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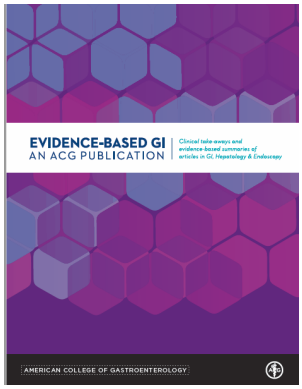

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Risankizumab, an Interleukin-23 Inhibitor, for Moderate-Severe Crohn's Disease: Advancing Care Beyond Anti-TNF Therapy

Bharati Kochar, MD, MS
Associate Editor

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

IBD

This summary reviews D'Haens G, Panaccione R, Baert F, et al. Risankizumab as Induction Therapy for Crohn's Disease: Results from the Phase 3 ADVANCE and MOTIVATE Induction Trials. Lancet 2022;399(10340):2015-30.

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

STRUCTURED ABSTRACT

Question: Is Risankizumab (Skyrizi, AbbVie Pharmaceuticals, San Francisco, CA), an interleukin (IL)-23 inhibitor, efficacious and safe for induction of remission in patients with moderate to severe Crohn's disease?

Design: Two multi-center, randomized, double-blind, placebo-controlled trials, ADVANCE and MOTIVATE, were conducted. The ADVANCE trial included patients who did not tolerate or did not have an adequate response to ≥1 approved conventional therapies (e.g., corticosteroids, 5-ASA products) or biologics and the MOTIVATE trial includes only patients with prior biologic failure. Patients exposed to ustekinumab (Stelara; Janssen Pharmaceuticals, Beerse, Belgium), a dual IL-12 and IL-23 inhibitor, were capped at 20% in both trials. The trial was conducted with a 35-day screening period with 12-week induction period. They required an ileocolonoscopy to determine eligibility during the screening period and then at week 12. Patients who had a clinical response went on to enroll in the FORTIFY maintenance trial, which is

summarized by Dalal and Allegretti in this issue of EBGI.

For patients receiving risankizumab who did not achieve clinical response at week 12, an additional exploratory 12-week induction period 2 was conducted with patients randomized 1:1:1 to Risankizumab 1200 mg intravenous (IV), Risankizumab 360 mg subq, or Risankizumab 180 mg subq at week 0, week 4, and week 8. Placebo-treated patients who did not achieve clinical response at week 12 during the first induction period were enrolled in induction period 2 and received Risankizumab 1200 mg IV at week 0, 4, and 8. However, these patients were not included in the primary analysis.

Setting: Patients were recruited from 297 academic centers, clinical research units and private practices in 44 countries between 2017 –2020.

Patients: Eligible patients were 16-80 years of age with a confirmed diagnosis of Crohn's disease for at least 3 months, with moderately to severely active disease defined by a Crohn's disease activity index (CDAI) of 220-450, average daily stool frequency of ≥4 and abdominal pain score ≥2. Initially only enrolled patients with endoscopic evidence of mucosal inflammation (simple endoscopic score for Crohn's disease [SES-CD] ≥6 or ≥4 for isolated ileal disease), but later amended to include patients with lower SES-CD scores. In the appendix, notable exclusion criteria are patients with HIV, active Clostridium difficile infection, hepatitis B or C, history of GI tract dysplasia, lymphoproliferative disease, current or previous malignancy, "severe, progressive or uncontrolled renal, hepatic, haematological, endocrine, disorder or symptoms thereof." Patients with ostomies, pouches, short bowel syndrome or surgical resections in the 3 months prior to enrollment, and women who were pregnant or lactating were also excluded.

Intervention: Patients were randomized to 1 of 3 arms: (1) Risankizumab 600 mg IV at week 0, 4 and 8; (2) Risankizumab 1200mg IV at week 0, 4 and 8; (3) placebo at week 0, 4 and 8. In the ADVANCE trial, patients were randomized 2:2:1, while patients were randomized 1:1:1 in the MOTIVATE trial.

Outcome: Both trials had the same 2 primary endpoints. The first is clinical remission at week 12 defined as (a) CDAI <150 in the United States or (b) patient reported average daily stool frequency ≤2.8 and abdominal pain score ≤1 in other countries. The second primary endpoint is endoscopic response at week 12. a >50% decrease from baseline based on central readers. While there were a number of key secondary endpoints, the one that is most clinically pertinent is safety. Safety outcomes are self-reported in this trial. Only cardiovascular events and anaphylactic events were adjudicated.

Data Analysis: Each trial was analyzed independently with an intention-to-treat (all patients who received at least one dose of the study drug) analysis. The sample size provided >87% power to detect significant differences in the co-primary endpoint.

Funding: AbbVie Pharmaceuticals, manufacturer of risankizumab.

Results: The ADVANCE Trial enrolled 931 patients, with 850 patients included in the primary efficacy endpoint. In this trial, 45% of patients treated with risankizumab 600 mg IV, 42% of patients treated with risankizumab 1200 mg IV, and 25% treated with placebo achieved clinical remission defined by CDAI. Similarly, using patient reported outcomes, 43% of patients treated with risankizumab 600 mg IV, 41% treated with risankizumab 1200mg IV, and 19% treated with placebo achieved clinical remission. **(Figure 1)**

The MOTIVATE Trial enrolled 618 patients, with 569 included in the primary efficacy analysis. Similar results were achieved in this trial with 42% of those treated with risankizumab 600 mg IV, 40% treated with risakizumab 1200 mg IV, and 21% treated with placebo achieved clinical remission by CDAI. Similarly, 35% of patients with Crohn's disease in the risankizumab 600 mg IV arm, 40% in the risankizumab 1200 mg IV arm, and 19% in the placebo arm achieved clinical remission by the stool frequency and abdominal pain scores. Also, in this trial there were significantly higher rates of week 12 endoscopic response with 29% of patients in the risankizumab 600mg IV, 34% in the risankizumab 1200 mg IV, and 23% in the placebo arms achieving this respectively. **(Figure 2)**

In both trials, mean disease duration for patients was just above 8 years and the drug arms and placebo arms were balanced across demographics factors. Additionally, in both studies, discontinuation was higher in the placebo arm than in the intervention arms.

Risankizumab was shown to be a minimally immunogenic medication with 1% of patients who were treated with riankizumab in the ADVANCE trial and 2% of patients treated with risankizumab in the MOTIVATE trial noted to have anti-drug antibodies to risankizumab. Overall adverse events were similar among all treatment groups. The most frequently reported adverse events (≥5% of patients in risankizumab arms) was headache and nasopharyngitis while most common adverse event in the placebo arm was worsening IBD. Across both trials, there were 3 deaths with 2 deaths in the placebo arm and 1 death unrelated to medication in the study drug arm. In ADVANCE, there were 5 serious infections in 5 separate patients while in MOTIVATE there were 3 serious infections in 3 separate patients.

None of the serious adverse events resulted in trial discontinuation.

NOTES

Although these 2 trials used a classic double-blind, placebo-controlled, randomized study design with modified intention-to-treat analysis, study methodology and results are too detailed to summarize comprehensively. Readers are encouraged to review the full study publication.

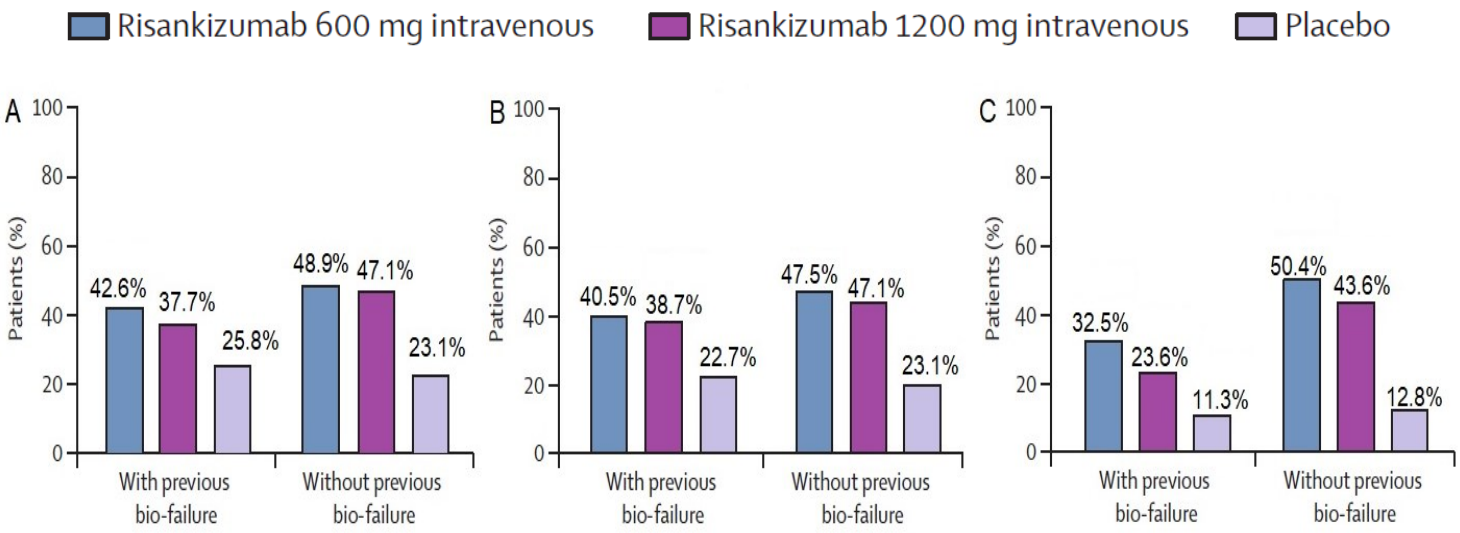

Figure 1. Coprimary endpoints at week 12 of ADVANCE
(**a**) CDAI clinical remission (**b***)* stool frequency and abdominal pain score clinical remission (**c**) endoscopic response.

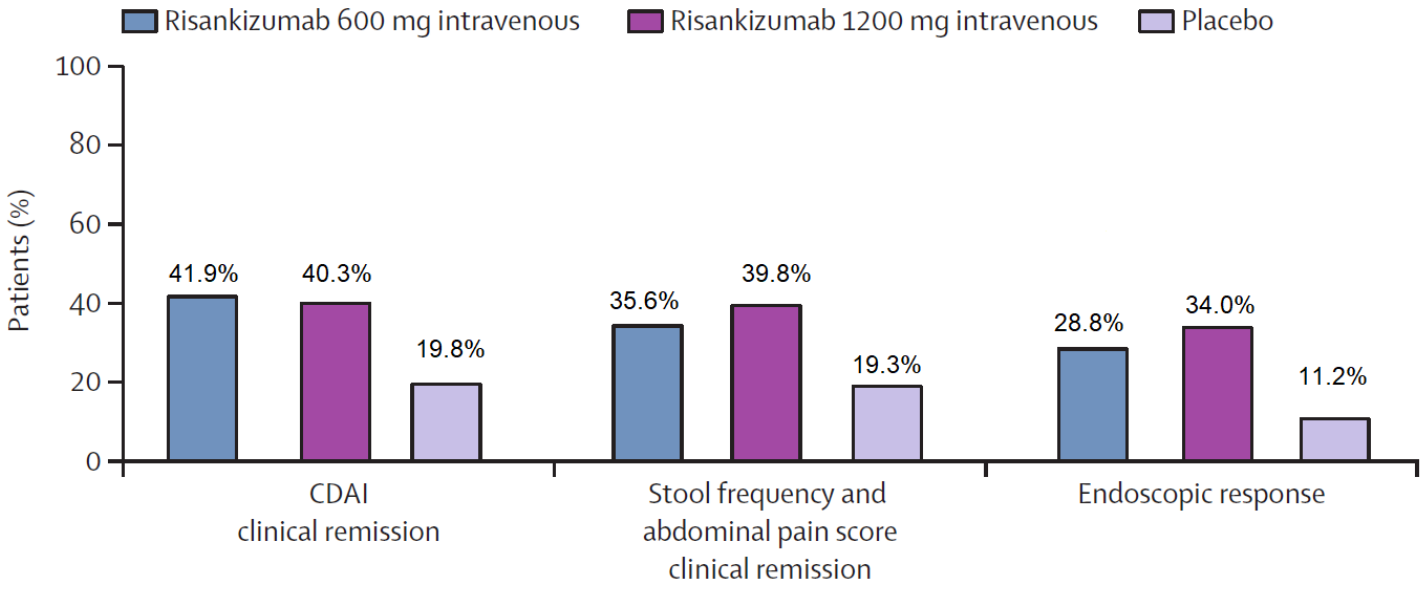

Figure 2. Coprimary endpoints at week 12 of MOTIVATE

COMMENTARY

Why Is This Important?

In 2018, ustekinumab, a dual IL-12 and IL-23 inhibitor, was the first anti-interleukin agent approved for the treatment of Crohn's disease.[1] The rationale is that IL-23 modulates intestinal inflammation through cytokines and elevated levels of IL-23 are present in the intestinal mucosa of Crohn's disease patients and there is a strong correlation between polymorphisms of the IL-23 or IL-23 receptor gene and inflammatory bowel disease (IBD). Therefore, agents that modulate IL-23 activity may impact Crohn's disease inflammation.

Approval of ustekinumab for use in Crohn's disease changed the therapeutic landscape for Crohn's patients who required a less systemic mechanism of immunosuppression than anti-tumor necrosis factor (TNF) therapy, but a more systemic mechanism than anti-integrin therapy with vedolizumab. Ustekinumab's mechanism of action is to target the p40 subunit which is shared by both IL-12 and 23. However, it is activation of IL-23 specifically that triggers differentiation of naïve T cells to produce a number of pro-inflammatory cytokines and suppress regulatory T cell activity. Therefore, risankizumab which targets the p19 subunit unique to IL-23 may confer added value to the expanding therapeutic armamentarium of anti-interleukin agents approved for Crohn's disease.

As the experience with risankizumab as the treatment for Crohn's disease is still in its nascency, it is reasonable to turn to the dermatology literature for longitudinal data on this medication. In fact, there has been a robust head-to-head trial of risankizumab and ustekinumab for the treatment of moderate to severe plaque psoriasis.[2] For the treatment of plaque psoriasis, risankizumab was more likely to result in reduction of the psoriasis disease activity score than ustekinumab by week 12 (90% vs 40%). Perhaps even more notable, 45% of psoriasis patients in the risankizumab arm had 100% reduction in the psoarisis disease activity index compared with 18% in the ustekinumab arm. These results, albeit using doses different than those approved to treat Crohn's disease, suggest that risankizumab may have a faster onset of action and could be more effective for the treatment of inflammatory conditions. This trial was conducted for 48 weeks and in all treatment arms, the most frequent adverse event was nasopharyngitis.

Key Study Findings

In the ADVANCE trial, 45% of patients treated with risankizumab 600 mg IV, 42% of patients treated with risankizumab 1200 mg IV, and 25% treated with placebo achieved clinical remission defined by CDAI. Similar results were achieved in the MOTIVATE trial with 42% of those treated with risankizumab 600 mg IV, 40% treated with risakizumab 1200 mg IV, and 21%

treated with placebo achieved clinical remission by CDAI.

Since the 1200 mg induction dosing did not yield better efficacy than the 600 mg dosing, prescribing information recommends 600 mg IV at week 0, 4, and 8 for induction.

Caution

Although adverse events were similar among all treatment groups, prescribing information for risankizumab notes that drug-induced liver injury has been reported and liver enzymes and bilirubin should be checked prior to administration as well as evaluating for tuberculosis.

My Practice

My initial risankizumab-treated patients in Summer 2022, shortly after formal FDA approval, were those who had failed a number of other biologic agents in 2-3 different classes, including ustekinumab, and were not good candidates for off-label treatment with small molecule agents. Since our state legislature finally voted to abolish step therapy laws, I became bolder in my requests for approval of risankizumab as a first line agent. Increasingly, guided by the SEAVUE trial and my own clinical experience, my practice (when allowed by payors) is to use anti-interleukin therapy as a first line agent for the treatment of Crohn's disease in patients who do not have perianal fistulizing Crohn's disease or a profound burden of extra intestinal manifestations. Now, instead of ustekinumab as that first line agent, I am requesting risankizumab. I counsel patients that the anti-interleukin class of medications may be slower in onset than the anti-TNF class of medications. However, I do have a number of patients reporting at least some improvement even after 1-2 infusions of risankizumab, suggesting that the increased potency and rapidity of action seen in psoriasis treatment compared with ustekinumab may be translatable to Crohn's disease as well.

Future Research

As the number of anti-interleukin therapies for the treatment of Crohn's disease increase[3], understanding comparative efficacy, safety and positioning will become increasingly important. Research about predictors of response to risankizumab are needed to identify patients that are optimal candidates for treatment. Additional data is also needed to clarify efficacy for small intestinal inflammation, strictures, and peri-anal disease as well as obtaining safety data in pregnant women.

Abbvie, the sponsor of the ADVANCE, MOTIVATE and FORTIFY trial, recently completed recruiting for SEQUENCE, a head-to-head trial of risankizumab and ustekinumab to assess change in Crohn's disease activity index. However, it is well established that patients recruited for clinical trials in IBD are not reflective of patients we treat in routine practice[4,5], therefore, understanding the real-world

applications for these novel agents will be very important as well.

Conflicts of Interest

Dr. Kochar reports servingas 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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Subcutaneous Risankizumab Is Effective and Safe for the Maintenance of Moderate-to-Severe Crohn's Disease

Dr Jessica Allegretti
Associate Editor

Dr Rahul S. Dalal
Guest Contributor

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IBD

This summary reviews Ferrante M, Panaccione R, Baert F,et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet 2022;399(10340):2031-2046.

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

STRUCTURED ABSTRACT

Question: Is subcutaneous Risankizumab (Skyrizi; AbbVie Pharmaceuticals, San Francisco, CA), a selective anti-interleukin (IL)-23 antibody, effective and safe for the maintenance of clinical remission of moderate-to-severe Crohn's disease?

Design: Phase 3 randomized, double-blind, placebo-controlled, 52-week maintenance withdrawal trial (FORTIFY).

Setting: The study was conducted in 273 clinical centers in 44 countries across North America, South America, Africa, Europe, Australia, and the Asia-Pacific regions.

Patients: In total, 542 patients with moderate-to-severe Crohn's disease and initial clinical response (defined as ≥ 30% reduction in mean stool frequency and mean

daily abdominal pain score in 7 days prior to assessment) or clinical remission (see definition in **Outcomes**) at week 12 or week 24 after intravenous (IV) risankizumab induction therapy from the ADVANCE and MOTIVATE trials were enrolled in FORTIFY between April 2018 and April 2020.

Interventions: All patients were randomized 1:1:1 to 360 mg of subcutaneous risankizumab, 180 mg of subcutaneous risankizumab, or subcutaneous placebo (referred to as "withdrawal") every 8 weeks.

Outcomes: Co-primary endpoints included week 52 clinical remission (stratified by 2 definitions of clinical remission: 1. Crohn's disease activity index [CDAI] <150 or 2. mean liquid/soft stool frequency $\leq$ 2.8/day and abdominal pain scores $\leq$1 and not worse than baseline) and endoscopic response (decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] by 50% from baseline). Secondary endpoints included stool frequency remission, abdominal pain remission, Crohn's Disease activity index (CDAI) response, endoscopic remission, and deep remission (clinical and endoscopic remission), among other outcomes. Adverse effects were also assessed through 52 weeks.

Data Analysis: Categorical primary and secondary endpoints were analyzed using the Cochran-Mantel-Haenszel test using a 2-sided significance level of 0.05. Continuous endpoints were assessed using mixed-effect models for repeated measures or analysis of covariance models in the absence of repeated measures.

Funding: AbbVie Pharmaceuticals, manufacturer of risankizumab.

Results: For 360 mg risankizumab versus placebo, risankizumab was associated with higher rates of clinical remission (CDAI clinical remission 52% vs 41%, P <0.05 and stool frequency/abdominal pain score clinical remission 52% vs 40%, P <0.05) and endoscopic response (47% vs 22%, P<0.05). For 180 mg risankizumab versus placebo, risankizumab was associated with higher rates of CDAI clinical remission and endoscopic response but not stool frequency/abdominal pain score clinical remission. Key outcomes from the study are summarized in **Figure 1.**

Among patients with previous biologic failure, clinical remission and endoscopic response were reduced in all groups (CDAI clinical remission: 48% risankizumab 360 mg, 49% risankizumab 180 mg, 35% placebo; stool frequency/abdominal pain score clinical remission: 48%, 41%, and 34%; endoscopic response: 44%, 41%, and 20%). Adverse events were similar across groups, and most commonly included worsening of Crohn's disease, arthralgia, and headache.

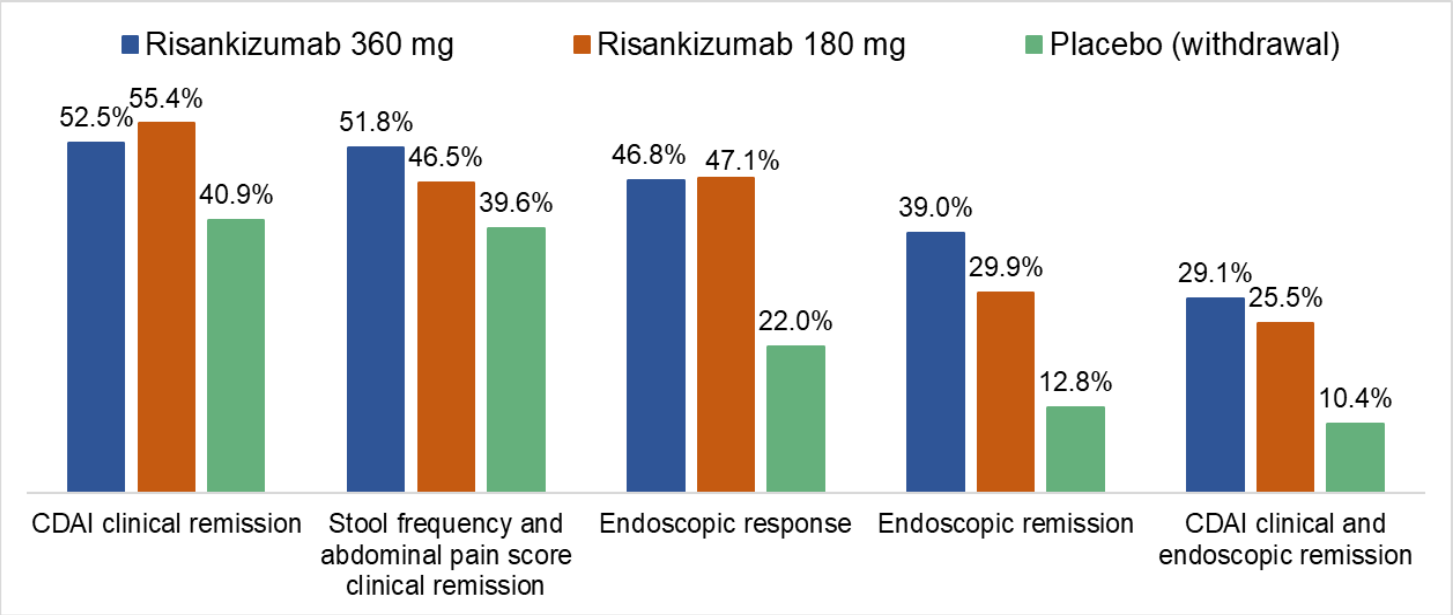

Figure 1. Key Outcomes at 52 Weeks. All comparisons are statistically significant with the exception of risankizumab 180 mg versus placebo for stool frequency and abdominal pain score clinical remission only. CDAI, Crohn's Disease activity index.

COMMENTARY

Why Is This Important?

Current biologic therapies for moderate-to-severe Crohn's disease target tumor necrosis factor α (infliximab, adalimumab), $\alpha_4\beta_7$ integrin (vedolizumab), and IL-12 and 23 (ustekinumab). Many patients do not have adequate response to existing biologic therapies, therefore additional agents with distinct mechanisms of action are needed. IL-23, a cytokine felt to be associated with chronic bowel inflammation, has been found in high concentrations in the gut mucosa of patients with Crohn's disease.[1,2] Ustekinumab (Stelara; Janssen Pharmaceuticals, Beerse, Belgium), which targets both IL-12 and 23 has been shown to be effective for induction and maintenance of moderate-to-severe Crohn's disease and ulcerative colitis.[3] Selective IL-23 inhibition may be a reasonable target for patients with prior non-response or loss of response to ustekinumab or other biologics.

Risankizumab is a selective anti-IL-23 monoclonal antibody that has recently been shown to be safe and effective for the induction of moderate-to-severe Crohn's disease in phase 3 trials (ADVANCE and MOTIVATE) compared to placebo.[4] (See preceding summary in this issue for full details about these randomized controlled trials (RCTs) and the mechanism of action for Risankizumab.) Additional clinical trial data is necessary to demonstrate the safety and efficacy of risankizumab during maintenance of moderate-to-severe Crohn's disease.

Key Study Findings

This RCT included 542 patients with initial response to risankizumab during induction. These patients were then randomized to 360 mg risankizumab, 180 mg risankizumab, and placebo (i.e.,

withdrawal of risankizumab). Greater clinical remission and endoscopic response rates were observed for 360 mg risankizumab compared to placebo. Similar findings were observed for the 180 mg dose of Risankizumab; however there appeared to be a positive dose-response relationship for more rigorous secondary endpoints such as endoscopic and deep remission. Risankizumab, like other biologics, appears to be less effective among those with prior biologic failures. Safety was similar between all treatment groups with no dose-dependent observations.

Caution

There were relatively high rates of clinical remission among patients in the placebo (i.e., withdrawal) group, suggesting prolonged pharmacodynamic effects from intravenous induction risankizumab. Therefore, study results may underestimate the efficacy of risankizumab compared to placebo. Additionally, endpoints were not stratified by Crohn's disease location or phenotype, so it remains unclear if risankizumab is similarly effective for small bowel, stricturing, or penetrating disease.

My Practice

So far, I am typically utilizing risankizumab for my patients with moderate-to-severe Crohn's disease with prior biologic failures, including ustekinumab, vedolizumab, and anti-tumor necrosis factor agents. It was only approved by the FDA for use in Crohn's disease about 6 months ago, in the summer of 2022. It is unknown if selective IL-23 inhibition performs superiorly to IL-12/23 inhibition. However, I have observed a clinical response to risankizumab among patients with prior loss of response ustekinumab. In the absence of adequate safety data, I do not yet recommend the use of risankizumab during pregnancy. In addition, this agent works very well in patients with concurrent psoriasis and we have appreciated a slight preference over ustekinumab from our dermatology colleagues.

For Future Research

Clinical predictors of response and failure of risankizumab therapy for Crohn's disease are largely unknown. Future observational research should attempt to assess the performance of risankizumab among patients with specific disease phenotypes, such as small bowel fistulizing disease, perianal disease, and stricturing disease. With a growing selection of biologic mechanisms, comparative effectiveness research is also needed to help position risankizumab relative to other agents in the treatment algorithm for moderate-to-severe Crohn's disease. The ongoing SEQUENCE trial will compare ustekinumab vs risankizumab in Crohn's disease.

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 Phar-

maceuticals, 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. Dr. Allegretti reports no conflicts.

Note: 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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EVIDENCE-BASED GI
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When It's Not Acid Reflux: Managing PPI-Resistant GERD Patients Based on Bravo Results

Ahmad Abu-Heija, MBBS,[1] Philip Schoenfeld, MD, MSEd, MSc (Epi)[2] and Kristle Lee Lynch, MD[3]


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This summary reviews Yadlapati R, Gyawali CP, Masihi M, et al. Optimal Wireless Reflux Monitoring Metrics to Predict Discontinuation of Proton Pump Inhibitor Therapy. Am J Gastroenterol. 2022 Oct 1;117(10):1573-1582.

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

STRUCTURED ABSTRACT

Question: What metrics from wireless reflux monitoring (Bravo; Medtronic, Minneapolis, MN) predict successful discontinuation of proton pump inhibitors (PPIs) in treatment-resistant individuals with gastroesophageal reflux (GERD) symptoms (i.e., heartburn, regurgitation, and/or non-cardiac chest pain)?

Design: A double-blinded single-arm prospective trial.

Setting: Two tertiary academic centers (Northwestern University, Chicago, IL and Washington University, St Louis, MO) during 2017-2021.

Patients: A total of 132 patients completed the trial. Eligible patients were adults with significant esophageal reflux symptoms (≥2 episodes of heartburn, regurgitation, and/or noncardiac chest pain per week) who remained symptomatic despite a

compliant trial of at least single-dose PPI therapy for a minimum of 8 weeks. Patients were excluded if they had endoscopic erosive GERD (Los Angeles grade C or D), long-segment Barrett's esophagus (BE) (≥3 cm), previous foregut surgery, active heart disease, pregnancy, major motility disorder on manometry, or eosinophilic esophagitis (EoE). Patients with insufficient pH monitoring (at least 14 hours a day for ≥3 days) were also excluded. Forty percent of the patients were males, mean age 47.3 years, mean body mass index 27.1 kg/m^2.

Interventions/Exposure: After being off PPI therapy for at least 1 week, patients underwent 96-hour wireless reflux monitoring using the Bravo pH probe, which was positioned 6 centimeters proximal to the squamo-columnar junction at the lower esophageal sphincter. Study patients were then instructed to refrain from resuming PPI therapy for an additional 2 weeks, although patients could use over the counter (OTC) antacids (e.g., Tums or Rolaids) up to 5 times per day. Indications to resume PPI was defined as high symptom burden with a desire to resume PPI and/or using an excess of maximal OTC antacids (i.e., more than 5 times per day). Study coordinators interviewed patients weekly to assess patients and PPI resumption. Patients, as well as study coordinators and investigators, were blinded to results of reflux testing during intervention.

Outcomes: The main outcome was inability to discontinue PPI therapy for 2 weeks.

Data Analysis: Primary analysis assessed acid exposure thresholds predictive of successful PPI discontinuation, including total, upright, supine, and daily acid exposure time (AET), defined as percent time with esophageal pH < 4.0. DeMeester score, number of reflux events, longest reflux event, symptoms reported, symptom index, and symptom association probability were also calculated.

Funding: The National Institute of Health RO1.

Results: The mean wireless reflux monitoring time was 3.4 days, and 30% of patients discontinued PPIs for the entire 3-week period. An AET threshold of 3.95% demonstrated optimal overall performance for PPI discontinuation (area under curve [AUC] 0.63 [95% confidence interval 0.52-0.73]; 75% sensitivity and 55%

specificity). (Figure 1) Total AET ≤4.0% had the greatest odds of predicting PPI discontinuation (odds ratio 2.9 [1.4-6.4]) with 96-hour monitoring providing optimal AUC to predict PPI discontinuation compared to 24 hours or 48 hours of monitoring. AET > 10.0% and/or DeMeester score > 50.0 were optimally predictive of patients resuming PPI therapy.

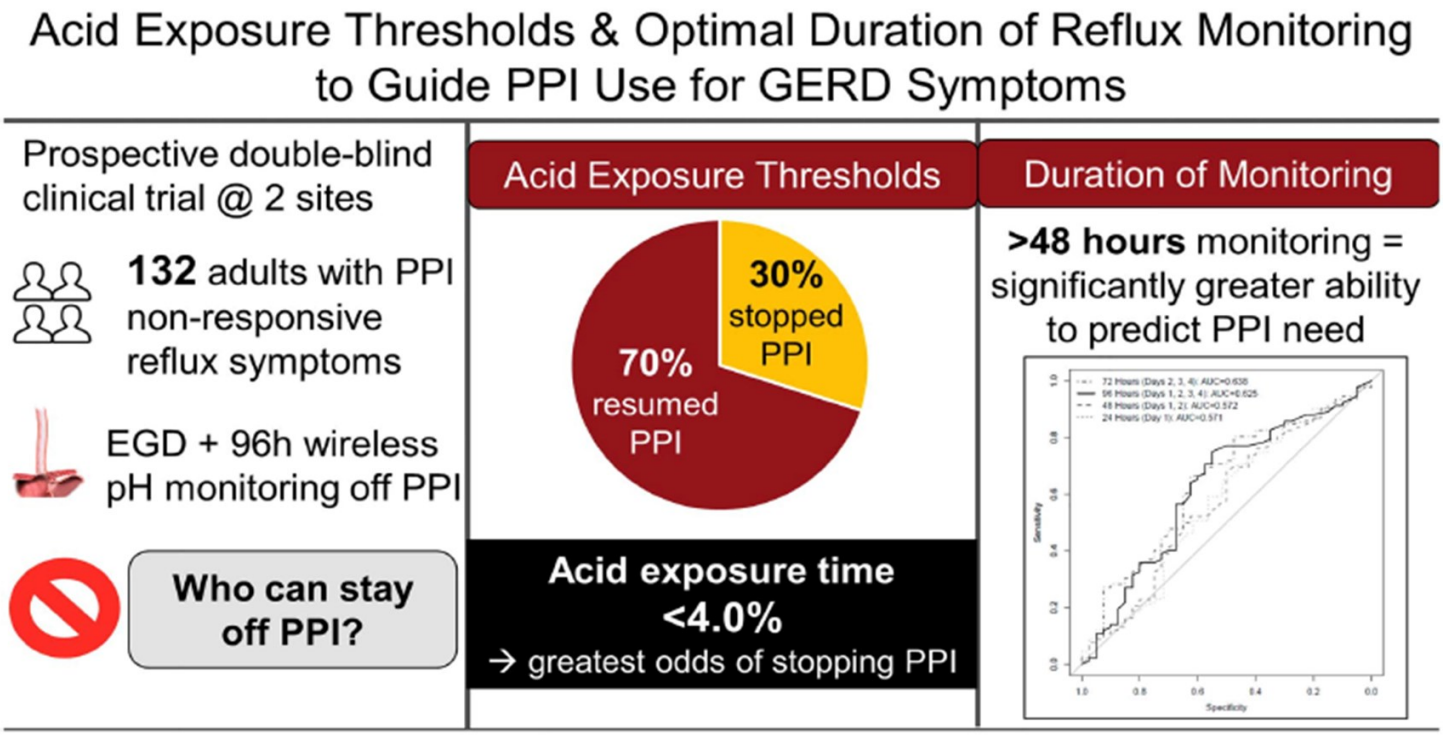

Figure 1: Study summary

COMMENTARY

Why Is This Important?

Nearly half of patients with GERD-type symptoms remain symptomatic despite PPI therapy.[1] These PPI-resistant patients are quite common in GI practice and create a management conundrum, especially when esophagogastroduodenoscopy (EGD) does not demonstrate erosive esophagitis. Are the ongoing symptoms of heartburn or regurgitation or non-cardiac chest pain due to insufficient acid reduction, non-acid regurgitation, or visceral hypersensitivity of the esophagus? Which patients can and should discontinue PPIs? This is a particularly important question since many of these PPI-resistant patients are routinely prescribed twice daily dosing and may soon be prescribed vonoprazan, a potassium-competitive acid blocker, which is pharmacologically more potent, longer-acting, and has a more rapid onset than PPIs. [2-3]

Although wireless reflux monitoring off PPI is a standard tool in these patients,

diagnostic criteria and optimal duration of this monitoring is inadequately defined. This research by Yadlapati and colleagues demonstrates that 96-hours of monitoring is optimal for identifying patients that can successfully discontinue PPIs while setting thresholds for patients that should be able to discontinue PPI (i.e., daily and total AET < 4.0%) versus patients that are most likely PPI-resistant due to inadequate acid suppression (i.e., AET > 10.0% and/or DeMeester score > 50).

Key Study Findings

Daily and total AET ≤4.0% had the greatest odds of predicting PPI discontinuation (odds ratio 2.9 [1.4-6.4]) with 96-hour monitoring providing optimal predictive power about PPI discontinuation compared to 24 hours or 48 hours of monitoring. AET > 10.0% and/or DeMeester score > 50 were optimally predictive of patients needing to resume PPI therapy.

Caution

The primary outcome, resuming PPI therapy, was subjectively decided by the patient. A minority of patients with daily and total AET < 4.0% resumed PPIs, which may reflect anxiety or hypervigilance.

My Practice

For my patients presenting with classic symptoms of heartburn, regurgitation, and/or non-cardiac chest pain who do not have sufficient symptom relief with single-dose PPI therapy after 8 weeks, I will perform an EGD. The main purposes of this test are to assess for erosive esophagitis and/or BE, characterize the diaphragmatic hiatus, as well as rule out eosinophilic esophagitis via esophageal biopsies. If there is no evidence of Grade B+ esophagitis, BE, or EoE, I order a 96-hour wireless pH monitoring probe with the patient off of PPIs for at least 1 week.

If the daily and total AET is <4.0%, then I typically have the patient remain off of PPIs . At this point, we consider neuromodulators, diaphragmatic breathing, and/or cognitive behavioral interventions. Alternatively, if the AET is >10.0%, then the goal is to enhance reflux control. PPI optimization via timing and agent selection is first done, followed by revision or enhancement of the hiatus if symptoms persist. Vonoprazan may also be considered after it becomes available as expected later this year.

For Future Research

Research about optimal diagnostic criteria are needed to identify PPI-resistant

GERD patients that would benefit from switch to a potassium channel acid blocker, like vonoprazan. Additionally, research towards early identification of patients with functional heartburn or other symptoms of visceral hypersensitivity is key, as these patients would benefit from neuromodulators or behavioral intervention.

Conflict of Interest

Dr. Abu-Heija reports no potential conflicts of interest. Dr. Schoenfeld has been an advisory board member and speaker for Phathom Pharmaceuticals. Dr. Lynch has been an advisory board member and speaker for Medtronic and an advisory board member for Lucid Diagnostics, Sanofi, and Takeda Pharmaceuticals.

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HEPATOLOGY

In Case You Missed It

Is Terlipressin for the Treatment of Hepato-renal Syndrome Ready for Primetime: Results of the CONFIRM Trial

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This summary reviews Wong F, Pappas SC, Curry MP, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med. 2021 Mar 4;384(9):818-828.

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STRUCTURED ABSTRACT

Question: Is terlipressin (Terlivaz; Mallinckrodt Pharmaceuticals, UK), a vasoconstrictor of splanchnic and peripheral vasculature, safe and effective in Type 1 hepatorenal syndrome (HRS-1)?
Design: A Phase 3 randomized, double-blind, placebo-controlled trial of 300 patients with HRS-1 randomized in a 2:1 ratio to receive terlipressin or placebo for up to 14 days.
Setting: The trial was conducted across 60 sites in the United States and Canada from July 2016 through July 2019.
Patients: The study included 300 patients with HRS-1, cirrhosis, ascites, and rapidly progressive kidney failure (doublings of serum creatinine level to at least 2.25 mg/dL) within 14 days; 199 patients were assigned to the terlipressin group and 101 to the placebo group. Patients were excluded if their creatinine level had a sustained reduction of more than 20% (or a decrease below 2.25 mg/dL) within 48 hours of diuretic withdrawal and albumin infusions. Patients on midodrine and oc-

treotide (current standard of care treatment for HRS-1) were eligible if both were discontinued prior to randomization. Other exclusion criteria included: serum creatinine level > 7.0 mg/dL, one or more large volume paracentesis (4 L within 2 days of randomization), sepsis or uncontrolled infection, cardiovascular disease, or initiation of renal replacement therapy (RRT) within 4 weeks. RRT includes hemodialysis, peritoneal dialysis, and other hemofiltration techniques to replace usual functions of kidneys.

Interventions/Exposure: Patients were randomly assigned in a 2:1 ratio to receive terlipressin (1 mg intravenous [IV] over 2 minutes every 5.5-6.5 hours) plus albumin (1 gram / kg to maximum of 100 grams on day 1, and 20-40 g/day daily after) or placebo plus albumin. In both groups, there were more males, the majority had alcohol associated liver disease as the cause of their cirrhosis (67% in terlipressin, 66% in placebo), with similar average model for end stage liver disease (MELD) score of 33.
Study participation could be stopped for several reasons: (1) day 4 creatinine was greater than or equal to their baseline, (2) RRT initiation, (3) vasopressors started, or (4) underwent liver transplant or TIPS procedure.

Outcome: The primary end point was verified HRS reversal (defined in this study as 2 consecutive serum creatinine measurements of 1.5 mg/dL or less at least 2 hours apart) and survival without renal-replacement therapy for at least 10 days after treatment completion.

Secondary endpoints included: (1) HRS reversal (defined as serum creatinine $\leq$ 1.5 mg/dL), (2) durability of HRS reversal (defined as HRS reversal without RRT to day 30), (3) HRS reversal among patients with systemic inflammatory response syndrome, and (4) verified reversal of HRS without recurrence of HRS by day 30.

Data Analysis: Intention-to-treat analysis.

Funding: Mallinckrodt Pharmaceuticals, manufacturer of terlipressin.

Results: More patients in the terlipressin group than placebo had verified HRS reversal (as defined above; 32% (n=63) vs 17% (n=17); *P*=0.006 respectively). The secondary endpoints also had greater success in the terlipressin group as compared to placebo (**Table 1**). Transplantation free survival up to 90 days did not differ significantly between the groups. However, there were more adverse events in the terlipressin group than placebo including abdominal pain, nausea, diarrhea, and respiratory failure. Notably, death from respiratory complications occurred more often in the terlipressin group (n=22, 11%) versus placebo (n=2, 2%).

End Point	Terlipressin n=199 % (n=)	Placebo n=101 (n, %)	*P*-value
Primary Endpoint: Verified HRS Reversal	**32 (n=63)**	**17 (n=17)**	**0.006**
Secondary Endpoints			
1. HRS Reversal	39 (n=78)	18 (n=18)	< 0.001
2. HRS Reversal without RRT at 30 days	34 (n=68)	17 (n=17)	0.001
3. HRS Reversal in SIRS patients	37 (n=31/84)	6 (n= 3/48)	< 0.001
4. Verified HRS Reversal with no recurrent at 30 days	26 (n=52)	17 (n=17)	0.008

Table 1. Primary and secondary endpoings in the CONFIRM trial
Abbreviations: HRS, hepatorenal syndrome; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome.

COMMENTARY

Why Is This Important?

Patients with decompensated cirrhosis and ascites are at risk for HRS-1, characterized by rapidly progressive kidney failure with high mortality rates in the absence of liver transplantation. Vasoconstrictors to increase mean arterial pressure have been used to combat the systemic vasodilation that is one of the main mechanisms leading to HRS. Although midodrine, an orally active vasoconstrictor, combined with octreotide is standard treatment in the US, it has limited efficacy.[1] Given the high mortality of HRS, effective treatments are needed.

Terlipressin, a synthetic vasopressin that constricts the splanchnic and systemic vasculature, has shown success in HRS treatment in Europe, but was not available in the US until September 2022 when the FDA approved it for treatment of HRS based largely on this randomly controlled trial and other parts of the world. However, side effects due to vasoconstriction, including abdominal pain or ischemia of fingers, skin, etc, as well as pulmonary edema when combined with albumin are common.[1]

Key Study Findings

More patients in the terlipressin group than placebo had verified HRS reversal (as defined above; 32% (n=63) vs 17% (n=17); *P*=0.006 respectively). Death from respiratory complications occurred more often in the terlipressin group (n=22, 11%) versus placebo (n=2, 2%).

Caution

Despite terlipressin improving HRS-1 in more patients than placebo, respiratory failure and death from respiratory failure also occurred in more patients receiving terlipressin.

Notably, the definition of HRS (creatinine > 2.25 mg/dL) in the trial does not follow the consensus definition of HRS which is an increase in the creatinine level of > 0.3 mg/dL from baseline that does not improve with volume expansion. If the consensus definition had been used, it is possible that terlipressin would show a larger response, as HRS reverses at lower creatinine levels.

My Practice

Any new or worsening renal insufficiency is worrisome in a patient with decompensated cirrhosis. A thorough work up ruling out other causes, discontinuation of diuretics, and initiation of volume expansion is required. HRS is diagnosed when there is no improvement in the creatinine after volume expansion. Standard treatment in the United States is midodrine, octreotide, and albumin in addition to a prompt liver transplant evaluation. If there is no improvement within 48 hours, I will transfer these patients to the intensive care unit for a trial of vasoactives, primarily norepinephrine, which has demonstrated similar efficacy to terlipressin although there is less data.[1] Given the significant cardiopulmonary complications associated with terlipressin, I do not currently recommend routine use and I individualize use on a case-by-case basis.

The question of renal replacement therapy is often brought up. In my practice, if they are a viable liver transplant candidate or if their MELD is being driven mainly by the creatinine (and bilirubin and INR are fairly preserved / improving), I will pursue this. However, in those that are not liver transplant candidates, it often becomes a bridge to nowhere (especially if unable to tolerate hemodialysis) and I often then focus on goals of care.

For Future Research

Future research and safety data is needed before universal use of terlipressin for HRS. Future studies could consider using the current consensus definition of HRS, as there may be a benefit in certain patient populations (perhaps lower creatinine levels indicating less sick patients).

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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