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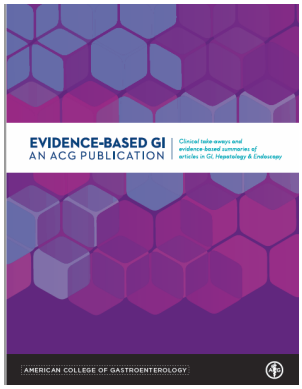

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EVIDENCE-BASED GI
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SEAVUE: A Sea of Change in Biologic Positioning for Crohn's Disease

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IBD

This summary reviews Sands BE, Irving PM, Hoops T, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. Lancet 2022;399(10342):2200-2211.

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STRUCTURED ABSTRACT

Question: Is biologic monotherapy with ustekinumab, an anti-interleukin-12/23 monoclonal antibody, superior to adalimumab, an anti-tumor necrosis factor (anti-TNF) monoclonal antibody, for clinical remission in biologic-naïve patients with moderately to severely active Crohn's disease?

Design: The SEAVUE study is a 56-week, randomized, double-blind, double dummy, parallel-group, active comparator, phase 3b trial, the first randomized controlled trial (RCT) to directly compare 2 biologic agents for the treatment of Crohn's disease (CD).

Setting: Patients were recruited from 121 practices in 18 countries.

Patients: Inclusion criteria included: (a) age ≥18 years; (b) confirmed diagnosis of Crohn's disease; (c) no previous biologic therapy; (d) non-response or intolerance to "conventional therapy" OR corticosteroid dependence; (e) moderately to severely active disease, Crohn's disease activity index (CDAI) of

220-450, for at least 3 months; and, (f) at least 1 ulcer of any size on ileocolonoscopy (Simple Endoscopy Score for Crohn's Disease [SES-CD] ≥3). Exclusion criteria included, but were not limited to: (a) pregnancy; (b) abscess in prior 3-8 weeks; (c) bowel resection in prior 6 months; (d) ongoing infection or malignancy. [CDAI includes assessment of frequency of liquid stools, use of anti-diarrheals, severity of abdominal discomfort, general well-being, presence of extra-intestinal symptoms, hematocrit, weight loss, presence/absence of abdominal mass, anal fissure, fistulae, or fever.]

Prior to study enrollment, eligible patients completed a 3 week wash out period for thiopurines, methotrexate and intravenous (IV) corticosteroids and a 4 week wash out period for other immunosuppression such as Janus kinase inhibitors and cyclosporine. If patients were using oral corticosteroids, they required that the dose be stable and ≤40mg of prednisone-equivalents or ≤9mg of budesonide equivalents for at least 3 weeks prior to randomization.

Intervention: Ustekinumab 6mg/kg IV dose at day zero and then 90mg subcutaneous (subq) every 8 weeks through week 56 vs adalimumab 160 mg subq on day 0, 80mg subq on week 2, and 40mg subq every 2 weeks without dose optimization due to double-blind, double-dummy protocol and without additional use of immunomodulators.

Outcomes: The primary outcome was clinical remission at week 52, defined as CDAI score <150. Major secondary endpoints included: (a) corticosteroid-free remission: CDAI <150 + no corticosteroids at week 52; (b) clinical response: CDAI decrease at least 100 points from baseline at week 52; (c) PRO-2 symptom remission: mean daily abdominal pain score ≤1 with mean daily stool frequency score ≤3 at week 52; (d) clinical remission at week 16; and, (e) endoscopic remission, SES-CD ≤3 (or SES-CD 0 for patients who were 3 at baseline) at week 52. If study patients had Crohn's disease related surgery, treatment discontinuation due to an adverse event or prohibited change in concomitant medications during the 52 week study period, then this was also considered failure to achieve primary outcome of clinical remission.

Data Analysis: The analysis was powered (80%) to detect superiority of ustekinumab over adalimumab by 15% for the primary outcome of clinical remission at week 52. Sample size was calculated using data from Phase 3/3b studies for each group, assuming response rates of 56% and 41%, respectively, for ustekinumab and adalimumab. Modified intention-to-treat analysis defined as patients who were randomized and received at least one dose of study medication was performed for the primary endpoint with Cochran-Mantel-Haenszel chi-square test. Continuous

variables were assessed with analysis of covariance. A hierarchical testing procedure was used for analysis, starting with the primary endpoint to control the inflation of type I error rate for multiple efficacy outcomes. If the primary endpoint did not demonstrate a significant difference, then all major secondary outcomes were considered not statistically significant and p values were nominal.

Funding: Janssen Biotech, the manufacturer of ustekinumab, had a role in study design and employed study statisticians.

Results: Between June 2018 and December 2019, 633 patients were screened. Of the 386 patients who enrolled, 191 were randomly assigned to the ustekinumab arm and 195 to the adalimumab arm. Baseline characteristics were similar in both arms with a mean age of 37; 51%-53% female; 86%-93% White; mean disease duration of 5 years; and, mean CDAI score was 300-301. Over 50% of patients in both arms had ileocolonic involvement, 9%-16% had upper GI involvement and 9%-10% patients had fistulae. At baseline, 22%-24% of patients were treated with systemic corticosteroids.

There was no significant difference in clinical remission at week 52 between ustekinumab and adalimumab: 65% vs 61%, respectively, and no significant differences in the treatment arms for the major secondary endpoints (**Figure 1**), including endoscopic remission (29% vs 31%, respectively). Time to treatment discontinuation was significantly shorter in the adalimumab arm (P=0.047), and treatment discontinuation prior to week 52 was numerically higher with adalimumab (24% vs 15%).

Adverse event data reported infection with adalimumab (41%) and ustekinumab (34%), and serious infection occurred with adalimumab (3%) and ustekinumab (2%). Only abdominal pain (13% vs 8%) and headaches (12% vs 7%) occurred more frequently in the ustekinumab arm than in the adalimumab. Notably, they included a category of “Crohn’s disease events” which occurred more frequently in the adalimumab arm (16% vs 12%).

COMMENTARY

Why Is This Important?

Prior to SEAVUE and VARSITY, which is also reviewed in this issue, the comparative effectiveness and safety of biologics for inflammatory bowel disease (IBD) were primarily derived from large retrospective claims-based data, smaller retrospective electronic medical record-based data, or network meta-analyses of published studies. Such studies are valuable in the absence of prospective RCTs and more reflective of patients in practice. However, they are also inherently biased, most notably by confounding by

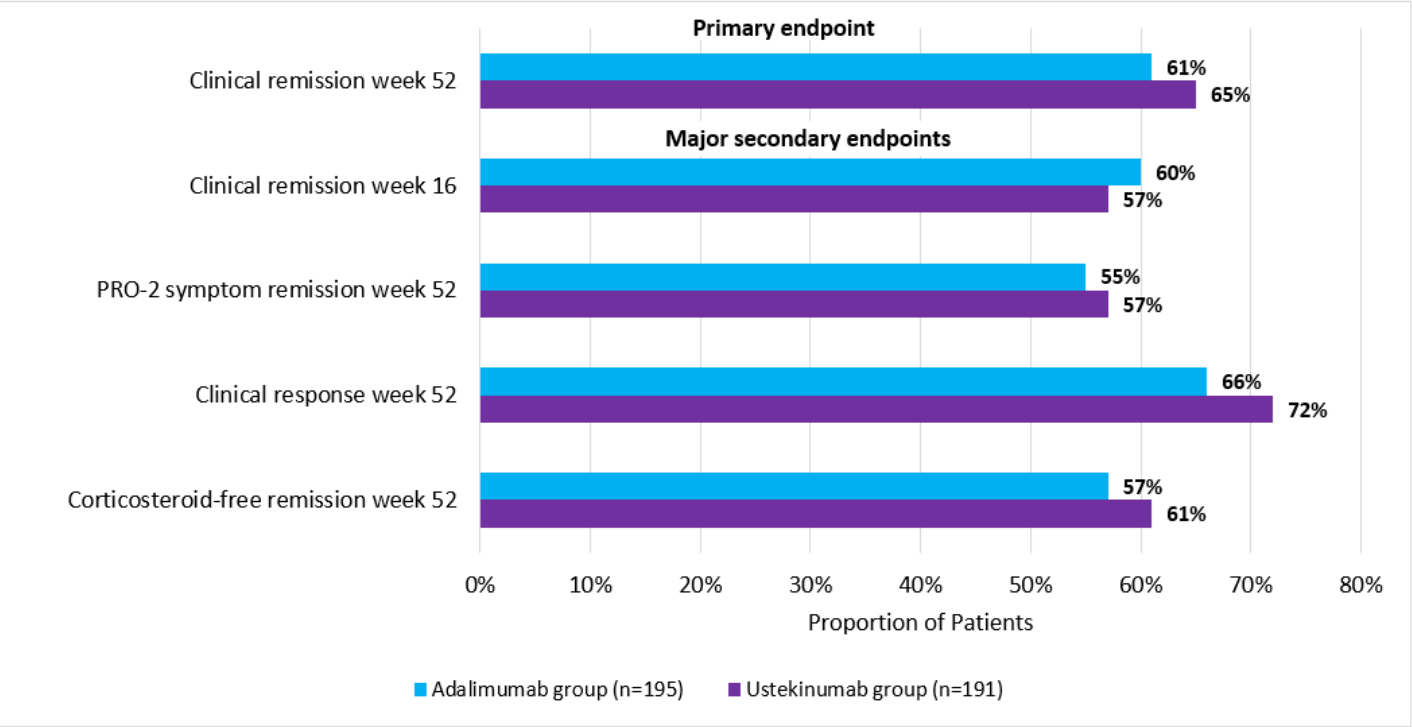

Figure 1. Primary and secondary study endpoints

indication which cannot be adequately adjusted for even by advanced statistical methodology.

SEAVUE is the first head-to-head RCT of biologic agents for the treatment of Crohn's disease, a seminal achievement. In the new therapeutic landscape of early biologic therapy and numerous treatment options for Crohn's disease, head-to-head trials more directly inform clinical care than the registration trials comparing a drug against placebo. When having a conversation with a patient about which medication to choose to treat their Crohn's disease in 2022, SEAVUE provides the most pertinent data to discuss. As with most rigorously -designed IBD clinical trials, many important details are limited to the appendix, although the manuscript itself is quite comprehensive. I encourage anyone treating patients with Crohn's disease to read the manuscript and appendices in their entirety.

Key Study Findings

In patients with moderate to severe Crohn's disease who have not been treated previously with a biologic agent, both ustekinumab and adalimumab have similar efficacy at achieving clinical remission at 52 weeks (65% vs 61%) without significant differences in clinical remission at 16 weeks, corticosteroid-free remission and improvement in patient-reported outcomes at 52 weeks.

Numerically, patients treated with ustekinumab had slightly lower rates of infections (34% vs 41%), serious infections (2% vs 3%), and Crohn's disease related adverse events (12% vs 16%) as well as longer time to treatment discontinuation.

Caution

Due to the double-blinded and double-dummy trial design, dose optimization of either biologic was not possible. Also, concurrent immunomodulator use (e.g., thiopurines) was not allowed. In real-world practice, dose optimization and immunomodulator use may positively influence clinical response. Since clinical remission rates are usually higher in biologically-naïve patients, these data may have limited generalizability to Crohn's disease patients who have tried and failed other biologic agents.

My Practice

The SEAVUE trial results had a pivotal impact on my clinical practice. Ustekinumab may confer an advantage related to treatment persistence and a numerically lower risk of infections, which is of great importance to patients, and I have been using these data in letters of medical necessity when requesting ustekinumab as a first-line biologic for the treatment of Crohn's disease. I do keep in mind that vedolizumab is also a great first line selective biologic agent for patients with colonic inflammation, whether it is Crohn's disease or ulcerative colitis.[1] While approximately 10% of the SEAVUE cohort did have fistulizing disease, I continue to prefer infliximab as first line therapy for penetrating Crohn's disease, as the ACCENT-II trial remains the largest dedicated trial of patients with fistulizing disease.[2] I also choose anti-TNF agents as first-line therapy if the patient has significant rheumatologic co-morbidities. For most other patients, especially for those with mild ileal Crohn's disease, anti-interleukin therapy with ustekinumab remains my preference for first-line therapy.

For Future Research

While SEAVUE and VARSITY helped us understand the most efficacious first line treatments, understanding the selection of the second biologic agent or identifying patients who benefit from combination biologic agents are other unmet needs. The ongoing VEGA trial, studying the combination of guselkumab with golimumab compared with guselkumab alone or golimumab alone, may shed some light on the role of combination biologics.[3] Despite the proliferation of treatments for IBD, durable response rates remain just above 50% and well under 90%, suggesting that we need to do better with selecting the right treatment for the patient. There is increasing work and investment in biomarker discovery for personalized therapy in IBD.

Conflicts of Interest

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

The authors of this article are active on social media. Tag them on Twitter to discuss this EBGI summary and other work:
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REFERENCES

1. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. ; VARSITY Study Group. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med 2019;381(13):1215-26.
2. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. N Engl J Med 2004;350(9):876-85.
3. Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol 2023;8(4):307-20.

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In Case You Missed It

Vedolizumab Is Superior to Adalimumab for Clinical Remission and Endoscopic Improvement of Ulcerative Colitis: The VARSITY RCT

IBD

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This summary reviews Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med 2019;381(13):1215-26.

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STRUCTURED ABSTRACT

Question: Is there a difference in efficacy and safety between vedolizumab, an anti-integrin monoclonal antibody, and adalimumab, an anti-tumor necrosis factor (anti-TNF) monoclonal antibody for moderate-severe ulcerative colitis (UC)?

Design: Phase 3b randomized, double-blind, double-dummy, 52-week trial (VARSITY trial), the first randomized controlled trial (RCT) to directly compare 2 biologic agents for the treatment of UC.

Setting: The trial included 245 centers across 34 countries from July 2015 through January 2019.

Patients: Included 769 adults (383 vedolizumab, 386 adalimumab) with moderate-to-severe UC, based on Mayo score $\geq$ 6 (scale 0-12) and endoscopic subscore of 2-3 (scale 0-3).

Interventions: Vedolizumab 300 mg intravenous (IV) at week 0, 2, 6 and then every 8 weeks vs adalimumab 160 mg subcutaneous (subq) on week 0, 80mg subq on week 2, and 40mg subq every 2 weeks without dose optimization due to double -blind, double-dummy protocol.

Outcomes: The primary outcome was clinical remission at week 52, defined as Mayo score 0-2 with no subscore >1. Mayo score includes rectal bleeding score (0 -3), stool frequency score (0-3), centrally-assessed endoscopy subscore (0-3), and Physician's Global Assessment (0-3). Additional outcomes included endoscopic improvement (Mayo endoscopic subscore of ≤1), corticosteroid-free remission at week 52, and adverse events (including infections), among others.

Data Analysis: Modified intention-to-treat analysis defined as patients who were randomized and received at least 1 dose of study medication was performed for the primary endpoint with Cochran-Mantel-Haenszel chi-square test. A hierarchical closed-testing procedure was used for analysis of secondary endpoints to control the inflation of type I error rate for multiple efficacy outcomes.

Funding: Takeda Pharmaceuticals, manufacturer of vedolizumab.

Results: Patient characteristics included male: 56-61%, mean age: 41; White: 88-90%; duration of UC: 6-7 years; prior anti-TNF treatment: 19-21%; concurrent use of corticosteroids only: 36%; concurrent immunomodulators only: 26%. At week 52, significantly more patients in the vedolizumab group achieved clinical remission (31.3% vs 22.5%, P=0.006) and endoscopic improvement (39.7% vs 27.7%, P<0.001) compared to adalimumab. Corticosteroid-free remission was numerically lower in the vedolizumab group vs the adalimumab group (12.6% vs 21.8%), which was not statistically significant (P>0.05). Infections occurred less frequently in the vedolizumab group (23.4 vs 34.6 events per 100 patient-years). Selected outcomes are presented in **Figure 1.**

COMMENTARY

Why Is This Important?

With a growing number of available biologic therapies for UC, treatment decisions have become increasingly complex. In addition to anti-TNF agents (e.g. infliximab and adalimumab), vedolizumab, a gut-selective, anti-integrin monoclonal antibody, and ustekinumab, an anti-interleukin-12/23 monoclonal antibody, are available, as are small molecules like ozanimod, a sphingosine-1 phosphate inhibitor, and upadacitinib, a selective JAK1 inhibitor. Without head-to-head comparisons, positioning was based primarily on network meta-analyses of placebo-controlled trials as well as real-world data.[1,2] VARSITY was groundbreaking as the first RCT to directly compare the efficacy and safety of 2 biologic agents for the treatment of moderate-to-severe ulcerative colitis, demonstrating generally greater efficacy and fewer infections for vedolizumab versus

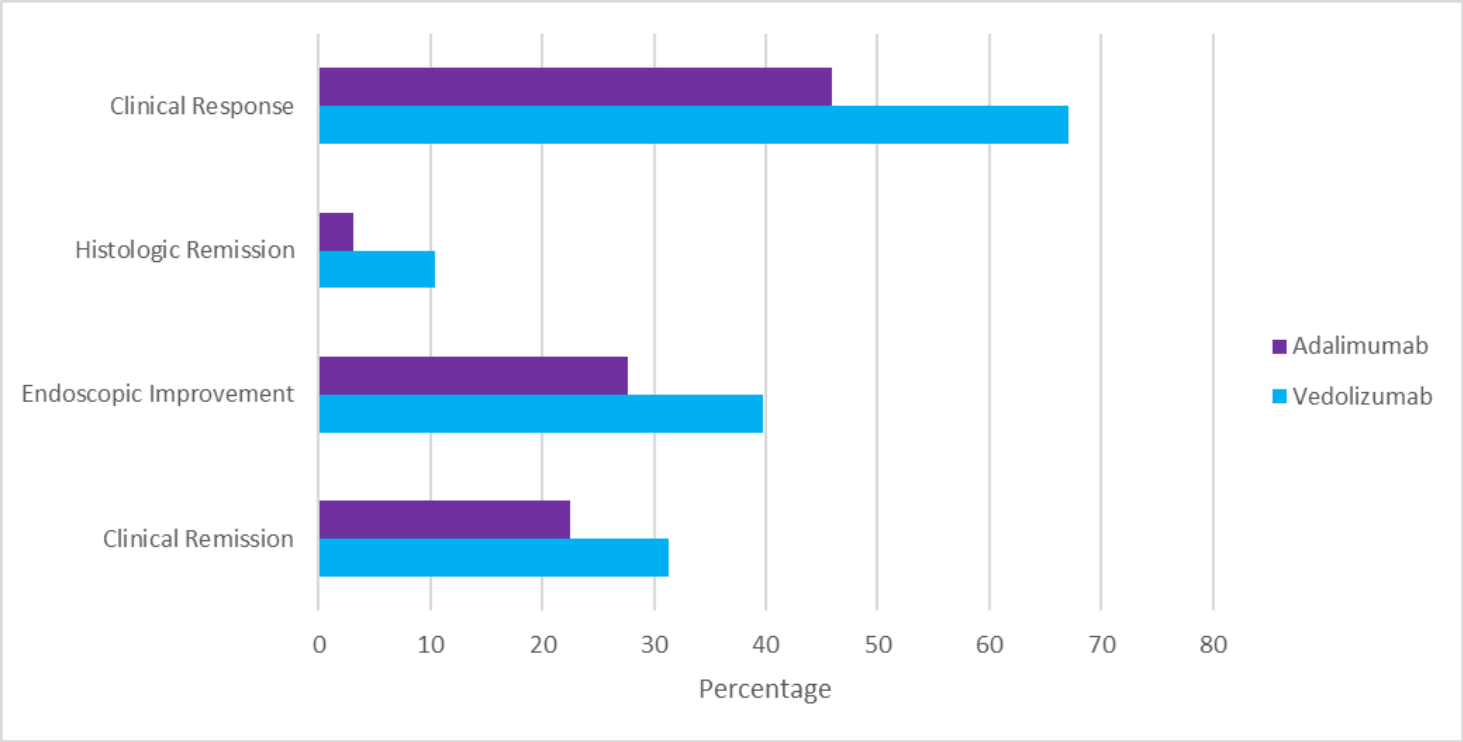

Figure 1. Selected outcomes of vedolizumab vs adalimumab for ulcerative colitis. Clinical response is at week 14 and clinical remission, endoscopic improvement, and histologic remission at week 52. vedolizumab statistically superior to adalimumab ($P< 0.05$) for all listed outcomes.

adalimumab.

Vedolizumab, which is only approved for treatment of UC and Crohn's disease, inhibits adhesion of gut-homing T lymphocytes to mucosal addressin-cell adhesion molecule 1, which should selectively down regulate gut inflammation while preserving systemic immune responses. Theoretically, this should make it particularly effective for gut inflammation while minimizing concurrent infections. This made it a particularly good comparator to the standard of care biologics, anti-TNF agents, when the VARSITY RCT was conducted.

Since VARSITY, a 2020 meta-analysis identified infliximab as the preferred first-line agent for ulcerative colitis, with ustekinumab and tofacitinib as preferred agents among those who were previously exposed to anti-TNF agents; vedolizumab had the lowest risk of infections.[3] Since the approval of upadacitinib, upadacitinib appears to be the most effective agent for the induction of clinical remission of ulcerative colitis, while vedolizumab still appears to be the safest according to a 2022 meta-analysis of clinical trials.[4] However, additional head-to-head comparisons are needed.

Key Study Findings

At week 52, significantly more patients in the vedolizumab group achieved clinical remission (31.3% vs 22.5%, P=0.006) and endoscopic improvement (39.7% vs 27.7%, P<0.001) compared to adalimumab, but not corticosteroid-free clinical remission, for patients in the vedolizumab group vs the adalimumab group. Fewer infections (23.4

vs 34.6 events per 100 patient-years) were also observed in the vedolizumab group.

Caution

It's unclear why corticosteroid-free remission was numerically higher with adalimumab while other outcomes demonstrated greater efficacy with vedolizumab over adalimumab. Due to the double-blinded and double-dummy trial design, dose optimization of either biologic was not possible. In real-world practice, dose optimization of either vedolizumab and adalimumab may positively influence clinical response. Therefore, these trial results may not reflect outcomes observed in clinical practice.

My Practice

Due to my own observations in clinical practice and the findings of VARSITY, I tend to favor vedolizumab over adalimumab as a first-line or later therapy for ulcerative colitis. However other considerations, such as patient preference regarding infusions and self-injections may factor into my decision. I may also consider adalimumab among individuals who had a robust response to infliximab, but developed anti-drug antibodies. These patients may benefit from a trial of another anti-TNF prior to switching out of class. The findings of VARSITY also do not affect my use of adalimumab for Crohn's disease, where it may be more effective.

For Future Research

Future research should prioritize head-to-head trials and real world studies directly comparing other biologics and small molecules for ulcerative colitis. Due to the challenges of comparing data from individual placebo-controlled trials, head-to-head comparisons are essential to guide biologic and small molecule positioning. Also, RCTs comparing dual biologic therapy in both UC and Crohn's disease are underway given the high rates of primary and secondary non-response among IBD patients.

Conflicts of Interest

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 Pharmaceuticals, 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 the to discuss their work and this EBGI summary.

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REFERENCES

1. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47(2):162-175.
2. Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2018; 47(4):454-465.
3. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: An updated network meta-analysis. Clin Gastroenterol Hepatol 2020;18(10):2179-2191.e6.
4. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: A systematic review and network meta-analysis. Lancet Gastroenterol Hepatol 2022;7 (2):161-170.

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Vibrating Capsules for Chronic Constipation: The New Non-Pharmacologic Approach

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This summary reviews Rao S, Quigley EMM, Chey WD, et al. Randomized Placebo-Controlled Phase 3 Trial of Vibrating Capsule for Chronic Constipation. Gastroenterology 2023; In Press. doi.org/10/1053/j.gastro.2023.02.013

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STRUCTURED ABSTRACT

Question: Is a vibrating capsule superior to placebo in chronic idiopathic constipation for symptoms based on FDA-defined responder endpoints?

Design: Multicenter, 8-week, double-blind, placebo-controlled randomized controlled trial (RCT).

Setting: Ninety-five United States centers, conducted from April 2019 through July 2021

Patients: Included 312 outpatients meeting Rome III criteria for chronic idiopathic constipation (CIC).

Interventions/Exposure: Vibrating capsule swallowed 5 evenings per week (skipped Wednesday and Saturday) vs sham dissolvable placebo capsule. Each capsule was programmed to begin vibrating at noon the following day, with 2 separate vibration cycles over 2 days. Each vibration cycle consisted of 3 seconds of oscillation followed by 16 seconds of rest (3 stimulations per minute) for 2 hours.

Outcome: Co-primary endpoints were the proportion of patients with: (a) increase of $\geq$ 1 weekly complete spontaneous bowel movements (CSBM) from baseline for

≥6 of 8 weeks (FDA-defined endpoint); and, (b) increase of ≥2 weekly CSBM from baseline for ≥6 of 8 weeks. Key secondary endpoints included changes in stool consistency, based on Bristol stool scale, straining, and bloating. A spontaneous bowel movement (SBM) was defined as a spontaneous bowel movement that occurred without using rescue medication in the preceding 48 hours and without use of digital maneuvers, and a CSBM was a SBM with a sense of complete evacuation.

Data Analysis: Intention-to-treat analyses were performed. Co-primary endpoints were assessed with Chi-square test and secondary endpoints which were continuous variables were assessed with analysis of covariance. A hierarchical approach was used for the co-primary and secondary endpoints to control for Type I errors due to multiple endpoints.

Funding: Vibrant Ltd, the manufacturer of the vibrating capsule Vibrant.

Results: Overall, 312 CIC patients were randomized (mean age: 46-47 years old; 85%-88% female; 40%-47% White; baseline symptoms: 0.4 CSBMs/week; 1.6-1.7 SBMs/week, mean Bristol stool scale=2.1). Patients using the vibrating capsule were more likely than placebo-treated patients to achieve both co-primary endpoints of increase of ≥1 weekly CSBM for ≥ 6 of 8 weeks (39.3% vs 22.1%, respectively, $P< 0.0001$) and increase of ≥2 weekly CSBM for ≥6 of 8 weeks (22.7% vs 11.4%, respectively, $P< 0.0008$). Significant improvements were also noted for adjusted mean change in Bristol stool scale score (0.92 vs 0.44, respectively, $P< 0.001$) and straining score, but not for bloating or change in mean SBMs per week. Adverse event data reported that 11% of vibrating capsule-treated patients reported vibrating sensation in abdomen, but this did not lead to study discontinuation. Diarrhea as an adverse event was uncommon in both groups (1.2% vs 0%, respectively).

COMMENTARY

Why Is This Important?

Although our therapeutic armamentarium for CIC has expanded in the past decade, many CIC patients fail to achieve adequate relief and seek out new treatments.[1] Vibrating capsules as a means to stimulate colonic motility while minimizing diarrhea is an intriguing idea. This trial reports the Phase 3 data which led to FDA-approval for this first-in-class vibrating capsule system, and this is a welcome addition to our treatment options.

This is a very well-designed trial, and the investigators should be congratulated for devising a trial with a rigorous definition of CSBM and utilizing a dissolvable sham capsule for use in the placebo group. Although the system to activate the capsules require an "Activation Pod" and a downloadable

app in addition to the capsules, more than 90% of study patients found the system easy to use.

Key Study Findings

Patients using the vibrating capsule were more likely than placebo-treated patients to achieve both co-primary endpoints of increase of ≥ 1 weekly CSBM for ≥ 6 of 8 weeks 39.3% vs 22.1%, respectively, $P< 0.0001$) and increase of ≥ 2 weekly CSBM for ≥ 6 of 8 weeks (22.7% vs 11.4%, respectively, $P< 0.0008$).

Caution

The study duration is relatively short (8 weeks) for a chronic condition. Appropriate blinding to treatment group could have been impacted in the 11% of vibrating capsule-treated patients who noted a vibrating sensation in their abdomen. However, exclusion of these patients did not change reported outcomes. The current trial only examined 1 activation mode or vibration cycle starting at noon on the day following administration, although a preliminary phase of the trial did assess efficacy of activating vibrations at 6 AM on the morning following ingestion.

My Practice

I have many CIC patients who are dissatisfied with currently available therapies, and many of these patients will be intrigued by a non-pharmacologic option that may trigger colonic motility. Since these vibrating capsules just became available, I have not prescribed them yet. I do plan to use it soon in CIC patients who have failed over-the-counter and prescription agents for CIC. For these difficult-to-treat patients, it is important to rule out pelvic floor dysfunction, which is best treated with biofeedback and not an appropriate option for IBS-C patients who have clinically important abdominal discomfort. Although combination therapy was not studied in this trial, I may combine this with other CIC treatments in some patients. I am uncertain about insurance coverage for this, although the manufacturer currently advertises a self-pay option for $89/month.

For Future Research

Longer clinical trials and real-world data is needed to define efficacy in this chronic condition. Since the vibrating capsule is programmable, further research may identify optimal vibration cycles, which might vary by patient. Identifying the sub-group of CIC patients most likely to benefit from this treatment will also be beneficial.

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Ardelyx Pharmaceuticals, and serving as an advisory board member for Salix Pharmaceuticals.

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

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REFERENCES

1. Oh SJ, Fuller G, Patel D, et al. Chronic Constipation in the US: Results from a Population-Based Survey Assessing Healthcare Seeking and Use of Pharmacotherapy. Am J Gastroenterol 2020; 115: 895-905.

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HEPATOLOGY

In Case You Missed It

Can We Prevent Hepatic Decompensation? Most Likely, With Nonselective Beta Blockers

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This summary reviews Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomized, double-blind, placebo-controlled, multicenter trial. Lancet. 2019 Apr 20;393(10181):1597-1608. doi: 10.1016/S0140-6736(18)31875-0.

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STRUCTURED ABSTRACT

Question: Can nonselective beta blockers decrease the risk of decompensation or death in compensated cirrhosis with clinically significant portal hypertension (defined as hepatic venous pressure gradient [HVPG] ≥10 mm Hg)?

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

Setting: Eight hospitals in Spain from January 2010 through July 2013. Patients were followed until June 2015.

Patients: Included 201 patients with compensated cirrhosis and clinically significant portal hypertension without high-risk varices (i.e., no esophageal varices or small esophageal varices without red spots).

Interventions/Exposure: During measurement of HVPG, study patients were

given intravenous (IV) propranolol with active measurement of HVPG. If HVPG-decreased ≥10%, the patients were randomly assigned to propranolol (40mg twice a day up to 160mg twice a day) vs placebo. If HVPG did not decrease ≥ 10%, the patients were labelled non-responders and were assigned to carvedilol (6.25 mg/day up to 25 mg/day) vs placebo. Doses were titrated to tolerance—ideally a heart rate of 55 beats per min and systolic blood pressure greater than 90 mm Hg. The median length of follow-up was 37 months. Surveillance upper endoscopy was performed annually. If patients developed high-risk varices, prophylactic banding was performed and the study drug continued. No preventive therapy for ascites or encephalopathy was allowed.

Outcome: The primary endpoint was incidence of cirrhosis decompensation (development of ascites, gastrointestinal (GI) bleeding related to portal hypertension, or overt encephalopathy) or death. Secondary outcomes included development of each decompensating event separately, spontaneous bacterial peritonitis, development of high-risk varices, and liver cancer development.

Data Analysis: Intention-to-treat analysis. Fisher's exact test was used to compare categorical variables and student's t test (for paired data within each group) was used for continuous variables. The primary and secondary outcomes were assessed as time-to-event variables. Data were censored at time of death, liver transplantation, last visit, or end of follow-up period, whichever came earliest. Patients lost to follow-up, who withdrew consent, or who started direct antiviral agents for hepatitis C virus (HCV) were censored after the last documented visit.

Funding: Spanish Ministries of Health and Economy.

Results: From January 2010 through July 2013, 631 patients were screened, 320 were excluded, and 110 declined to participate/withdrew, leaving 201 patients to be randomized. Study patients' mean age: 59-60; male: 59-63%; Child's Pugh A: 80%; etiology of cirrhosis: HCV (54-58%), alcohol (14-19%), HCV plus alcohol (8-9%), and nonalcoholic steatohepatitis (NASH; 5-8%). One hundred and thirty-five patients had HVPG-decrease ≥10% in response to IV propranolol during HVPG measurement and were randomized to propranolol (n=67) or placebo (n=67). An additional 66 patients were non-responders to IV propranolol and were randomized to carvedilol (n=33) or placebo (n=33).

Patients receiving nonselective beta blockers had less decompensation or death: 27% vs 16%; hazard ratio (HR) 0.51, (95% confidence interval [CI] 0.26–0.97, *P*=0.041) (**Figure 1**). Specifically, the incidence of ascites was reduced in those taking beta blockers compared to placebo: 20% vs 9%; HR = 0.42, (95% CI 0.19–

0.92, *P*=0·03). Additionally, the benefit of nonselective beta blockers for ascites was slightly higher in the carvedilol group compared to those receiving propranolol. Similar results were also found for death from any case. However, these were not statistically significant. GI bleeding due to portal hypertension was low in groups treated with beta blockers and placebo: 4% vs 3%, respectively. Development of high-risk esophageal varices was numerically less common in the beta blocker group during study follow-up: 16% vs 25%, respectively, although approximately 70% of these patients received prophylactic esophageal band ligation of varices which would reduce the risk of GI bleeding.

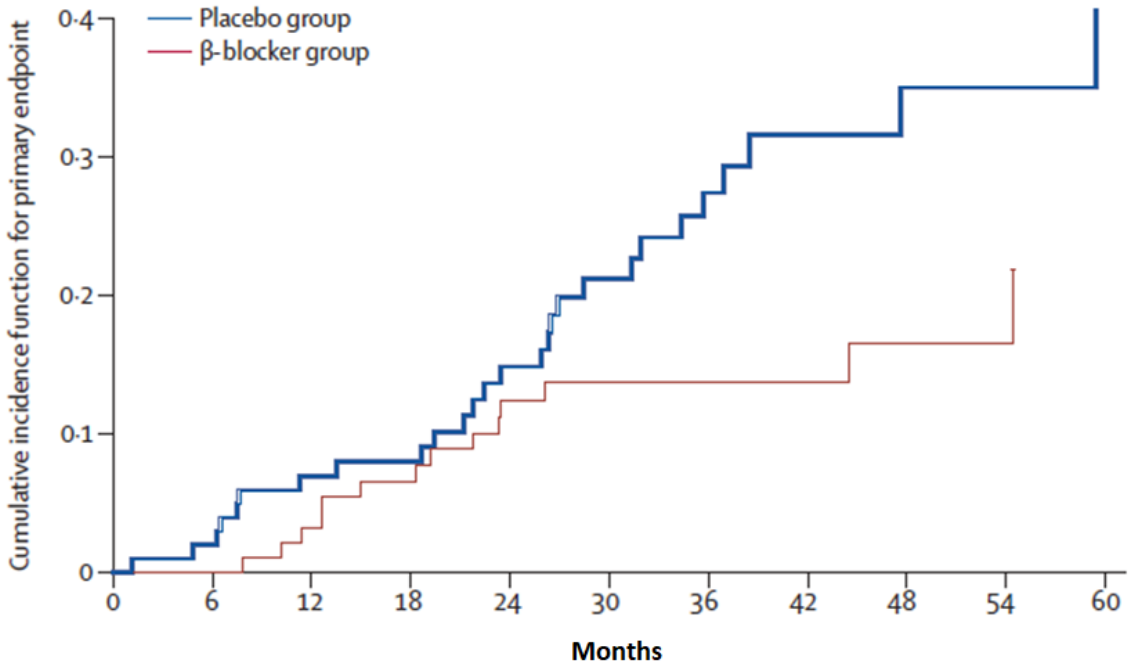

Figure 1. Time to hepatic decompensation or death.

COMMENTARY

Why Is This Important?

Decompensated cirrhosis, as defined by ascites, variceal bleeding, and hepatic encephalopathy is associated with high mortality and poor prognosis. Clinically significant portal hypertension (HVPG ≥10 mm Hg) has been found to be the main determinant of decompensation. Beta blockers decrease portal venous inflow thereby reducing portal pressures, especially in those who have clinically significant portal hypertension. Methods to reduce this gradient are needed. Nonselective beta blockers decrease portal flow through a decrease in cardiac output and through splanchnic vasoconstriction. It is common practice to start nonselective beta blockers in those with compensated cirrhosis and varices that are at high risk of bleeding (medium/large, small varices with red wale signs) as primary prophylaxis.[1] Ascites prevention is also important as this event is associated with transplant-free mortality rates ranging from 15%-20% in 1 year to nearly 50%-60% in 5 years.[2,3]

Key Study Findings

Patients receiving nonselective beta blockers had less decompensation or death: 27% vs 16%; HR 0.51, 95% CI 0.26–0.97, *P*=0.041. Specifically, the incidence of ascites was reduced in those taking beta blockers compared to placebo: 20% vs 9%; HR 0.42, 95% CI 0.19–0.92, *P*=0.03.

Caution

Patients with compensated cirrhosis should be screened for clinically significant portal hypertension. However, the methods used in this paper are unrealistic in real practice. Not every patient with cirrhosis has their HVPG measured. Certainly, even if they have clinically significant portal hypertension, IV propranolol is not routinely used to assess response. The applicability of these results to real world practice is difficult. However, the role of beta blockers is still important, especially since there are now non-invasive methods of assessing this[4] (see *My Practice* below). Additionally, the majority of patients studied had HCV since this study was done before routine use of direct acting anti-viral therapies. It is unclear if this will translate to other causes of liver disease, importantly alcohol and nonalcoholic/metabolic-associated fatty liver disease. Specifically, based on the new Baveno VII Consensus guidelines released in 2022, a small percentage of patients with NASH-related cirrhosis may have signs of clinically significant portal hypertension with HVPG values < 10mmHg.[4]

My Practice

In those patients with compensated cirrhosis who have had formal HVPG testing at diagnosis, I routinely administer nonselective beta blockers. My preference is carvedilol as it is more effective in reducing HVPG (as it not only decreases portal flow, but has vasodilatory effects), preventing decompensation, and improved tolerance compared to other nonselective beta blockers.[4] However, I am often limited by blood pressure in these patients. Propranolol or nadolol are alternatives as they affect blood pressure less. Each is titrated to goal heart rate 55-60 beats/minute as tolerated.

For those without direct HVPG measurements, I use the Baveno guidelines to determine who should initiate nonselective beta blockers.[4] Liver stiffness measurements (LSM) by transient elastography can help differentiate the presence of clinically significant portal hypertension in patients with compensated cirrhosis. The previous Baveno VI criteria (and current AASLD guidelines[1]) use LSM > 20kPa and platelets count $<150x10^9$/L to diagnose clinically significant portal hypertension and determine the need for variceal screening. The updated Baveno VII guidelines are more nuanced:

- LSM $\leq$15 kpa and platelet count $\geq 150x10^9$/L rules out clinically significant portal hypertension with a sensitivity and negative predictive value of >90%.
- In those with viral or alcohol related cirrhosis and non-obese NASH related cirrhosis, LSM $\geq$25 rules in

clinically significant portal hypertension. I routinely start these patients on non-selective beta blockers.

- For those that cannot tolerate non-selective beta blockers (low baseline heart rate, low blood pressures, or other reasons), I determine the need for endoscopy if the LSM $\geq$ 20 or platelet count $\leq 150 \times 10^9$/L. However, using this strategy requires annual LSM and platelet counts to assess changes and endoscopy needs overtime.

Of note, the above only applies to those with compensated cirrhosis. I do not routinely prescribe nonselective beta blockers in those with decompensated cirrhosis and perform variceal screening on every patient with any form of decompensation.

For Future Research

While transient elastography is a fantastic tool to screen for fibrosis and clinically significant portal hypertension, in some patients it is inaccurate because of body habitus and/or the interquartile range is high. In these situations, magnetic resonance elastography is used. However, we do not yet have magnetic resonance elastography measurements to define clinically significant portal hypertension and administration of nonselective beta blockers.

Conflict of Interest

Dr. Paul has no relevant conflicts of interest.

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

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References

1. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2017; 65 (1):310-35.
2. Planas R, Montoliu S, Ballesté B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006 ;4(11):1385-94.
3. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44 (1):217-31.
4. De Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII–Renewing consensus in portal hypertension. J Hepatol 2022; 76 (4):959–74.