EVIDENCE-BASED GI
AN ACG PUBLICATION

Clinical take-aways and evidence-based summaries of articles in GI, Hepatology & Endoscopy

AMERICAN COLLEGE OF GASTROENTEROLOGY

EVIDENCE-BASED GI

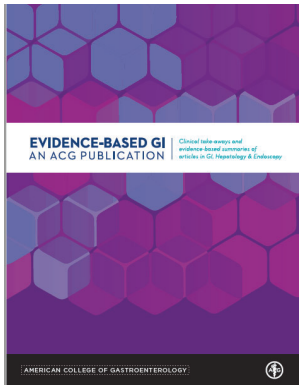
An ACG Publication

EDITORIAL BOARD

CONTACT

We'd love to hear from you!
Send comments and feedback to the editorial office at ebgi@gi.org.

Full issue archives available at gi.org/ebgi



The American College of Gastroenterology (ACG) is an international organization with more than 14,000 physician members representing some 85 countries. The College's vision is to be the pre-eminent professional organization that champions the evolving needs of clinicians in the delivery of high-quality, evidence-based and compassionate health care to advance world-class care for patients with gastrointestinal disorders through excellence, innovation, and advocacy in the areas of scientific investigation, education, prevention, and treatment. *Evidence-Based GI* is a member publication of the American College of Gastroenterology.

EVIDENCE-BASED GI
AN ACG PUBLICATION

SOCIAL MEDIA AMBASSADORS

Taiwo Ajose, MD
Michelle Baliss, DO
Aileen Bui, MD
Romy Chamoun, MD
Kashyap Chauhan, MD
Aastha Chokshi, MD
Arjun Chatterjee, MD
Sophia Dar, MBBS, MSEd
Jalpa Devi, MBBS
Lovekirat Dhaliwal, MD
Anoushka Dua, MD
Chukwunonso Benedict Ezeani, MD
Aimen Farooq, MD
Umer Farooq, MD
Hannah Winthrop Fiske, MD
Devika Gandhi, MD
Dheera Grover, MBBS
Maryam Bilal Haider, MD
Mohamad I. Itani, MD
Carl Kay, MD
Muhammad Zarrar Khan, MD
Zubair Khan, MD, FACP
Frances Lee, MD
Camille Lupianez Merly, MD
Clive Jude Miranda, DO
Jack F. Mlabasati, MD
Mouhand Mohamed, MD, MSc
Eleazar Montalvan-Sanchez, MD
Nazli Begum Ozturk, MD
Omar Tageldin, MD
Sean-Patrick Prince, MD, MPH
Jassimran Singh, MD
Noor Syed, MD
Fnu Vikash, M.Med, MD
Muhammad Sheharyar Warraich, MBBS

Social Media Associate Editors
Noor Syed, MD and Romy Chamoun, MD

Subcommittee Leaders

CRC Awareness Month Team
Aileen Bui, MD Romy Chamoun, MD
Frances Lee, MD

Twitter & Patient Advocate
Aimen Farooq, MD

International GI Fellowship Outreach
Jalpa Devi, MBBS

Ambassador Training Committee
Lovekirat Dhaliwal, MD
Zubair Khan, MD, FACP

Tweetorial Review
Michelle Baliss, DO

National GI Fellowship Outreach
Mouhand Mohamed, MD, MSc

Trainee #SoMe Impact Study Lead
Noor Syed, MD
Muhammad Sheharyar Warraich, MBBS

EBGI **Volume 4, Issue 1**

January 2024

TABLE OF CONTENTS

1//IBD

Mirikizumab Is Effective for Induction and Maintenance of Ulcerative Colitis

Rahul Dalal, MD, MPH

7//IBD

Is Early Ileo-cecal Resection for Crohn's Disease an Appropriate Primary Treatment?

Bharati Kochar, MD, MS

15//CRC SCREENING

Which Endoscopists Benefit from Using Computer-Aided Detection of Polyps During Colonoscopy?

Philip Schoenfeld, MD, MSEd, MSc (Epi)

19//CRC SCREENING

Post-Colonoscopy Colorectal Cancer Due to Missed Polyps in Proximal Colon or Rectum with Sub-Optimal Bowel Cleansing

Jeffrey Lee, MD, MPH

Discover the possibilities for your patients with inflammatory bowel disease.

View AbbVie's IBD portfolio online at ibd.abbvie.net.

Immunology

Gastroenterology
Dermatology
Rheumatology

abbvie

IBSRELA®
(tenapanor) tablets
50 mg BID

DISCOVER FIRST-IN-CLASS IBSRELA

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

Consider IBSRELA for your adult patients with IBS-C.

Visit **IBSRELA-hcp.com/discover**

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)*].

ardelyx®

Manufactured for and distributed by Ardelyx, Inc. Waltham, MA 02451 USA

EVIDENCE-BASED GI
AN ACG PUBLICATION

Mirikizumab Is Effective for Induction and Maintenance of Ulcerative Colitis

Dr. Rahul Dalal
Associate Editor

Rahul Dalal, MD, MPH

Instructor, Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

IBD

This summary reviews D'Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2023 ;388(26):2444-2455. Erratum in: N Engl J Med. 2023 Aug 24;389 (8):772.

Correspondence to Rahul Dalal, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is mirikizumab (Omvoh; Eli Lilly, Indianapolis, IN), a monoclonal antibody directed at the p19 subunit of interleukin-23, a proinflammatory factor, superior to placebo for induction and maintenance of clinical remission for moderate-to-severe ulcerative colitis (UC)?

Design: LUCENT-1 and LUCENT-2 were phase 3, randomized, double-blind, placebo-controlled trials (RCTs) of mirikizumab for moderate to severe UC. In the 12-week induction trial (LUCENT-1), patients were randomized 3:1 (mirikizumab: placebo). Patients who responded to mirikizumab induction were included in the 40-week maintenance trial (LUCENT-2), in which patients were randomized 2:1 (mirikizumab:placebo).

Setting: LUCENT-1 included 383 centers in 34 countries, and LUCENT-2

included 367 centers in 34 countries.

Patients: Inclusion criteria included: 18-80 years old; moderate-to-severe ulcerative colitis based on modified Mayo score ≥4 (0-9 scale); prior history of inadequate response, loss of response or intolerant of conventional therapy (glucocorticoids or immunomodulators) or biologic therapy. Exclusion criteria included: prior exposure to anti-interleukin (IL)-12 or anti-IL 23 monoclonal antibodies or prior treatment failure with ≥3 different biologic therapies. Note that the modified Mayo Score assesses rectal bleeding score (0-3), stool frequency score (0 -3), endoscopy subscore (0-3), so the score range is 0-9 with 9 representing most severe UC.

Interventions: In the 12-week induction RCT (LUCENT-1), mirikizumab 300 mg intravenously (IV) or placebo IV every 4 weeks for 12 weeks. In the subsequent 40 -week maintenance of remission RCT (LUCENT-2), mirikizumab 200 mg or placebo subcutaneously every 4 weeks.

Outcomes: Primary endpoints were clinical remission at week 12 for LUCENT-1 and clinical remission at week 40 (week 52 overall) for LUCENT-2. Clinical remission was defined as stool frequency subscore of 0-1, rectal bleeding subscore of 0, and an endoscopic subscore of 0-1, based on the modified Mayo Score. Secondary endpoints included clinical response, endoscopic response, and improvement in bowel movement urgency, which was assessed with the Urgency Numeric Rating Scale (Urgency NRS), a newly validated scale from 0 (no urgency) to 10 (worst possible urgency). Safety events were also assessed.*

Data Analysis: Primary and secondary endpoints were analyzed in modified intention-to-treat populations, including all patients who underwent randomization and received any amount of mirikizumab or placebo (but excluding those who were affected by an electronic clinical outcomes transcription error). Safety events were assessed in all patients who underwent randomization and received any amount of mirikizumab or placebo (including those affected by the transcription error). Binary endpoints were assessed using the Cochran-Mantel-Haenszel test with adjustment for stratification factors. Continuous endpoints were compared using mixed-effects models with repeated measures analysis. *

Funding: Eli Lilly, manufacturer of mirikizumab.

Results: A total of 1,281 patients were randomized for the 12-week induction of remission RCT (LUCENT-1): mean age 41-43; male sex 56%-61%; disease duration 6.9-7.2 years; left sided colitis 63%-64%; previous treatment failure with biologics 40%-42% or inadequate response to biologics 23%-24%. A significantly higher percentage of patients receiving mirikizumab achieved clinical remission at week 12 vs placebo (24.2% vs 13.3%, respectively). Clinical response, endoscopic remission, bowel urgency, and steroid-free remission were also significantly more common with mirikizumab compared to placebo **(Figure 1).** A total of 544 with response to mirikizumab were randomized for the 40-week maintenance of remission RCT (LUCENT-2), and a significantly higher percentage of patients receiving mirikizumab maintained/achieved clinical remission at week 40 vs placebo (49.9% vs 25.1%, respectively) and achieved secondary endpoints **(Figure 2**).

Incidence of adverse events were similar in the mirikizumab and placebo group. There were 15 opportunistic infections (including 6 herpes zoster) and 8 diagnoses of cancer in the mirikizumab group compared to 1 opportunistic infection (herpes zoster) and no diagnoses of cancer in the placebo group.*

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

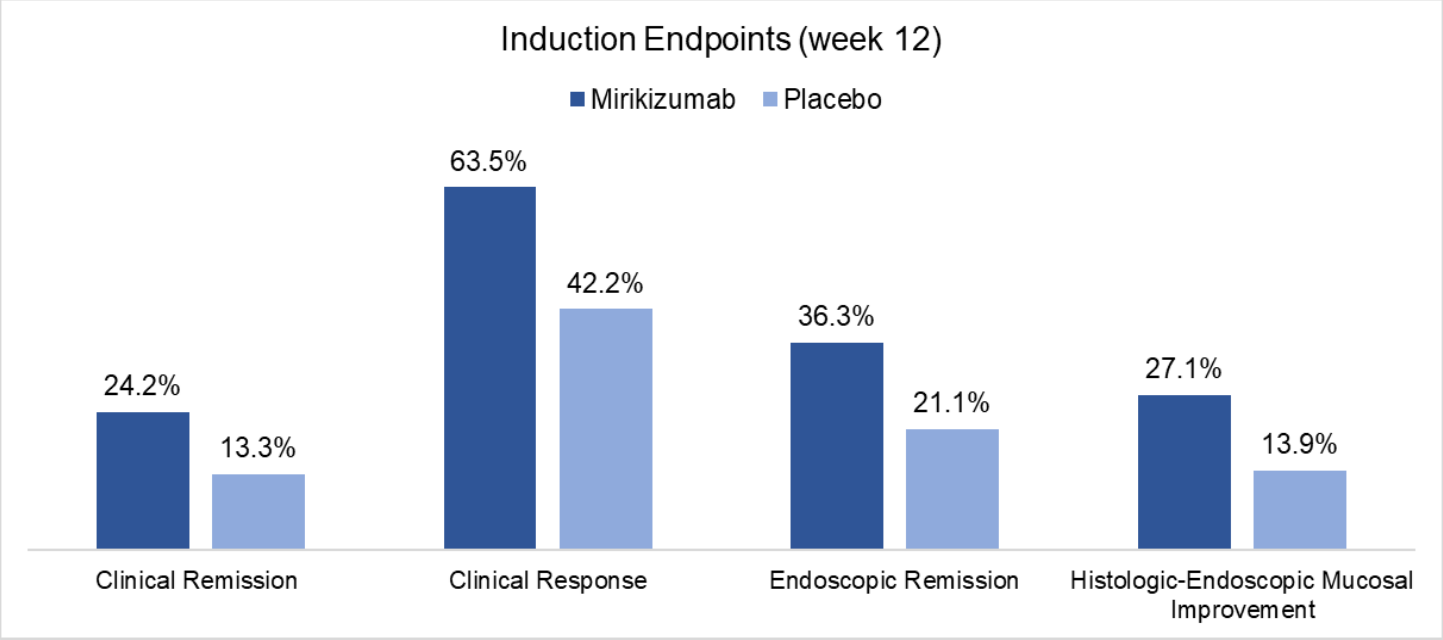


Figure 1. LUCENT-1. 12-week induction of remission randomized controlled trial.

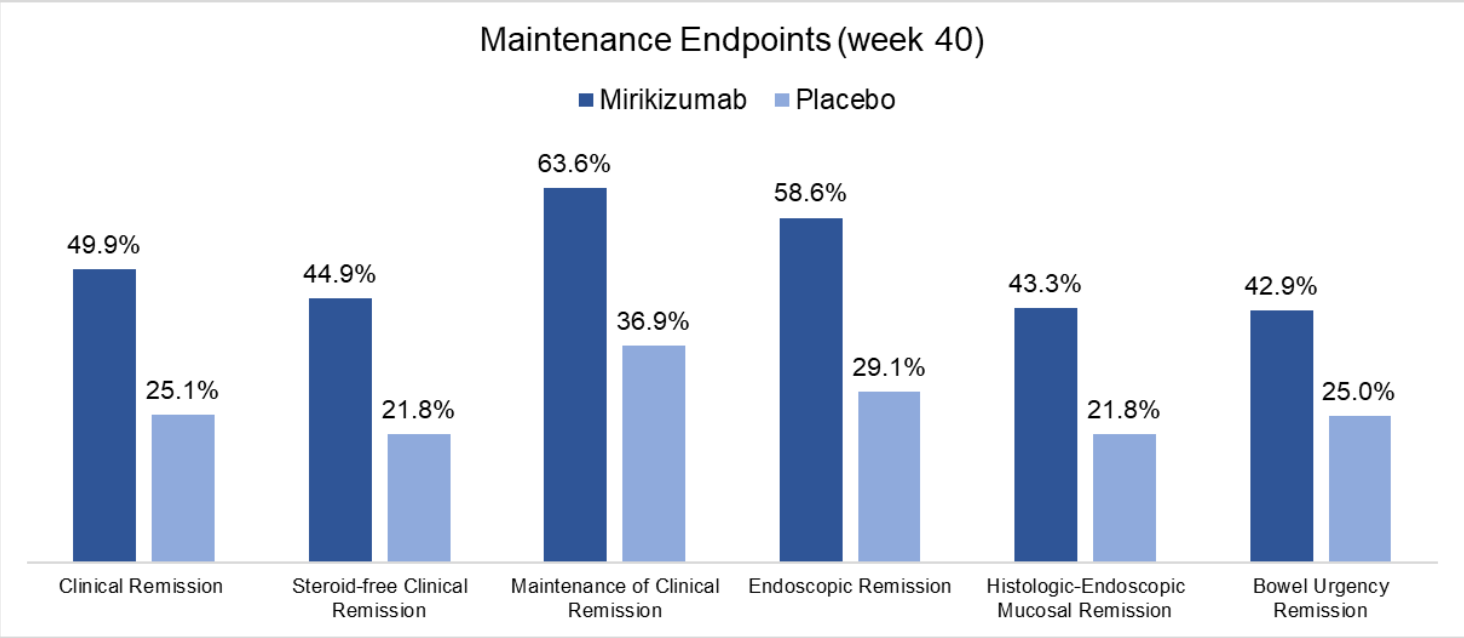


Figure 2. LUCENT-2. 40-week maintenance of remission randomized controlled trial.

COMMENTARY

Why Is This Important?

Despite an increasing number of approved therapies for moderate-to-severe UC, many patients will fail to achieve adequate response or lose response to therapy over time.[1] Additionally, the use of many treatments is limited due to the risk of infection and malignancy. The IL-23 pathway has become an important pathway to balance the effective treatment of autoimmune disease while minimizing adverse effects. Ustekinumab (Stelara; Janssen Pharmaceuticals, Beerse, Belgium) was the first drug approved for both Crohn's disease and UC that targets this pathway, specifically blocking the shared p40 subunit of IL-12 and IL-23,[2,3] while mirikizumab is the first drug approved for UC that selectively blocks the p19 subunit of IL-23.

The study assessed typical endpoints such as clinical remission, clinical response, and endoscopic remission. Other endpoints reflecting modern treatment goals in UC were also assessed. Mirikizumab was effective for these endpoints, including histologic-endoscopic mucosal remission and resolution of bowel urgency, which is increasingly recognized as the most important symptom for many patients with UC.[4] The LUCENT-1 and LUCENT-2 trials are unique as the first phase 3 RCTs to utilize the newly validated Urgency NRS to evaluate this endpoint. Given its effectiveness and favorable safety profile, mirikizumab will serve as another reasonable treatment consideration for patients with moderate-to-severe UC.

It's been hypothesized that the selective blockade of the p19 subunit of IL-23 would produce better outcomes in IBD

than blockade of the shared p40 subunit of IL-12 and IL-23. Risankizumab (Skyrizi; AbbVie Pharmaceuticals, Chicago, IL), which also selectively blocks the p19 subunit and has been approved for Crohn's disease, did demonstrate superiority vs ustekinumab for endoscopic and clinical remission of Crohn's disease in the SEQUENCE trial.[5] Thus, future comparative trials of ustekinumab vs mirikizumab in UC will be beneficial.

Key Study Findings

This study found that mirikizumab had greater efficacy than placebo for induction and maintenance of clinical response, clinical remission, and endoscopic remission of UC through 52 weeks of therapy.

Caution

There were numerically more opportunistic infections and cancer in the mirikizumab group compared to placebo. Long-term data is needed to better understand the safety of mirikizumab, particularly in relation to other agents targeting the IL-23 pathway (e.g. ustekinumab).

My Practice

At this time, there is insufficient comparative data for me to routinely use mirikizumab over ustekinumab, and ustekinumab may be more convenient for my patients since it has a less frequent maintenance dosing schedule (every 8 weeks). As always, insurance coverage will also play a role in my prescribing. I may also consider mirikizumab in individuals who had secondary loss of response to ustekinumab and have also exhausted other classes of therapy.

For Future Research

Future research is needed to compare the effectiveness and safety of mirikizumab to ustekinumab and other classes of therapy (e.g. vedolizumab, Janus kinase inhibitors) to determine the optimal positioning of this agent for patients with moderate-to-severe UC.

Conflicts of Interest

Dr. Dalal has received grant support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs.

REFERENCES

1. Raine T, Danese S. Breaking through the therapeutic ceiling: What will it take? Gastroenterology 2022;162(5):1507-1511.
2. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 2012;367(16):1519-28.
3. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381(13):1201-1214.
4. Dubinsky MC, Irving PM, Panaccione R, et al. Incorporating patient experience into drug development for ulcerative colitis: development of the urgency numeric

rating scale, a patient-reported outcome measure to assess bowel urgency in adults. J Patient Rep Outcomes 01 2022;6(1):31.

5. Peyrin-Biroulet L, Chapman JC, Colomber JF, et al. Risankizumab versus ustekinumab for patients with moderate to severe Crohn's disease: results from the Phase 3b SEQUENCE study. United European Gastroenterol J 2023;11: 919-940. Abstract LB01.

EVIDENCE-BASED GI
AN ACG PUBLICATION

Is Early Ileo-cecal Resection for Crohn's Disease an Appropriate Primary Treatment?

Dr Bharati Kochar
Associate Editor

Bharati Kochar, MD, MS

Assistant Professor of Medicine, Division of Gastroenterology, Massachusetts General Hospital; Investigator, The Mongan Institute, Harvard Medical School, Boston, MA

IBD

This summary reviews Agrawal M, Ebert AC, Poulsen G, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared with anti-tumor necrosis factor therapy: A population-based cohort study. Gastroenterology 2023; 165:976-985.

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

STRUCTURED ABSTRACT

Question: What are the long-term outcomes of ileo-cecal resection (ICR) and anti-tumor necrosis factor (TNF)-α therapy as the initial primary treatment for ileal and ileo-cecal Crohn's disease (CD) within 1 year of diagnosis?

Study Design: Retrospective cohort study in a population-based cohort's cross-linked national registers.

Setting: All people living in Denmark between January 1, 2003 and December 31, 2018.

Patients: Study inclusion criteria included: (a) patients with Crohn's disease in ileal or ileocecal region were identified based on *International Classification of Disease -10th Edition (ICD-10)* diagnoses and cross-linked with the Danish Pathology

Register to ensure pathologic confirmation of disease; and (b) primary treatment was ileocecal resection (ICR) or anti-TNF therapy within 30 days before and 1 year after CD diagnosis based on medication and hospital procedure codes identified using Anatomical Therapeutic Chemical (ATC) codes and Nordic Classification of Surgical Procedures. Patients were excluded if CD was diagnosed before the start of the study period, did not receive ICR or anti-TNF therapy within 30 days before or 1 year after CD diagnosis, were treated with other biologic medications or CD-related operations before ICR or anti-TNF primary treatment, had perianal Crohn's disease before primary treatment, and individuals who did not live in Denmark for at least 1 year prior to primary treatment.

Intervention/Exposure: The primary exposure was primary treatment of Crohn's disease with anti-TNF therapy versus ileo-cecal resection within 30 days before or 1 year after CD diagnosis. Cohort assignment was done by the first of the 2 treatments received, regardless of whether the other treatment was received at a later time.

Outcomes: The primary outcome was a composite of ≥1 of the following >30 days after primary treatment: (a) CD-related hospitalization; (b) systemic corticosteroid exposure; (c) major CD-related surgery; or (d) perianal CD.

Data Analysis: Kaplan-Meier survival analyses were conducted to compare proportion of individuals who experienced the primary outcome in both arms (anti-TNF therapy vs ICR). Cox proportional hazards regression analyses were used to estimate adjusted hazard ratios for the composite outcome. Their models were adjusted for age at CD diagnosis, sex, and year of treatment, as well as variables that were different between the 2 intervention arms: all-cause hospital contacts, unique prescription medications, systemic corticosteroid and immunomodulator exposure. They tested for interaction for a number of variables and conducted a number of sensitivity analyses. Finally, to adjust as much as possible for confounding by indication, they conducted propensity-weighted analysis with a propensity score including age at CD diagnosis, sex, number of unique prescription medications, number of hospital contacts and systemic corticosteroid and immunomodulator exposures in the year prior to primary treatment.

Funding: Supported by a grant from the Danish National Research Foundation. Dr. Agrawal and Dr. Ungaro are supported by National Institutes of Health K23 Career Development Awards.

Results: From 2003 to 2018, 1,279 Danish CD patients met inclusion criteria with 45% (n=581) receiving ICR and 55% (n=698) receiving anti-TNF as primary therapy within 12 months of CD diagnosis. Other demographic data included 58% female (both groups); median age was 30 (interquartile range [IQR] 22-51) and 22 (IQR 17-31), respectively. Patients in the ICR group were more likely to have complicated CD, defined as stricture, ileus, internal fistula, or abscess (21% vs 2%), but less likely to have received corticosteroids (34% vs 68%) or immunomodulators (18% vs 56%) in the preceding 12 months. Total follow-up was 2,474 person-years with median follow-up of 1.7 years per patient.

Patients getting ICR as primary treatment were less likely to suffer from the composite primary outcome compared to patients getting anti-TNF agents: incidence rate: 110/1000 person-years vs 202/1000 person-years; adjusted hazard ratio (aHR) = 0.67 (95% confidence interval [CI]: 0.54-0.83) (**Figure 1**). After adjusting for age, sex, and calendar year, ICR as primary therapy was also associated with lower risk of corticosteroid exposure (aHR = 0.61; 95% CI: 0.49-0.77) and CD-related surgery (aHR = 0.49; 95% CI: 0.36-0.67), but only trended toward lower rates of CD-related hospitalization (aHR = 0.84; 95% CI: 0.68-1.04) or perianal CD diagnosis (aHR = 0.62; 95% CI: 0.37-1.04). Also, among ICR-treated patients with 5 years of follow-up, 49.7% were on no therapy with 46% only on immunomodulator and 17% on anti-TNF agents.

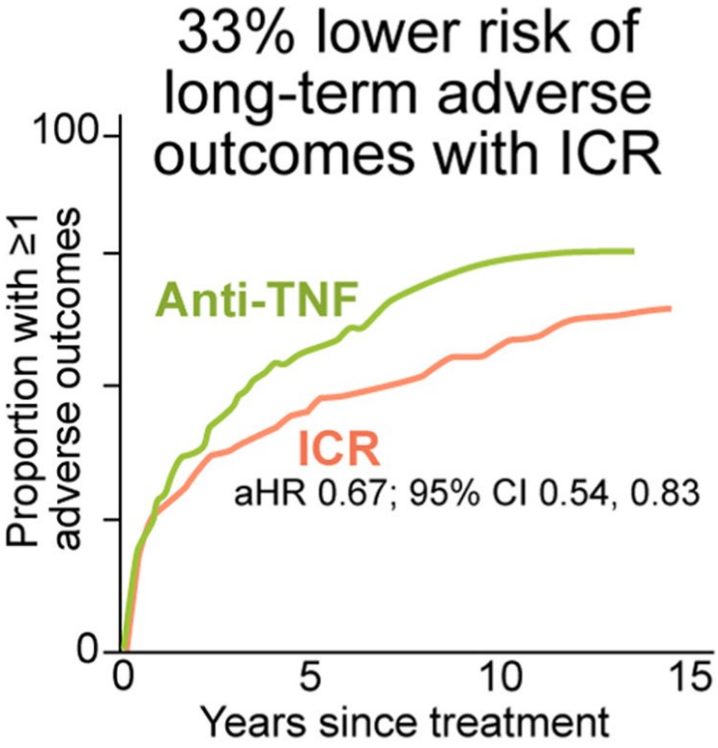


Figure 1. The risk of long-term adverse outcome, including hospitalization, repeat Crohn's disease-related surgery, systemic corticosteroid exposure, and perianal Crohn's disease was 33% lower with ileocaecal resection compared with anti-tumor necrosis factor agents as primary therapy.

ICR, ileocecal resection; TNF, tumor necrosis factor.

Reprinted from *Gastroenterology,* 165. Agrawal M, Ebert AC, Poulsen G, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared with anti-tumor necrosis factor therapy: A population-based cohort study. " pages 976-985, copyright 2023, with permission from Elsevier

COMMENTARY

Why Is This Important?

This is a very well done, robust retrospective cohort study which demonstrates that early ileo-cecal resection is a reasonable first line option for select patients with isolated terminal ileal or limited ileo-cecal inflammation. In the era of expanding inflammatory bowel disease (IBD) treatments and declining rates of surgery, this trial highlights that Crohn's disease remains a disease process that merits true medical-surgical interdisciplinary collaboration.

The findings from this analysis are not entirely surprising. In 2017, the LIR!C trial, a prospective open-label randomized controlled trial (RCT), assigned 143 patients with limited (<40 cm) inflammatory ileo-cecal CD that was not responsive to conventional therapy to laparoscopic ileocecal resection or infliximab[1]. The primary outcome was quality of life at 12 months with morbidity as a secondary outcome. While this small RCT did not detect a difference in the primary outcome, the anti-TNF arm had a higher number of unscheduled hospital admissions. Four patients in the resection arm had serious surgical-complications and 2 patients in the TNF arm had treatment-related serious adverse events. During long-term follow-up (median 64 months) of 94% of study patients[2], 48% in the ICR arm were treated prophylactically with an immunomodulator, 26% were eventually started on an anti-TNF, and none of the patients required a second resection, while 48% of patients in the anti-TNF treatment arm eventually required a resection for Crohn's disease.

This study includes a much larger cohort (1,279 versus 143 patients), assessed objective outcomes, and found that early surgical resection has a lower risk than anti-TNF therapy for the composite of 4 objective outcomes. This is certainly a more definitive finding than the LIR!C study, and CD patients are identified with high validity in the Danish registers given the robust national data collection and cross-linking of databases. However, the limitations of a retrospective studies must be kept in mind when applying these results to the patient in your clinical practice. Disease behavior, radiologic or endoscopic extent, severity of disease and such details that inform treatment decision making are not available with high validity in such databases. Therefore, despite robust methodological techniques, there is residual confounding by indication. It was likely a highly selective group of patients with limited and mild disease who were offered first -line surgical management and an even more selective group of patients who elected for this option. It is also likely that patients with either more robust inflammation or systemic disease were only offered medical therapy. Given the inherent and unmeasurable differences between the 2 study arms in a retrospective analysis, it is difficult to say with great confidence that ileocecal resection is a superior first line treatment option

for these patients.

Key Study Findings

Ileo-cecal resection was associated with a 33% reduction in long-term adverse outcomes (CD-related hospitalization, systemic corticosteroid exposure, major CD-related surgery, or perianal CD) versus patients receiving anti-TNF agents as primary treatment within 12 months of CD diagnosis. At 5-year follow-up, almost 50% of ICR-treated patients were on no CD therapy.

Caution

As noted above, findings from this retrospective analysis may be biased because there may be residual confounding by indication. In other words, many factors like disease behavior, radiologic and endoscopic findings, and severity of disease may have led physicians to offer ICR only to a highly selective group of CD patients, which could account for more adverse outcomes in the anti-TNF group.

My Practice

In my practice, I discuss limited ileal resection as a treatment option for patients with short segment, non-stricturing, non-penetrating ileal Crohn's disease. While many patients shy away from first line surgical treatment, some express interest in learning more about this. For these patients, I will request a visit with one of our expert IBD surgeons—even if it's mainly for educational value. I also emphasize to my patients that just because they meet a surgeon doesn't mean they have to have surgery.

However, in the era of selective anti-interleukin agents (ustekinumab, risankizumab) which are effective and seem to have a similar, if not lower concern, for serious adverse events compared with anti-TNF agents, first line anti-interleukin therapy is a much more reasonable treatment option. The loss of an ileo-cecal valve can have significant ramifications with regards to bacterial overgrowth syndromes and bile acid homeostasis. Therefore, despite both the LIR!C RCT and this larger, retrospective Danish study, I have a much higher threshold for recommending surgery. Nevertheless, these studies highlight that surgery for CD can be safe, effective, and transformative for quality of life.

For Future Research

Identifying the right patient for the right treatment, including surgical treatment, remains the holy grail for IBD management. Additionally, understanding patient concerns about early resections for IBD is an important and understudied topic. Further qualitative research may facilitate better communication around medical versus surgical decision making, especially early in the course of disease.

Conflicts of Interest

Dr. Kochar has served on advisory boards for Pfizer and Bristol Myers Squibb.

REFERENCES

1. Ponsioen CY, de Groof EJ, Eshuis EJ, et al. Laparascopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol 2017; 2: 785-92.
2. Stevens TW, Haasnoot ML, D'Haens G, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial. Lancet Gastroenterol Hepatol 2020; 5: 900-907.

EVIDENCE-BASED GI
AN ACG PUBLICATION

CRC SCREENING

Which Endoscopists Benefit from Using Computer-Aided Detection of Polyps During Colonoscopy?

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 Shaukat A, Lichtenstein DR, Chung DC, et al. Endoscopist-level and procedure-level factors associated with increased adenoma detection with the use of a computer-aided detection device. Am J Gastroenterol 2023; 118: 1891-94.

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

STRUCTURED ABSTRACT

Question: Does computer-aided detection device (CADe) improve adenomas found per colonoscopy (APC) in all endoscopists or in any specific groups of endoscopists based on their experience, withdrawal time, clinical setting, or baseline adenoma detection rate (ADR)?

Design: Multicenter, randomized controlled trial (RCT) with 1:1 randomization stratified by individual endoscopists (n=22).

Setting: Five US academic and community endoscopy centers. Study endoscopists (n=22) were required to have completed a minimum of 1,000 colonoscopies with ADR $\geq$ 25%.

Study Patients: Inclusion criteria included: (a) $\geq$ 40 years old; (b) screening or surveillance as indication for colonoscopy; and (c) colonoscopy complete to cecum with adequate bowel preparation.

Interventions/Exposure: CADe device is a software as a medical device tool

that uses a deep neural network to identify potential polyps during colonoscopy in real-time. Endoscopists completed an orientation video and performed up to 10 run -in cases with the device prior to study initiation.

Outcome: Primary outcome for the original study[1] was adenomas per colonoscopy. The prespecified secondary outcome, which is the focus of the current study, was association of procedure-related (academic vs community site of procedure, morning vs afternoon procedure, withdrawal time < 8 minutes vs ≥ 8 minutes, bowel preparation fair/good vs excellent) and endoscopist-related factors (baseline ADR < 45% vs ≥ 45%, 1-10 years of experience vs 11-20 vs > 20 years of experience) with APC.

Data Analysis: Modified intention-to-treat (mITT) analysis. APC was compared between standard colonoscopy arm and CADe arm with simple Z-statistic for procedure-related and endoscopist-related factors.

Funding: Iterative Health, Inc, manufacturer of the CADe device under investigation.

Results: Between January 2021-September 2021, 1,423 patients were included in mITT analysis. Among study patients, mean age was 60 years old; 53% male; 83% White; 65% had screening colonoscopies. Among endoscopists (n=22), 50% were community-based; mean years of experience 21; mean baseline ADR 46%; 98% of colonoscopies had adequate bowel preparation; mean withdrawal time 11 minutes; 72% of procedures were performed in the morning.

Although no statistically significant differences in procedure-related or endoscopist-related factors were identified, numeric increases in APC were noted when withdrawal time was ≥ 8 minutes vs < 8 minutes (0.21 vs -0.03), endoscopist's baseline ADR < 45% vs ≥ 45% (0.30 vs 0.10), and for endoscopists with > 20 years of experience vs ≤ 10 years of experience (0.28 vs -0.04).

COMMENTARY

Why Is This Important?

The benefit of CADe on ADR is variable based on current research. Although most RCTs demonstrate increases in ADR,[2] RCTs performed in populations with high prevalence of adenomas, such as fecal immunochemical test positive individuals,[3] have not demonstrated benefit. Clearly, it's easier to show improvement in ADR if the endoscopists have a low ADR, such as GI fellows who are learning to perform colonoscopy,[4] or if the patient population has lower prevalence of adenomas, such as average-risk 45-49 year olds getting colorectal cancer screening.

Pragmatic trials, which have not consistently demonstrated ADR improvement,

have led many endoscopists to question the benefit of CADe. In these trials, endoscopists in real-world settings are randomized to start using CADe at various times or at various locations in routine practice. Some have demonstrated benefit[5], but only when the endoscopists made a commitment to using it in most of their cases. Endoscopists with high ADRs (> 45%) frequently complained that CADe identification of potential polyps--which pop up as little green boxes on the endoscopy display--was distracting and unhelpful. For these high performers, the addition of CADe did not seem to improve performance. Thus, our goal is to better understand which endoscopists and which patient populations would most benefit from the addition of CADe tools.

Key Study Findings

The use of the CADe device numerically increased APC for endoscopists with baseline ADR < 45%, when withdrawal time was ≥ 8 minutes, and for endoscopists with > 20 years of experience.

Caution

Although this was a prespecified secondary outcome, it is a *post hoc* analysis of a relatively small sample size. The relatively small sample size may account for results only showing numeric trends for improvement in APC for specific categories.

My Practice

In my colonoscopy practice, I routinely use CADe tools for polyp identification. However, I haven't seen a statistically significant increase in my ADR, but that's probably because my composite ADR (screening and surveillance) is >45% and CADe tools only increases ADR by a few percentage points. Nevertheless, I've found it helpful for identifying smaller and flatter polyps, which I might have missed. This benefit may have occurred because I committed myself to training with introductory videos and training my eyes to assess the little green boxes that pop up on the endoscopy display whenever a potential polyp is identified by the software. It can be distracting, and even counterproductive, to see these little green boxes pop up on your endoscopy display. Proper use of CADe tools probably prolongs my withdrawal time. CADe tools certainly are not a substitute for proper colonoscopy technique during withdrawal, working the folds to expose colonic mucosa and taking a second look in the right side of the colon and rectum. If endoscopists think that they can speed up withdrawal time because the CADe tool will identify polyps, then that may be a misuse of the tool.

Distal attachment mucosal exposure devices (e.g., Endocuff Vision; Olympus America, San Jose, CA), which are clear caps attached to the tip of the colonoscope, may be analogous to CADe tools for improving polyp detection. RCTs clearly demonstrate that

they increase ADR, but real-world experience data is minimal. Endoscopists must be committed to performing colonoscopy consistently with these tools and take the time to work the folds and expose mucosa in order to benefit ADR. Personally, I've found it distracting to use these distal clear caps and don't routinely use them. Again, each individual endoscopist has to make a commitment to learning and utilizing a specific tool in order to see an improvement in polyp detection. We need to figure out which endoscopists might benefit the most from using different specific tools.

For Future Research

Implementation research could assess obstacles to utilizing CADe tools, how endoscopists should be trained to use these tools and become committed to routinely using them in real-world settings. Additional prospective studies should identify specific groups of endoscopists that will benefit from the addition of CADe devices, including endoscopists with ADRs < 25%. Finally, as CADe devices improve, additional studies will be needed to determine effectiveness of future, improved versions.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest related to this study.

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

@AasmaShaukatMD

Aasma Shaukat

REFERENCES

1. Shaukat A, Lichtenstein DR, Somers S, et al. Computer-aided detection improves adenomas per colonoscopy for screening and surveillance colonoscopy: A randomized trial. Gastroenterology 2022;163:732-41.
2. Samarasena J, Yang D, Berzin T. AGA clinicalpPractice update on the role of artificial intelligence in colon polyp diagnosis and mangement: Commentary. Gastroenterology 2023;165:1568-73.
3. Mangas-Sanjuan C, de-Castro L, Cubiella J, et al. Role of artificial intelligence in colonoscopy detection of advancing neoplasias: a randomized controlled trial. Ann Intern Med 2023;176:1145-52.
4. Yao L, Li X, Wu Z, et al. Effect of artificial intelligence on novice-performed colonoscopy: a multicenter randomized controlled tandem study. Gastrointest Endosc 2024;99:91-9.
5. Keswani RN, Thakkar U, Sals A, Pandolfino J. A computer-aided detection (CADe) system significantly improves polyp detection in routine practice. Clin Gastroenterol Hepatol 2023; In Press.

EVIDENCE-BASED GI
AN ACG PUBLICATION

Post-Colonoscopy Colorectal Cancer Due to Missed Polyps in Proximal Colon or Rectum with Sub-Optimal Bowel Cleansing

Jeffrey Lee, MD, MPH
Associate Editor

Jeffrey Lee, MD, MPH

Research Scientist and Attending Gastroenterologist, Kaiser Permanente San Francisco Medical Center, San Francisco, CA

This summary reviews Troelsen FS, Sørensen HT, Pedersen L, et al. Root-cause analysis of 762 Danish post-colonoscopy colorectal cancer patients. Clin Gastroenterol Hepatol 2023;21(12):3160-3169.e5.

Correspondence to Jeffrey Lee, MD, MPH. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: What are the causes of post-colonoscopy colorectal cancer (PCCRC), defined as first-time colorectal cancer (CRC) diagnosis > 6 months to 48 months after a negative colonoscopy (i.e., no evidence of CRC on index colonoscopy)?

Design: Retrospective cross-sectional study.

Setting: Central Denmark Region, which covers approximately 1.3 million individuals.

Patients: Using the Danish Cancer Registry and the Danish National Patient Registry from 1995-2021, 762 individuals with PCCRCs were identified. Among these PCCRC cases, 46.5% were females, 4.1% had a family hereditary colorectal cancer syndrome, 52.6% had a prior polypectomy, and 2.5% had an inflammatory bowel disease diagnosis.

Exposure: For each PCCRC case, manual chart review was performed to extract detailed information from colonoscopy reports, including colonoscopy

indication, quality of bowel preparation, cecal intubation, colonoscopy findings and pathology reports. The most plausible cause of the PCCRC was then determined by performing a root-cause analysis using the new World Endoscopy Organization (WEO) consensus recommendations.

Outcome: Each PCCRC case were categorized as: a) possible missed lesion, prior examination adequate (i.e., cecum was reached, and the bowel preparation was adequate); (b) possible missed lesion, prior examination inadequate; (c) detected lesion, not resected; or (d) likely incomplete resection of previously identified lesion.

Data Analysis: Indication for colonoscopy was only provided on colonoscopy reports from 2014-2021, so analyses assumed that all colonoscopies performed from 1995-2013 were performed on symptomatic patients. Also, an additional 175 PCCRC cases were eliminated from analysis because insufficient data was available for root-cause analysis.

Funding: Danish Cancer Association and Novo Nordisk Foundation.

Results: Of the 762 PCCRCs, 15.2% of PCCRCs were located in the cecum, 15.7% in the ascending colon, and 23% in the rectum. The most plausible explanation for these PCCRCs were: Category A: 80.8% (possible missed lesion with a prior adequate examination); Category B: 4.7% (possible missed lesion with a prior inadequate examination); Category C: 3.4% (detected lesion but not resected); and, Category D: 11% (likely incomplete resection of previously identified lesion) (**Figure 1**).

Bowel preparations were recorded as: poor, fair, good, or excellent. For root-cause analysis, “fair” prep was considered adequate. When “fair” bowel preparation was re-classified as “inadequate,” then Category A (possible missed lesion-adequate exam) decreased from 80.8% to 63.4% and Category B (possible missed lesion-inadequate exam) rose from 4.7% to 22.2%.

COMMENTARY

Why Is This Important?

Multiple studies have shown that colonoscopy reduces CRC incidence and mortality.[1] In the United States, colonoscopy is the most common screening test for CRC and is the primary diagnostic procedure for follow up after a positive fecal-based screening test and for evaluating signs and symptoms related to CRC. Unfortunately, colonoscopy is not perfect, and cancers can be diag-

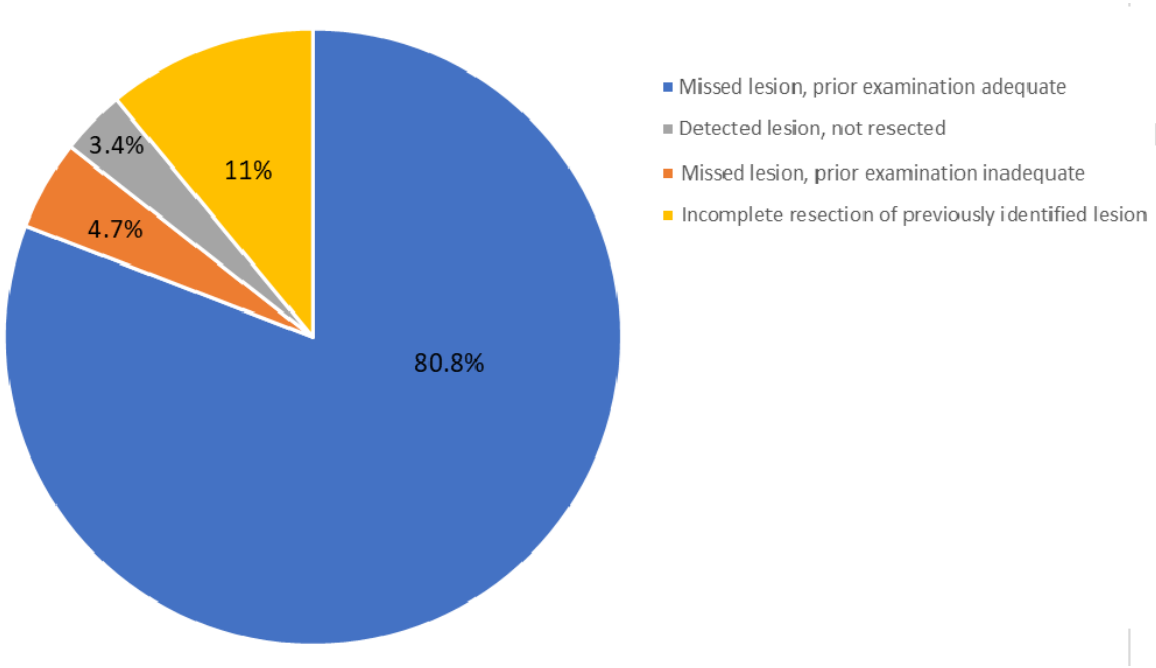


Figure 1. Plausible explanations of 762 post-colonoscopy colorectal cancer in Central Denmark.

nosed after a negative colonoscopy which did not detect cancer, or PCCRC.[2,3] Recently, the WEO developed a consensus statement and methodology to better classify PCCRCs into their most plausible explanations.[4] By understanding the root cause of PCCRC, endoscopists may better improve colonoscopy quality.

Only a few studies have utilized this methodology, and they demonstrated that most PCCRCs are likely due to missed lesions in the proximal colon. However, these studies were limited by their relatively small sample size.[5,6] To address these limitations, the authors performed a root cause analysis for 762 PCCRC cases diagnosed in Central Denmark.

Key Study Findings

Most PCCRCs were due to missed lesions, which is similar to past studies. However, missed lesions in the rectum were almost as common as missed lesions in the proximal colon as the location of PCCRC. Also, when "fair" bowel preparation was classified as an inadequate bowel preparation, the proportion of PCCRC due to missed lesions from inadequate exam rose from 4.7% to 22.2%. These findings re-emphasize the importance of careful inspection of the rectum, including retroflex exam of rectum and good/excellent

Caution

The WEO methodology for classifying PCCRC etiology does not adequately describe some situations where the root cause of the PCCRC is due to patient- or system-related failures (e.g., failure to schedule a surveillance colonoscopy). Insufficient data was available for multiple colonoscopies. Also, there was no reporting of adherence to quality

standards for most colonoscopies (e.g., withdrawal time, performance of second view of rectum in retroflex view).

My Practice

As seen in this study and other prior studies,[5,6] missed lesion is the most common explanation for PCCRCs diagnosed within 48 months after a clearing colonoscopy. This finding highlights the need for careful inspection of the colon during withdrawal, particularly in the right colon and rectum.

There are several tools and techniques that I use to optimize pre-cancerous lesion detection during withdrawal. First, it is critical to use a high definition colonoscope with image enhancement (e.g., narrow band imaging) capabilities to help detect and evaluate subtle lesions. Second, it is important to have a mindset for detecting flat polyps since these lesions are often missed. Third, I maximize mucosal exposure by "working the folds" (i.e., deflecting the tip of the colonoscope into the inner-haustral valley and exposing the proximal sides of each haustral folds), cleaning and suctioning any stool debris, and distending the lumen adequately. Fourth, I perform 2 or 3 passes in the right colon and rectum since adenomas, especially flat lesions, are often missed in this location. Lastly, when available, I often use a distal attachment device such as a clear translucent cap to help expose the proximal sides of each haustral fold and improve mucosal exposure.

In addition to missed lesions, incomplete resection is a critical modifiable factor for PCCRC that deserves more attention. There are several tips and techniques I like to share with my colleagues and fellows to reduce the chances of adenoma recurrence. First, give yourself time--never tackle a polyp you cannot finish during your assigned time slot. Second, be humble and refer any complex polyp to a colleague or referral center that specializes in advanced tissue resection. Third, always aim for *en bloc* resection using conventional or underwater EMR or ESD technique. Fourth, if *en bloc* is not feasible, make sure to take wide margins and ablate the edges of the defect with soft tip coagulation after piecemeal EMR. Fifth, carefully inspect the piecemeal EMR defect and remove any residual or visible islands using hot forceps avulsion. Lastly, emphasize to your patients that it is critical to come back for your surveillance colonoscopy in 6 months following your EMR or ESD.

For Future Research

Additional studies evaluating the root cause of PCCRC are needed, particularly PCCRC cases diagnosed after 4 years following a clearing colonoscopy. Studies about successful implementation of quality improvement of colonoscopy procedures with an emphasis on improving adenoma detection and performing high-quality resection of pre-cancerous lesions would also be useful.

Conflict of Interest

None to report.

REFERENCES

1. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315 (23):2564-2575.
2. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370(14):1298-1306.
3. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362(19):1795-1803.
4. Rutter MD, Beintaris I, Valori R, et al. World Endoscopy Organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. Gastroenterology 2018 Sep;155(3):909-925.e3.
5. Leung LJ, Lee JK, Merchant SA, et al. Post-Colonoscopy Colorectal Cancer Etiologies in a Large Integrated US Health Care Setting. Gastroenterology 2023;164 (3):470-472.e3.
6. Anderson R, Burr NE, Valori R. Causes of Post-Colonoscopy Colorectal Cancers Based on World Endoscopy Organization System of Analysis. Gastroenterology 2020 Apr;158(5):1287-1299.e2.