EVIDENCE-BASED GI
AN ACG PUBLICATION

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

AMERICAN COLLEGE OF GASTROENTEROLOGY

Attend an upcoming
ACG POSTGRADUATE COURSE

2025

2025 ACG/LGS Regional Postgraduate Course & Women Leading with Guts Course
March 14–16, 2025
DoubleTree by Hilton, New Orleans, LA

2025 ACG's Endoscopy School & Eastern Regional Postgraduate Course
June 6–8, 2025
Washington Marriott Metro Center, Washington, DC

2025 ACG's Functional GI and Motility Disorders School & Midwest Regional Postgraduate Course
August 22–24, 2025
Marriott Indianapolis Place, Indianapolis, IN

2025 ACG's NEW Esophagus School & ACG/VGS/MASGNA Regional Postgraduate Course
September 5–7, 2025
Williamsburg Lodge, Williamsburg, VA

2025 ACG Hepatology School & Southern Regional Course
December 6-7, 2025
Renaissance Hotel, Nashville, TN

&

ACG 2025 Annual Meeting & Postgraduate Course
October 24-29, 2025
Phoenix Convention Center, Phoenix, AZ

ACG Weekly Virtual Grand Rounds

REGISTER NOW: gi.org/ACGVGR

Plus our monthly webinar series focused on career-based topics!

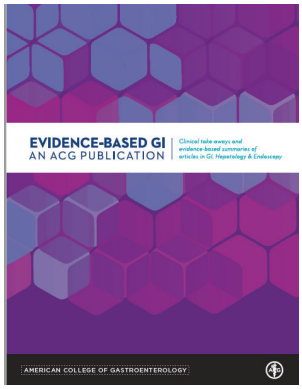
FOR MORE INFORMATION VISIT:
gi.org/regional-meetings

EVIDENCE-BASED GI

An ACG Publication

EDITORIAL BOARD

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
AN ACG PUBLICATION

SOCIAL MEDIA AMBASSADORS

Peter Bhandari, MD
Kuntal Bhowmick, MD
Romy Chamoun, MD
Arjun Chatterjee, MD
Kashyap Chauhan, MD
Aastha Chokshi, MD
Benjamin Clement, MD
Sophia Dar, MD
Jalpa Devi, MD
Anoushka Dua, MD
Chukwunonso Ezeani, MD
Aimen Farooq, MD
Umer Farooq, MD
Hannah Fiske, MD
Devika Gandhi, MD
Dheera Grover, MBBS
Maryam Bilal Haider, MD
Tessa Herman, MD
Mohamad Itani, MD
Camille Lupianez-Merly, MD
Clive Miranda, DO
Eleazar Montalvan, MD
Chidiebele E. Omaliko, MD
N. Begum Ozturk, MD
Mythili Menon Pathiyil, MD
Sean-Patrick Prince, MD, MPH
Daryl Ramai, MD
Muhammad Sheharyar Warraich, MD
Grecia Santaella Mendez, MD
Jassmiran Singh, MD
Noor Syed, MD
Fnu Vikash, MD
Natalie Wilson, MD

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

Subcommittee Leaders

CRC Awareness Month Team
Mohamad I. Itani, MD
Chukwunonso Benedict Ezeani, MD
Jassimran Singh, MD
Camille Lupianez Merly, MD

Media Operations Aimen Farooq, MD
Kashyap Chauhan, MD

GI Fellowship Outreach
Jalpa Devi, MBBS

Trainee #SoMe Impact Study Lead
Sophia Dar, MD

EBGI **Volume 6, Issue 4**

April 2025

TABLE OF CONTENTS

EVIDENCE-BASED GI
AN ACG PUBLICATION

Optimizing Bowel Preparation for Colonoscopy: Insights from the USMSTF

Rachael Hagen
Contributing Writer

Joseph Anderson
Co-Editor-in-Chief

Rachael Hagen DO[1] and Joseph C. Anderson, MD, FACG[1,2]

[1]*University of Connecticut School of Medicine, Farmington, CT*

[2]*VA Medical Center, White River Junction, VT; Geisel School of Medicine at Dartmouth, Hanover, NH.*

COLON

This summary reviews Jacobson BC, Anderson JC, Burke CA, et al. Optimizing Bowel Preparation Quality for Colonoscopy: Consensus Recommendations by the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2025;120(4):738-64.

Correspondence to Joseph C. Anderson, MD, FACG, Co-Editor-in-Chief. Email: EBGI@gi.org

Keywords: bowel prep, colonoscopy; colorectal cancer screening, USMSTF

STRUCTURED ABSTRACT

Questions:

Pre-Colonoscopy. What pre-colonoscopy interventions can enhance bowel preparation adequacy? How should bowel purgatives and adjuncts be selected to optimize preparation quality?

During Colonoscopy. What techniques can improve bowel preparation quality during colonoscopy? How should bowel cleanliness be assessed and reported?

Post-Colonoscopy. What is an appropriate bowel preparation adequacy rate? What strategies should be used to manage high-risk patients for inadequate bowel preparation?

Design: A panel of content experts formulated clinical questions using the Patient, Intervention, Comparison, and Outcomes (PICO) framework. Research

librarians conducted a literature review search across EMBASE, PubMed, Cochrane Reviews, and the Cochrane Central Register of Controlled Clinical Trials from January 2013 to September 2023.

The United States Multi-Society Task Force (USMSTF) includes 3 representatives from each of the following societies: The American College of Gastroenterology (ACG), the American Gastroenterology Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE). Leadership from all 3 organizations reviewed the recommendations, which were subsequently approved by each society's governing board.

As the statements were developed through expert consensus rather than the traditional guideline development process, they are designated as "Recommendations" rather than "Guidelines." Additionally, key concepts were established based on expert consensus for topics where evidence-based recommendations could not be formulated.

Patients: Outpatients at low risk for inadequate bowel preparation.

Outcome: Improved bowel preparation quality enhances colonic mucosa visualization, facilitates precancerous lesion detection, and optimizes colorectal cancer monitoring.

Data Analysis: Recommendations were created by an expert consensus as described above. A literature review was conducted to develop recommendations. The quality of evidence supporting each recommendation was also assessed. Strong recommendations indicate that most patients should be managed accordingly and are typically associated with high or moderate-quality evidence from well-designed clinical trials and systematic reviews. In contrast, weak recommendations serve as suggestions due to limited evidence or a smaller clinical impact and are generally based on low or very low-quality evidence. When evidence-based recommendations could not be formulated, key concept statements were developed through expert consensus.

Funding: None.

Summary: Authors recommend assessing a patient's medical history, including prior bowel preparation adequacy, to help predict preparation quality. Adherence to instructions is crucial and should be reinforced through written and verbal guidance, along with patient navigation. Dietary restrictions should be limited to the day before the procedure. Preparation regimens should be tailored to medical history, patient preference, and comorbidities, with a preference for low-volume (≤2 L) solutions to improve tolerability.[1] Split-dose preparation is preferred, except for afternoon colonoscopies.

Oral simethicone is recommended to enhance visibility by reducing bubble formation, thereby improving procedural quality. The lowest effective dilution (e.g. 0.5 mL simethicone in 99.5 mL water) at a minimum dose of 320 mg should be used and administered only through an instrument channel that undergoes routinely brushing during endoscope reprocessing. The routine use of other adjuncts is not advised.

When inadequate bowel preparation is suspected, confirmation should be made by assessing preparation quality to the sigmoid colon. Bowel cleanliness should be evaluated and clearly described following endoscopist cleansing maneuvers. Endoscopists should employ strategies to enhance visualization, such as irrigation pumps, same-day rescue therapy, and the lowest effective dilution of simethicone. The term "adequate" preparation should be reserved for cases when standard surveillance intervals can be assigned based on examination findings.

Following colonoscopy, bowel preparation adequacy rates should be tracked at the level of the individual endoscopist and the endoscopy unit, with a target of at least 90%. This includes procedures cancelled for presumed inadequate preparation. Significant differences in adequacy rates may indicate deficiencies in cleansing methods during colonoscopy or inconsistencies in assessing preparation quality. When bowel preparation is insufficient for standard screening or surveillance, repeat colonoscopy should be performed within 12 months, or sooner for patients with alarm symptoms or positive non-endoscopic colorectal cancer screening tests.

For patients with a history of inadequate preparation or those at high risk, proactive interventions should be implemented to augment bowel cleansing. These may include improved patient communication, stricter dietary limitations, use of promotility agents, and methods to prevent constipation. High-risk patients should begin dietary modifications 2-3 days prior and consume 4L PEG-ELS with 15 mg

of bisacodyl the afternoon before. If visualization of the ascending or transverse colon is poor but the remainder of the colonic mucosa is well visualized, the procedure should be considered equivalent to flexible sigmoidoscopy, with repeat screening recommended in 5 years or via non-endoscopic methods.

USMSTF recommendations are listed in Table 1 along with the strength of recommendation and quality of evidence.

Table 1. USMSTF Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
RECOMMENDATIONS PRE-COLONOSCOPY		
Patient Education and Navigation		
1. Provide both verbal and written instructions of colonoscopy preparation.	Strong	High
2. Use patient navigation (e.g. telephone calls, electronic messaging) to improve bowel preparation quality.	Weak	Moderate
Dietary Modifications		
3. Limit dietary modifications to the day before colonoscopy.	Strong	High
4. Use low-residue and low-fiber foods or full liquids for early/ midday meals on the day before colonoscopy with split-dose bowel preparation.	Strong	High
Bowel Preparation Purgatives		
5. No single bowel preparation purgative is considered superior.	Strong	High
6. Low volume, 2 L bowel regimens are preferred to higher volume, 4 L preparations.	Weak	Moderate
7. Consider medical history, medications, and prior preparation adequacy when selecting a regimen.	Strong	Moderate
8. Avoid hyperosmotic regimens in individuals at risk for volume overload or electrolyte imbalances.	Strong	High
Dosing and Timing of Bowel Preparation Regimens		
9. Split-dose preparations are recommended for all patients.	Strong	High
10. Same-day preparation rather than split-dose is acceptable for afternoon colonoscopies.	Strong	High
11. Same-day regimen is inferior to split dosing for morning colonoscopies.	Weak	Low
12. The second dose in split preparations should start 4–6 h before the procedure and finish at least 2 h prior.	Strong	Moderate
Adjuncts for Bowel Preparation		
13. Oral simethicone is suggested as an adjunct to bowel preparation regimens.	Weak	Moderate
14. The routine use of non-simethicone adjuncts is not recommended.	Weak	Low

Table 1 (Continued). USMSTF Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
RECOMMENDATIONS DURING COLONOSCOPY		
Assessing Bowel Preparation		
15. When there is suspicion for incomplete adherence to the bowel preparation regimen, advance the colonoscope to the sigmoid colon to confirm inadequacy before aborting the procedure.	Weak	Low
16. Assess bowel preparation quality only after all washing and suctioning, using clear descriptors.	Very Low	Conditional
17. “Adequate bowel preparation” should indicate that standard screening or surveillance intervals are appropriate.	Strong	Moderate
Improving Bowel Preparation Quality After Colonoscope Insertion		
18. Use irrigation pumps routinely to assist with bowel preparation.	Weak	Very low
19. Implement same-day salvage maneuvers when possible.	Weak	Moderate
RECOMMENDATIONS POST-COLONOSCOPY		
Bowel Preparation Adequacy Rate as a Quality Measure		
20. Track the rate of adequate bowel preparations at both the level of the endoscopist and the endoscopy unit.	Strong	Moderate
21. Target ≥90% adequacy rate for both individual endoscopists and endoscopy units.	Strong	Moderate
Management of Patients with Inadequate and Non-Salvageable Bowel Preparation		
22. Reschedule colonoscopy within 12 m for screening or surveillance, and as soon as possible for abnormal non-colonoscopic colorectal cancer screening tests.	Strong	Moderate
23. Modify the regimen by communicating instructions; using patient navigators; implementing dietary restrictions days prior and clear liquids the day before; promotility agents; treating constipation; holding constipating medications; and using high-volume regimens.	Strong	Moderate
Bowel Preparation for Patients at High Risk for Inadequate Bowel Preparation		
24. Manage individuals at high risk for inadequate bowel preparation quality similarly to those with prior inadequate bowel preparation.	Strong	Moderate
25. For high-risk patients, prescribe split-dose 4 L PEG-ELS + 15 mg bisacodyl the afternoon before, a low-residue diet 2-3 d prior, and clear liquids the day before.	Weak	Low

PEG-ELS: polyethylene glycol-electrolyte lavage solution.

COMMENTARY

Why Is This Important?

High-quality colonoscopy is essential for evaluation of the colon, such as detecting and monitoring precancerous lesions. Suboptimal bowel preparation decreases colonoscopy efficacy and is associated with significant adenoma and advanced adenoma miss rates.[2] These recommendations update the 2014 USMSTF recommendations on optimizing bowel preparation for colonoscopy. Over the last decade, significant advancements have been made to improve bowel cleansing adequacy, patient tolerability, and procedural outcomes. In addition, many new bowel purgative options continue to emerge. Updated recommendations emphasize split-dose low-volume (≤2 L) regimens, which provide bowel preparation quality comparable to higher volume solutions while offering better tolerability. These regimens have been shown to increase adenoma and potentially sessile serrated lesion detection rates, ultimately improving the effectiveness of colorectal cancer screening and surveillance.[3,4,5,6]

Key Study Findings

Updated USMSTF recommendations emphasize a patient-centered approach that promoting split-dose regimens (except for patients undergoing afternoon colonoscopies) and greater flexibility in dietary modifications.

Bowel preparation purgative options have expanded, favoring low-volume (≤2 L) solutions for improved tolerability. The use of oral simethicone is now supported by evidence to improve visualization, while other adjuncts should be avoided.

The term "adequate bowel preparation" should refer to a colonoscopy of sufficient quality to allow for the application of standard screening or surveillance intervals. A benchmark of ≥90% adequate bowel preparation rates is suggested for both individual endoscopists and endoscopy units to improve colonoscopy quality and detection rates. Additionally, innovations such as patient navigators, enhanced instructional methods, and artificial intelligence-driven tools have been introduced to further optimize bowel preparation quality.

Caution

The key concepts are expert panel suggestions and some recommendations are not supported by substantial evidence. They should be applied to patients on an individual basis when managing bowel preparation for colonoscopy.

My Practice

My approach for optimizing bowel preparation for colonoscopy includes prescribing low-volume, split-dose regimens to enhance patient compliance and preparation quality, reserving full-dose regimens for afternoon colonoscopies, which still demonstrate effective cleansing. To minimize ambiguity in bowel preparation assessment, I prefer

standardized scoring systems with clear descriptors, such as the one used in the New Hampshire Colonoscopy Registry scale.[7] Scales with clear descriptions allow for endoscopists as well as other physicians reading the note to determine whether the bowel preparation was adequate.

When inadequate bowel preparation is suspected, I confirm that the quality is inadequate by endoscopically examining the distal colon before cancelling the procedure. I also document inadequate preparation with photographs of poorly cleansed segments for improvement efforts. While salvage therapies, such as enemas, may provide additional cleansing, logistical constraints often limit reassessment.

During the colonoscopy, I perform thorough cleaning maneuvers, utilizing a vigorous water exchange approach. The use of copious water infusion in exams with residual stool can help improve the quality. I also find that removing the suction button helps to increase the rate of aspiration, making sure that I point the handle down to avoid splattering. Finally, if I snare a polyp, I will leave the snare in the biopsy channel to avoid clogging.

Bowel preparation adequacy rates are routinely tracked at our endoscopy unit to drive quality improvement. When patients present with inadequate bowel preparation despite additional cleansing efforts, we will reschedule, ideally for next-day colonoscopy. However, scheduling conflicts often preclude same-day colonoscopy completion with additional purgatives. To mitigate these issues, I proactively identify high-risk patients before their procedures, ensuring early interventions through patient navigation, enhanced communication, and reinforcement of preparation instructions. Although not preferred, for average risk patients with repeated inadequate preparation, I discuss alternative colorectal cancer screening options.

For Future Research

Future research should explore strategies to enhance bowel preparation adequacy while maintaining the improved patient tolerability of low-volume, split-dose regimens.[1,8,9,10] This includes the use of novel adjuncts to optimize cleansing with smaller solution volumes. Further research is needed to evaluate the clinical impact of simethicone and its efficacy when combined with other bowel regimens. As our understanding of GLP-1 receptor agonists evolves, the approach to pre-procedure management of patient's using these medications should be refined.

In addition, data on same-day dosing of morning colonoscopies remain limited and warrants investigation. Identifying patients at high risk for inadequate bowel preparation is essential, and artificial intelligence-based tools may play a key role in this effort. Some have already been developed to evaluate bowel

preparation quality by analyzing photographs of stool before the procedure.[11]

Conflict of Interest

The authors have no reported conflicts of interest.

Abbreviations

ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; ASGE, American Society for Gastrointestinal Endoscopy; PEG-ELS, polyethylene glycol-electrolyte lavage solution; PICO, Patient, Intervention, Comparison, and Outcomes; USMSTF, United States Multi-Society Task Force.

REFERENCES

1. Oldfield EC, Johnson DA, Rex DK. Prescribing colonoscopy bowel preparations: Tips for maximizing outcomes. *Am J Gastroenterol*. 2023;118 (5):761-764.
2. Lebwohl B, Kastrinos F, Glick M, Rosenbaum AJ, Wang T, Neugut AI. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc*. 2011;73(6):1207-1214.
3. Hassan C, East J, Radaelli F, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline—Update 2019. *Endoscopy*. 2019;51 (8):775-794.
4. Jover R, Zapater P, Polanía E, et al. Modifiable endoscopic factors that influence the adenoma detection rate in colorectal cancer screening colonoscopies. *Gastrointest Endosc*. 2013;77(3):381-389.e1.
5. Gurudu SR, Ramirez FC, Harrison ME, Leighton JA, Crowell MD. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. *Gastrointest Endosc*. 2012;76 (3):603-608.e1.
6. Horton N, Garber A, Hasson H, Lopez R, Burke CA. Impact of Single- vs Split-Dose Low-Volume Bowel Preparations on Bowel Movement Kinetics, Patient Inconvenience, and Polyp Detection: A Prospective Trial. *Am J Gastroenterol*. 2016;111(9):1330-1337.
7. Anderson JC, Butterly L, Robinson CM, Goodrich M, Weiss JE. Impact of fair bowel prep on adenoma and serrated polyp detection: Data from the New Hampshire Colonoscopy Registry using a standardized preparation quality rating. *Gastrointest Endosc*. 2014;80(3):463-470.
8. Martel M, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A. Split-dose preparations are superior to day-before bowel cleansing regimens: A meta-analysis. *Gastroenterology*. 2015;149(1):79-88.
9. Shafer LA, Walker JR, Waldman C, et al. Predictors of patient reluctance to wake early in the morning for bowel preparation for colonoscopy:

A precolonoscopy survey in city-wide practice. *Endoscopy International Open*. 2018;6(6):E706.

10. Menees SB, Kim HM, Wren P, et al. Patient compliance and suboptimal bowel preparation with split-dose bowel regimen in average-risk screening colonoscopy. *Gastrointest Endosc*. 2014;79(5):811-820.e3.
11. Zhu Y, Zhang DF, Wu HL, et al. Improving bowel preparation for colonoscopy with a smartphone application driven by artificial intelligence. *npj Digit Med*. 2023;6(1):1-9.

EVIDENCE-BASED GI
AN ACG PUBLICATION

HEPATOLOGY

Increased ATTENTION to Early Initiation of Antiviral Therapies in Chronic Hepatitis B Based on Viral Load

Leandro Sierra, MD
Contributing Writer

Nikki Duong, MD
Associate Editor

Leandro Sierra, MD[1] and Nikki Duong, MD[2]

[1]*Internal Medicine Resident, Department of Internal Medicine, Cleveland Clinic, Cleveland, OH*

[2]*Clinical Assistant Professor of Medicine, Gastroenterology & Hepatology, Stanford University School of Medicine, Stanford, CA*

This summary reviews Lim YS, Yu ML, Choi J, et al. Early antiviral treatment with tenofovir alafenamide to prevent serious clinical adverse events in adults with chronic hepatitis B and moderate or high viraemia (ATTENTION): Interim results from a randomised controlled trial. Lancet Gastroenterol Hepatol 2025; 10(4):295-305.

Correspondence to Nikki Duong, MD. Associate Editor. Email: EBGI@gi.org

Keywords: chronic, HBV, tenofovir alafenamide, RCT

STRUCTURED ABSTRACT

Question: Does early antiviral treatment with tenofovir alafenamide reduce liver-related serious adverse events in adults with non-cirrhotic chronic hepatitis B (CHB) and moderate or high viremia (serum HBV DNA ≥10,000 IU/mL), but normal or mildly elevated alanine aminotransferase (ALT) concentrations?

Design: A randomized controlled trial.

Setting: From February 8, 2019 to October 17, 2023, 22 centers in South Korea and Taiwan were included.

Patients: Adults aged 40-80 years with non-cirrhotic CHB, serum HBV DNA

concentrations between 4 $\log_{10}$ IU/mL and 8 $\log_{10}$ IU/mL, either HBeAg positive or HBeAg negative, and with normal ALT concentrations or lower than 70 U/L for males and 50 U/L for females. Key exclusion criteria included co-infection with hepatitis C or D, previous exposure to anti-HBV treatment, evidence of cirrhosis, hepatic decompensation, malignancy, or organ transplantation.

Intervention: Oral tenofovir alafenamide (25 mg daily) or no antiviral treatment (observation) for a median follow up time of 17.7 months.

Outcomes: The primary endpoint was a composite of the rate of hepatocellular carcinoma (HCC), hepatic decompensation, liver transplantation, or death from any cause. Secondary outcomes included the incidence of each individual component of the composite endpoint, achievement of viral response (i.e., undetectable serum HBV DNA [<10 IU/mL]), ALT normalization (defined as serum ALT ≤35 U/L for males or ≤25 U/L for females), and HBeAg seroconversion. In addition, virological, biochemical, and serological responses—including HBsAg seroclearance and HBeAg seroclearance in patients who were HBeAg positive at baseline—were assessed every 6 months at local laboratories.

Data Analysis: The statistical analysis plan included 2 interim analyses, scheduled at 4 years and 8 years after the enrollment of the first participant, with a final analysis planned at the 12-year mark, contingent upon the interim results. All analyses were performed on an intention-to-treat basis.

The cumulative incidence of the primary endpoint was estimated using Kaplan–Meier, with differences between treatment groups assessed via log-rank test. HRs for the primary outcome were derived from Cox proportional hazards regression models, considering the treatment group (tenofovir alafenamide vs observation) as the primary independent variable. To maintain a 2-sided type I error rate of 0.025—given the 2 planned interim analyses and a final analysis—the nominal significance level was determined using the O'Brien–Fleming spending function. Accordingly, stopping boundaries were set based on the timing of the interim analyses (e.g., at the first interim analysis, the stopping boundary for the log-rank test was $Z_1 = 4.17$, corresponding to a nominal α_1 of 0.00003), and 2-sided 97.5% CIs were reported for the primary outcome.

The secondary endpoints were analyzed with either the χ^2 test or Fisher's exact test, as appropriate, with treatment effects for binary outcomes estimated as risk

differences alongside 95% CIs, and prespecified subgroup analyses were conducted (including stratification by baseline HBeAg status, sex, and other criteria).

Funding: This study was funded by the late Kang Jeong-Ja, the Government of South Korea, and Gilead Sciences (which supplied tenofovir alafenamide), with funders having no role in study design, data collection, analysis, interpretation, or publication decisions.

Results: Overall, 798 individuals were screened and 734 were randomized (369 to the tenofovir alafenamide group and 365 to the observation group), with baseline characteristics well balanced between groups. The composite primary endpoint—comprising HCC, hepatic decompensation, liver transplantation, or death—occurred in 2 (1%) participants in the tenofovir alafenamide group (0.33 per 100 person-years) compared to 9 (2%) in the observation group (1.57 per 100 person-years), yielding a hazard ratio of 0.21 (97.5% CI 0.04–1.20; P=0.027). (**Table 1)** Notably, among participants with normal ALT concentrations at baseline, no primary endpoint events were observed in the tenofovir alafenamide group versus 4 events in the observation group, with similar trends evident when applying European and Asia-Pacific ALT criteria.

Secondary endpoints showed that significantly more participants in the tenofovir alafenamide group achieved virological response and ALT normalization (both P<0.0001) compared to those under observation, while HBeAg and HBsAg seroclearance rates were comparable between groups. Treatment adherence in the tenofovir alafenamide group was high (mean 98.4%), and the frequency of serious adverse events was similar between groups, with no new safety concerns identified during the follow-up period.

COMMENTARY

Why Is This Important?

Chronic HBV is a major global health concern, ranking as the third most common cause of cirrhosis and affecting nearly 300 million people worldwide, including approximately 2.4 million in the United States[1, 2] The cornerstone of management are antivirals such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir, which inhibit HBV polymerase activity to reduce viral replication.[2]

Although there is slight variation amongst the major international liver

societies regarding thresholds for treatment initiation, the common theme is that the main driver for HCC risk and disease progression (ie. development of fibrosis) is the viral load.[3-5] These findings have led to a growing consensus that treatment decisions should be driven primarily by HBV DNA levels, independent of ALT values.[5, 6]

To our knowledge, this is the first RCT to assess the efficacy of early antiviral treatment with tenofovir alafenamide in patients with non-cirrhotic chronic HBV and moderate to high viremia who do not meet current treatment criteria due to normal or only mildly elevated ALT levels. It challenges the conventional approach and suggests that treatment indications should be expand-

	Tenofovir alafenamide group (n=369)	Observation group (n=365)	Hazard ratio (97·5% CI)	p value
Composite primary endpoint				
Number (%)	2 (1%)	9 (2%)	0·21 (0·04 to 1·20)	0·027
Incidence rate per 100 person-years	0·33	1·57	..	..
Secondary endpoints				
Hepatocellular carcinoma	2 (1%)	7 (2%)	0·27 (0·04 to 1·62)	0·079
Hepatic decompensation	0	1 (<1%)	NE	0·31
Death	0	1 (<1%)	NE	0·29
Liver transplantation	0	0	NE	NE
Virological response*	295/325 (91%)	96/310 (31%)	59·8 (53·8 to 65·8)	<0·0001
Biochemical responses*				
Normal ALT†	261/325 (80%)	192/310 (62%)	18·4 (11·5 to 25·3)	<0·0001
ALT normalisation‡	124/171 (73%)	86/173 (50%)	22·8 (12·8 to 32·8)	<0·0001
Serological responses*				
HBsAg seroclearance	1/325 (<1%)	2/310 (1%)	−0·3 (−1·4 to 0·7)	0·62
HBeAg seroclearance	13/57 (23%)	8/45 (18%)	5·0 (−10·6 to 20·6)	0·53
HBeAg seroconversion	8/57 (14%)	6/45 (13%)	0·7 (−12·7 to 14·1)	0·92

Data are n/N (%) unless otherwise indicated. NE=not estimable. ALT=alanine aminotransferase. HBeAg=hepatitis B e antigen. HBsAg=hepatitis B surface antigen. *Participants who were followed up for at least 6 months were evaluated. †Normal ALT was defined as ≤25 U/L for females and ≤35 U/L for males. ‡Among participants with abnormal ALT concentrations at baseline.

Table 1. Primary and secondary efficacy endpoints.

ed based primarily on HBV DNA concentrations, considering patients with moderately high viremia, independent of the degree of fibrosis and ALT levels.

Expanding treatment criteria would increase the number of people eligible for therapy. For example, a recent study in South Korea showed that removing ALT restrictions for treatment in patients with viral loads of 2,000 IU/mL or higher increased eligibility from 25% to 54% of the CHB population, potentially reducing decompensated cirrhosis, HCC, and liver-related deaths by 68%, 33%, and 35%, respectively, by 2035.[7]

Key Study Findings

Patients treated with tenofovir alafenamide had a 79% lower risk of the overall composite primary endpoint (including HCC, hepatic decompensation, liver transplantation, or death) compared with patients in the observation group.

These findings suggest that antiviral therapy should be considered early on for individuals with non-cirrhotic chronic HBV and moderate to high viremia, even if ALT levels are not elevated, to prevent hepatocellular carcinoma and other serious liver-related events.

Caution

Although this study does show significant improvement in risk reduction of the composite endpoint with tenofovir alafenamide, we are only looking at 2 out of 369 participants who developed a liver-related endpoint in the treatment arm. Further, the median age in this study was 53 years, whereas in the US, due to the opioid crisis leading to rising cases of incident HBV in younger patients, this study may not be generalizable to our patients.

The median follow-up time of 17.7 months on average is relatively short for assessing outcomes such as HCC or death, however we do acknowledge that the trial is still ongoing and we look forward to long-term results.

The composite primary endpoint is almost entirely driven by HCC, with only one event each for hepatic decompensation and death, and no events for liver transplantation. Given this, it may be more accurate to say that the tenofovir alafenamide group could decrease the rate of HCC, while its impact on the other secondary endpoints remains questionable. In addition, 36% of patients in the observational group were eventually moved into the treatment arm as they met treatment criteria. This absolutely affected the incidence of the composite outcome in the observational arm.

Finally, the study evaluated only one agent, although other widely used agents, such as entecavir, have not yet been evaluated.

My Practice

Though in 2025 our armamentarium of antivirals is limited to drugs that are highly potent, efficacious and safe, they often can be cost-prohibitive. Though the thresholds are different, this study essentially aligns with the recent WHO guidelines which aim to eliminate hepatitis B as a major public health threat by 2030. They suggest treatment if the DNA is > 2,000 IU/mL and the ALT is above the upper limit of normal, thus treating before there is significant inflammation. In my practice, undoubtedly I utilize NILDA to risk-stratify patients first, obtain a full history, and understand their unique social determinants of health in a culturally competent manner to tailor my plan for them. If there is significant fibrosis, cirrhosis, co-infections, or a family history of HCC or cirrhosis, we opt for treatment (if they can follow-up and the medication is affordable). If there are multiple time points that demonstrate a rise in viral load, irrespective of ALT levels and fibrosis stage, I highly consider treatment initiation after a discussion with the patient and the individuals who identify as their support system.

CHB is arguably one of the most challenging topics for trainees to understand and master. Often, confusion can arise due to the varying guidelines put forth by the different international societies. As such, we must recall that guidelines are meant to guide us as clinicians, but at the end of the day, treatment decisions should be tailored to each individual patient based on shared decision making and by weighing the overall risks and benefits.

For Future Research

Future studies should aim to validate these findings in multi-center studies with diverse populations ideally with longer follow-up periods that allow for the development of more complications, making comparisons more meaningful. It would also be interesting to see more granularity in terms of patient reported outcomes such as the impact on quality of life after treatment with antivirals. Furthermore, in this study, tenofovir alafenamide was chosen. Given the frequently encountered concerns surrounding prescription drug coverage costs, the efficacy of alternatives such as entecavir or tenofovir disoproxil fumarate would add to this body of literature.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval ; HBeAg, hepatitis B e-antigen; HBV, hepatits B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; NILDA, Non-Invasive Liver Disease Assessment; RCT, randomized controlled trial; WHO, World Health Organization.

Social Media

The authors of this summary are active on social media. Tag them on X to discuss their work.

@leandrosierraca
Leandro Sierra

@doctornikkid
Nikki Duong

REFERENCES

1. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: A review. *JAMA*. 2018;319 (17):1802-1813. Erratum in: *JAMA*. 2018 Sep 18;320(11):1202.
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. *Lancet*. 2015;386(10003):1546-1555.
3. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. March 29, 2024. https://www.who.int/publications/i/item/9789240090903. Accessed Apr 6, 2025.
4. Liu J, Wang J, Yan X, et al. Presence of liver inflammation in Asian patients with chronic hepatitis B with normal ALT and detectable HBV DNA in absence of liver Fibrosis. *Hepatol Commun*. 2022;6(4):855-866
5. Kim GA, Han S, Choi GH, Choi J, Lim YS. Moderate levels of serum hepatitis B virus DNA are associated with the highest risk of hepatocellular carcinoma in chronic hepatitis B patients. *Aliment Pharmacol Ther* 2020; 51: 1169–79.
6. Kim GA, Lim YS, Han S, et al. Viral load-based prediction of hepatocellular carcinoma risk in noncirrhotic patients with chronic hepatitis B: A multinational study for the development and external validation of a new prognostic model. *Ann Intern Med* 2024; 177: 1308–18.
7. Lim YS, Ahn SH, Shim JJ, Razavi H, Razavi-Shearer D, Sinn DH. Impact of expanding hepatitis B treatment guidelines: A modelling and economic impact analysis. *Aliment Pharmacol Ther.* 2022; 56(3):519-528.

EVIDENCE-BASED GI
AN ACG PUBLICATION

Challenges of Full FDA Approval for Obeticholic Acid Based on Reduction of Hepatic PBC Clinical Events

Paul Kwo
Co-Editor-in-Chief

Paul Y. Kwo, MD, FACG

Professor of Medicine and Director of Hepatology, Stanford University School of Medicine, Stanford, CA

HEPATOLOGY

This summary reviews Kowdley KV, Hirschfield GM, Coombs C, et al. COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls. Am J Gastroenterol. 2025;120 (2):390-400.

Correspondence to Paul Y. Kwo, MD, FACG, Co-Editor-in-Chief. Email: EBGI@gi.org

Keywords: obeticholic acid; primary biliary cholangitis; liver disease; RCT

STRUCTURED ABSTRACT

Question: The goal of this phase 3B/4 study was to determine whether obeticholic acid (OCA) administration could reduce hepatic decompensation events in patients with primary biliary cholangitis (PBC) and advanced liver disease.[1]

Design: This was a prospective randomized controlled study (RCT) combined with a contemporaneous external cohort (EC) of patients derived from a healthcare claims database with 330 million members. The study is registered with ClinicalTrials.gov identifier NCT02308111.

Setting: A RCT in the United States and Europe enrolled patients prospectively. The external cohort was derived from the Komodo Healthcare Map, US health claims database.

Patients: Patients aged ≥18 years diagnosed with PBC were enrolled at 137 sites in 27 countries starting in February 2015. Original entry criteria included mean ALP >5× ULN and mean total bilirubin > ULN and ≤3× ULN. Subsequently, these criteria were revised to ALP >3× ULN and mean total bilirubin > ULN and ≤5× ULN to increase patient recruitment. Eligible patients included those who had either discontinued ursodeoxycholic acid >3 months earlier or who were taking ursodeoxycholic acid >12 months with an approved, stable dose ≥3 months before enrollment. The external cohort used Komodo Healthcare Map, a large US healthcare claims database with approximately 330 million unique patients

Exposure: Patients were randomized to OCA (5–10 mg) were compared with placebo (RCT) or external control (EC)

Outcomes: The primary composite endpoint was time to death, liver transplant, model for end-stage liver disease (MELD) score ≥15, uncontrolled ascites, or hospitalization for hepatic decompensation. A prespecified propensity score–weighted EC group was derived from a US healthcare claims database and analyzed for similar outcomes other than MELD score ≥15.

Data Analysis: In the COBALT RCT, the intention-to-treat (ITT) analysis was a log-rank test of the randomized OCA and placebo cohorts with respect to the primary composite endpoint, stratified by the randomization stratification factors. The EC analysis was a log-rank test of OCA patients in COBALT and comparable non-OCA–treated EC individuals with respect to the primary composite endpoint (excluding MELD score).

Funding: This study was funded by Intercept Pharmaceuticals.

Results: In the RCT, the primary endpoint occurred in 28.6% of OCA (n = 168) and 28.9% of placebo patients (n= 166; ITT analysis hazard ratio [HR]= 1.01, 95% CI 0.68–1.51). Functional unblinding and crossover to commercial therapies occurred, especially in the placebo arm. Correcting for these using inverse probability of censoring weighting and as-treated analyses shifted the HR to favor OCA over placebo. In the EC (n= 51,051), the weighted primary endpoint occurred in 10.1% of OCA and 21.5% of non-OCA patients (HR 50.39; 95% CI 0.22–0.69; *P*=0.001). No new safety signals were identified in the RCT.

COMMENTARY

Why Is This Important?

Ursodiol is effective in the treatment of PBC, although up to 40% of individuals fail to have an adequate response. In 2016, the FDA and EMA granted accelerated approval for OCA as a second-line therapy to treat those with PBC and inadequate response to ursodiol using the surrogate output of reduction of alkaline phosphatase ≤1.67 ULN and normal total bilirubin that was believed to reflect improved survival based on results of the POISE trial.[2] Full approval of OCA was to be based on the long-term confirmatory trial demonstrating improved clinical outcomes in OCA patients with PBC. The COBALT PBC trial was designed to confirm clinical benefit but faced multiple challenges that will likely occur with other therapies that require confirmatory endpoint trials including recently including other recently approved therapies for primary biliary cholangitis (seladelpar and elafibranor) and other in other diseases such as MASH.[3,4]

In the COBALT trial, patients with PBC had more advanced liver disease than those in the initial POISE trial in order to enrich for likelihood of clinical events. However, the data monitoring committee, in conjunction with regulatory authorities, recommended the termination of the study due to the disproportionate exit of patients in the placebo arm. This was due to substantial functional unblinding and initiation of other adjunctive PBC therapies, which occurred at greater rates in the placebo arm than in the OCA arm. This led to a remarkable reduction in alkaline phosphatase in the placebo arm of the COBALT trial, with no difference in hepatic events being demonstrated between the OCA and placebo arms in the ITT analysis. The EC analysis demonstrated reduced primary endpoints in the OCA-treated arm compared to untreated controls, a result that has been replicated in other real-world cohorts[5]

Key Study Findings

EC analysis demonstrated that OCA treatment is associated with a significant reduction in risk of negative clinical outcomes. Confounding in the RCT ITT analysis demonstrates the value of EC data in confirmatory trials of rare diseases.

Caution

The high dropout rate greatly influenced the negative findings of the randomized trial. Based on these results, the FDA advisory panel declined to grant long-term approval for OCA for non-responders to PBC first-line therapy. The external cohort in the setting is beneficial in that the response rates appear comparable to other PBC non-responder trials and represent an attractive option to generate post-conditional approval data confirming long-term benefits and clinical outcomes. High dropout rates may be a challenge for all

therapies that will be conducted in populations with more advanced liver disease who are at risk for decompensation, liver transplant, hepatocellular carcinoma, and death. Indeed, many physicians may choose not to put these at-risk patients in clinical trials even though these are the populations where the therapeutic intervention will likely demonstrate the greatest benefit.

There is not a regulatory approval pathway yet finalized using real-world evidence to confirm clinical outcome efficacy.

My Practice

OCA was the first approved second-line therapy for PBC based on the POISE trial. Recently 2 therapies have been approved as second line therapy for PBC. Both seladelpar and elafibranor have also been shown to meet their primary endpoint, including a reduction in alkaline phosphatase to less than 1.67 times the upper limit of normal. These therapies now must also undergo similar prospective trials to determine whether these therapies can also prevent clinical decompensation and improve long-term outcomes in those with primary biliary cholangitis and will face similar challenges of the COBALT trial, particularly in those with advanced liver disease who must remain on placebo. OCA should no longer be used in those with advanced cirrhosis and portal hypertension due to an FDA safety update, and compared to seladelpar and elafibranor, does not have the same improvement in pruritus. I have been utilizing the newer agents for my PBC patients who require adjunctive therapy, and offer those who are responding and tolerating OCA therapy well the option to transition to these agents, though there is no data that seladelpar and elafibranor are effective in treating those who have responded to OCA as a second line therapy.

For Future Research

An important priority is for drug developers, investigators, and regulatory authorities is to come together to address the challenges of conducting confirmatory trials in those with advanced liver disease where placebo arms are highly likely to fail as occurred in the Coldwell trial. The EMA has recently released initial guidance about this issue with a potential path forward[6], and it is hoped that the FDA will also address this important issue.

Conflict of Interest

Dr. Kwo has the following disclosures: Consultant for Abbvie, Durect, Genentech, HepQuant, Inventiva, LyGenesis, Madrigal, Mirum, PB Gene, Tune Therapeutics; advisory board member for Aligos, Amgen, Arbutus, Galapagos, Gilead, Mallinckrodt, Novo Nordisk, Ocelot, and Surrozen; research support from Altimmune, Ausper Bio, Inventiva, Novo Nordisk, Salix, Takeda, Target Registries, and Ultragenyx.

Abbreviations

ALP, alkaline phosphatase; CI, confidence interval; EC, external cohort; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; MELD, model for end-stage liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; RCT, randomized controlled trial; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

REFERENCES

1. Kowdley KV, Hirschfield GM, Coombs C, et al. COBALT: A confirmatory trial of obeticholic acid in primary biliary cholangitis with placebo and external controls. *Am J Gastroenterol* 2025; 120(2): 390-400.
2. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375(7):631-643.
3. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):783-794.
4. Kowdley KV, Bowlus CL, Levy C, et al. Efficacy and safety of elafibranor in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):795-805.
5. Perez CFM, Fisher H, Hiu S, et al. Greater transplant-free survival in patients receiving obeticholic acid for primary biliary cholangitis in a clinical trial setting compared to real-world external controls. *Gastroenterology.* 2022;163(6):1630-1642. e3.
6. European Medicines Agency. Reflection paper on regulatory requirements for the development of medicinal products for primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). EMA/CHMP/299976/2018. Published December 19, 2023. Accessed April 15, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-development-medicinal-products-primary-biliary-cholangitis-pbc-primary-sclerosing-cholangitis-psc_en.pdf

EVIDENCE-BASED GI
AN ACG PUBLICATION

Tulisokibart: A New Drug for Moderate-to-Severe UC That May Come With Personalized Medicine

Ellen Axenfeld, MD[1] and Elie S. Al Kazzi, MD, MPH[2]

Dr Ellen Axenfeld
Guest Contributor

Elie Al Kazzi
Associate Editor

[1]*Clinical Instructor, Division of Gastroenterology & Hepatology, New York University Langone Health, New York, NY*

[2]*Assistant Professor of Medicine, New York University Grossman School of Medicine, New York, NY*

IBD

This summary reviews Sands BE, Feagan BG, Peyrin-Biroulet L, et al and the ARTEMIS-UC Study Group. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. N Engl J Med. 2024;391(12):1119-1129 .

Correspondence to Elie S. Al Kazzi, MD, MPH, Associate Editor Email: EBGI@gi.org

Keywords: Ulcerative colitis, tulisokibart, RCT, IBD

STRUCTURED ABSTRACT

Questions: Among patients with moderate to severe ulcerative colitis (UC), is induction therapy with tulisokibart more effective than placebo? Is there a benefit to genetic-based testing for likelihood of response?

Design: Phase 2, multicenter, double blind, placebo-controlled trial with 12 weeks of follow-up. Eligible patients were enrolled in cohort 1 regardless of their status on a genetic-based diagnostic test. Enrollment in cohort 2 was limited to patients with a positive test for likelihood of response.

Setting: This trial was conducted in 14 countries.

Patients: Patients included in the study were adult patients with a diagnosis of moderately to severely active disease extending at least 15 cm from the anal verge. Moderately to severely active disease was defined by a 3-component modified Mayo score. Patients were eligible if they had glucocorticoid dependence. Patients were excluded if prior failure of more than 3 classes or more than 4 advanced therapies approved for UC.

Interventions: Participants received intravenous tulisokibart at a dose of 1,000 mg on day 1, followed by 500 mg at weeks 2, 6, and 10, or placebo at the same time points.

Outcomes: The primary efficacy end point was clinical remission at week 12, defined as a modified Mayo endoscopic subscore of 0 or 1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0 or 1 and not greater than the baseline value. Prespecified secondary end points that were assessed at week 12 were endoscopic improvement, clinical response, symptomatic remission, histologic improvement, histologic-endoscopic mucosal improvement, mucosal healing, and Inflammatory Bowel Disease Questionnaire response improvement.

Data Analysis: Analysis was based on the modified intention-to-treat principle, with the inclusion of all randomly assigned patients (for cohort 1) who had received at least 1 dose of tulisokibart or placebo. Analyses of the primary and secondary end points were prespecified and were conducted with the use of a sequential hierarchical testing procedure to control for multiple comparisons with a familywise alpha level (2-sided) of 0.05.

Funding: This study was supported by Prometheus Biosciences, a subsidiary of Merck.

Results: A total of 135 out of 198 screened patients were randomized. The baseline characteristics of the patients indicated a relatively refractory population with moderately to severely active ulcerative colitis. About half of the patients had prior exposure to advanced therapies. The trial sample was broadly representative of the demographic characteristics of individuals with ulcerative colitis in the countries where the patients were enrolled.

In cohort 1, 135 patients were randomized. A significantly higher proportion of pa-

tients who received tulisokibart achieved clinical remission compared to those who received placebo (26% vs 1%; 95% CI, 14 to 37; *P* <0.001). Tulisokibart also demonstrated significant benefits over placebo across all ranked secondary endpoints.

In the group of 75 patients with a positive likelihood of response test, a higher percentage of those who received tulisokibart achieved clinical remission at week 12 compared to those who received placebo (32% vs 11%; 95% CI, 2 to 38; *P*=0.02).

The incidence of adverse events was similar between the two groups, with 46% of patients in the tulisokibart group and 43% in the placebo group reporting adverse events.

	Tulisokibart (N= 68)	Placebo (N=67)	Δ
Clinical remission	**26%**	**1%**	**25%**
Endoscopic improvement	37%	6%	31%
Clinical response	66%	22%	44%
Symptomatic remission	19%	6%	13%
Histologic improvement	46%	18%	29%
Histologic-endoscopic musical improvement	31%	4%	27%
Mucosal healing	31%	4%	27%
IBDQ response	82%	49%	33%

Table 1. Outcomes at week 12.

IBDQ, inflammatory bowel disease questionnaire.

COMMENTARY

Why Is This Important

Despite the explosion of new medications and mechanisms in recent years in the field of inflammatory bowel disease (IBD), disease remission remains far from a universal experience for patients living with IBD. Most of our medical therapies only achieve a clinical remission rate of approximately 40% at week 52.[1] This underscores the importance of continued advancement in therapeutic options to break through this "efficacy ceiling." There are several strategies working towards this goal, but this study highlights two important tactics: (1) a novel mechanism targeting a new molecule in the inflammatory pathway and (2) personalized medicine. This exploration of personalized medicine is what is particularly unique to this study. Although this was a negative study in the clinical utility of a genetic-based

diagnostic test which was designed to identify patients with an increased likelihood of response, this is a concept that will almost certainly become a common theme in future research in IBD therapeutics.

Key Study Findings

At week 12, a significantly higher percentage of patients in cohort 1 who received tulisokibart had clinical remission than those who received placebo. A significant benefit of tulisokibart as compared with placebo was also observed for all ranked secondary end points for cohort 1.

Subgroup analyses for clinical remission and endoscopic improvement showed a consistent benefit of tulisokibart as compared with placebo in prespecified subgroups, including patients receiving concurrent glucocorticoids and immunosuppressants

A greater percentage of patients with a positive test for the likelihood of response who received tulisokibart had clinical remission at week 12 than those who received placebo. The between-group difference for endoscopic improvement in patients with a positive test for likelihood of response was not significant. Among all the enrolled patients for both cohorts, the percentage of patients reporting an adverse event was similar in the 2 trial groups (46% and 43% in the tulisokibart and placebo groups, respectively).

Caution

As a phase 2 trial, this study is inherently limited in the inability adequately evaluate the therapeutic index or the positioning of tulisokibart in the IBD medications armamentarium. Future assessment of larger numbers in a phase 3 trial with longer-term follow will provide more precise efficacy and safety evaluations. The analysis of patients with a positive test for likelihood of response was based on pooled patients from cohorts 1 and 2 and is therefore limited by the small sample size and may be susceptible to selection bias due to cohort differences. Additionally, caution should be exercised when analyzing cohort 2 which selected for patients with a positive test for likelihood of response, and has therefore lost randomization.

My Practice

At our institution, we are enrolling patients in the phase 3 study for tulisokibart. The typical patient that is enrolled is a relatively refractory phenotype that, from a clinical perspective, closely reflects that of the population studied in the phase 2 trial. Patients are often considered for enrollment with moderate to severe disease, higher Mayo endoscopic subscores, and most importantly prior failure several lines of therapy. At this point it is unclear where tulisokibart would fit into the treatment algorithm compared to other biologics/small molecules for the treatment of ulcerative colitis based on this study. It should also be noted that our practice is guided by treat-to-target

guidelines outlined by STRIDE II that support the use of endoscopic healing rather than this study's primary outcome of clinical remission as the therapeutic target.[2]

For Future Research

The currently underway phase 3 trials of tulisokibart in treatment of moderate-to-severe UC will elucidate where this patient falls in the treatment algorithm for UC. With a larger patient population, it will be interesting to see if there is benefit to using the genetic-based diagnostic test. Beyond a larger cohort size to increase power of the study, the cohort used to evaluate the genetic-based testing for likelihood of response should be designed to maintain randomization for more accurate results.

Conflict of Interest

The authors report no potential conflicts of interest related to this study.

Abbreviations

CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.

REFERENCES

1. Peyrin-Biroulet L, Lémann M. Review article: Remission rates achievable by current therapies for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33(8):870-9.
2. Turner D, Ricciuto A, Lewis A, et al. and the International Organization for the Study of IBD. STRIDE-II: An update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583.

Advance to Fellowship of the AMERICAN COLLEGE OF GASTROENTEROLOGY (FACG)

Criteria for an ACG Physician Member to Advance to Fellowship:

- **Demonstration of scholarly activities**, which include continuing education experience, professional leadership, and excellence in the fields of clinical practice and/or academic medicine.
- **Current uninterrupted membership** or international membership in the College for a period of no less than five years (Post Resident/Trainee Membership).
- Minimum of 3 distinct* ACG managed and sponsored CME courses within the last six years:
  - Three in-person meetings are required.
  - *Attendance at multiple courses in the same meeting, e.g., PG Course and Annual Meeting, or Regional Meeting plus Hepatology School counts as one program
- **Evidence of ongoing involvement in ACG activities**: Committees, Courses, Annual Meeting attendance, etc.
- **Letters of recommendation** from two Fellows of the College.
- **Documentation of initial certification** by one or more of the following specialty boards recognized by the Council on Graduate Medical Education of the American Medical Association: American Board of Internal Medicine, (subspecialty Boards in Gastroenterology), or its equivalent, e.g., American Board of Pediatrics (subspecialty Board in Gastroenterology), American Board of Surgery, American Board of Radiology, American Board of Pathology, the American Osteopathic Board of Internal Medicine or the Canadian equivalent qualifications, Fellow of the Royal College of Physicians and Surgeons.

Benefits of ACG Fellowship:

- You can run for elected office on the Board of Governors
- You can serve as the Chair of an ACG Committee
- You can be nominated for the Board of Trustees
- You can be nominated for a Master Award or the Samuel S. Weiss Award
- Add FACG to your credentials, on business cards, and on your CV
- Recognition at the ACG Annual Meeting and on the ACG website
- Certificate of Advancement to Fellowship signed by the ACG President and Secretary

Complete the application online:
members.gi.org/acgmembership

Application fee is $50