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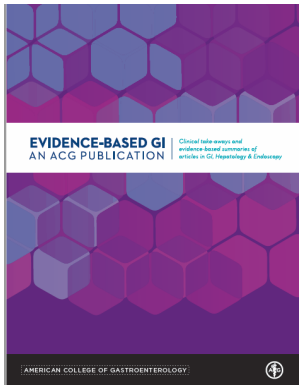

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Upadacitinib Is Effective for the Induction and Maintenance of Moderate-to-Severe Crohn's Disease

Dr Jessica Allegretti
Associate Editor

Dr Rahul S. Dalal
Guest Contributor

Rahul S. Dalal, MD, MPH[1] and Jessica R. Allegretti, MD, MPH, FACG[2]

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IBD

This summary reviews Loftus EV Jr, Panés J, Lacerda AP, Peyrin-Biroulet L, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2023 May 25;388(21):1966-1980.

Correspondence to Jessica Allegretti, MD, MPH. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is upadacitinib effective for the induction and maintenance of moderate-to-severe Crohn's disease?

Design: Three clinical trials were included: U-EXCEL, U-EXCEED, and U-ENDURE. U-EXCEL and U-EXCEED were both 12-week, double-blinded placebo -controlled, induction of remission trials with 12-week extended treatment periods for those without initial clinical response. In U-EXCEED, all patients had prior failure of biologic therapies, while in U-EXCEL, patients had to have failed either biologic (approximately 45%) or conventional therapies (approximately 55%). U-EXCEED included an additional 12-week open-label single-group induction period. Patients with clinical response or clinical remission after 12 weeks of upadacitinib induction were enrolled in U-ENDURE, which was a 52-week double-blinded, placebo-controlled maintenance of remission trial.

Setting: Two hundred seventy-seven sites across 43 countries.

Patients: Adults age 18-75 years with a diagnosis of moderate-to-severe Crohn's disease for at least 3 months.

Interventions: Upadacitinib (45 mg once daily for U-EXCEL and U-EXCEED; 15 mg once daily or 30 mg once daily for U-ENDURE) vs placebo.

Outcomes: The primary outcomes were clinical remission (Crohn's Disease Activity Index [CDAI] < 150) and endoscopic response (decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] of >50% from baseline) at week 12 of induction and week 52 of maintenance. Secondary outcomes included, but were not limited to: clinical response (decrease of ≥100 point in CDAI from baseline), steroid-free CDAI clinical remission, endoscopic remission, resolution of extraintestinal manifestations, deep remission (both clinical remission and endoscopic remission), and maintenance of CDAI clinical remission.

Data Analysis: U-EXCEL and U-EXCEED analyses were performed using modified intention-to-treat populations, which included all patients who were randomized and received at least one dose of upadacitinib or placebo. Analyses for U-ENDURE were performed for those who completed the week 52 visit. Categorical data were analyzed using Cochran-Mantel-Haenszel models and continuous data were analyzed using mixed-effects repeated-measures models.

Funding: The study was funded by AbbVie, manufacturer of upadacitinib.

Results: In total, 526 patients were randomized in U-EXCEL, 495 in U-EXCEED, and 502 in U-ENDURE. At week 12, significantly higher proportions of patients who received 45 mg upadacitinib achieved clinical remission (50% vs 29% in U-EXCEL, 39% vs 21% in U-EXCEED) and endoscopic response (45% vs 13% in U-EXCEL, 35% vs 4% in U-EXCEED) compared to placebo. At week 52 (U-ENDURE only), higher proportions of patients achieved clinical remission and endoscopic response with 15 mg upadacitinib or 30 mg upadacitinib compared to placebo (37% and 48% vs 15% for clinical remission; 28% and 40% vs 7% for endoscopic response). In U-ENDURE RCT, the 30mg upadacitinib arm also demonstrated a significant reduction in extra-intestinal manifestations of Crohn's disease. Herpes zoster infections were more common in the 45 mg and 30 mg upadacitinib groups compared to placebo. There was no evidence of cardiovascular or thromboembolic complications with upadacitinib. A summary of key efficacy outcomes is presented in **Figure 1**.

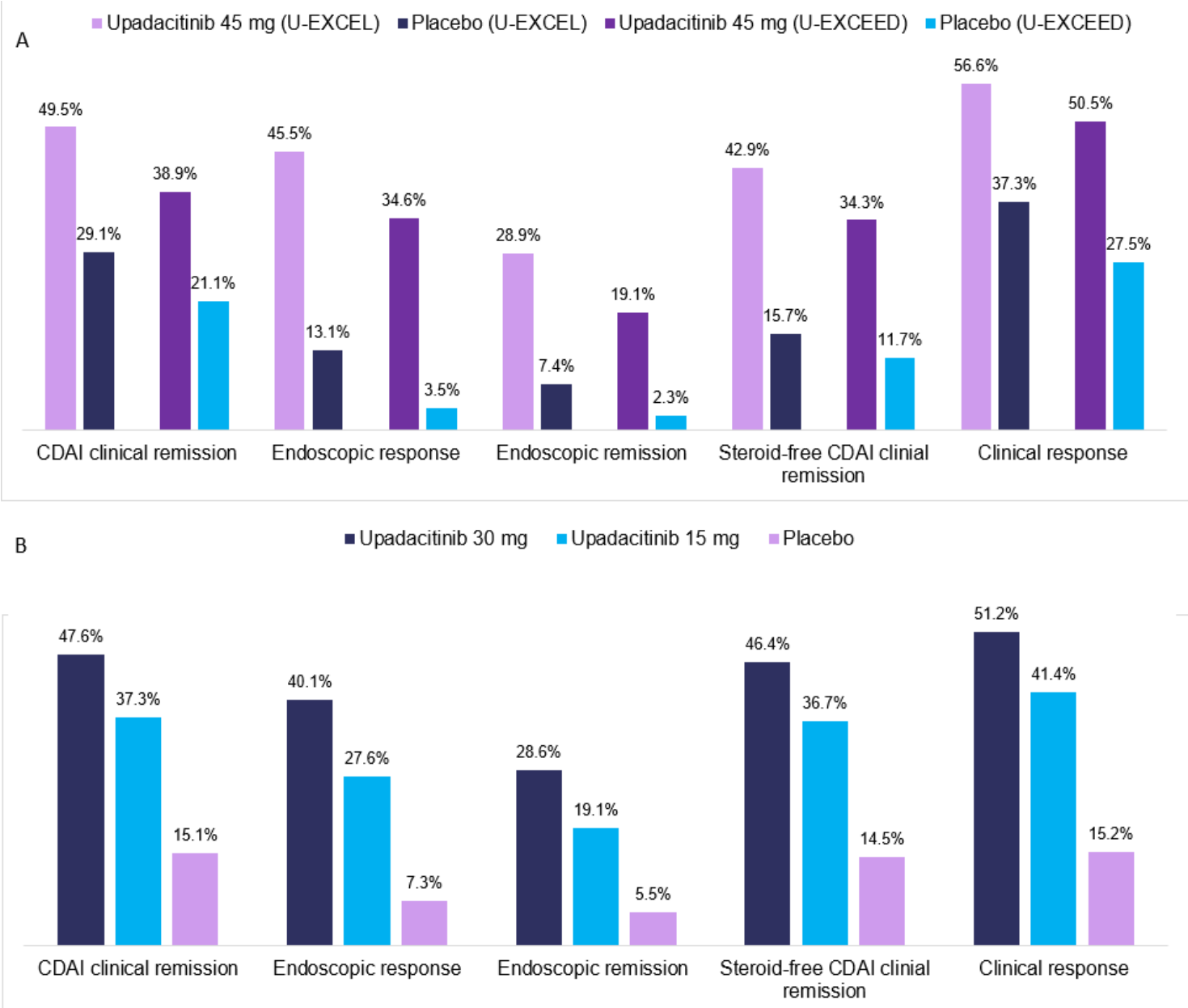

Figure 1. (A) Selected 12-week induction outcomes (U-EXCEL and U-EXCEED). (B) 52-week maintenance outcomes (U-ENDURE) of upadacitinib vs placebo for Crohn's disease.

CDAI, Crohn's Disease Activity Index.

COMMENTARY

Why Is This Important?

The available number of advanced therapies for inflammatory bowel diseases has rapidly expanded over the last decade to include biologics as well as small molecule agents. Prior to upadacitinib, only biologics, which are susceptible to immunogenicity and subsequent loss of efficacy, have been available for the treatment of moderate-to-severe Crohn's disease.[1] Tofacitinib, a Janus kinase inhibitor approved for the treatment of ulcerative colitis, did not demonstrate efficacy for Crohn's disease compared to placebo.[2] Upadacitinib represents the first Janus kinase inhibitor and small molecule agent that has received FDA-approval for Crohn's

disease. The novel mechanism of action presents an opportunity to successfully treat cases of Crohn's disease that have been refractory to anti-tumor necrosis factor (TNF), anti-integrin, and/or anti-interleukin agents, but may also be used immediately after anti-TNF failure. It is also the only orally administered maintenance treatment available for this population that can be stopped and started without the risk of anti-drug antibody formation.

Key Study Findings

These clinical trials identified significantly higher rates of clinical remission and endoscopic response for 45 mg upadacitinib vs placebo at 12 weeks aswell as for 15 mg and 30 mg upadacitinib vs placebo at 52 weeks among patients with moderate-to-severe Crohn's disease where the majority, approximately 75%, had already failed other biologic agents.

Infections such as herpes zoster occurred more commonly in upadacitinib treatment groups compared to placebo.

Caution

While the safety outcomes of upadacitinib appear to be similar to the known safety profile of Janus kinase inhibitors, the limited sample sizes and follow-up period cannot exclude a significantly higher risk of rare or delayed adverse effects, such as cancer. Additionally, based on the data presented in these trials, it is not clear how effective upadacitinib is for certain Crohn's disease phenotypes, such as fistulizing disease.

My Practice

Due to our own observations regarding the effectiveness of upadacitinib in the treatment of moderate-to-severe ulcerative colitis, including those refractory to other advanced therapies, we are inclined to utilize upadacitinib in cases of luminal colonic Crohn's disease after anti-TNF failure. However, in certain populations, such as the elderly and those at higher risk for infection or malignancy, we may first consider biologics with more established and favorable safety profiles (i.e., vedolizumab, ustekinumab, and risankizumab).

For Future Research

Future research should examine the efficacy and safety of upadacitinib for challenging Crohn's disease phenotypes, such as perianal fistulizing disease, as well as in pregnancy. Head-to-head clinical trials and real-world comparative effectiveness studies are also needed to help determine the optimal positioning of upadacitinib relative to other advanced therapies for Crohn's disease.

Conflict of Interests

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

Dr. Allegretti has received grant support from Janssen Pharmaceuticals, Pfizer Pharmaceuticals, and Merck Pharma-

ceuticals, and has served as a consultant for Janssen Pharmaceuticals, Pfizer Pharmaceuticals, AbbVie Pharmaceuticals, Ferring Pharmaceuticals, Merck Pharmaceuticals, Bristol Myers Squibb, Seres Therapeutics, Finch Therapeutics, Iterative Scopes, and Takeda Pharmaceuticals.

Note: The authors of the article published in NEJM are active on social media. Tag them to discuss their work and this EBGI summary.

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@JeanFredericCo1
@RPanaccione

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EVIDENCE-BASED GI
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Vedolizumab: An EARNEST Option for the Management of Chronic Pouchitis

Kristin E. Burke
Guest Contributor

Bharati Kochar
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IBD

This summary reviews Travis S, Silverberg MS, Danese S, et al. Vedolizumab for the treatment of chronic pouchitis. N Engl J Med 2023;388(13):1191-1200.

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

STRUCTURED ABSTRACT

Question: Is vedolizumab a safe and effective treatment for patients with chronic pouchitis after ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC)?

Design: The EARNEST study is 34-week, multicenter, randomized, double-blind, placebo-controlled phase 4 trial. It is the first randomized controlled trial (RCT) to study the efficacy and safety of a biologic therapy in management of pouchitis after IPAA for UC.

Setting: Patients were recruited from 13 sites in North America and 18 sites in Europe.

Patients: Inclusion criteria were: (a) 18- to 80-year-old patients; (b) status post IPAA for UC at least 1 year prior to screening; (c) active chronic pouchitis defined as a modified pouchitis disease activity index (mPDAI)* score of at least 5 with a subscore of at least 2 on the endoscopic domain; and (d) at least 3 episodes of pouchitis within 1 year before the screening visit treated with at least 2 weeks of an antibiotic or other therapy, or continuous antibiotics for at least 4 weeks.

Primary exclusion criterion was previous vedolizumab use.

Intervention: Vedolizumab 300 mg intravenous on day 1, and at weeks 2, 6, 14, 22, and 30. All patients received oral ciprofloxacin 500 mg twice daily from the time of randomization through week 4. Subsequently, antibiotics were not permitted from weeks 5-14. Additional antibiotics were permitted for pouchitis flares after week 14. Oral corticosteroids were also permitted throughout the trial if the patient had been on a stable dose for at least 4 weeks prior to randomization.

Outcomes: The primary outcome was mPDAI remission at week 14, defined as total mPDAI score of ≤ 4 with a reduction of at least 2 points from baseline. Secondary endpoints included, but not limited to: (a) mPDAI remission at week 34; (b) PDAI remission at weeks 14 and 34 (PDAI ≤ 6 with a reduction of at least 3 points from baseline); (c) time to PDAI remission; (d) partial mPDAI response (reduction from baseline mPDAI total score of at least 2 points at weeks 14 and 34); and (e) mean changes in the total mPDAI score, endoscopic subscore, and histologic subscore at weeks 14 and 34.

Data Analysis: Modified intention-to-treat analysis, including patients who were randomized and received at least 1 dose of vedolizumab or placebo, was performed. For the primary endpoint, the incidence of mPDAI remission at week 14 was compared using a Fisher's exact test. Stratified analyses for the primary endpoint according to additional antibiotic use were also performed with a Cochran-Mantel-Haenszel chi-square test. For other dichotomous variables, unadjusted and adjusted between-group differences were calculated using a Cochran-Mantel-Haenszel test with corresponding 95% confidence intervals.

Funding: Takeda, the manufacturer of vedolizumab, had a role in study design and funded study investigators.

Results: Between October 2016 and March 2020, 165 patients were assessed for eligibility. Of these, 102 patients were enrolled, underwent randomization (51 vedolizumab group, 51 placebo group), and received at least 1 dose of vedolizumab or placebo. Eight patients in each group discontinued treatment due to lack of efficacy. Baseline characteristics were similar in both arms: with 84% White, median age 42-45 years of age, 69% male, mean mPDAI score 8.1. At baseline, 10% of patients in the vedolizumab group and 16% of patients in the placebo group were receiving stable doses of steroids. Overall, 59% of patients in the vedolizumab group and 37% of patients in the placebo group received additional antibiotics during weeks 15-34 of the study in addition to the universally prescribed ciprofloxacin from weeks 0-4.

At week 14, a significantly higher proportion of patients in the vedolizumab group achieved mPDAI remission as compared to those in the placebo group: 31% vs 10%, *P*=0.01 (Figure 1). The percentage of patients who achieved mPDAI remission at week 34 (35% vs 18%, respectively), PDAI remission at weeks 14 and 34, and mPDAI response at weeks 14 and 34 favored vedolizumab.

As compared to the placebo group, the incidence of upper respiratory infection (10% vs 2%) and headache (20% vs 6%) was numerically higher in the vedolizumab group.

Note: **mPDAI includes clinical assessment of stool frequency, rectal bleeding, fecal urgency or abdominal cramping, fever; and endoscopic assessment for edema, granularity, friability, loss of vascular pattern, mucosal exudate, and ulcerations in the pouch body. It excludes 1 domain that is part of the original PDAI: histologic assessment of severity of polymorphonuclear inflammatory infiltrate and number of ulcers per lower power field.*

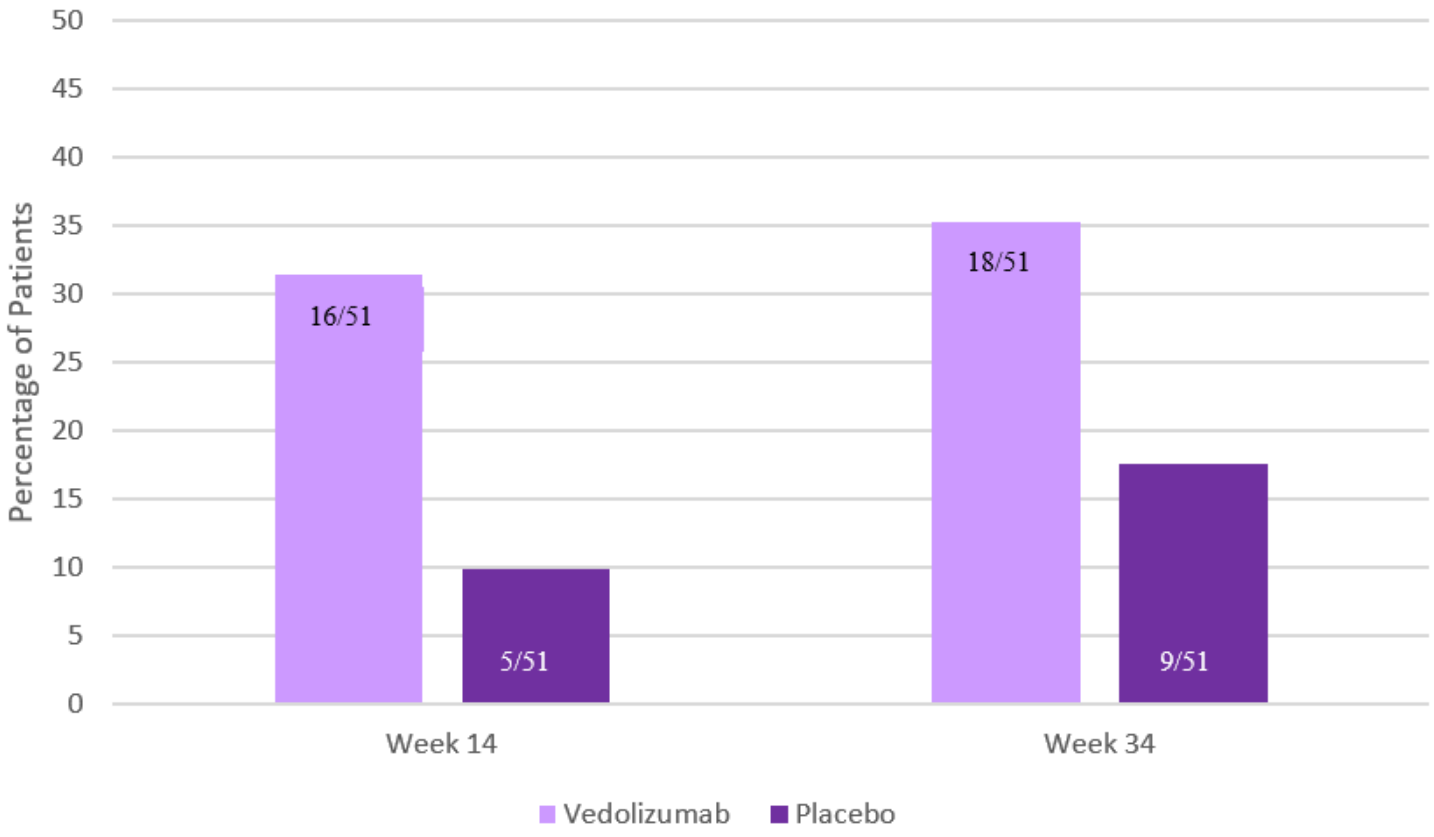

Figure 1. mPDAI-defined remission at week 14 and week 34.

COMMENTARY

Why Is This Important?

Chronic pouchitis is a common complication of IPAA for UC that greatly impairs quality of life. Acute pouchitis, characterized by fecal urgency, diarrhea, and/or abdominal-pelvic discomfort, occurs in more than 50% of patients within 5 years, and approximately 20% develop chronic symptoms that last longer than 4 weeks. The mainstay of therapy is recurrent or chronic use of antibiotics, usually ciprofloxacin or amoxicillin-clavulanic acid, for 14- to 28-day courses. Antibiotic-resistant patients may be treated with oral corticosteroids, specifically budesonide, or topical corticosteroids, although these patients are frequently hesitant to use enemas or suppositories. While uncontrolled studies suggest that biologic therapies are safe and effective for long-term management of chronic pouchitis[1], there are no FDA-approved therapies for chronic pouchitis. This is the first RCT demonstrating the safety and efficacy of a biologic therapy for treatment of chronic pouchitis.

Key Study Findings

As compared to placebo, vedolizumab is a more effective therapy for the management of chronic pouchitis, with mPDAI remission in 31% of patients on vedolizumab vs 10% of placebo-treated patients at week 14.

This effect appeared sustained over the 34-week trial. While vedolizumab appeared overall safe, a higher rate of headaches and upper respiratory infections were reported in the vedolizumab group vs placebo.

Caution

While all patients in the trial received 4 weeks of ciprofloxacin with no antibiotics allowed during weeks 5-14, additional antibiotic use was allowed during weeks 15-34. The trial reported higher rates of additional antibiotic use in the vedolizumab group vs the placebo group (59% vs 37%, respectively). As antibiotics are the current mainstay of therapy for chronic pouchitis, their use may have confounded the results of this trial. The authors used a stratified analysis by additional antibiotic use to try to account for this, and did not find a substantial difference between groups, although the number of patients in each group was small.

My Practice

The EARNEST trial is an important step in the treatment algorithm of chronic pouchitis after IPAA for UC and substantiates uncontrolled data that vedolizumab is a safe and effective therapy for antibiotic-refractory or -dependent disease. However, my enthusiasm for this trial is tempered by the rate of additional antibiotic use in the vedolizumab group. I consider vedolizumab the initial biologic agent for chronic pouchitis after IPAA for UC in antibiotic-refractory or -dependent patients.

Clinicians should do pouchoscopy and ensure that no clear stricturing or pene-

trating features of Crohn's disease of the pouch is present since occasional patients may be diagnosed with Crohn's after their IPAA. If stenoses are present in the pouch inlet, mid-pouch body, or neo-terminal ileum, I would treat the patient for stricturing small bowel Crohn's disease and consider first-line treatment with an anti-TNF or anti-IL12/23 or IL-23 depending on co-morbidities and prior biologic exposure.

For Future Research

While the EARNEST trial supports that vedolizumab is superior to placebo for the management of chronic pouchitis over 34 weeks, head-to-head trials of biologic therapies are required to better define the management algorithm for this debilitating disease. Furthermore, long-term trial data is required to understand the role of biologic therapy in long-term outcomes including patient quality of life, and need for repeat surgery such as end-ileostomy or pouch revision.

Conflicts of Interest

Dr. Burke is a consultant for OM1 and has participated in an advisory board for Bristol Myers Squibb.

Dr. Kochar is an advisory board member for Pfizer Pharmaceuticals.

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Note: The authors of the article published in NEJM are active on social media. Tag them to discuss their work and this EBGI summary!

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EVIDENCE-BASED GI
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Bariatric Surgery Is Superior to Lifestyle Changes + Best Medical Care for Metabolic Dysfunction-Associated Steatohepatitis: The BRAVES Study

LIVER

Yichin Fu
Guest Contributor

Sonali Paul
Associate Editor

Yichin Fu, MD[1] and Sonali Paul, MD, MS[2]

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[2]*Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, Pritzker School of Medicine, the University of Chicago, Chicago, IL*

This summary reviews Verrastro O, Panunzi S, Castagneto-Gissey L, et al. Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. Lancet 2023;401(10390):1786-1797.

Correspondence to Sonali Paul, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does bariatric surgery (Roux-en-Y gastric bypass [RYGB] or sleeve gastrectomy) result in histologic resolution of metabolic-dysfunction associated steatohepatitis (MASH; previously known as nonalcoholic steatohepatitis [NASH][1]) compared to lifestyle modification plus best medical care (i.e., Vitamin E supplements plus pioglitazone and liraglutide 1.8 g daily if patient had type 2 diabetes mellitus [DM])?

Design: Open-label trial randomizing participants to RYGB, sleeve gastrectomy, or lifestyle modification plus best medical care for 52 weeks. All patients received lifestyle modification counseling on diet and exercise.

Setting: Three centers in Rome, Italy.

Patients: Individuals aged 25-70 years of age with obesity (body mass index [BMI] 30-55 kg/m) with or without type 2 DM and histologically confirmed

metabolic-dysfunction associated steatohepatitis. Key exclusion criteria included hemoglobin A1c ≥10%, significant cardiac comorbidity and familial dyslipidemia.

Exposure/Intervention: Eligible patients were randomized 1:1:1 to RYGB vs sleeve gastrectomy vs optimal medical care. All patients in the study received lifestyle modification counseling, defined as counseling to improve adherence to a diet containing two-thirds of the calorie expenditure per day, 10,000 steps per day, and 2-3 hours of moderate-intensity physical activity per week. In the best medical care arm, participants received vitamin E 800 IU/day plus pioglitazone and liraglutide 1.8 g daily if they also had type 2 DM since these agents have demonstrated positive effects on MASH. Surgical participants did not receive pharmacotherapy.

Outcome: The primary endpoint was histological MASH resolution without worsening of fibrosis at week 52. The main secondary outcome was improvement by at least 1 stage of the MASH fibrosis score with no worsening of MASH.

Data Analysis: Both intention-to-treat (ITT) and per-protocol analyses were reported.

Funding: The participating hospitals (Fondazione Policlinico Universitario A Gemelli, Policlinico Universitario Umberto I and S Camillo Hospital, Rome, Italy) funded the study.

Results: Overall, 288 adults with histologically confirmed MASH were included in the study and 236 (67%) completed the trial. Participants were 100% White, 44% women, mean age 47 years old, 32% with diabetes, mean body weight of 87.31 kg, BMI 41.8. While 88% of participants had stage F1 or 2 fibrosis, 11% (n=32) had F3 fibrosis. In ITT analysis, 56% and 57% of participants achieved resolution of MASH without worsening fibrosis with RYGB and sleeve gastrectomy, respectively, compared to 16% achieving resolution with lifestyle modification with best medical care (P<0.0001 for all comparisons among all 3 groups) (**Figure 1a**). Participants in the RYGB group and the sleeve gastrectomy group had 3.60 times (95% confidence interval [CI] 2.19–5.92; P<0.0001) and 3.67 times higher (2.23–6.02; P<0.0001) calculated probability of MASH resolution compared with the lifestyle modification plus best medical care group. Similar results were found in the per protocol analysis. Mean weight loss at 52 weeks was superior with RYBG and sleeve gastrectomy versus lifestyle modification plus best medical care: 31.8% vs 24.0% vs 5.5%, respectively (P< 0.0001).

In the ITT analysis, 37%, 39% and 23% of participants had improvement of fibrosis by at least 1 stage without worsening of MASH in the RYGB, sleeve

gastrectomy, and lifestyle modification with best medical care, respectively (*P*=0.034) (**Figure 1b**). Nine percent of the RYGB group and 12% of the sleeve gastrectomy group had regression to Stage 0 fibrosis compared to 3% with lifestyle modification (*P*=0.0003).

Significantly more participants in the bariatric surgery groups had remission of their diabetes and improvement in liver biochemistries. There was no death or life-threatening complications, and 6% of the participants had severe adverse events but did not require re-operations.

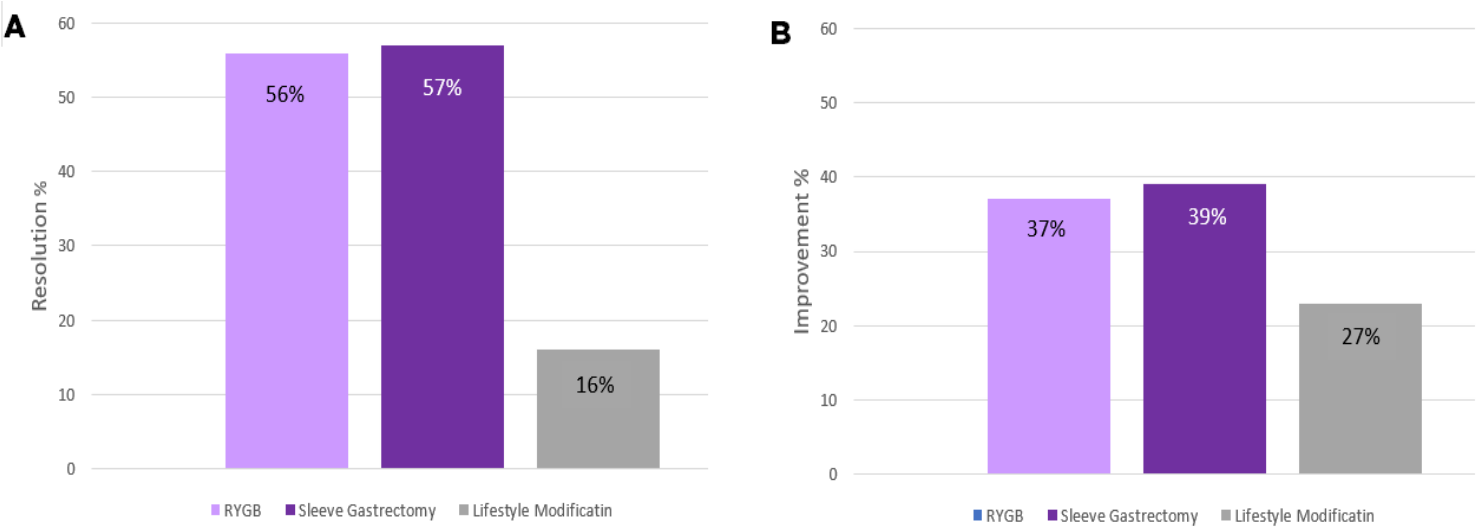

Figure 1. Resolution of MASH without worsening of fibrosis **(A)** and improvement of at least one stage of fibrosis without worsening of MASH **(B)**.

Abbreviations: ITT, intention-to-treat; MASH, metabolic-dysfunction associated steatohepatitis; NASH, non-alcoholic steatohepatitis.

COMMENTARY

Why Is This Important?

Metabolic dysfunction-associated steatotic liver disease (MASLD; previously known as nonalcoholic fatty liver liver disease [NAFLD][1]) is a growing public health concern globally, affecting not only liver health, but also cardiovascular mortality, and is quickly becoming the leading indication for liver transplantation. By 2030, approximately 30 million Americans will have MASH and approximately 5% will develop cirrhosis. Although no pharmacologic therapy is approved by the US Food and Drug Administration for the treatment of MASLD or MASH, weight loss is beneficial, with 3% weight loss reversing steatosis and 10% reversing fibrosis. Historically, bariatric surgery has had the most efficacious weight loss compared to pharmacotherapy, resulting in 25% to 30% weight reduction at 1-2 years. Patients with MASH and MASLD are often told about lifestyle interventions, with infrequent success. This randomized controlled trial is the first to demonstrate the benefits of bariatric surgery not only for weight loss, but also on MASH and fibrosis

reversal, which are the ultimate goals of MASH treatment.

Key Study Findings

Bariatric surgery (RYGB or sleeve gastrectomy) is more effective than lifestyle modifications with best medical care (i.e., Vitamin E supplements plus pioglitazone and liraglutide for type 2 DM) for resolution of MASH and improvement in MASH fibrosis score.

Caution

While the results of this study are very promising, we need to be thoughtful of who we send to bariatric surgery for the treatment of MASH. First, the results may not be entirely generalizable to our patients, as the participants were all White and in Italy, where lifestyles are certainly different from the US. Also, best medical care patients with diabetes were given pioglitazone, which is not often used in clinical practice, and liraglutide 1.8mg daily. While liraglutide can be effective for weight loss, a higher dose (3.0 mg) is needed. Additionally, newer pharmacotherapies which can achieve ≥20% reduction in body weight, including semaglutide and tirzepatide,[2-3] were not studied. Ongoing trials are investigating their efficacy for MASH.[4] These weight loss therapies remain an option for individuals with MASH and obesity, especially if they also have type 2 DM. However, it remains unknown if newer pharmacotherapies can achieve similar weight loss as bariatric surgery.

My Practice

BMI ≥ 35 or presence of metabolic disease with a BMI ≥ 30 are indications for bariatric surgery. MASLD is a metabolic disease, but coverage based on MASLD alone is variable depending on insurance plan. However, most patients with MASLD have obesity, diabetes, or other components of metabolic syndrome. With the introduction of semaglutide and tirzepatide (off-label use) for weight loss into my practice, I try and use pharmacotherapy first before bariatric surgery. However, insurance often dictates medication coverage, making it not available to many patients.In those cases, bariatric surgery is considered. Insurance coverage is also variable for endoscopic sleeve gastrectomy. Whether surgery or pharmacotherapy, each is paired with important lifestyle interventions and counseling from a registered dietician. I am cautious in those with compensated cirrhosis given the risk of hepatic decompensation, but it could be done in select compensated patients.

For Future Research

In addition to better data across all racial/ethnic groups, more patients with F3 fibrosis need to be studied (there were only 11% in this study). Comparing efficacy of the newer anti-obesity medications to bariatric surgery in both the treatment of obesity and MASLD is also needed.

Conflicts of Interest

The authors have no reported conflicts of interest.

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CRC SCREENING

Colonoscopy for Colon Polyp Surveillance: Avoid Recommending Early Surveillance

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This article reviews reviews Dong J, Wang LF, Ardolino E, Feuerstein J. Real-World Compliance with the 2020 US Multi-Society Task Force on Colorectal Cancer Polypectomy Surveillance Guidelines: An Observational Study. Gastrointest Endosc 2023; 97:350-56.

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STRUCTURED ABSTRACT

Question: Are endoscopists complying with 2020 US Multi-Society Task Force Guidelines by recommending repeat colonoscopy in 7-10 years after finding 1-2 small adenomas on average-risk screening colonoscopy?

Design: Retrospective cohort study from November 2019 through May 2022.

Setting: Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Study Population: Thirty-three gastroenterologists performing average-risk screening colonoscopy, who were also asked to complete a survey to assess knowledge of new polypectomy surveillance guidelines.

Exposure: Recommendation for timing of surveillance colonoscopy after finding 1 -2 small (<1 cm) adenomas during first average-risk screening colonoscopy.

Outcome: Primary endpoints were adherence to recommendations from 2020 US Multi-Society Task Force Polypectomy Surveillance Guidelines, which extended the timing of repeat colonoscopy from 5-10 years to 7-10 years in low-risk adenomas (i.e., 1-2 small adenomas), high-risk adenomas, sessile serrated polyps, and hyperplastic polyps. Compliance was stratified based on whether gastroenterologists demonstrated knowledge of new guideline recommendations in their survey responses.

Frequency of compliance was calculated for 3 separate periods after publication of updated 2020 US Multi-Society on Colorectal Cancer Polypectomy Surveillance Guidelines: March-May 2021; November 2021-January 2022; and April 2022-May 2022. This was compared to a baseline period, November 2019 to January 2020, which was just prior to publication of updated guideline recommendations.

Data analysis: Compliance with guideline recommendations between the baseline and post-guideline periods were assessed with Fisher's Exact Test and improvement in compliance during the three intervals was assessed with chi-square tests. A mixed-effects logistic regression was used to identify factors associated with non-compliance.

Funding: None reported

Results: Among the 33 gastroenterologists, 58% (19/33) completed the survey with 53% (10/19) and 37% (7/19) correctly stating 7-10 years surveillance intervals for patients with 1 small adenoma or 2 small adenomas, respectively. Among 266 first-time screening colonoscopies performed in the baseline period and 532 during the combined post-guideline period, 43% of patients had low-risk adenomas, 18% had high-risk adenomas, and 19% had serrated polyps.

Compliance with guideline recommendations was 8.3% for low-risk adenomas, 88.3% for high-risk adenomas, and 63% for sessile serrated polyps. Compliance with guideline recommendations for low-risk adenomas (i.e., 1-2 small adenomas) increased to 18.6% when limited to gastroenterologists who knew that guidelines recommended 7-10 year intervals based on survey responses. The vast majority of patients with low-risk adenomas were advised to get surveillance colonoscopy in 5 years. There was no significant increase in compliance with guideline recommendations during the three separate periods of analysis in 2021-2022. Noncompliance was associated with finishing training >10 years ago (odds ratio [OR] 1.7; 95% confidence interval [CI]: 1.2-2.3) and endoscopists performing >800 colonoscopies per year (OR 2.0; 95% CI: 1.5-2.6).

COMMENTARY

Why Is This Important?

An old aphorism from Abraham Maslow states that "when all you have is a hammer, then you see every problem as a nail," meaning that we may develop an over-reliance on a familiar or favorite tool. As gastroenterologists, this can lead to an over-reliance on colonoscopy for colorectal cancer (CRC) prevention. However, our focus should be on performing high-quality colonoscopy instead of recommending that it be repeated too frequently! High-quality colonoscopy for CRC screening means that the cecum is intubated with photo confirmation, that the bowel preparation is adequate/good, and that the endoscopist has an adequate adenoma detection rate (ADR), which is facilitated by simply auditing and providing feedback to endoscopists about their ADR, along with doing a second-look in the right side of the colon, and training endoscopists to look for flat serrated polyps.

Unfortunately, as illustrated by this study, many gastroenterologists instruct patients to return for repeat colonoscopy sooner than recommended by guidelines even when they understand and know the guidelines.[1-2] Why does this happen? Although multiple explanations have been offered, many gastroenterologists worry about post-colonoscopy or "missed" CRC and believe that recommending repeat colonoscopy at earlier intervals will prevent this from happening.[1-2] If this is true, then it's an education gap that needs to be addressed. The vast majority of post-colonoscopy or missed CRC occur within 3 years of the index colonoscopy because adenomas were missed.[3] Thus, recommending that a patient with 1-2 small adenomas return in 5 years instead of 7-10 year intervals won't have much impact on reducing post-colonoscopy or missed CRC. In fact, multiple studies demonstrate that these patients with 1-2 small adenomas can wait 10 years or more between colonoscopies[4], and the United Kingdom and European Society of Gastrointestinal Endoscopy recommend intervals of $\geq$10 years when patients have 1-4 small adenomas on index colonoscopy.

Having said that, we also need to ensure that patients with large ($\geq$1 cm) or high-risk villous adenomas actually return for colonoscopy at 3-year intervals. Unfortunately, our piecemeal US health system may let many of these patients slip through the cracks. A recent study from same health care system looked at the Mass General Brigham Colonoscopy Cohort and found that 36% of patients with large or high-risk villous adenomas had not received any surveillance colonoscopy during median follow-up of almost 5 years and that only 21% of these patients had received colonoscopy at the appropriate 3-year interval.[5]

Ultimately, you can't fix a problem unless it's first identified. Therefore, I commend the investigators for identifying this issue, which is the first step in quality

improvement processes.

Key Study Findings

In 2020, a minority of gastroenterologists at one institution knew that the 2020 US Multi-Society Task Force on Colorectal Cancer Guidelines had extended colonoscopy surveillance intervals to 7-10 years if only 1-2 small adenomas were found on average-risk screening colonoscopy. Among gastroenterologists who knew the correct interval based on survey responses, their real-world compliance with this recommendation was only 18.6%.

Caution

This is a single institution study that assessed only 33 gastroenterologists from 2021-2022, and only 57% (19/33) completed the survey assessing their knowledge of 2020 colon polyp surveillance guidelines. Therefore, the frequency of noncompliance with guideline recommendations more broadly is unclear.

My Practice

In my Veterans Affairs (VA) Medical Center practice, I routinely recommend 10-year intervals when I find 1-2 diminutive (1-4 mm) adenomas on average-risk screening colonoscopy. If I find 1-2 small (5-9 mm) adenomas, then I'll usually recommend a 7-year interval. As part of our quality assessment program, a sample of colonoscopy reports are reviewed quarterly to determine the frequency of guideline-adherent recommendations for repeat colonoscopy along with other quality indicators (e.g., cecal intubation rate, adenoma detection rate, frequency of adequate bowel preparation rate, etc).

More importantly, since the VA is a closed health system, I'm fortunate to utilize an automated computer reminder system where primary care providers are alerted and required to send a referral for colon polyp surveillance colonoscopy at the appropriate interval. Therefore, as long as a patient with large or high-risk adenomas continues to see their primary care provider, these patients routinely get repeat colonoscopy at an appropriate 3-year interval. Since most of our patients are dependent on the VA system for their health care needs, this system works well and formal audits of these reminders are also part of our continuous quality improvement processes.

For Future Research

Larger studies about compliance with colon polyp surveillance guideline recommendations may be helpful to quantify the magnitude of this issue. However, qualitative mixed methods research to identify factors that minimize compliance and to develop effective educational or incentive programs to overcome those factors are needed. This would be more beneficial for our patients, especially if that work is followed by implementation research to improve compliance broadly.

Conflict of Interest

Dr. Schoenfeld reports no potential

conflicts of interest.

Note: The authors of the article published in Gastrointestinal Endoscopy are active on social media. Tag them to discuss their work and this EBGI summary!

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