EVIDENCE-BASED GI
AN ACG PUBLICATION

Risankizumab Is Superior to Ustekinumab for Induction and Maintenance of Crohn's Disease: The SEQUENCE Trial

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IBD

This summary reviews Peyrin-Biroulet L, Chapman JC, Colombel JF, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease. N Engl J Med 2024;391:213-223 .

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Keywords: Crohn's disease, risankizumab, Ustekinumab, RCT

STRUCTURED ABSTRACT

Question: Is risankizumab (Skyrizi, AbbVie Pharmaceuticals, San Francisco, CA), a p19 subunit-specific interleukin (IL)-23 monoclonal antibody, as efficacious and safe as ustekinumab (Stelara; Janssen Pharmaceuticals, Beerse, Belgium), a dual IL-12/23 inhibitor, in the treatment of patients with moderate-to-severe Crohn's disease who previously had unacceptable side effects or an inadequate response to at least one anti-tumor necrosis factor (TNF) therapy?

Design: Phase 3b, multicenter, open label, randomized comparator trial for 48 weeks.

Setting: Patients were recruited from 187 sites in 28 countries between September 2020-July 2023.

Patients: Inclusion criteria included: age 18-80 years; moderate-to-severe Crohn's

disease, based upon Crohn's disease activity index (CDAI) score of 220-450 with average daily stool frequency of ≥4 and/or an average abdominal pain score ≥2; endoscopic evidence of mucosal inflammation based upon simple endoscopic score for Crohn's disease (SES-CD) score ≥ 6 for ileocolonic or colonic disease or SES-CD ≥ 4 for isolated ileal disease; and history of unacceptable side effects or an inadequate response to at least one anti-tumor necrosis factor (TNF) therapy.

Multiple exclusion criteria included, but were not limited to: presence of ostomy or ileoanal pouch; short bowel syndrome; surgical bowel resection within 3 months of enrollment; and prior use of small molecules or biologics other than anti-TNFs.

Intervention: Patients were randomly assigned in 1:1 ratio to receive risankizumab or ustekinumab. In the risankizumab group, patients received 600 mg intravenous (IV) induction dose at week 0, 4, 8 followed by 360 mg subcutaneous (SQ) maintenance dose every 8 weeks from week 12 to 48. Patients in the ustekinumab group received the approved single weight-based induction IV dose followed by 90 mg SQ maintenance dose every 8 weeks until week 48. All enrolled patients also underwent a mandatory steroid taper starting at week 2.

Outcome: The 2 primary endpoints of this study were: (1) clinical remission at week 24 (defined as CDAI score ≤ 150) and (2) endoscopic remission at week 48 (defined as SES-CD of ≤ 4, and at least 2-point reduction from baseline and no subscore > 1 in any individual variable).

Secondary endpoints were tested hierarchically for superiority of risankuzimab to ustekinumab in the following order: clinical remission at 48 weeks (defined as reduction in SES-CD ≥50% from baseline, or at least 2-point reduction from baseline for patients with isolated ileal disease); endoscopic response at week 24; steroid-free endoscopic remission at week 48; and, steroid-free clinical remission at week 48. Safety events were assessed among all patients who received at least one dose of risankizumab or ustekinumab.

Data Analysis: Intention-to-treat analyses were performed. Since risankizumab was not approved for use when the trial was designed, noninferiority of risankizumab to ustekinumab in achieving clinical remission at week 24 was the primary analysis and was established with the 95% confidence interval (CI) for the risk difference between risankizumab and ustekinumab group set at greater than 10 percentage points. Superiority of risankuzimab compared to ustekinumab was evaluated using a 2-sided significance level of 0.05. Categorical variables were analyzed using the Cochran-Mantel-Haenszel test to assess common risk difference, stratified by the number of previous anti-TNF therapies that failed (1 or >1), and by

steroid use at baseline.

Funding: AbbVie Pharmaceuticals, manufacturer of risankuzimab.

Results: Among 520 patients randomized to risankuzimab (n =255) and ustekinumab (n= 265), demographic data included mean age 38-years-old; 49% female; 74% White, 20% Asian, 10% Hispanic; ileocolonic disease 43%, ileal disease only 17%, colonic disease only 40%; median duration of disease was 7.3 years; and, mean CDAI score was 307. Overall, 90.2% of patients in the risankuzimab group (230/255) and 72.8% of patients in the ustekinumab group (193/265) completed all the assigned treatment.

Risankuzimab was noninferior to ustekinumab with regards to clinical remission at week 24 (58.6% vs 39.5%; -18.4% [95% CI, 6.6-30.3]). Risankuzimab was superior to ustekinumab with regards to endoscopic remission at week 48 (31.8% vs 16.2%; -15.6% [95% CI, 8.4-22.9; P<0.001]; Figure 1).

Risankuzimab demonstrated superior efficacy to ustekinumab across all secondary endpoints (Table 1). Furthermore, the incidence of hospitalization related to Crohn's disease, or any other cause was significantly lower in the risankizumab group compared to the ustekinumab group (4% vs 13%, -8.45% [95% CI, 3.31-13.60]; 11% vs 19%, -7.13% [95% CI, 0.25-14.01]).

Adverse events were similar in the 2 groups. The incidence of serious adverse events was lower in the risankizumab compared to the ustekinumab group (10.3% vs 17.4%). Infection rates were similar in the 2 groups. One case of skin squamous -cell carcinoma (in the risankizumab group) and one case of anal squamous cell carcinoma (in the ustekinumab group) was reported.

	Risankizumab (n=255)	Ustekinumab (n=265)
Clinical Remission-Week 48	60.8%	40.8%
Glucocorticoid-Free Remission-Week 48	60.8%	40.4%
Endoscopic Response-Week 48	45.1%	21.9%

Table 1: Secondary trial endpoints.

$P < 0.001$ for all secondary endpoints

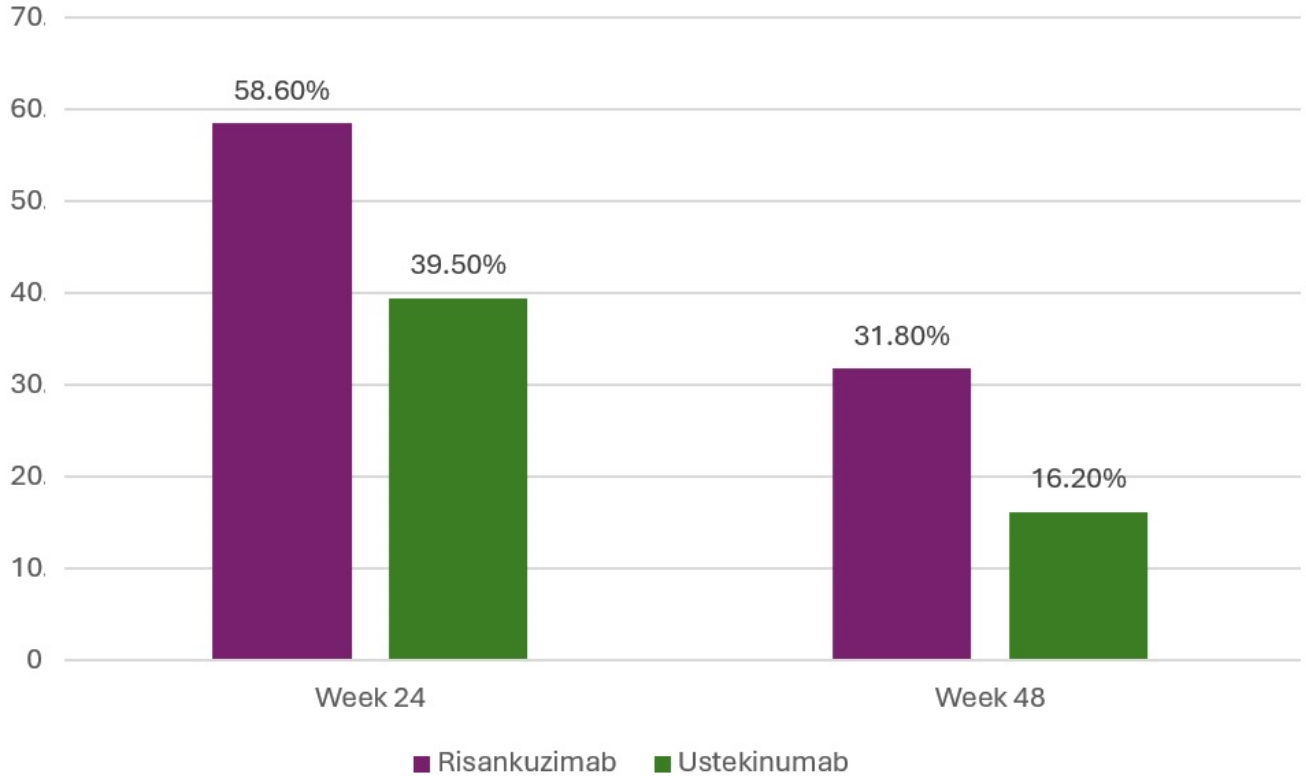

Figure 1. Co-Primary Endpoints: Clinical remission at week 24 and endoscopic remission at week 48.

COMMENTARY

Why Is This Important?

Head-to-head trials, comparing treatment options for IBD, are arguably the most practice changing studies. Yet to date we have very few published head-to-trial trials in IBD: SONIC, NORSWITCH, SEAVUE[1], and VARSITY[2] are the prominent ones since 2000. Head-to-head clinical trials are the most clinically pertinent to patients, providers and insurers. These trials answer the every day question of which medication should we use to treat this disease in this patient and what are the risks and benefits of each choice compared with the other choice, the true counterfactual, instead of compared with placebo, which is not a realistic counterfactual for patients who need to start advanced therapies. Unlike VARSITY and SEAVUE, which are trials to investigate the most efficacious first line advanced therapy in ulcerative colitis and Crohn's disease respectively, SEQUENCE helps position second line agents for Crohn's disease.

Key Study Findings

Risankizumab is non-inferior to ustekinumab in achieving clinical remission at 24 weeks in patients who have already been treated with an anti-TNF agent.

Importantly, risankizumab was superior to ustekinumab for clinical remission at 48 weeks (60.8% vs 40.8%, $P< 0.001$) and for endoscopic remission (31.8% vs 16.2%, $P< 0.001$).

There was no significant difference in adverse events between the study drugs and rates of opportunistic infections were less than 1% in both groups, reinforcing the relative safety of this class of biologic agents.

Caution

This was an open label study, so patients knew if they were receiving risankizumab and ustekinumab, which might impact their subjective assessment of abdominal discomfort and bowel habits. However, the reviewers were blinded to the treatment arm when assessing endoscopic healing. Also, risankizumab maintenance dosing was the higher 360 mg dose instead of the 180 mg maintenance dose, while dose escalation of ustekinumab to every 6 weeks or even every 4 weeks was not allowed. Finally, the drop-out rate was 28% in the ustekinumab arm versus 10% in the risankizumab arm, and this difference was primarily due to lack of efficacy in the ustekinumab arm, which may impact interpretation of results.

Whether the superior efficacy of risankizumab is due to binding on the p19 subunit or if there are specific properties of the drug itself that allow for better tissue penetration or another feature that result in greater endoscopic efficacy is unclear.[3] Finally, the superiority of risankizumab to ustekinumab in these moderate-severe Crohn's disease patients whose anti-TNF agents had failed to treat their condition is not generalizable to ulcerative colitis.

My Practice

These data are not surprising as the findings are parallel to what has been published in 2017 for the treatment of moderate to severe plaque psoriasis.[4] However, head-to-head trials like this must influence clinical practice. While ustekinumab may be a great first line biologic for Crohn's disease as the SEAVUE trial demonstrated, SEQUENCE shows us that when used as a second line agent after failure with an anti- TNF agent, risankizumab should be preferred for the greater efficacy for the stringent endpoint of endoscopic remission. It's not clear whether this increased efficacy can be extrapolated to the use of an anti-interleukin agent as a first line agent.

While SEQUENCE clarifies the positioning of risankizumab, ustekinumab will continue to have a large role in IBD treatment. There is likely to be a ustekinumab biosimilar available in the US by 2025 which should make ustekinumab more affordable. Furthermore, starting in 2024, ustekinumab has been covered by Medicare prescription drug plans as part of the Inflation Reduction Act of 2022 covering high cost medications. Since the financial burdens of biologic therapy are an important consideration and ustekinumab is an efficacious anti-IL 23 agent, it would be short sighted to overlook ustekinumab in the treatment of Crohn's disease.

Nevertheless, especially if I am starting an anti-IL 23 agent after failure of other advanced therapy for CD, it is worth appealing for risankizumab, citing this

paper if it is denied with the initial request.

Future Research

The number of head-to-head clinical trials are increasing, which is very useful for the IBD community. Two such trials, VIVID-1 and GALAXI-2/3, have presented preliminary data, although we're awaiting full publications. VIVID-1 compared mirikizumab, another anti-IL targeting the p19 subunit of IL-23, vs ustekinumab for the treatment of Crohn's disease in patients who have been previously treated with an anti-TNF agent. GALAXI-2/3 compared guselkumab, another anti-IL 23 monoclonal antibody, vs ustekinumab in patients with Crohn's disease who were both biologic naïve and exposed.

This trial was quite traditional in its inclusion and exclusion criteria, excluding patients with abnormal anatomy, advanced age, etc. Future investigation should also focus on novel clinical trial analytics and methodology to allow for these important sub-groups of patients who are the most challenging in the clinical practice to be assessed in a rigorous prospective manner.

Conflict of Interest

Dr. Ghoneim notes no conflicts of interest. Dr Kochar has received consulting fees from Pfizer, Inc and Bristol Meyers Squibb.

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