65% (95% CI 41-83) since only 11 of 17 individuals with Stage I CRC had a positive test. This is not a useful test for identifying advanced adenomas since the sensitivity is 13.2% (95% CI 11-15) with only 147 of 1,116 individuals having a positive test.

Caution

Although the manufacturer of cf-DNA blood-based tests recommends performance every 3 years, it's unclear to me how that interval was determined. Also, since approximately 10% of average-risk individuals will have a false-positive test and since other solid-tissue tumors may release abnormal cf-DNA fragments into blood, it's unclear if any additional cancer screening or diagnostic testing should be performed when a patient has a positive test followed by a normal colonoscopy.

My Practice

The mainstay of CRC screening for gastroenterologists is colonoscopy, a CRC prevention tool. I do see average-risk individuals in clinic who are fearful of colonoscopy, sedation, or simply doing the bowel preparation and want a non-invasive alternative. For these individuals, annual FITs are certainly appropriate cancer detection tools, although the new version of multi-target stool DNA tests are also reasonable, especially since the latest version has superior sensitivity to FIT for CRC and advanced adenomas.

Nevertheless, when explaining the benefits and limitations of different CRC screening tests to patients, the best test is one that the patient completes. If the patient wants a non-invasive test but doesn't want to obtain a sample from voided stool, then I might offer a blood-based test as long as the patient agreed to get a colonoscopy if the blood-based test was positive and if the patient could pay out-of-pocket for the test, which is not currently covered by Medicare and most commercial insurers.

For Future Research

Although this version of the cf-DNA blood-based test may not be appropriate for widespread use, the development of this technology is a huge advance. Again, the investigators

should be congratulated for their efforts and ongoing research in fragmentomics is likely to advance our ability to perform cancer screening with blood-based tests. In the interim, research about how to manage or advise individuals with a false positive test and data to validate a 3-year interval between screening tests is needed.

Conflict of Interest

Dr. Schoenfeld previously served as a speaker for EXACT Sciences.

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

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Samir Gupta

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Rachel Issaka

REFERENCES

1. Lo YMD. Cell-free DNA for colorectal cancer screening. N Engl J Med 2024; 390: 1047-50.
2. Imperiale TF, Porter K, Zella J, et al. Next-generation multi- target stool DNA test for colorectal cancer screening. N Engl J Med 2024;390:984-93.

EVIDENCE-BASED GI
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First FDA-Approved NASH Treatment Produces NASH Resolution and Decreases Fibrosis: Results From the Landmark Phase 3 MAESTRO-NASH Trial

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LIVER

This summary reviews Harrison SA, Bedossa P, Guy CD et al. A phase 3, randomized controlled trial of resmetirom in NASH with liver fibrosis. NEJM 2024; 390(6): 497-509.

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

Keywords: Steatotic liver disease, liver fibrosis, metabolic associated liver disease, clinical trials

STRUCTURED ABSTRACT

Question: Does the oral thyroid hormone receptor beta-selective agonist resmetirom decrease fibrosis and produce resolution of nonalcoholic steatohepatitis (NASH; now also known as metabolic-dysfunction associated steatohepatitis [MASH]) with fibrosis?

Design: Multicenter, phase 3, double-blind, randomized, placebo-controlled clinical trial.

Setting: Two hundred and forty-five centers across 15 countries (United States, Australia, Austria, Belgium, Canada, France, Germany, Hungary, Israel, Italy, Mexico, Poland, Spain, Switzerland, and the United Kingdom) between March 2019 and July 2021.

Patients: Adults aged ≥18 years with metabolic syndrome and biopsy-confirmed NASH. Screening biopsies were performed within 6 months of randomization, and

participants were required to have a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage ranging from stage F1B to F3. At least 50% of the total enrollment was required to have fibrosis stage F3. Participants were also required to have stable weight (<5% change in 3 months) with stable doses of glucagon-like peptide-1 (GLP-1) agonists for ≥ 6 months prior to biopsy, if applicable. Exclusion criteria included: 1) alcohol consumption (≥30 g/day for men, ≥20 g/day for women), 2) hemoglobin (Hgb) A1c >9%, 3) presence of other, concomitant chronic liver disease, and 4) fibrosis stage F0 (no fibrosis) or F4 (cirrhosis).

Interventions: Participants randomized 1:1:1 to 1 of 3 study arms: 1) resmetirom 80 mg once daily, 2) resmetirom 100 mg once daily, or 3) placebo with stratification for presence of type 2 diabetes mellitus (DM) and fibrosis stage (F1, F2, F3). All participants received nutrition and exercise counseling according to current recommendations. A second liver biopsy was performed at 52 weeks.

Outcomes: Dual primary endpoints were assessed at week 52, including: 1) NASH resolution, defined as ballooning score of 0, lobular inflammation score of 0 or 1, and reduction in NAS by ≥2 points with no worsening of fibrosis and 2) Improvement in fibrosis by at least 1 stage with no worsening of NAS. Outcomes were assessed by central, independent review by 2 pathologists. A secondary end point was percent change in baseline low-density lipoprotein (LDL) cholesterol at week 24.

Data Analysis: Intention-to-treat analysis using Cochran-Mantel-Haenszel test.

Funding: Madrigal Pharmaceuticals (West Conshohocken, PA), manufacturer of resmetirom.

Results: Nine hundred and fifty-five patients were randomized: mean age was 56.6 years, mean body mass index (BMI) was 35.7, 89% White, and most had metabolic risk factors (78% hypertension, 71% dyslipidemia, and 67% type 2 diabetes). Most patients (60%) had F3 fibrosis, with 33% having F2 fibrosis and only 5% having F1B fibrosis.

For NASH resolution with no worsening of fibrosis, resmetirom 80mg and resmetirom 100 mg was superior to placebo: 25.9% and 29.9% vs 9.7%, respectively, $P<0.001$ for both comparisons). For decrease in fibrosis score by at least 1 with no worsening of NAFLD activity score, resmetirom 80mg and resmetirom

100mg were also superior to placebo: 24.2% and 25.9% vs 14.2%, respectively, $P<0.001$ for both comparisons (**Figure 1**). For both NASH resolution and fibrosis improvement by ≥1 stage, resmetirom 80 mg and resmetirom 100mg was superior to placebo: 14.2% and 16% in the 100 mg vs 4.9%, respectively, $P<0.001$ for both comparisons.

Beneficial effects on LDL cholesterol levels were observed in both intervention groups at week 24 (-13.6% in the 80 mg resmetirom group and -16.3% in the 100 mg resmetirom group) but not in the placebo group (0.1%; $P<0.001$ for both comparisons). Additionally, larger decreases in levels of other atherogenic lipids and lipoproteins (e.g., triglycerides, non-high density lipoprotein (HDL) cholesterol, apolipoprotein B) compared to baseline were observed in the resmetirom groups compared to placebo.

Most adverse events (AEs) were mild or moderate, with diarrhea (27.0% and 33.4% vs 15.6%, respectively) and nausea (22.0% and 18.9% vs 12.5%, respectively) occurring more commonly in the resmetirom 80mg and 100 mg groups compared to placebo. Diarrhea was generally self-limited with duration. However, AEs led to trial discontinuation in more patients in the 100 mg resmetirom group (6.8%) compared to those in the 80 mg group (1.8%) and those in the placebo group (2.2%).

COMMENTARY

Why Is This Important?

NAFLD, recently renamed metabolic-dysfunction associated liver disease (MASLD),[1] is highly prevalent, affecting 30% of the global population.[2] It is the fastest rising cause of hepatocellular carcinoma (HCC)[3, 4] and the most rapidly increasing indication for liver transplant in the US.[5] MASLD encompasses a spectrum of disease, from simple steatosis (i.e., excess fat accumulation in hepatocytes) to its more severe form, MASH, characterized by hepatocyte ballooning, inflammation, and progressive fibrosis.[1] An estimated 25% of patients with MASH will eventually develop cirrhosis, but fibrosis progression is incompletely understood and varies significantly between patients.[6] Fibrosis stage is the most important predictor of all-cause mortality, liver-related events and cardiovascular disease in MASLD.[7] Liver biopsy remains the gold standard for diagnosis and to assess disease severity (evaluated with the NAS) and stage (fibrosis), but is not routinely performed in clinical practice given its invasiveness.

The pathophysiology of MASH is complex with several potential therapeutic

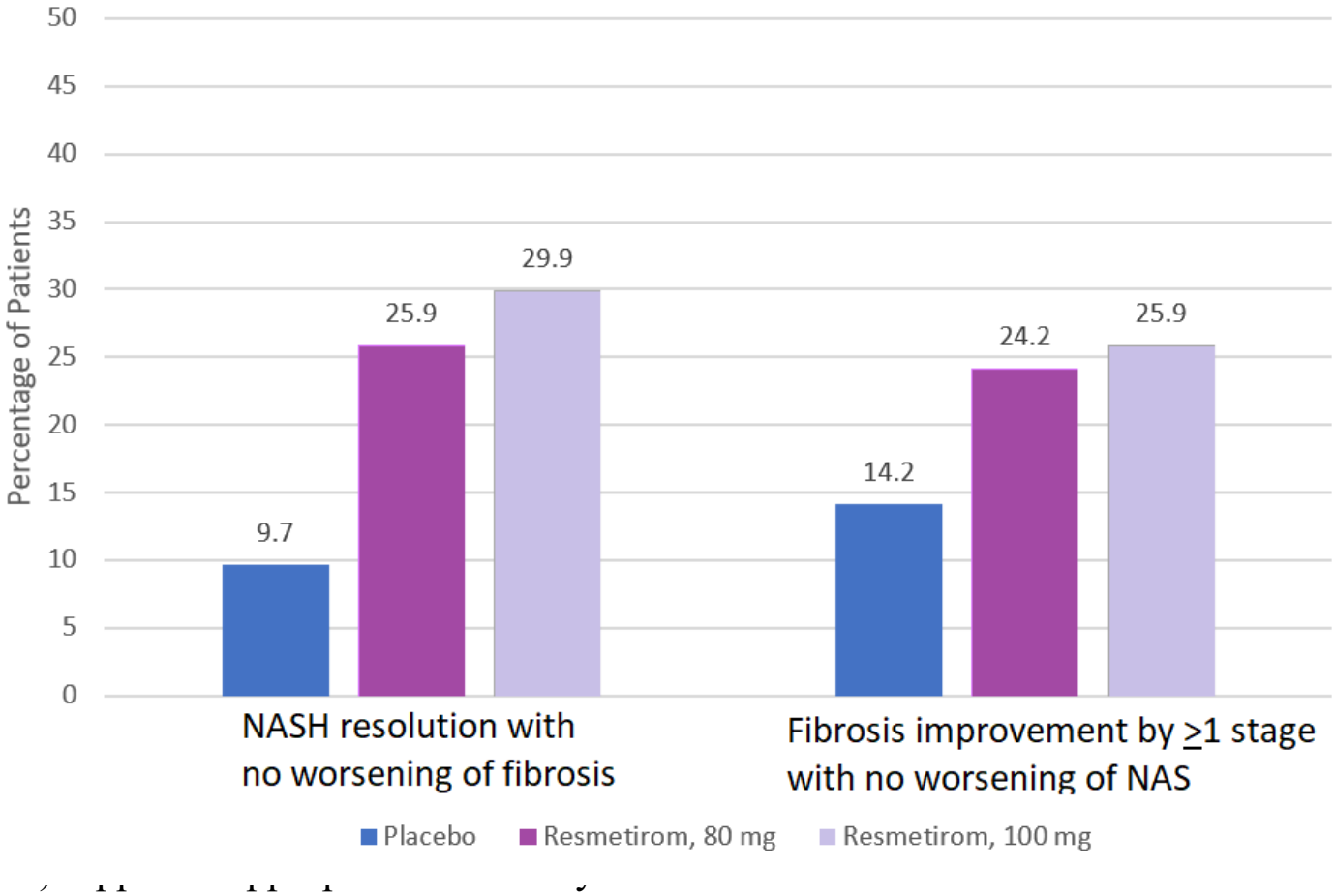

Figure 1. Percentage of patients reaching primary end points at week 52. Placebo N= 318; resmetirom, 80 mg N= 316; resmetirom, 100 mg N=321. NAS, nonalcoholic fatty liver disease activity score. NASH, nonalcoholic steatohepatitis.

targets.[8] Despite an active research landscape and promising novel pharmacologic agents, none had shown safety and efficacy in phase 3 trials to date. As fibrosis stage is the key driver of clinical outcomes and survival in MASH, the US Food and Drug Administration (FDA) endpoints for late-stage MASH trials have focused on improvement in histology (that is, MASH resolution without worsening fibrosis or improvement of fibrosis stage without worsening MASH), resulting in at least 2 liver biopsies being required (at entry and end of treatment).[9] Given the lack of FDA-approved drugs for MASH, treatment has relied on lifestyle modifications (i.e., diet and aerobic exercise) and weight loss with varying efficacy.[10] Resmetirom, an oral selective thyroid hormone receptor beta (THR-b) agonist, is the first investigational drug to achieve both fibrosis improvement and NASH resolution in a phase 3 trial.[11] Data from the landmark MAESTRO-NASH trial have led to resmetirom becoming the first FDA-approved therapy for the treatment of patients with noncirrhotic MASH with moderate to advanced fibrosis (i.e., stage F2-F3 fibrosis) in March 2024.

Key Study Findings

Among patients with biopsy-proven MASH and liver fibrosis, resmetirom

(both 80 mg and 100 mg doses) was superior to placebo regarding both histologic primary endpoints: improvement in MASLD activity score and fibrosis stage.

Results favoring resmetirom were consistent across key subgroups; further, changes in lipid profiles, liver biochemistries, and non-invasive steatosis and fibrosis assessments all favored resmetirom. Resmetirom appears to be safe and well-tolerated, with most common adverse events being self-limited diarrhea and nausea at treatment initiation; serious adverse events were similar across all 3 arms, including the placebo arm (10.9% to 12.7%).

Caution

The primary limitation of MAESTRO-NASH to date is the lack of clinical outcomes data, as both primary endpoints were histologic and assessed at 52 weeks from baseline. Long-term safety and durability of histologic response beyond 52 weeks have also yet to be assessed. However, the trial is planned to continue for a total 54 months of treatment to accrue and evaluate potential benefits, including all-cause mortality and liver-related clinical outcomes (i.e., progression to cirrhosis, hepatic decompensation, need for liver transplantation). Additionally, results from this trial may not be generalizable to all populations, including Black patients and those with an overlap of MASH and alcohol-related liver disease (i.e., those classified within the newly termed metALD group, which encompasses a spectrum across which the relative contribution of MASLD and ALD varies). It should be noted that this trial was published shortly after new nomenclature for steatotic liver disease was endorsed by the American Association for the Study of Liver Diseases (AASLD) and other professional societies.[1] It also remains unclear whether patients with cirrhosis and those that have not yet developed fibrosis (stage F0) may benefit from resmetirom.

My Practice

As a hepatologist, it is incredibly exciting to (finally!) see the first FDA-approved medication for MASH, a disease impacting many of our patients. Identifying the subset of patients most likely to benefit from resmetirom (and anticipated future NASH therapies) will be the next challenge facing both subspecialty and primary care clinicians. Gastroenterology and hepatology clinics alone lack the capacity to diagnose and risk stratify the entire large population of patients with MASLD. Provider education and proposed primary care pathways will be critical to risk stratify patents and minimize the number of patients requiring biopsy.

The 2023 AASLD clinical practice guidance recommends an algorithm wherein patients at higher risk for advanced fibrosis due to MASH (i.e., patients with 2 or more metabolic risk factors, particularly those with pre-diabetes or diabetes) are screened with FIB-4 testing every 1-2 years.[12, 13] Patients with moderate or high risk based on FIB-4 are recommended to undergo second-line testing like vibration-

controlled transient elastography or enhanced liver fibrosis testing, and, if still consistent with moderate or higher risk of fibrosis, the patient is referred to a subspecialist for possible intervention. As non-invasive tests have excellent negative predictive value, patients identified to be low riskcan be managed in primary care. We have begun to implement this care pathway at our health system.

It is not feasible to biopsy the entire population of patients with MASH and suspected fibrosis. While non-invasive testing is useful to rule in or rule out patients with severe disease, liver biopsy remains the gold standard for grading MASH severity and staging fibrosis, it is not without limitations including sampling variability, reader variation and safety. These limitations and access become a greater concern when considering the need to monitor treatment response. Fortunately, the FDA-approved label does not include a requirement for biopsy to diagnose moderate-to-severe fibrosis, and most clinicians have access to some sort of non-invasive testing.

Given the close correlation between MASLD and metabolic syndrome and diabetes, it will also be important to continue to counsel patients on lifestyle modifications for healthy weight loss, consider pharmacologic or surgical therapies for treatment of obesity, and cardiac risk factor modification.

For Future Research

Given the sheer number of patients with MASH that may potentially benefit from resmetirom (and anticipated future novel therapeutics), there is an urgent need to refine patient care pathways and implement strategies to identify patients at greatest risk of MASH progression and adverse clinical outcomes. As the leading causes of death among patients with MASLD are still cardiovascular events and extra-hepatic malignancies,[14] the benefits and risks of long-term therapy must be considered in patients with low-risk NASH and those with concomitant severe comorbidities and limited life expectancy. Cost-effectiveness studies that consider competing risks (e.g., comorbidities, liver transplantation) are needed to estimate the expected burden of long-term therapy on healthcare systems. Proactive strategies and interventions to address individual out-of-pocket costs and provide equitable access to new, high-cost therapeutics will be critical to prevent widening of existing racial, ethnic, and socioeconomic disparities in MASH severity and outcomes.[15]

Finally, there remains an unmet need for non-invasive tests to monitor treatment response and assess risk of important clinical outcomes, including progression to cirrhosis, liver decompensation, development of HCC and mortality. While there are several promising serum- and imaging-based biomarkers, most are limited regarding positive predictive value and require further validation in diverse patient populations and practice settings. As the landscape of therapeutics for MASH continues to evolve, accurate and widely available tools for non-invasive risk

stratification and monitoring of treatment response will only become more crucial.

Conflicts of Interest

Dr. Rich has served as consultant or on advisory boards for AstraZeneca, Eisai, Exelixis and Genentech, unrelated to the present work. Dr. Leff reports no conflicts of interest.

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

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REFERENCES

1. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023;78:1966-1986.
2. Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77:1335-1347.
3. Huang DQ, Singal AG, Kono Y, et al. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab 2022;34:969-977.e2.
4. Rich NE. Changing epidemiology of hepatocellular carcinoma within the United States and worldwide. Surg Oncol Clin N Am 2024;33:1-12.
5. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19:580-589.e5.
6. Zhai M, Liu Z, Long J, et al. The incidence trends of liver cirrhosis caused by nonalcoholic steatohepatitis via the GBD study 2017. Scientific Reports 2021;11:5195.
7. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-97.e10.
8. Parlati L, Régnier M, Guillou H, et al. New targets for NAFLD. JHEP Rep 2021;3:100346.
9. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology 2011;54:344-53.
10. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight

loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367-78.e5; quiz e14-5.
11. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390:497-509.
12. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77.
13. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology 2021;161:1657-1669.
14. Konyn P, Ahmed A, Kim D. Causes and risk profiles of mortality among individuals with nonalcoholic fatty liver disease. Clin Mol Hepatol 2023;29:S43-s57.
15. Rich NE, Oji S, Mufti AR, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:198-210.e2.

EVIDENCE-BASED GI
AN ACG PUBLICATION

How Effective are Obesity Medications for Reducing Hepatic Decompensation in MASH?

Dr Philip Schoenfeld
Editor-in-Chief

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LIVER

This summary reviews EngströmA, Wintzell V, Melbye M, et al. Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes mellitus: A Scandinavian cohort study. Hepatology 2024; In Press doi: 10.1097/HEP.0000000000000712

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Keywords: obesity, GLP-1, type 2 diabetes, MASH, MASLD

STRUCTURED ABSTRACT

Question: Do glucagon-like peptide-1 (GLP-1) receptor agonists decrease serious liver events in patients with type 2 diabetes mellitus (DM)?

Design: Retrospective cohort study using active-comparator and nationwide health and administrative databases.

Setting: Sweden, Denmark, and Norway.

Patients: Individuals aged 35-54 years who were started on GLP-1 receptor agonists or dipeptidyl peptidase-4 (DPP4) inhibitors, a common treatment for type 2 DM that does not appear to have any impact on hepatic function, between 2007-2020. Although presence of type 2 DM was not an explicit inclusion criterion due to limitations in patient registries, individuals receiving GLP-1 receptor agonists for obesity indication were excluded. Additional exclusion criteria included history of any chronic liver disease except non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD)*.

Interventions/Exposure: Patients were followed from treatment initiation until the first occurrence of one of the following: emigration, death, end of the study period, initiation of a DPP4 inhibitor among patients who entered the study on a GLP-1 receptor agonist or vice versa, or the occurrence of a study outcome.

Outcome: Primary outcome was serious liver events, defined as incident diagnoses of compensated or decompensated cirrhosis or hepatocellular carcinomas that was captured by patient registries. Compensated and decompensated cirrhosis were defined as presence of esophageal varices, portal hypertension, liver failure, liver transplantation, hepatorenal syndrome, liver cirrhosis, but not ascites or hepatic encephalopathy. Secondary outcomes were: (a) compensated and decompensated cirrhosis; and (b) hepatocellular carcinoma (HCC).

Data Analysis: Standardized mortality ratio weighting based on propensity score was used to adjust for confounding. Adjusted hazard ratios (aHR) calculated using Cox proportional hazards model.

Funding: Swedish Research Council, Region Stockholm, and Dr. Margaretha Nilsson foundation for medical research.

Results: The study cohort included 91,479 new users of GLP-1 receptor agonists (81% oral liraglutide, 4% subcutaneous semaglutide) and 244,004 new users of DPP4 inhibitors (73% sitagliptin). Demographic data demonstrated a mean age of62 years old; 415 females; median follow-up time of 3 to 3.6 years (interquartile range 1.2-6.1), and 0.6% diagnosed with NASH/NAFLD at study inception. Among new users of GLP-1 receptor agonists, 21% also carried a diagnosis of obesity while only 8.4% of new users of DPP4 inhibitors had this diagnosis at study inception.

New users of GLP-1 receptor agonists had 16.9 serious liver events per 10,000 person years compared with 19.1 serious liver events per 10,000 person years among new users of DPP4 inhibitors (aHR 0.85; 95% confidence intervals [CIs] 0.75-0.97). In sub-group analysis, new users of GLP-1 receptor agonists had less compensated or decompensated cirrhosis compared to new users of DPP4 inhibitors (aHR 0.85; 95% CIs 0.75-0.97), but no difference in HCC was demonstrated.

***Note:** As per recent nomenclature change, NASH is now labelled as metabolic-dysfunction associated steatohepatitis (MASH) and NAFLD is labelled metabolic-dysfunction associated steatotic liver disease (MASLD).

COMMENTARY

Why Is This Important?

Per the National Institute of Health, approximately 24% of the US population has MASLD and up to 6% have MASH. Estimates about the progression from MASLD to decompensated cirrhosis vary widely, with some experts estimating that up to 20% of patients with MASLD may progress to serious liver events.[1] However, data from the largest prospective natural history study of MASH patients demonstrated hepatic decompensation rates are very small among patients with stage F0-F2 fibrosis (0.05 per 100 person-years), but increase significantly with stage F3 fibrosis (0.99 per 100 person-years, crude HR 18.6; 95% CI 5.4-62.6).[2] Despite this low rate of progression, the high prevalence of MASLD means that this will lead to decompensated cirrhosis in many individuals and effective treatments are sorely needed.

The 2023 American Association for the Study of Liver Disease (AASLD) guideline on NAFLD[1] recommends the following treatments: cessation of alcohol if MASH with ≥F2 fibrosis score, weight loss, increased exercise, Mediterranean diet, consideration of bariatric surgery for obese patients, and consideration of pioglitazone if a patient also has Type 2 DM or consideration of semaglutide (a subcutaneous GLP-1 receptor agonist) if patient also has obesity or Type 2 DM. As summarized in this issue of EBGI, the US Food and Drug Administration (FDA) just approved the first treatment for MASH, resmetirom, an oral thyroid hormone beta-selective agonist that is liver-directed and demonstrated to be more effective than placebo at MASH resolution and reduction in fibrosis. However, could GLP-1 receptor agonists be a better option for most patients with MASH?

Phase 2 randomized controlled trial (RCT) data of 320 MASH patients with F1-F3 fibrosis scores demonstrated that daily semaglutide produced MASH resolution versus placebo, but did not achieve statistical significance for decrease in hepatic fibrosis.[3] The value of the study by Engström et al is that it demonstrates a reduction in serious liver events associated with GLP-1 receptor agonist use in patients with Type 2 DM. However, as discussed below, the study has many limitations. Another retrospective cohort study from South Korea is currently in press in the *Journal of the American Medical Association Internal Medicine*[4] produces similar results, albeit with similar study limitations. Ultimately, the most common cause of death among patients with MASLD are cardiovascular disease and non-hepatic malignancy. Thus, for these conditions, effective treatment of obesity with substantial weight loss may be more effective than specific liver-directed treatments for MASH, like resmetirom.

Key Study Findings

In this observational study, patients with Type 2 DM who were treated with GLP-1 receptor agonists were less likely to develop serious liver events compared to patients receiving DPP4 inhibitors (aHR 0.85; 95% CIs 0.75-0.97).

Caution

Given substantial study design limitations, this should be considered a hypothesis-generating study as opposed to a study which guides management. Specifically, the study design was limited because the vast majority of patients treated with GLP-1 receptor agonists received oral liraglutide, which has not demonstrated similar impact on weight loss as semaglutide. Also, assessment of presence/absence of MASH or MASLD at baseline and change in weight over time were not assessed. Fewer than 1% of study patients had confirmed MASH/MASLD during study inception. The study was limited to patients with Type 2 DM, although the ideal population would be patients with MASH.

My Practice

Since I'm not an obesity specialist, I again consulted with an EBGI former Associate Editor, Sonali Paul, MD, who is certified in obesity medicine and has expertise in using these medications for management of MASH and MASLD patients with obesity and/or Type 2 DM. She noted that the results of this study will not change her practice, but it's helpful to quote this and other studies when educating her patients about the potential benefits of GLP-1 receptor agonists for MASH/MASLD. Dr. Paul noted one issue is insurance coverage for GLP-1 receptor agonists. Based on her anecdotal experience, this has improved over time, especially for patients with Type 2 DM. However, shortages of GLP-1 receptor agonists as well as tirzepatide, a GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide, has made it difficult to start new patients on these agents.

For gastroenterologists who see patients experiencing gastroinstestinal side effects from GLP-1 receptor agonists, Dr. Paul emphasized the following pearls, which we have discussed in prior EBGI summaries.[5-6] First, when she prescribes GLP-1 receptor agonists, like semaglutide, she usually increases the dose gradually in 2.5 mg increments every 4 weeks based on tolerability. Therefore, if clinically important nausea develops, the next step should be to revert to a lower dose as opposed to starting an anti-nausea agent or simply discontinuing the medication totally. Remember, continued treatment will be required to maintain weight loss in most patients since obesity is a chronic disease. If patients develop mild constipation, then treatment with an osmotic laxative without lowering the dose is acceptable.

Finally, she also follows other recommendations in the AASLD guideline. She encourages MASH/MASLD patients to limit alcohol consumption or

stop drinking alcohol completely, to modify their diets to lose weight and frequently recommends the Mediterranean diet and advises patients to exercise regularly.

For Future Research

Ongoing research will clarify if GLP-1 receptor agonists do decrease hepatic decompensation in in MASH/MASLD patients with obesity and define the magnitude of any benefit. The ongoing MAESTRO-NASH RCT will also determine if resmetirom, which produces histologic improvement in MASH and is the only FDA-approved treatment for MASH, decreases hepatic decompensation, although those results will not be available for several years.

Conflict of Interest

Dr. Schoenfeld reports no relevant conflicts of interest.

REFERENCES

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77.
2. Schoenfeld P, Paul S. Hepatic decompensation rate is 0.05 per 100 person-years in NAFLD with Stage F0-F2 fibrosis, but rises to 1 per 100 person-yeard with Stage F3. Evidence-Based GI April 2022. https://gi.org/journals-publications/ebgi/april_schoenfeld/
3. Paul S. Inching closer to a NASH cure: Daily semaglutide achieves resolution of NASH but not fibrosis after 72 weeks. Evidence-Based GI Nov 2021. https://gi.org/journals-publications/ebgi/inching-closer-to-a-nash-cure-daily-semaglutide-achieves-resolution-of-nash-but-not-fibrosis-after-72-weeks/.
4. Jang H, Kim Y, Lee DH, et al. Outcomes of various classes of oral antidiabetic drugs on nonalcholic fatty liver disease. JAMA Intern Med 2024;184:375-83.
5. Paul S. Tirzepatide for obesity: "Mounting" evidence for substantial weight loss. Evidence-Based GI; Aug 2022. https://gi.org/journals-publications/ebgi/paul_august_2022/
6. Schoenfeld P, Paul S. GI adverse events with GLP-1 receptor agonists for weight loss: Understanding the risks. Evidence-Based GI: Nov 2023. https://gi.org/journals-publications/ebgi/phil_paul_nov2023/.

EVIDENCE-BASED GI
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Ustekinumab and Vedolizumab Demonstrate Safety During Pregnancy-Updates From the PIANO Registry

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Associate Editor

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IBD

This summary reviews Chugh R, Long MD, Jiang Y, et al. Maternal and neonatal outcomes in vedolizumab and ustekinumab exposed pregnancies: Results from the PIANO registry. Am J Gastroenterol. 2024; 119(3):468-476.

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Keywords: Ustekinumab, vedolizumab, pregnancy, PIANO

STRUCTURED ABSTRACT

Question: Are ustekinumab, an interleukin (IL)-23 monoclonal antibody, and vedolizumab, an anti-integrin monoclonal antibody, safe during pregnancy in patients with inflammatory bowel disease (IBD)?

Design: This multicenter, prospective observational study included pregnant women with singleton pregnancies and a diagnosis of IBD, and is otherwise known as the "Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes" (PIANO) study. This article provides an updated analysis through November 2022 and specifically focuses on pregnant women exposed to ustekinumab and vedolizumab. Patients were administered questionnaires at enrollment, each trimester, delivery, and 4, 9, and 12 months post-delivery (**Figure 1**).

Setting: The PIANO registry has enrolled patients from more than 30 centers in the United States since 2007.

Patients: Through November 2022, 1,669 completed singleton pregnancies with 1,610 resulting in the birth of a baby were included. Spontaneous abortion or miscarriage occurred in 2.5% of patients. Among these pregnant women, 47 were exposed to ustekinumab and 66 were exposed to vedolizumab.

Exposures: IBD medications, including ustekinumab, vedolizumab, anti-tumor necrosis factor (TNF) agents, immunomodulators, combination anti-TNF/thiopurine therapy, and no exposure to biologics or thiopurines.

Outcomes: Primary outcomes included congenital malformations, spontaneous abortion, preterm birth, Cesarean section (C-section), small for gestational age, low birth weight, neonatal intensive care unit (NICU) stay, intrauterine growth restriction, placental events, neonatal/infant infections, and infant developmental milestones.

Data Analysis: Bivariate analyses were utilized to determine the association of biologic therapy class with pregnancy and neonatal outcomes. Fisher's exact test and Kruskal-Wallis test were also used to compare categorical and continuous data.

Funding: The Crohn's and Colitis Foundation and the Leona M. and Harry B. Helmsley Charitable Trust.

Results: Among the 1,669 pregnancies in the registry, demographic data included mean maternal age: 32; IBD duration: 8.5 years; disease type: 62% Crohn's disease, 35% ulcerative colitis, 2% IBD unclassified; mean total pregnancies, including current: 2.1; IBD drug exposure during pregnancy: anti-TNF: 43%; immunomodulator: 14%; combination of anti-TNF/immunomodulator: 11%; no IBD drug exposure: 26%; ustekinumab: 3%; and vedolizumab: 4%.

There was no observed increased risk in congenital malformations, spontaneous abortion, small for gestational age, low birth weight, NICU stay, placental complications, or intrauterine growth restriction with either vedolizumab or ustekinumab compared to other therapy exposures. Ustekinumab was associated with a lower rate of pre-term birth compared to all other therapies, including vedolizumab. Rates of serious infections in infants within 12 months were similar between all groups, though non-serious infections were less common for ustekinumab.

COMMENTARY

Why Is This Important?

Prior data from the PIANO registry demonstrated that corticosteroid use in IBD patients during pregnancy was associated with increased adverse maternal and fetal outcomes, confirming the importance of achieving and maintaining IBD remission prior to pregnancy. Further data from the PIANO registry confirmed the safety of anti-TNF agents and thiopurines during pregnancy, demonstrating no increased

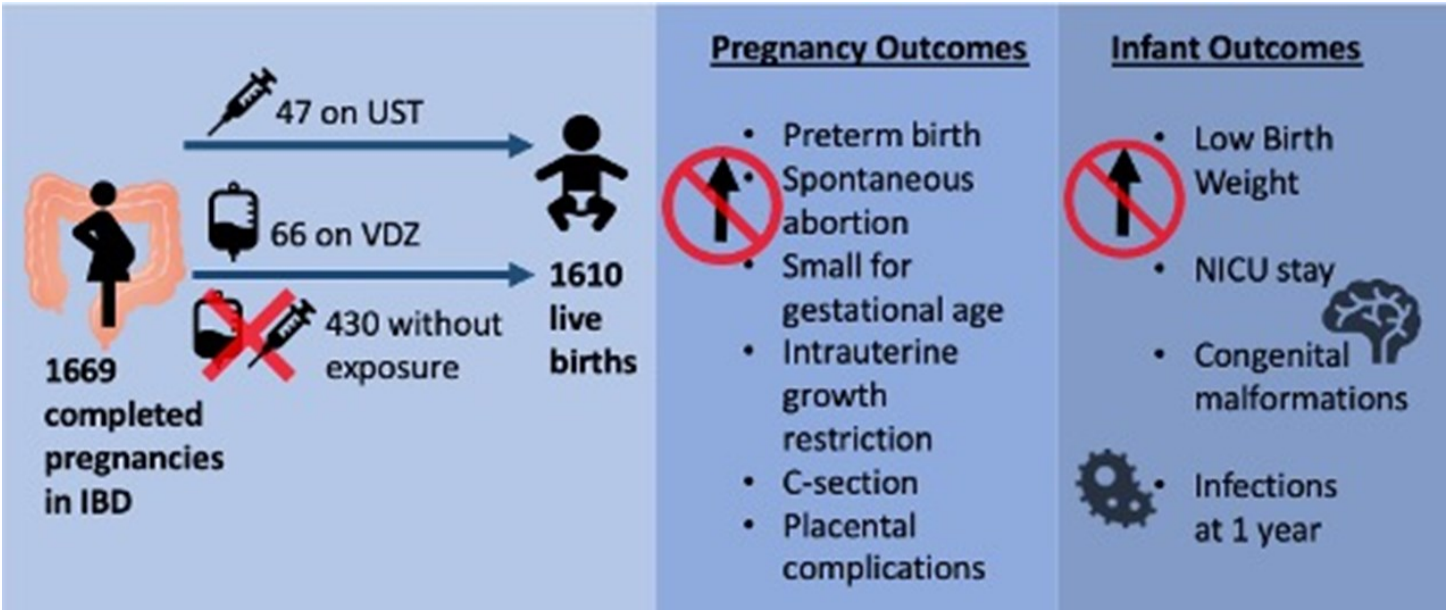

Figure 1. Visual abstract showing study design and pregnancy/infant outcomes. Abbreviations: IBD, inflammatory bowel disease; NICU, neonatal intensive care unit; PIANO, Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes

risk of spontaneous abortion/ miscarriage, congenital malformations, or infant infections.[2] Until this updated analysis, prior studies reporting pregnancy outcomes with vedolizumab and ustekinumab exposure during pregnancy were limited due to small sample sizes.[3-4]

This prospective study by Chugh et al is the largest study to assess maternal and infant outcomes after exposure to ustekinumab or vedolizumab while also providing comparators of IBD patients with no IBD drug exposure and IBD patients treated with anti-TNF agents or immunomodulators. Since there was no increased risk of adverse pregnancy or infant outcomes after exposure to ustekinumab or vedolizumab, these data provide critical reassurance to both patients and providers who are either considering these therapies or already receiving them near the time of pregnancy. Patients can be counseled that these biologics, like anti-TNFs, should be continued and uninterrupted during pregnancy with no expectation for an increased risk of adverse outcomes.

Key Study Findings

Ustekinumab and vedolizumab exposure during pregnancy were not associated with an increased risk of adverse pregnancy (preterm birth, spontaneous abortion, small for gestational age, intrauterine growth restriction, C-section, and placental complications) or neonatal/infant (low birth weight, NICU stay, congenital malformations, and infections at 1 year) outcomes when compared to no exposure, anti-TNFs, and combination therapy with anti-TNFs and thiopurines.

Ustekinumab exposure was associated with a lower risk of pre-term birth when compared to other therapies, though this potential benefit needs to be confirmed

in larger cohorts.

Caution

This was a relatively small study with only 113 patients exposed to either ustekinumab or vedolizumab. This could lead to type 2 error, i.e., failure to observe significant rates of adverse events that could be identified in larger cohorts. Additionally, the findings of this study are based on patient questionnaires, which are subject to selection, sampling, and recall bias.

My Practice

In my practice, I now counsel patients that they should continue ustekinumab or vedolizumab during pregnancy if these agents had been controlling their disease well prior to pregnancy. Additionally, I now encourage these agents (when clinically appropriate) as options in women who are contemplating pregnancy and need to initiate biologic therapy for either Crohn's disease or ulcerative colitis. I also emphasize important findings from other studies of the PIANO registry, particularly that flares of disease and use of corticosteroids are associated with adverse perinatal outcomes.[1,5] This underscores the importance of continuing anti-TNF agents, ustekinumab, and vedolizumab during pregnancy to maintain remission of IBD.

For Future Research

Larger, prospective cohorts are needed to confirm the findings of this study. Additionally, research is needed regarding the comparative effectiveness and safety of other biologic therapies, including sphingosine-1-receptor modulators and JAK1 inhibitors, to maintain remission of IBD during pregnancy without any increase in adverse pregnancy or neonatal outcomes.

Conflict of Interest

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

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

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REFERENCES

1. Schoenfeld P, Charabaty A. Achieve IBD remission before pregnancy: PIANO registry data shows adverse perinatal outcomes for infants associated with IBD flares and steroid use. Evidence-Based GI 2022. https://gi.org/journals-publications/ebgi/schoenfeld_september_2022/
2. Mahadevan U, Long MD, Kane SV, et al. Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among women with inflammatory bowel disease.

Gastroenterology 2021;160(4):1131-1139.
3. Mitrova K, Pipek B, Bortlik M, et al. Safety of ustekinumab and vedolizumab during pregnancy-pregnancy, neonatal, and infant outcome: A prospective multicentre study. J Crohns Colitis 2022;16(12):1808-1815.
4. Gisbert JP, Chaparro M. Safety of new biologics (vedolizumab and ustekinumab) and small molecules (tofacitinib) during pregnancy: A review. Drugs 2020;80(11):1085-1100.
5. Odufalu FD, Long M, Lin K, Mahadevan U. Exposure to corticosteroids in pregnancy is associated with adverse perinatal outcomes among infants of mothers with inflammatory bowel disease: results from the PIANO registry. Gut 2022;71(9):1766-1772.