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

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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.

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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.

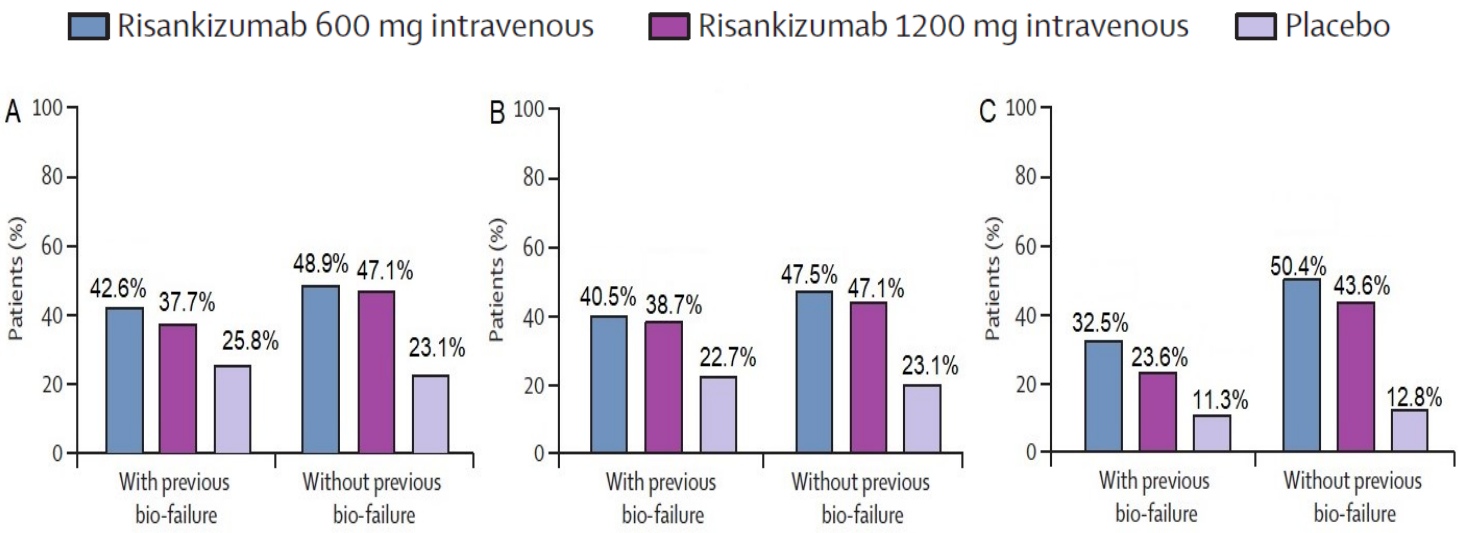

Figure 1. Coprimary endpoints at week 12 of ADVANCE
(**a**) CDAI clinical remission (**b***)* stool frequency and abdominal pain score clinical remission (**c**) endoscopic response.

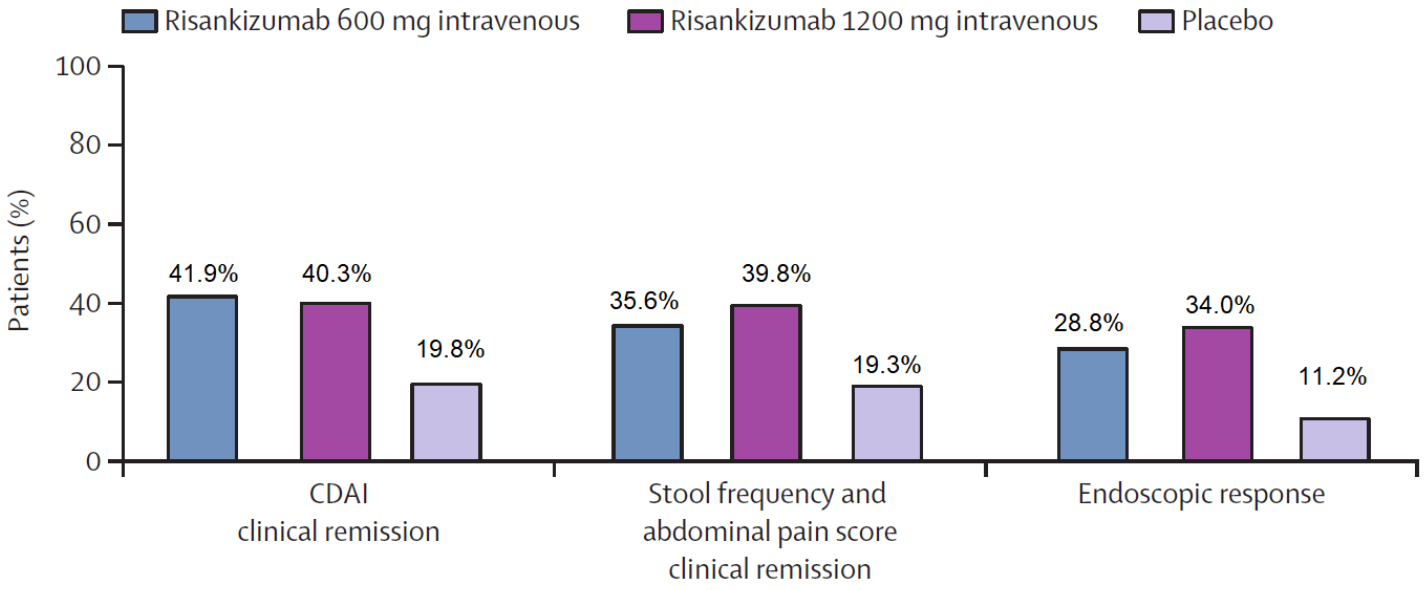

Figure 2. Coprimary endpoints at week 12 of MOTIVATE

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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