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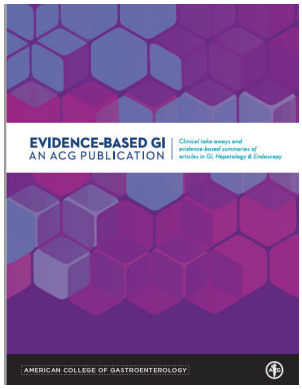

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EBGI **Volume 3, Issue 12**

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IBSRELA®
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INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

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

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx

IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

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

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

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

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

5.2 Diarrhea

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

Most Common Adverse Reactions

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

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

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

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

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

Adverse Reaction of Special Interest – Severe Diarrhea

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

Patients with Renal Impairment

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

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

Adverse Reactions Leading to Discontinuation

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

Less Common Adverse Reactions

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

Hyperkalemia

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

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

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

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

Juvenile Animal Toxicity Data

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Diarrhea

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

Accidental Ingestion

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

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Overt Evidence for the Efficacy and Safety of Thalidomide in Gastrointestinal Bleeding from Small Intestinal Angiodysplasia

Philip N. Okafor, MD, MPH

Philip N. Okafor, MD, MPH

Senior Associate Consultant, Department of Gastroenterology, Mayo Clinic, Jacksonville, Florida

This summary reviews Chen H, Wu S, Tang M et al. Thalidomide for Recurrent Bleeding Due to Small Intestinal Angiodysplasia N Engl J Med 2023 Nov 2;389(18):1649-1659.

Correspondence to Philip N. Okafor, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does a 4-month treatment course of oral thalidomide (50 mg or 100 mg daily) reduce the number of bleeding episodes in patients with recurrent bleeding from small intestinal angiodysplasia?

Design: Randomized, multicenter, double-blind, placebo-controlled study, conducted between April 2016 and December 2020.

Setting: Ten hospitals in China.

Participants: Adults with at least 4 episodes of recurrent bleeding in the previous year from small intestinal angiodysplasia (SIA) were enrolled. The existence of SIA had to be confirmed via capsule endoscopy, balloon-assisted enteroscopy, or both.

Intervention/Exposure: Fifty mg or 100 mg oral thalidomide vs placebo for 4 months with 1:1:1 randomization.

Outcomes: The primary endpoint was a reduction of at least 50% in the

number of bleeding episodes occurring during a 1-year follow-up period compared with the number of bleeding episodes in the 1-year observation period before 4-months of treatment with thalidomide. Secondary endpoints included cessation of bleeding during 1-year follow-up period; blood transfusion during 1-year follow-up period; hospitalization for bleeding during 1-year follow-up period. Changes during the 1-year follow-up period compared to the initial 1-year observation period were calculated for transfusion volume of red cells, duration of bleeding in days, hemoglobin level, number of hospitalizations for bleeding, duration of hospital stay (in days) for bleeding, and number of bleeding episodes.

Data Analysis: Intention-to-treat analysis and a Fisher exact test were used to compare the primary endpoint across all 3 groups. There was no adjustment for multiple comparisons. The sample size was calculated for comparison of 100 mg thalidomide group and 50 mg thalidomide group vs placebo, but not intended to determine if 100 mg thalidomide was superior to 50 mg thalidomide.

Funding: The National Natural Science Foundation of China and the Shanghai Municipal Education Commission, Gaofeng Clinical Medicine.

Results: The median age of participants was 62.2 years (range 26-69.6 years), 59.3% (n=89) were women, and all 3 groups were comparable in demographics and clinical characteristics. The primary endpoint, a reduction of at least 50% in the number of bleeding episodes occurring during a 1-year follow-up period compared with the number of bleeding episodes in the 1-year observation period before 4-months of treatment, was significantly better for thalidomide 100 mg and thalidomide 50 mg treatment groups vs placebo: 68.6% and 51% vs 16%, respectively, $P<0.001$. The incidence of rebleeding was also significantly lower with 100 mg thalidomide and 50 mg thalidomide vs placebo: 27.5% and 42.9% vs 90%, respectively.

Among other secondary outcomes, hospitalization due to recurrent bleeding was also significantly lower with 100 mg thalidomide and 50 mg thalidomide vs placebo: 27% and 35% vs 74%, respectively, as well as need for blood transfusion: 18% and 25% vs 62%, respectively. Other secondary outcomes followed the same trend (**Table 1**).

Although only 3 patients stopped treatment due to side effects (1 for abnormal liver function and 2 due to dizziness), adverse events were common with thalidomide, including constipation (22%-26%), limb numbness (14%) and dizziness (10%-20%).

		Relative Risk (100 mg Thalidomide vs Placebo) [95% CI]
Primary end point	Reduction of at least 50% in the number of bleeding episodes occurring during the 1-year follow-up	4.29 (2.21 to 8.31)
Secondary end points	Cessation of bleeding without rebleeding during first follow-up	12.75 (3.19 to 50.88)
	Receipt of a blood transfusion during the first follow-up period	0.28 (0.15 to 0.54)
	Hospitalization for bleeding during first follow -up period	0.37 (0.23 to 0.60)
	Median change in transfusion volume of red blood cells	−2.43 (−3.49 to −1.37)
	Median change in duration of bleeding	−3.63 (−4.21 to −2.51)
	Median change in hemoglobin level (g/l)	34.05 (26.98 to 41.13)
	Median change in number of hospitalizations for bleeding	−1.74 (−2.26 to −1.21)
	Median change in duration of hospital stays for bleeding	−4.89 (−6.72 to −3.05)
	Median change in number of bleeding episodes	−3.46 (−4.22 to −2.70)

Table 1: Effectiveness of thalidomide for the treatment of gastrointestinal bleeding from small intestinal angiodysplasia. CI, confidence interval.

COMMENTARY

Why Is This Important?

The increasing use of antiplatelet agents and novel anticoagulants has been met with an uptick in hospitalizations for gastrointestinal (GI) bleeding.[1] In particular, small bowel bleeding presents a treatment challenge for clinicians with rebleeding rates as high as 45%.[2] With the advancement in endoscopy technology, balloon-assisted enteroscopy (BAE) has become an important option for treating small-intestinal angiodysplasias, but it isn't available in many hospitals. Even when available, BAE can be challenging to perform, may not identify a bleeding source, is associated with complications including bowel perforations, and may not be suitable for medically unstable patients.[3] Therefore, it's also crucial to explore pharmacological therapies, too, especially because SIA are believed to recur over time. An effective pharmacological option for SIA has the potential to be a game changer by reducing hospitalizations, transfusion requirements, and endoscopy utilization.

Somatostatin analogs, such as octreotide 40 mg IM, every 28 days, decrease blood flow to splanchnic vasculature in the GI tract and may decrease transfusion requirements in these patients. However, most of the evidence supporting its use comes from small observational studies,[4] and it does not have any disease-modifying effects on eradicating or preventing SIAs.

SIAs are essentially collections of dilated arterial and/or venous capillaries. Thalidomide decreases expression of vascular endothelial growth factor, which are at high levels in patients with angiodysplastic lesions.[4-5] Thus, it's considered antiangiogenic and may be a disease-modifying agent whose benefit persists even after medication is stopped. However, there has been a paucity of evidence on therapeutic efficacy,[4] appropriate dose and duration of use, and significant concerns about dose-dependent side effects. In this landmark study, Chen et al conducted the first well-designed, large, randomized, placebo-controlled trial of thalidomide for the treatment of bleeding from small intestinal angiodysplasia.

Key Study Findings

Hospitalization due to recurrent bleeding was significantly lower with 100 mg thalidomide and 50 mg thalidomide vs placebo: 27% and 35% vs 74%, respectively, as well as need for blood transfusion: 18% and 25% vs 62%, respectively. Adverse events were common with thalidomide, including constipation (22%-26%), limb numbness (14%) and dizziness (10%-20%).

Caution

The authors highlight some limitations of this clinical trial. They emphasize that a positive fecal occult blood (used to identify GI bleeding) in patients who are not hospitalized or who do not receive any intervention may not be clinically meaningful. They also did not compare the 2 doses of Thalidomide (100 mg and 50 mg) against each other. Importantly, they excluded patients with aortic stenosis and hereditary hemorrhagic telangiectasia, 2 SIA risk factors. They also excluded patients on anticoagulation and antiplatelet therapy, who account for a significant proportion of patients hospitalized for small bowel bleeding. In addition, their study population was not as diverse as the US population which may limit the generalizability of the results. Finally, among the "responders" without rebleeding in the follow-up period, 20 out of 42 re-bled in the subsequent 3 months-27 months, suggesting a loss of effect and potential need for re-treatment with thalidomide.

My Practice

In my clinical practice, I have rarely used thalidomide for small bowel bleeding attributable to SIA, partly because I have easy access to BAE at my center. Also, thalidomide is still regarded as a chemotherapeutic agent at some hospitals and

prescription privileges are reserved for oncologists. In the rare clinical situations I have had to recommend thalidomide for GI bleeding, I have referred those patients to the hematology-oncology clinic, where it is prescribed and monitored for side effects. For these reasons, I have preferentially used long-acting somatostatin analogs when a pharmacological option is indicated for SIA bleeding. This can be administered monthly, increasing medication adherence.

For Future Research

This excellent study provides level I evidence on the efficacy and safety of 2 different thalidomide doses in reducing the risk of bleeding in patients with known small intestinal angiodysplasia. Future studies powered to compare both doses (and even lower doses), identify the ideal duration of treatment, and role of re-treatment are needed. In addition, more data are needed on patients with a higher cardiovascular disease burden who tend to be disproportionately affected with small intestinal angiectasia. Comparative trials between thalidomide, somatostatin and other antiangiogenic agents would also be helpful.

Conflict of Interest

Dr. Okafor reports no conflicts of interest.

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Low-dose Tricyclic Antidepressants for Irritable Bowel Syndrome: Definitive Evidence of Benefit from ATLANTIS

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

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

This summary reviews Ford AC, Wright-Hughes A, Alderson S, et al. Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment in Primary Care (ATLANTIS): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet 2023; 402: 1773-85.

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

STRUCTURED ABSTRACT

Question: Is amitriptyline 10 mg-30 mg nightly superior to placebo for improvement in irritable bowel syndrome (IBS) symptoms at 6 months in the primary care setting?

Design: Multicenter, double-blind, placebo-controlled randomized controlled trial (RCT) with 1:1 randomization.

Setting: Fifty-five general practices/primary care centers in England.

Patients: Inclusion criteria included: (a) ≥ 18 years old; (b) IBS based on ROME IV criteria; (c) IBS-Symptom Severity Score (IBS-SSS) >75 (0-500); (d) failure to respond to first-line treatments defined as dietary modification, soluble fiber, antispasmodics, or laxatives/ antidiarrheals; and, (e) normal hemoglobin, normal c-reactive protein, negative anti-tissue transgluaminase (TTG) antibodies to exclude celi-

ac disease, and no evidence of suicidal ideation since amitriptyline can be fatal in overdoses.

Interventions/Exposure: Amitriptyline 10 mg nightly (qhs) vs placebo. Patients were educated to titrate their dose upward to a maximum of 3 tablets (30 mg amitriptyline or 3 placebo tablets) over 3 weeks based on improvement in IBS symptoms. Throughout the study, patients could further titrate their dose up or down based on severity of IBS symptoms or side effects.

Outcome: The primary outcome was change in IBS-SSS from baseline at 6 months. The IBS-SSS requires patients to quantify severity of abdominal pain, abdominal distention, satisfaction with bowel habits, impact of IBS symptoms on quality of life based on a visual analog scale of 0-100 plus number of days with abdominal pain in past 10 days (X 10). The IBS-SSS range is 0-500, with mild IBS 75-175, moderate IBS 176-300, and severe IBS >300. A change of 35 points in IBS-SSS was considered to be a minimal clinically important difference.[1]

The key secondary outcome was subjective global assessment of relief of IBS symptoms at 6 months, which was defined as having somewhat relieved or better (ordinal scale of global IBS symptoms being worse, unchanged, somewhat relieved, considerably relieved, completely relieved compared to baseline).

Data Analysis: Intention-to-treat analysis. Primary outcome assessed using a linear regression model.

Funding: National Institute for Health and Care Research (NIHR) Health Technology Assessment Program.

Results: Between October 2019 and April 2022, 463 IBS patients were enrolled. The mean age was 48-49 years old; 67%-69% female; mean IBS-SSS at baseline 273. Over 80% of patients had IBS with diarrhea (IBS-D) or IBS-mixed (IBS-M), 84% had normal scores on HADS-Depression instrument, and 85% had moderate-severe IBS based on baseline IBS-SSS score with median IBS duration of 10 years.

At 6 months, mean IBS-SSS decreased from 273 to 170 in amitriptyline group versus decrease from 272 to 200 in the placebo group for mean difference in IBS-SSS score of -27.0; 95% confidence interval (CI) -46.9 to

-4.6, $P = 0.008$. Similar reduction was also seen after 3 months of treatment. For the key secondary outcome, amitriptyline-treated patients were more likely to achieve at least somewhat relief of global IBS symptoms (odds ratio [OR] 1.78, 95% CI 1.19-2.66) or for considerable/complete relief of global IBS symptoms (OR 1.88, 95% CI 1.20-2.95). (**Figure 1**) There was no evidence of effect on HADS-Depression scores at 3 or 6 months.

Discontinuation of study medication due to adverse events was 13% vs 9% for amitriptyline vs placebo, respectively. The most common adverse events were due to known anticholinergic effects in the amitriptyline group, including dry mouth (54%), drowsiness (53%), blurred vision (17%), and difficulty with urination (22%).

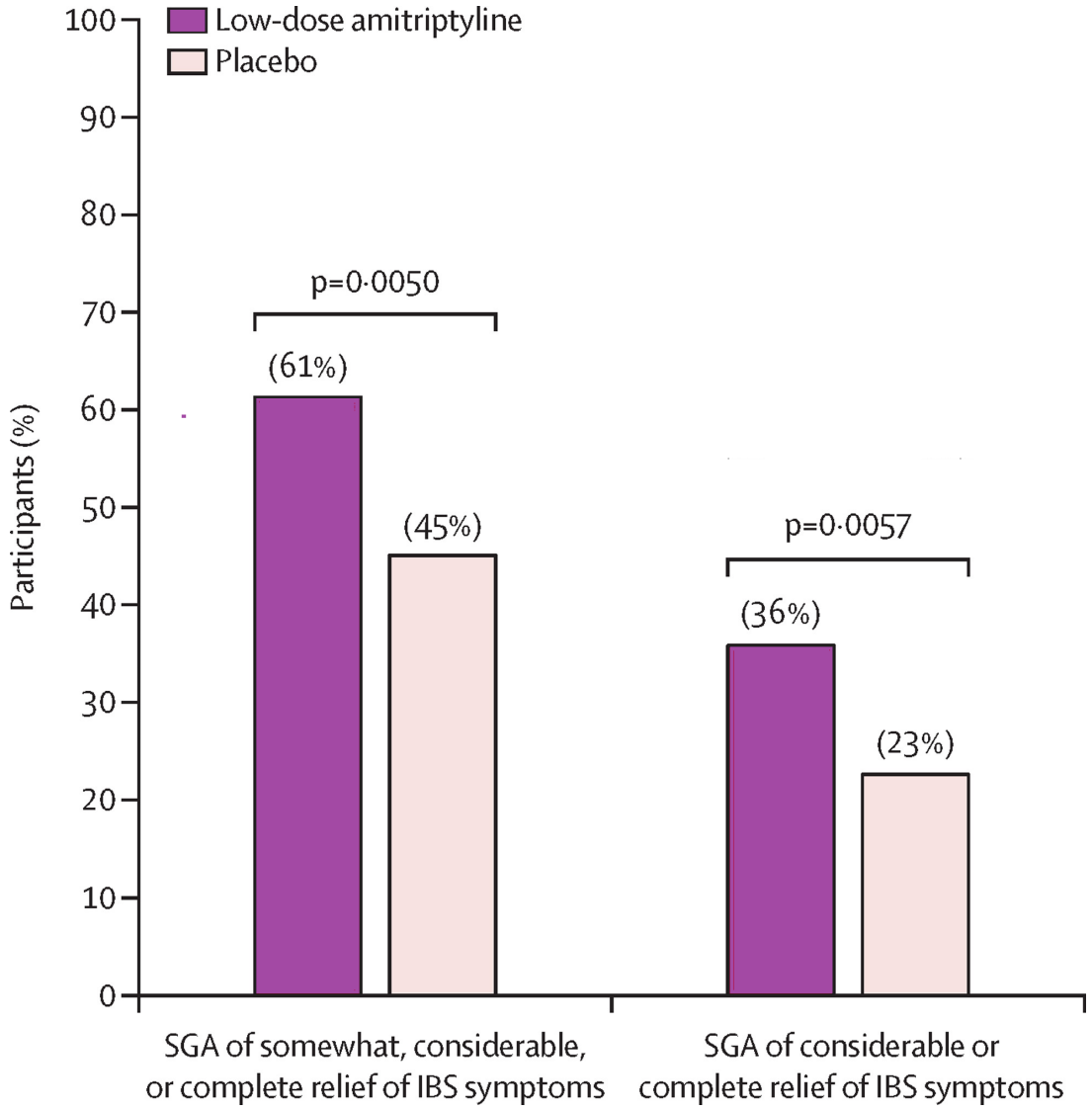

Figure 1. Key secondary outcome of subjective global assessment (SGA) of relief of irritable bowel symptoms (IBS symptoms at 6 months).

COMMENTARY

Why Is This Important?

Optimal treatment of IBS requires improvement in abdominal discomfort symptoms as well as bowel symptoms. The American College of Gastroenterology (ACG) guidelines on management of IBS[2] as well as the American Gastroenterological Association (AGA) guidelines on management of IBS-D[3] provide conditional recommendations suggesting that tri-cyclic antidepressants (TCAs) may be used for global IBS symptoms. Low-dose TCAs are used for neuropathic pain, including fibromyalgia, chronic pelvic pain, and migraines, because they modify central nervous system-mediated pain signaling.

There is limited RCT data supporting the use of TCAs in IBS. Although 12 RCTs have evaluated these agents, only about 650 patients have been enrolled and 6 different TCAs have been examined. These studies also have various design limitations, which is why the ACG and AGA guidelines only provide conditional recommendations that suggest TCA use in IBS. Therefore, the ATLANTIS study is a major achievement that quantifies the benefit of amitriptyline in a large, methodologically rigorous RCT which assessed patients over 6 months. Ford and colleagues should be commended for this effort.

Key Study Findings

Amitriptyline was superior to placebo for decreasing IBS-SSS and for achieving somewhat, considerable, or complete relief of global IBS symptoms at 6 months.

Caution

Since TCAs may cause constipation, I do not use them in IBS-C or IBS-M patients and reserve them for IBS-D patients where the constipation side effect is beneficial. The inclusion of IBS-C patients in this trial may have decreased the observed benefit of amitriptyline in the overall IBS population, although only 17% of study patients had IBS-C.

Since the study was performed in the primary care setting in a diverse IBS population, the more rigorous responder endpoints required by the US Food and Drug Administration and the European Medicines Agency for drug trials in IBS -D and IBS-C were not used. Ultimately, the benefit observed with amitriptyline was modest and did not meet the minimal clinically important difference in IBS-SSS reduction of 35 points compared to placebo.

My Practice

In my practice, TCAs are a cornerstone of IBS-D treatment: nortriptyline 25 mg every evening at bedtime and I may increase to 50 mg every evening at bedtime. Nortriptyline, which is a secondary amine, is my preferred agent

because it generally has less antihistaminic and anticholinergic side effects compared to a tertiary amine, like amitriptyline. I educate patients that TCAs modify their perception of central nervous system-mediated pain and that's helpful since defects in brain-gut communication and visceral hypersensitivity lead to abdominal pain in IBS. I also educate patients that low-dose TCAs are not appropriate nor intended to treat depression or anxiety symptoms, while also proactively communicating that they may feel drowsy, feel a little fatigued or get a dry mouth with these agents. It may take at least 12 weeks to see abdominal pain improvement. Furthermore, set appropriate expectations: "success" means decrease in frequency of abdominal discomfort and decrease in severity of symptoms when they do occur. Near-total resolution of symptoms is not the expected goal, although it does happen for some patients.

I do not prescribe selective serotonin reuptake inhibitors (SSRIs), like fluoxetine or paroxetine, which have not demonstrated clear benefit in some small RCTs with study design limitations. The ACG and AGA guidelines[2-3] both suggest against using SSRIs for IBS. However, if a patient can't tolerate TCAs or if the patient has IBS-C, then I frequently prescribe serotonin and norepinephrine reuptake inhibitors (SNRIs), which are effective neuromodulators of chronic pain. My preferred agent is duloxetine, which is FDA-approved for diabetic neuropathic pain and fibromyalgia. I start at 30 mg daily and will increase to 60 mg daily after 2 months depending on symptom response. However, it's important to note that there are no well-designed, large RCTs of duloxetine in IBS-C patients.

For Future Research

Future research should assess frequency and efficacy of TCAs in real-world settings, especially among IBS-D patients. Implementation research could assess why gastroenterologists may be hesitant to use TCAs for IBS and what interventions would overcome any barriers.

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards or speakers bureaus for Ironwood Pharmaceuticals, Salix Pharmaceuticals, AbbVie Pharmaceuticals, and Ardelyx Pharmaceuticals.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

HEPATOLOGY

Hepatocellular Carcinoma Incidence Rates Are 2%-3% in US Patients with Cirrhosis Regardless of Etiology

Dr Nicole Rich
Associate Editor

Dr Ashwini Arvind
Guest Contributor

Ashwini Arvind, MBBS[1] and Nicole E. Rich, MD MSCS[2]

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This article reviews Reddy KR, McLerran D, Marsh T et al. Incidence and risk factors for hepatocellular carcinoma in cirrhosis: the multicenter Hepatocellular Carcinoma Early Detection Strategy (HEDS) study. Gastroenterology 2023;165(4): 1053-1063.e6.

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STRUCTURED ABSTRACT

Question: What is the incidence of hepatocellular carcinoma (HCC) among US patients with cirrhosis and which demographic and clinical characteristics predict the development of HCC?

Design: Multicenter, prospective cohort study.

Setting: Seven centers across the US between April 2013 and December 2021.

Patients: Study patients had cirrhosis (diagnosed using histology or a combina-

tion of imaging and laboratory findings) and a Model for End-Stage Liver Disease (MELD) score <15. Exclusion criteria included: (a) clinically significant hepatic decompensation (defined as Grade 3–4 encephalopathy, refractory ascites, Child-Turcotte-Pugh class C); (b) listing for transplant; (c) history of cancer within 5 years; (d) unexplained liver masses; and (e) significant comorbid conditions with life expectancy <1 year.

Patients were followed every 6 months (per standard of care at each site) until HCC development, liver transplant, or death. Patients underwent HCC surveillance according to provider preference (or the respective site's protocol) and included bi-annual ultrasound or computed tomography/magnetic resonance imaging (CT/MRI) with or without serum alpha-fetoprotein (AFP). Baseline clinical, demographic and laboratory data were collected, and lifestyle exposures were assessed through validated questionnaires.

Outcomes: The primary endpoint was development of HCC, defined per AASLD guidelines (i.e., diagnosed either on biopsy or by radiographic identification of an LI-RADS 5 lesion). Incident HCC were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system, the most widely used staging system which includes tumor burden, liver function, and performance status. The BCLC system includes 5 stages: 0 (very early), A (early), B (intermediate), C (advanced), and D (terminal). Stage 0 indicates the tumor is less than 2cm, patient feels well and is active, and Child-Pugh A. Stage A means there is a single tumor of any size or up to 3 tumors all less than 3cm, patient feels well and are active, and Child-Pugh A or B.

Data Analysis: The annual incidence rate of HCC was estimated per 100 person-years and reported with 95% Poisson confidence intervals. Fisher's exact test, Wilcoxon test and multivariable logistic regression were used to examine the association between risk factors and incident HCC. All risk factor analyses excluded patients diagnosed with HCC within 6 months of study enrollment and patients with <6 months of follow-up.

Funding: National Institutes of Health.

Results: Among 1,723 patients followed for a median of 2.2 years (range, 0–8.7 years), the annual incidence rate of HCC was 2.4% (95% confidence interval [CI], 1.8%-3.1%). Among the 109 patients that developed HCC, 81% had very early or

early-stage HCC, defined as BCLC stage 0/A. Patients included in analyses evaluating risk factors for HCC development included 95 patients with HCC diagnosed >6 months after study enrollment and 1,230 patients without HCC with at least 6 months of study follow-up.

HCC incidence rates differed by cirrhosis etiology, with highest rates seen in Hepatitis C virus (HCV) infection (3.02%, 95% CI 2.04%– 4.26%) and alcohol-related liver disease (2.69%, 95% CI 1.37%–4.6%), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) (2.06%, 95% CI 1.01%–3.61%), and lower rates observed in Hepatitis B virus (HBV) infection (1.08%, 95% CI 0%–8%), autoimmune hepatitis (0.69%, 95% CI 0.02–3.22), and cholestatic liver disease (1.78%, 95% CI 0.37–4.74).

In univariate analysis, the following clinical characteristics and laboratory parameters were significantly associated with HCC: male gender (70.5% vs 51.9%; $P<0.001$), age (median, 62 years vs 59.5 years; $P=0.03$), obesity (63.2% vs 50.3%; $P=0.02$), smoking history (ever vs never; $P=0.04$), family history of liver cancer (9% vs 3.9%; $P=0.05$), baseline AFP ($P<0.001$), albumin, aspartate aminotransferase (AST), total bilirubin ($P=0.01$), international normalized ratio (INR) ($P=0.004$), platelet count ($P=0.002$), MELD score (10.0 vs 8.0; $P=0.004$), history of HCV (56.4% vs 40.9%; $P=0.005$) and years with cirrhosis (median, 3.85 vs 2.73 years; $P=0.004$). In multivariate analysis, male gender (odds ratio [OR] 2.47; 95% CI 1.54–4.07), obesity (OR 1.7; 95% CI 1.08–2.73), older age (per 5 years; OR 1.17; 95% CI 1.03–1.33), family history of liver cancer (OR 2.69; 95% CI 1.11–5.86), and years with cirrhosis (OR 1.06; 95% CI 1.02–1.1) predicted incident HCC.

COMMENTARY

Why is This Important?

HCC, the most common type of primary liver cancer, is the fastest rising cause of cancer-related deaths in the U.S., and >80% of cases occur in patients with cirrhosis.[1,2] Major risk factors for HCC, aside from male sex and older age, include hepatitis B virus (HBV) infection, HCV infection, MASLD (previously known as non-alcoholic fatty liver disease-NAFLD), alcohol consumption, diabetes and smoking. The risk of HCC varies across cirrhosis etiologies, and the landscape of HCC is shifting from predominately viral (HCV, HBV) to eradicated HCV and non-viral (MASLD and alcohol-related liver disease) etiologies with lower annual incidence rates.[3] These lower incidence rates hinder surveillance effectiveness in patients with MASLD, ALD, and eradicated HCV, by increasing the number needed to screen

(NNS)—the number of patients that must be screened to identify one early-stage HCC. Thus, better risk stratification tools are needed to identify at risk patients.

Most prior studies on HCC incidence and risk factors have been retrospective, performed outside of the US, and/or conducted in cohorts of patients lacking diversity in liver disease etiology. This decade-long, NIH-funded study is the largest prospective cohort to date to examine the magnitude of HCC risk and risk factors for HCC in contemporary patients with cirrhosis. Additionally, this study used validated surveys and manual chart reviews to evaluate risk factors not included in other studies, including family history of liver cancer, tobacco use, alcohol consumption, coffee/tea consumption, etc.

Key Study Findings

In a geographically diverse cohort of patients with cirrhosis enrolled from 2013 to 2021 with median follow-up time of 2.2 years (4,510 person-years), the annual incidence rate for HCC was 2.4% (95% CI 1.8%–3.1%).

HCC incidence rates differed by cirrhosis etiology with highest rates seen in HCV (3.02%, 95% CI 2.04%–4.26%) and alcohol-related liver disease (2.69%, 95% CI 1.37- 4.6), followed by MASLD (2.06%, 95% CI 1.01%–3.61%). Obesity OR 1.7 (95% CI 1.08–2.73) was the only modifiable risk factor identified in this study.

Caution

The study cohort, while geographically diverse, lacked racial and ethnic diversity and included only 7.1% Black, 2.1% Asian/Pacific Islander, and 9.5% Hispanic/Latino participants. Data on aspirin use, which has been associated with reduced HCC risk in population-based studies,[4-5] was not collected.

My Practice

We follow the updated 2023 AASLD guidance for HCC surveillance,[6] which recommends performing biannual ultrasound in addition to AFP in all patients with cirrhosis, regardless of etiology. This practice is supported by this prospective study, as the annual incidence rate for HCC exceeded 1% for all etiologies of cirrhosis, exceeding the established threshold for which surveillance is currently considered to be cost-effective. We also perform surveillance in patients with cirrhosis and treated HCV who have achieved viral cure (i.e., sustained viral response), as well as those with chronic HBV who are at high risk (determined by PAGE-B score $\geq$10 or age + endemic country of origin from Asia or Africa).[6]

Obesity was the only modifiable risk factor identified for HCC in this study. This reiterates the importance of counseling patients on lifestyle modifications and healthy weight loss to mitigate HCC risk. As only a minority of patients can lose weight and maintain weight loss with lifestyle modifications

alone, it will become increasingly important to 1) identify and risk stratify patients with MASLD; and 2) refer patients early for multidisciplinary treatment, including bariatric surgery or pharmacologic obesity treatment and pharmacologic MASLD treatment once available.

For Future Research

The burden of HCC is not equally distributed in the US, with higher incidence and mortality rates observed among Black, Hispanic, Asian/Pacific Islander and American Indian/Alaskan Native populations compared to non-Hispanic Whites.[3,7] Thus, future studies should be performed in racially and ethnically diverse cohorts. Additionally, limited information is available to guide clinicians on how to counsel patients regarding their individual risk of HCC. While some risk stratification tools are available, none have been sufficiently externally validated and it remains unclear how to implement these tools into clinical practice.

Conflicts of Interest

Dr. Arvind reports no conflicts of interest. Dr. Rich has served as consultant for AstraZeneca, Eisai, and Elevar Therapeutics.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

CRC SCREENING

In Case You Missed It

Lynch Syndrome: An Aspirin a Day Keeps Colorectal Cancer Away!

Dr. Swati G. Patel
Associate Editor

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Associate Professor of Medicine, University of Colorado Anschutz Medical Center; Rocky Mountain Regional Veterans Affairs Medical Center, Denver, Colorado

This summary reviews Burn J, Sheth H, Elliot F, et al for CAPP2 Investigators. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomized, placebo-controlled trial. The Lancet 2020;395:1855-63.

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STRUCTURED ABSTRACT

Question: Does aspirin decrease the risk of colorectal cancer (CRC) in Lynch Syndrome patients?

Study Design: Double-blind, placebo controlled, randomized controlled trial (RCT).

Setting: Forty-two international centers

Patients: Eight-hundred sixty-one individuals with Lynch Syndrome from Europe (82%), Australasia (13%), Africa (4%) and the Americas (<1%).

Intervention: Aspirin 600 mg versus placebo between 1999-2005 for 25 months.

Outcomes: The primary endpoint was time to first occurrence of CRC. CRC incidence and non-colorectal Lynch-associated cancer incidence at 10-year follow up (20-year follow up was available for participants from England,

Finland, and Wales).

Data Analysis: Intention-To-Treat and Per-Protocol Analyses were performed. For time to first occurrence of CRC, life-table methods, Cox proportional hazards adjusted for age and gender, and Kaplan-Meier curves were used.

Funding: Cancer Research UK, European Union, MRC, NIHR, Bayer Pharma AG, Barbour Foundation.

Results: There was no significant difference between the placebo and intervention arm in terms of geography, genotype, or other baseline characteristics.[1] Mean follow up was 10 years approximating 8,500 person-years. There was a lower proportion of patients who developed CRC in the aspirin group vs placebo group (9% vs 13%). In the intention-to-treat analysis, there was a significantly reduced hazard ratio (HR) for developing CRC in aspirin group vs placebo: HR 0.65, 95% confidence interval (CI) 0.43–0.97, *P*=0.035, with risk diverging starting at 5 years (**Figure**). Accounting for those with multiple primary CRCs, the incidence rate ratio (IRR) was 0.58, 95% CI 0.39–0.87, *P*=0.0085. For those who were adherent to aspirin over the study period (per-protocol analysis), the HR was 0.56, 95% CI 0.34–0.91, *P*=0.019, and IRR 0.50, 95% CI 0.31–0.82, *P*=0.0057. There was no significant difference in non-CRC Lynch associated cancers between aspirin and placebo group. There was also no significant difference in adverse event rates between the 2 groups while on treatment (cerebrovascular events: 2 out of 427 vs 3 out of 434; cardiovascular events: 1 out of 427 vs 5 out of 434; gastrointestinal bleeding: 11 out of 427 vs 9 out of 434).[1]

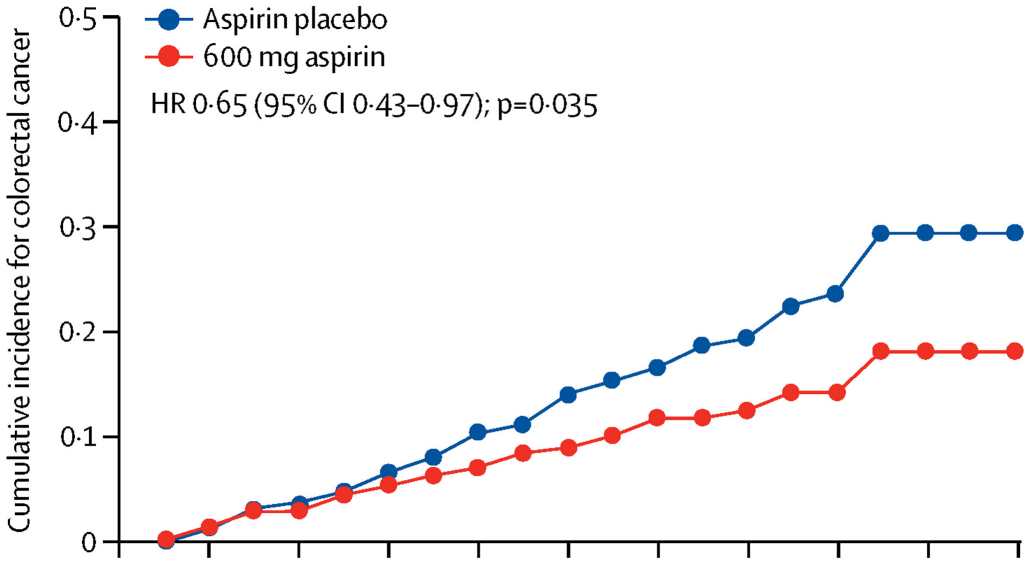

Figure 1. Cox proportional hazards (HRs and 95% CIs) comparing those on aspirin *vs* those on placebo and depicted by Kaplan-Meier analysis (n=861). Intention-to-treat analysis (n=427 aspirin, 434 placebo) by randomization group.

COMMENTARY

Why Is This Important?

Lynch syndrome is common, affecting every 1 out of 279 individuals,[2] and is caused by a pathogenic variant in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). It is associated with an up to 61% lifetime risk of CRC.[3] Although regular, high-quality colonoscopy and polypectomy are cornerstones for CRC prevention, post-colonoscopy CRCs occur.[4] This may, in part, be due to accelerated carcinogenesis due to defective mismatch repair or due to progression via non-polypoid pathways.[5] Adjuncts to colonoscopy are needed to reduce CRC risk in this common, high-risk condition. Aspirin is associated with decreased risk of CRC in the general population,[6] though not routinely recommended due to overall low absolute risk in average-risk individuals, risk of short-term adverse effects, and delayed potential benefit.[7] Given the high absolute CRC risk in Lynch Syndrome, aspirin use may provide adjunct benefit to this high-risk population that outweighs potential harms.

Key Study Findings

Aspirin 600 mg daily for 25 months significantly reduces the long-term risk of developing CRC during 10 years of follow up: HR = 0.65, 95% CI 0.43–0.97; *P*=0.035, with risk starting to split between the 2 groups at 5 years from start of intervention. Based on this study, we need to treat 24 Lynch Syndrome patients with aspirin to prevent one CRC.

Serious adverse event rates were low in both groups, and there was no significant difference between aspirin (11 out of 427, 2.6%) and placebo (9 out of 434, 2.1%) for those who developed peptic ulcer or bleeding over the treatment period.

Caution

The study was designed in an era when high doses of aspirin (600 mg) were thought to be required for various indications (cardiovascular, etc.). Although the adverse event rates were low in the study and there was no difference between aspirin and placebo, 600 mg is a high dose and providers and patients should exercise caution and close monitoring if this high dose is used. Data from the general population suggests that lower doses may be just as protective against cancer. However, a head-to-head comparison of different aspirin dosages is not available for Lynch Syndrome patients yet. This study did not include *PMS2* patients, who have a lower lifetime risk of CRC (up to 20%).[3] Thus, it is unclear if they would derive the same relative benefit, and if they do, whether it is still advised to use aspirin given their absolute risk is lower than *MLH1*/*MSH2* patients. This study kept patients on aspirin for 25 months. It is unclear what the optimal duration of therapy is.

My Practice

Based on this well-designed RCT, I discuss aspirin therapy with every Lynch Syndrome patient I see. I explain that the optimal dose is still under study. Unless there is an allergy or contraindication, I recommend adults >60 kg start 325 mg daily and monitor for any adverse effects. I also test and treat for *Helicobacter pylori* in all patients to minimize peptic ulcer risk. For those unable to tolerate 325 mg daily due to side effects, I encourage trial of 81 mg daily. I inform them that a dose finding study comparing 100 mg vs 300 mg vs 600 mg completed recruitment in 2019 (CAPP3). Thus, I will update them on optimal dose when those results are available. I explain that the benefit is delayed with expected benefit starting 5 years after initiating therapy. I advise patients to stay on aspirin as long as they are tolerating it but explain that this study demonstrated durable 10-year benefit after just 2 years of use. For patients with co-morbidities, on antithrombotics, or approaching age 60, I have an annual discussion about risks/benefits and discuss stopping it for those with limited life expectancy or where short-term risk begins to outweigh potential long-term benefit, knowing that patients will derive 10 years of protection. For my *PMS2* patients, I explain that no *PMS2* patients were included in this trial, thus it is unclear if there is similar benefit, especially in context of their overall lower absolute risk of CRC.

For Future Research

We will likely have 5-year outcome data from the dose finding CAPP3 study in the coming 1-2 years, which will guide what the best dose of aspirin is for our Lynch Syndrome patients. Other areas of research include understanding the mechanism of the long-term protection aspirin appears to confer. Current hypotheses include salicylate mediated modulation of the microbiome, pro-apoptotic properties of salicylate on aberrant progenitor cells or effect of salicylate on upregulation of immune surveillance.

Conflict of Interest

Dr. Patel reports no conflicts of interest.

The authors of CAPP2 are active on social media. Tag them to discuss their work and this EBGI summary!

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