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Risankizumab Is Superior to Placebo for Induction and Maintenance of Moderate-Severe Ulcerative Colitis (UC): Assessing the UC Treatment Paradigm

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IBD

This summary reviews Louis E, Schreiber S, Panaccione R, et al. Risankizumab for ulcerative colitis: Two randomized clinical trials. JAMA. 2024:e2412414.

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STRUCTURED ABSTRACT

Question: Is risankizumab (Skyrizi; AbbVie Pharmaceuticals, San Francisco, CA), a p19 subunit-specific interleukin (IL)-23 monoclonal antibody, superior to placebo for induction of remission and maintenance of remission of moderate-severe ulcerative colitis (UC)?

Design: INSPIRE and COMMAND were phase 3, double-blind, placebo-controlled, randomized clinical trials (RCT) of risankizumab for moderate to severe UC. In the 12-week induction trial (INSPIRE), patients were randomized 2:1 (risankizumab:placebo) to 1,200 mg risankizumab or placebo administered intravenously at 0, 4, and 8 weeks. Patients who had clinical response or clinical remission to risankizumab induction were included in the maintenance trial (COMMAND) conducted from week 12 to week 52, in which patients were randomized 1:1:1 to

180 mg risankizumab, 360 mg risankizumab, or placebo administered subcutaneously every 8 weeks.

Setting: INSPIRE, the induction of remission RCT, was conducted in 261 centers in 41 countries from November 2020 through August 2022. The maintenance of remission RCT, COMMAND, was conducted in 238 centers in 37 countries.

Patients: Inclusion criteria included: 18-80 years old; moderate-severe ulcerative colitis based on adapted Mayo score ≥5 (0-9 scale) which consists of rectal bleeding score (0-3), stool frequency score (0-3), endoscopy subscore (0-3); endoscopic subscore of 2-3 based on central review of endoscopic images; prior history of inadequate response, loss of response, or intolerant of conventional therapy (glucocorticoids or immunomodulators) or biologic therapy. Exclusion criteria included prior exposure to ustekinumab, mirikizumab, or risankizumab.

Interventions: For the induction of remission RCT, INSPIRE, 1,200 mg risankizumab or placebo was administered intravenously at 0, 4, and 8 weeks. For the maintenance of remission RCT, COMMAND, 180 mg risankizumab, 360 mg risankizumab, or placebo were administered subcutaneously every 8 weeks.

Outcomes: For the induction trial, the primary outcome was clinical remission at week 12. For the maintenance trial, the primary outcome was clinical remission at week 52. Clinical remission was defined as a stool frequency score ≤1 and not higher than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1 without friability. Secondary outcomes included endoscopic and histologic improvement as well as endoscopic remission, among others.

Data Analysis: Intention to treat (ITT) analysis. Categorical outcomes were analyzed using the Cochran-Mantel-Haenszel test. Continuous outcomes were analyzed using mixed-effect models with a repeated-measures method or analysis of covariance.

Funding: AbbVie Pharmaceuticals, manufacturer of risankizumab.

Results: Of 975 UC patients in the induction of remission trial, 60% were male, mean age was 42 years, 70% were White, mean disease duration of 7 years, and mean adapted Mayo score of 7. Clinical remission rates at week 12 were 20.3% (132/650) for 1,200 mg risankizumab vs 6.2% (20/325) for placebo ($P < 0.01$).

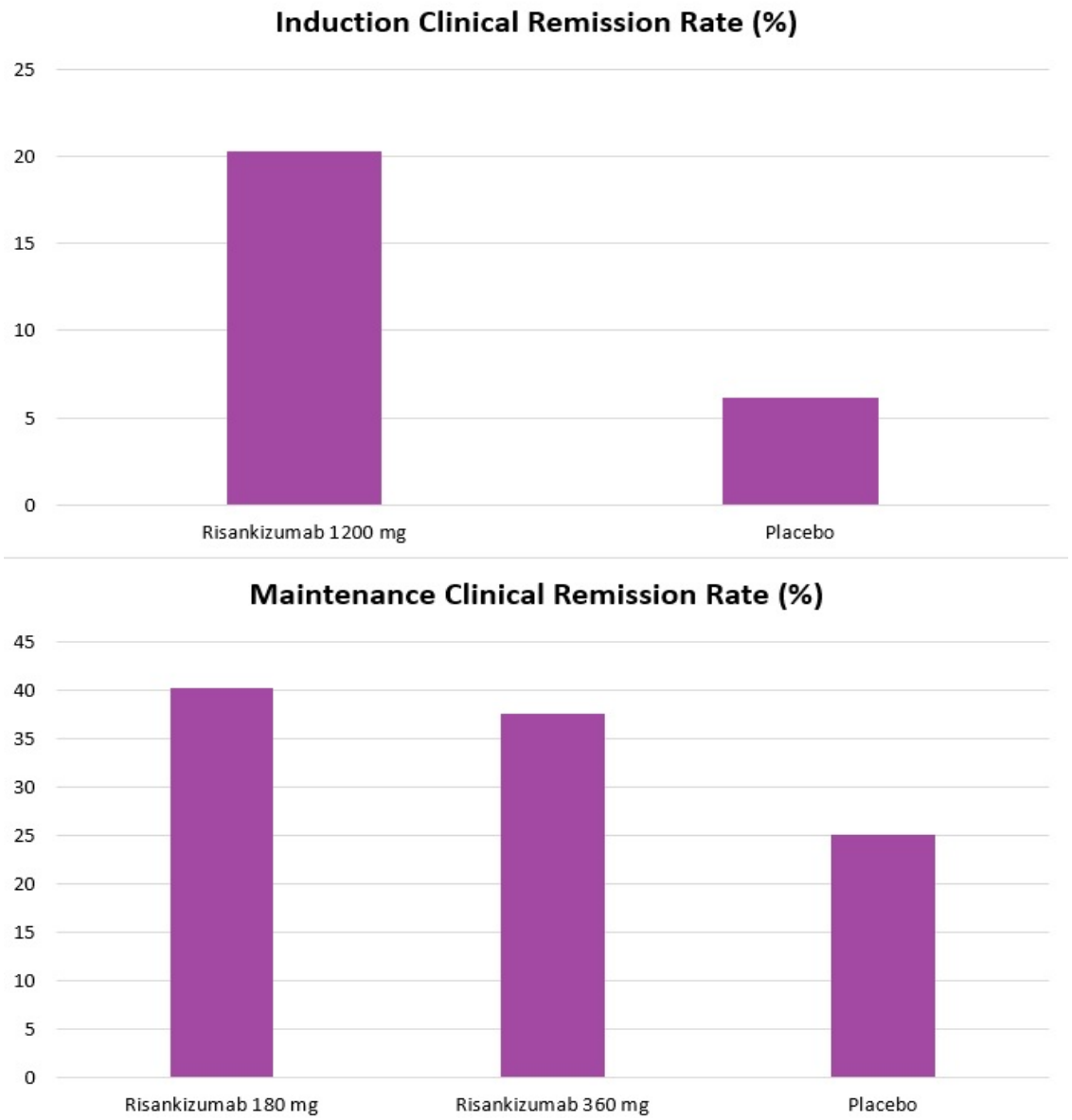

Figure 1. Results of induction and maintenance risankizumab compared to placebo.

(Figure 1) Endoscopic improvement was observed in 36.5% for risankizumab vs 12.1% for placebo ($P<0.01$). UC patients that were treatment-naïve to biologic therapy demonstrated numerically higher remission rates compared to treatment-experienced patients who had a history of inadequate response to biologic therapy. Specifically, in treatment-naïve patients, clinical remission rates for risankizumab and placebo were 29.7% vs 8.4%, respectively, while clinical remission rates in treatment-experienced patients were 11.4% vs 4.3%, respectively.

Of 548 UC patients in the maintenance of remission trial, 57% were male, mean age was 41 years, 74% were White, mean disease duration of 8-9 years, and mean adapted Mayo score of 7. Clinical remission rates at week 52 were 40.2% (72/179) for 180 mg risankizumab vs 37.6% (70/186) for 360 mg risankizumab vs 25.1% (46/183) for placebo ($P < 0.01$). **(Figure 1)** Endoscopic improvement was observed in 50.8% for 180 risankizumab vs 48.3% for 360 mg risankizumab vs

31.7% for placebo. Again, UC patients that were treatment-naïve to biologic therapy demonstrated numerically higher maintenance of remission rates compared to treatment-experienced patients who had a history of inadequate response to biologic therapy. Specifically, in treatment-naïve patients, maintenance of remission rates were 50.9% for 180 risankizumab vs 61.7% for 360 mg risankizumab vs 31.1% for placebo, while maintenance of remission rates were 36.6% vs 29.5% vs 23.2%, respectively, in treatment-experienced patients.

A post-hoc analysis demonstrated significantly suppressed levels of IL-22 (a downstream cytokine of the IL-23 pathway) in the risankizumab treatment group compared to placebo. Incidence of adverse events were similar in the risankizumab and placebo group. Rates of both herpes zoster and serious infection were similar between risankizumab and placebo groups during induction and maintenance of remission.

Note

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

COMMENTARY

Why Is This Important?

Risankizumab is the first p19 subunit-specific interleukin (IL)-23 monoclonal antibody approved for the treatment of inflammatory bowel disease, and the second p19 subunit-specific interleukin (IL)-23 monoclonal antibody approved specifically for ulcerative colitis (UC) in the United States.[1,2] While anti-tumor necrosis factor (anti-TNF) agents have an established role as first-line therapy for moderate-to-severe UC, approximately one-third of patients fail to respond and up to 50% lose clinical response to anti-TNFs over time.[3] The introduction of p19 subunit-specific interleukin (IL)-23 monoclonal antibodies offers a new mechanistic option with subcutaneous administration to treat UC effectively with a favorable safety profile that may be appealing to many patients and providers. In Crohn's disease, risankizumab has been shown to have greater efficacy than ustekinumab, an inhibitor of both IL-12 and 23, though it is unclear how a p19 subunit-specific interleukin (IL)-23 monoclonal antibody will compare to ustekinumab for the treatment of UC.[4]

Ultimately, clinicians now have an expanded menu of options to treat

moderate-severe UC, including oral sphingosine 1-phosphate (S1P) receptor modulators (e.g., etrasimod), oral Janus kinase 1 (JAK1) inhibitors (e.g., upadacitinib), intravenous (IV)/ subcutaneous (subq) anti-integrin monoclonal antibodies (e.g., vedolizumab), IV/subq anti-TNF agents (e.g., infliximab), as well as the anti-interleukin-12/23 monoclonal antibodies. Given this expanding menu of therapies, new algorithms are needed to help gastroenterologists choose preferred treatment for individual UC patients by accounting for the strengths and limitations of individual agents.

Key Study Findings

For the induction trial, clinical remission rates at week 12 were 20.3% (132/650) for 1,200 mg risankizumab vs 6.2% (20/325) for placebo ($P < 0.01$). For the maintenance trial, clinical remission rates at week 52 were 40.2% (72/179) for 180 mg risankizumab vs 37.6% (70/186) for 360 mg risankizumab vs 25.1% (46/183) for placebo ($P < 0.01$).

Caution

Patients with prior treatment with ustekinumab were excluded from this trial. Therefore, it is difficult to extrapolate these results to patients with previous exposure to ustekinumab.

My Practice

In my practice, I commonly prescribe risankizumab as a first-line therapy for moderate-to-severe UC. I will consider this therapy in older adults in whom a more favorable safety profile is needed (e.g. as compared to anti-TNF agents) or in those who prefer a subcutaneous option. Due to the results of the SEQUENCE trial in Crohn's disease, I typically favor prescribing risankizumab over ustekinumab for UC as well, though comparative data in UC are lacking. I also counsel my patients that dose intensification of risankizumab (i.e. reduction of the maintenance dosing interval to more frequent than every 8 weeks) could be needed for loss of response or partial response, similar to ustekinumab.[5]

With respect to other UC therapies, I may consider oral S1P receptor modulators in patients with moderate UC that prefer an oral option. Due to FDA requirements, I usually limit JAK1 inhibitors to UC patients that have failed anti-TNF agents. For older UC patients with multiple co-morbidities, vedolizumab may be a good option because of its safety profile, although I don't limit vedolizumab just to this population. Finally, infliximab is still a very good option, especially in patients with extra-intestinal symptoms, and is now available in subq formulations.

For Future Research

Randomized comparator trials are needed to compare the effectiveness of risankizumab to other advanced therapies for UC, particularly ustekinumab,

vedolizumab, and JAK1 inhibitors. Large cohort studies are needed to explore long-term outcomes of risankizumab for UC beyond 52 weeks and the effectiveness of p19 subunit-specific IL-23 monoclonal antibody in those with prior ustekinumab exposure. Since we have multiple approved treatments for UC with different mechanisms of action, studies of biologic markers that predict response to specific therapies would be helpful to guide treatment. Also, since monotherapy of UC with biologic agents fails to achieve remission in many patients, further research about combination biologic therapy will be helpful to assess the benefits and potential risks of different combinations of treatment.

Conflict of Interest

Dr. Dalal has research grant support from Janssen and Pfizer and has served as a consultant for Janssen, Takeda, and Centaur Labs.

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