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Clinical insights into IL-23 inhibition: risankizumab for Crohn's disease through a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background and aims: Crohn's disease is a chronic inflammatory disorder with rising global prevalence, marked by abdominal pain, diarrhea, and fatigue. Interleukin (IL)-23 plays a pivotal role in Crohn's disease pathogenesis, making it a therapeutic target. Risankizumab, a monoclonal antibody targeting the IL-23 p19 subunit, has shown potential in clinical trials.

Objectives: This meta-analysis evaluates the efficacy and safety of Risankizumab in achieving clinical remission, clinical response, and endoscopic remission in patients with moderate-to-severe Crohn's disease.

Design: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines.

Data sources and methods: A comprehensive search of PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov was performed to identify randomized controlled trials (RCTs) assessing Risankizumab in Crohn's disease. Primary outcomes were clinical remission, clinical response, and endoscopic remission, with secondary outcomes focusing on treatment-related adverse events. A random-effects model estimated odds ratios (ORs) with 95% confidence intervals. Meta-regression analyzed dose- and duration-dependent effects.

Results: Four RCTs involving 1774 participants showed that Risankizumab significantly improved clinical remission (OR = 2.223), clinical response (OR = 2.483), and endoscopic remission (OR = 4.112). Dose-dependent improvements were observed, with treatment duration affecting clinical remission ($p = 0.0158$) but not clinical response or endoscopic remission. Adverse event rates were comparable between Risankizumab and placebo groups (OR = 0.872, $p = 0.592$).

Conclusion: Risankizumab is effective in achieving clinical and endoscopic outcomes in moderate-to-severe Crohn's disease, demonstrating dose-dependent benefits and a favorable safety profile, supporting its use as a therapeutic option. However, the limited number of studies may affect the robustness of these findings. Further large-scale RCTs are needed to validate its long-term efficacy, safety in elderly populations, and effectiveness in biologic-naïve patients.

Trial registration: This systematic review and meta-analysis were registered with the INPLASY database under registration number INPLASY202530014. The full protocol is accessible at DOI: 10.37766/inplasy2025.3.0014.

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Plain language summary

How Risankizumab helps treat Crohn's disease: a review of clinical trial results

Crohn's disease is a long-term condition that causes inflammation in the digestive system. People with Crohn's disease often experience symptoms like stomach pain, diarrhea, and tiredness, which can significantly affect their daily lives. Researchers have found that a protein called interleukin-23 (IL-23) plays a key role in this disease. Targeting IL-23 may help control the inflammation. Risankizumab is a medicine designed to block a part of IL-23, and it has been tested in clinical trials to see if it can help people with moderate-to-severe Crohn's disease. To understand how well it works and whether it is safe, we combined the results of multiple high-quality studies in a process called a metaanalysis. Our analysis included four studies with a total of 1,774 patients. We found that Risankizumab significantly improved three key outcomes: Clinical remission: Fewer or no symptoms of Crohn's disease. Clinical response: Noticeable improvement in symptoms. Endoscopic remission: Healing of the digestive tract, confirmed by a camera test. Patients who received Risankizumab were more likely to achieve these outcomes compared to those who received a placebo. The benefits were stronger with higher doses of the medication and with longer treatment durations for clinical remission. Importantly, the medicine was found to be safe. The rates of side effects were similar between patients taking Risankizumab and those taking a placebo. In conclusion, Risankizumab is an effective and safe treatment for people with moderate-to-severe Crohn's disease. It helps reduce symptoms, promotes healing in the digestive tract, and works better at higher doses. This makes it a promising option for managing this challenging condition.

Keywords: clinical remission, Crohn's disease, endoscopic remission, IL-23 inhibitors, meta-analysis, Risankizumab

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Introduction

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract with rising global prevalence, affecting approximately 1 million individuals in the United States alone.[1] Common symptoms include abdominal pain, chronic diarrhea, weight loss, and fatigue. Diagnosis is typically established through clinical evaluation, imaging studies, endoscopic procedures, and histological analysis.[2] Patients with Crohn's disease often experience significantly lower health-related quality of life compared to healthy individuals, driven by factors such as disease activity, work disability, and frequent hospitalizations.[3] Despite advances in treatment, many patients experience inadequate responses or intolerance to current therapies, highlighting the need for more effective and targeted treatment options.

Current treatment options for Crohn's disease include advanced biological therapies. Anti-TNF agents (e.g., infliximab, adalimumab, and golimumab) are widely used for moderate-to-severe cases. Anti-integrin therapies—such as vedolizumab—block the migration of inflammatory cells and are associated with favorable safety profiles. Recently, interleukin (IL)-23 inhibitors have emerged as promising alternatives. IL-23, part of the IL-12 cytokine family, plays a central role in the pathogenesis of Crohn's disease by promoting T helper 17 cell differentiation and survival. These cells produce pro-inflammatory cytokines, including IL-17A and IL-22, which drive intestinal inflammation. Structurally, IL-23 comprises a unique p19 subunit and a shared p40 subunit (with IL-12).[4,5]

Several IL-23 inhibitors—Risankizumab, Guselkumab, Brazikumab, and Mirikizumab—are currently in clinical use or under investigation for Crohn's disease treatment. Guselkumab has shown promise in inducing clinical and

endoscopic remission, although the study did not demonstrate a dose-dependent effect.[6] Brazikumab has demonstrated clinical benefits in patients with prior anti-TNF failure and has sustained long-term efficacy for over 100 weeks without significant safety concerns.[7] Mirikizumab has demonstrated superior endoscopic response compared to Ustekinumab, further supporting the therapeutic potential of IL-23 inhibition.[8]

Risankizumab, a monoclonal antibody that selectively targets the IL-23 p19 subunit, prevents its interaction with the IL-23 receptor complex. This therapeutic agent is already approved for treating psoriatic arthritis.[9] Compared to other IL-23 inhibitors, risankizumab has been evaluated in more randomized controlled trials (RCTs), providing a more extensive clinical evidence base. While all IL-23 inhibitors share a common mechanism of action, risankizumab has demonstrated significant efficacy in achieving clinical remission, clinical response, and endoscopic remission, with emerging data suggesting potential advantages in dose optimization and long-term safety.

This systematic review and meta-analysis aim to comprehensively assess the efficacy and safety of risankizumab in Crohn's disease by integrating data from multiple RCTs. Additionally, we aim to explore dose- and duration-dependent effects to provide insights into optimal treatment strategies. By synthesizing the available evidence, this study seeks to inform clinical decision-making and support the role of risankizumab as a targeted therapy for Crohn's disease.

Materials and methods

Protocol and registration

This meta-analysis was conducted in accordance with the PRISMA 2020 guidelines (see Supplemental Table S1) and registered with INPLASY (http://INPLASY.com) under registration number INPLASY202530014.[10]

Search strategy and data collection

The authors independently conducted electronic searches in the PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov databases, ("Risankizumab") AND ("Crohn's Disease" OR "Inflammatory Bowel Disease" OR "IBD") AND ("efficacy" OR "treatment outcome" OR "clinical trial") AND ("safety" OR "adverse effects" OR "side effects") AND ("quality of life" OR "QOL") AND ("endoscopic remission" OR "mucosal healing") AND ("biologics" OR "Interleukin-23 inhibitor"). The search covered all available records from each database's inception up to the search date (December 31, 2024). The full search strategy for this systematic review and meta-analysis is provided in the Supplemental Table S2.

Author conducted an initial screening of titles and abstracts to determine eligibility through a consensus-based approach. The PubMed and EMBASE databases were reviewed meticulously for any potentially relevant studies. In cases of disagreement, consensus was sought. No language restrictions were applied to this search.

Eligibility criteria and outcomes

This meta-analysis followed the P (Population): Participants with Crohn's disease. I (Intervention): Risankizumab treatment. C (Comparison): Placebo or standard treatment (e.g., TNF inhibitors, corticosteroids). O (Outcome): Changes in disease activity (e.g., Crohn's Disease Activity Index (CDAI)), endoscopic remission, or adverse events. Inclusion criteria included: (1) RCTs involving human participants, (2) RCTs with quantitative assessments of outcome before and after Risankizumab, and (3) trials providing data on pre- and post-intervention changes in disease activity. Exclusion criteria were: (1) non-RCT studies, (2) studies lacking quantitative disease activity assessments, and (3) studies with participant overlap with previously published trials.

Risk of bias and evidence quality

To evaluate the methodological quality of the included studies, we used the Cochrane Risk of Bias tool for randomized trials (version 2; RoB 2, London, UK). This tool assesses six key domains: randomization process, adherence to intervention, missing outcome data, outcome measurement, selective reporting, and overall risk of bias. For the intervention adherence aspect within RoB 2, two assessment approaches are available: intention-to-treat (based on intervention assignment) and per-protocol (based on adherence). We chose the per-protocol approach for this meta-analysis, as it better aligns with the study designs of our included trials.[11]

Primary outcome (clinical remission, clinical response, and endoscopic remission)

This study primarily assessed changes in clinical remission, clinical response, and endoscopic remission following treatment with Risankizumab or placebo. Additionally, the validity and appropriateness of the scales used in each trial were evaluated,[12–14] or trials employing multiple scoring systems, the score included in the meta-analysis was determined through author consensus.

Secondary outcome (treatment-associated adverse event rates)

As a secondary outcome, this investigation also examined the rate of treatment-related adverse events. The outcomes were measured using odds ratios (ORs).

Data extraction and management

Data were extracted by the author from each study included in this meta-analysis, capturing demographic details, study design elements, information on Risankizumab and placebo treatments, and both primary and secondary outcome values. To maintain accuracy, evaluators carefully verified the direction of effect for each scale used. When data were unavailable in published reports, corresponding authors were contacted for original data. Data extraction, transformation, and consolidation across study arms with differing Risankizumab strategies followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and related medical literature.[15] When multiple post-treatment data points were available, we used the outcome reported at the intervention's conclusion for statistical analysis. In crossover studies, only data from the initial study period were included to avoid carry-over effects.[16]

Statistical analysis

Given the variability of the target populations in the studies, we conducted this meta-analysis using a random-effects model with Comprehensive Meta-Analysis software (version 4; Biostat, Englewood, NJ, USA).[17] Primary outcomes, such as changes in clinical remission, were measured using ORs with 95% confidence intervals (CIs). For secondary outcomes, including treatment-related adverse event rates, ORs with 95% CIs were calculated. Study heterogeneity was assessed using I^2 and Cochran's Q statistics, with I^2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.[18] Meta-regression analyses explored the relationship between Risankizumab's effects and treatment dose or duration.[19] Sensitivity analyses using the one-study removal method were conducted to confirm the robustness of the meta-analysis.[20] Publication bias was evaluated following Cochrane Handbook guidelines, with funnel plots visually inspected for asymmetry.[21] These methodological approaches ensured a comprehensive assessment of Risankizumab's efficacy and safety across diverse study populations.

Results

Study selection and characteristics

Figure 1 illustrates the PRISMA flowchart detailing the literature search process. After removing duplicates and excluding non-relevant articles based on title and abstract screening, we included four RCTs (one study included two RCTs) in the final analysis.[12–14] Supplemental Table S3 lists excluded articles from the final stage, along with exclusion reasons. The 4 eligible RCTs comprised 1774 participants with a mean age of 38.3 ± 13.4 years, 48.2% ($n = 964$) of whom were male. Study durations ranged from 4 to 52 weeks, and all participants had moderate-to-severe Crohn's disease. A summary of the trials is provided in Table 1.[12–14]

Risk of bias and quality of evidence

Among the included studies, 33.3% were rated as low risk of bias, 66.6% as having some risk of bias, and none as high risk (Figure 2). Two studies were classified as having "some" risk of bias due to insufficient information on allocation concealment and loss of follow-up participants. Details of the risk of bias assessment are summarized in Table 2.[12–14]

Primary outcome: effects of Risankizumab on clinical remission, clinical response, and endoscopic remission

In the pooled analysis of four RCTs (Figure 3), Risankizumab demonstrated significant efficacy in achieving clinical remission (OR = 2.223, 95% CI = 1.630–3.033, $p < 0.001$, $I^2 < 0.01\%$), clinical response (OR = 3.618, 95% CI = 2.361–5.545,

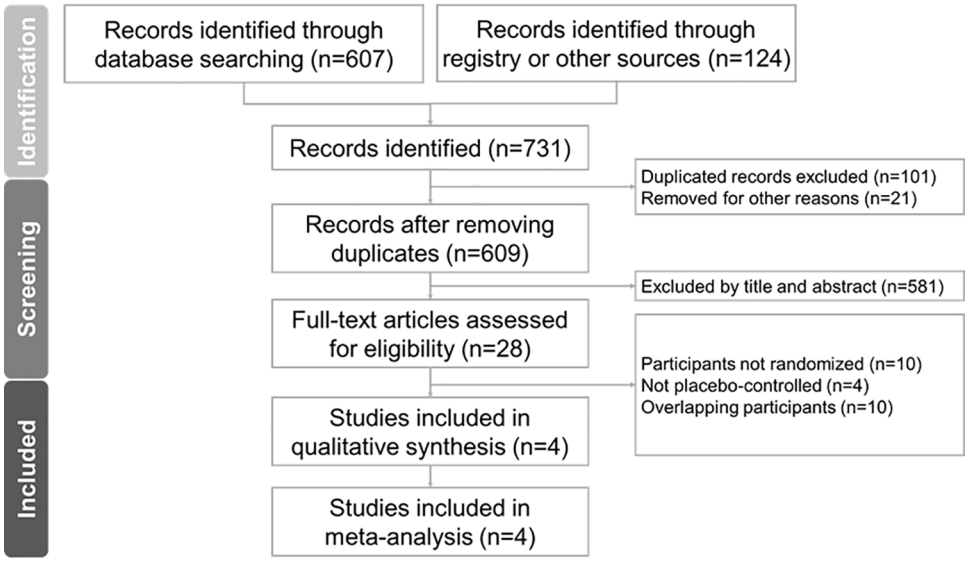

Figure 1. The PRISMA flowchart.

$p < 0.001$, $I^2 = 50.95\%$), and endoscopic remission (OR = 5.741, 95% CI = 2.603–12.66, $p < 0.001$, $I^2 < 0.01\%$). Moderate-to-high heterogeneity was observed in clinical response. Sensitivity analysis using the one-study removal method confirmed the robustness of these findings, with statistical significance remaining stable upon exclusion of any single study (Figure 4).

Meta-regression revealed that higher treatment dosage significantly correlated with improvements in clinical remission (coefficient = 0.0008 per mg, $p = 0.0491$), clinical response (coefficient = 0.0018 per mg, $p = 0.0004$), and endoscopic remission (coefficient = 0.0012 per mg, $p = 0.0001$; Figure 5). Treatment duration was significantly associated with clinical remission (coefficient = 0.0034 per day, $p = 0.0158$), but not with clinical response (coefficient = 0.0055 per day, $p = 0.0670$) or endoscopic remission (coefficient = 0.0026 per day, $p = 0.3171$; Figure 6).

We conducted subgroup analyses to account for variations in disease duration and prior treatments, both of which can influence remission rates. For disease duration, we categorized studies based on a 10-year threshold and performed subgroup analyses accordingly. The association between Risankizumab and placebo remained consistent across both subgroups. In patients with a disease duration of less than 10 years, the ORs were as follows: clinical remission (OR = 2.454, 95% CI = 1.662–3.622, $p < 0.001$), clinical response (OR = 2.116, 95% CI = 1.438–3.115, $p < 0.001$), and endoscopic remission (OR = 3.710, 95% CI = 2.478–5.554, $p < 0.001$). Similarly, in patients with a disease duration exceeding 10 years, the ORs were: clinical remission (OR = 1.872, 95% CI = 1.119–3.132, $p = 0.017$), clinical response (OR = 1.872, 95% CI = 1.119–3.132, $p < 0.001$), and endoscopic remission (OR = 5.827, 95% CI = 2.772–12.248, $p < 0.001$; Supplemental Figure S1).

Regarding prior treatments, all patients had received conventional therapy, while 42% of participants in the D'Haens 2022 (ADVANCE) study were bio-naïve.[12] We conducted a subgroup analysis to compare outcomes between patients previously treated with biologic agents and bio-naïve patients. Among those with prior biologic exposure, the ORs were: clinical remission (OR = 2.344, 95% CI = 1.614–3.404, $p < 0.001$), clinical response (OR = 2.413, 95% CI = 1.358–4.287, $p = 0.003$), and endoscopic remission (OR = 4.851, 95% CI = 3.087–7.622, $p < 0.001$). In contrast, the ORs for bio-naïve patients were: clinical remission (OR = 1.974, 95% CI = 1.127–3.456, $p = 0.017$), clinical response (OR = 2.582, 95% CI = 1.071–6.226, $p = 0.035$), and endoscopic remission (OR = 3.157, 95% CI = 1.782–5.591, $p < 0.001$; Supplemental Figure S2).

Table 1. Summary of the retrieved trials investigating the effect of Risankizumab on Crohn's disease in the enrolled participants.

First author and year	Country	Population	Participants (female/male)	Age[a]	Study design	Allocation concealment	Randomization	Funding/ grants/ support
Feagan 2017	North America, Europe, and Southeast Asia	• Moderate-to-severe Crohn's disease • diagnosed for at least 3 months	200 mg Risankizumab: 26/15[b] 600 mg Risankizumab: 25/16[b] Placebo: 23/16	39 ± 13[b] 40 ± 13 36 ± 14	RCT, double-blind	Independent statistician	Stratified by prior TNF antagonist exposure	N/A
Ferrante 2022	North and South America, Europe, Oceania, Africa, and the Asia-Pacific region	Moderately to severely active Crohn's disease	180 mg Risankizumab: 89/68[b] 360 mg Risankizumab: 60/81 Placebo: 75/89	39.1 ± 14.8[b] 37 ± 12.8 38 ± 13	RCT, double-blind	Independent statistician	Stratified	AbbVie
D'Haens 2022 (ADVANCE)	39 countries	• Moderate-to-severe Crohn's disease • Intolerance to one or more previous treatments	Risankizumab 600 mg: 147/189 Risankizumab 1200 mg: 156/183 Placebo: 87/88	38.3 ± 13.3[b] 37 ± 13.2 37.1 ± 13.4	RCT, double-blind	Not mentioned	Stratified the number of previous biologics that had failed, corticosteroid use at baseline, and the Simple Endoscopic Score for Crohn's disease	AbbVie
D'Haens 2022 (MOTIVATE)	40 countries	• Moderate-to-severe Crohn's disease • Diagnosed for at least 3 months • Inadequate response or intolerance to at least one approved biologic therapy	Risankizumab 600 mg: 99/92 Risankizumab 1200 mg: 89/102 Placebo: 88/99	40.2 ± 13.6[b] 39.3 ± 12.9 39.3 ± 13.5	RCT, double-blind	Not mentioned	Stratified the number of previous biologics that had failed, corticosteroid use at baseline, and the Simple Endoscopic Score for Crohn's disease	AbbVie

[a]Age is presented as means ± standard deviations or as medians (ranges).
[b]Allocated participants.
RCT, randomized controlled trial.

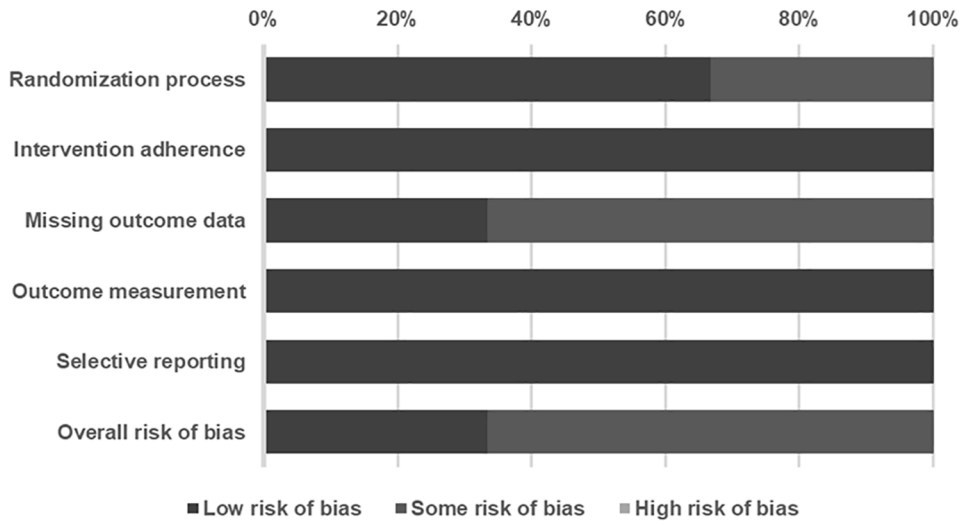

Figure 2. Summary of quality assessment of studies included in the meta-analysis using Cochrane risk of bias 2 tool.

Table 2. Detailed quality assessment of included studies using Cochrane RoB 2 tool.

First author	Year	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB
Ferrante	2022	L	L	S[a]	L	L	S
Feagan	2017	L	L	L	L	L	L
D'Haens	2022	S[b]	L	S[c]	L	L	S

[a]The study excluded two subjects from risankizumab group because of lost follow-up.
[b]The studies didn't provide allocation concealment details.
[c]The study excluded one subject from risankizumab group and two from placebo group because of lost follow-up.
H, high risk of bias; L, low risk of bias; RoB, risk of bias; S, risk of bias.

The funnel plot showed slight asymmetry in effect size distributions (Supplemental Figure S3), and Egger's regression test ($p = 0.73410$) indicated no evidence of publication bias.

Secondary outcome: treatment-associated adverse event rates

Of the 1437 participants receiving Risankizumab, 892 (62.07%) reported adverse events, including nasopharyngitis, arthralgia, headache, nausea, and diarrhea.[12–14] Similarly, adverse events were reported in placebo groups (385 of 616 participants, 62.5%). Meta-analysis of treatment-related adverse events (Supplemental Figure S4) revealed no significant difference between Risankizumab and placebo groups (OR = 0.872, 95% CI: 0.695–1.093, $p = 0.592$, $I^2 < 0.01\%$).

Discussion

Principal findings

In this systematic review and meta-analysis, we synthesized data from four RCTs to evaluate the efficacy of Risankizumab in Crohn's disease. Our findings demonstrate that Risankizumab significantly improves clinical remission, clinical response, and endoscopic remission outcomes. Clinical remission was defined as a CDAI score of <150, while clinical response was defined as a reduction in CDAI of $\geqslant 100$ points from baseline.

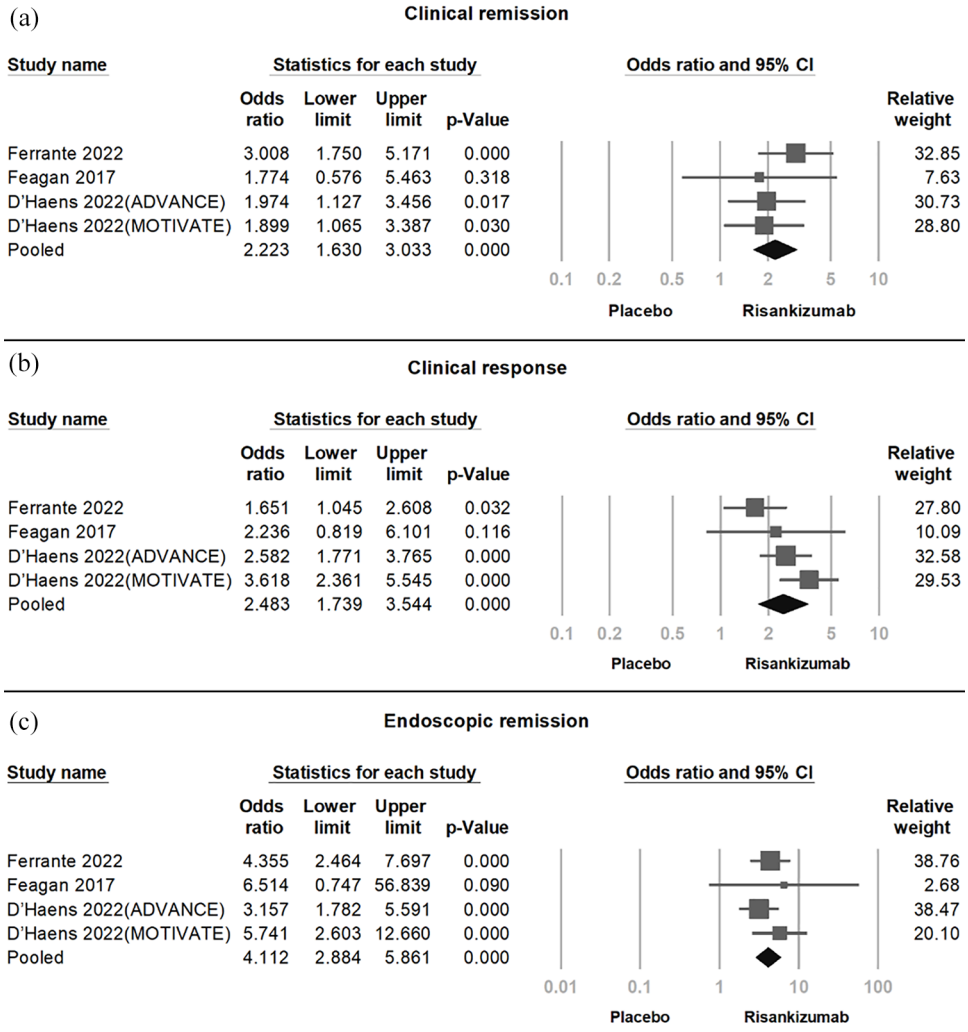

Figure 3. Forest plot showing the significant efficacy of Crohn's disease with Risankizumab across four trials. (a) Clinical remission (OR = 2.223, 95% CI = 1.630–3.033, $p < 0.001$, $I^2 < 0.01\%$). (b) Clinical response (OR = 2.483, 95% CI = 1.739–3.544, $p < 0.001$, $I^2 = 50.95\%$). (c) Endoscopic remission (OR = 4.112, 95% CI = 2.884–5.861, $p < 0.001$, $I^2 < 0.01\%$).
CI, confidence interval; OR, odds ratio.

Endoscopic remission was characterized by a Simple Endoscopic Score for Crohn's Disease ⩽4, with at least a 2-point reduction from baseline and no individual subscore >1, as assessed by central reviewers. These metrics are established benchmarks for assessing therapeutic outcomes in Crohn's disease.[22] Unlike anti-TNF agents, the role of therapeutic drug monitoring for small-molecule agents is more complex. Drug clearance is influenced by individual factors such as low albumin levels, high fecal calprotectin (FCP) levels, and corticosteroid use at the time of induction.[23] Regarding the efficacy of IL-12/23 antagonists as induction therapy, the UNISTAR pediatric RCT study demonstrated that the high-dose arm of Ustekinumab (9 mg/kg or 390 mg) at 16 weeks resulted in better clinical remission compared to the low-dose arm (3 mg/kg or 130 mg).[24] Similarly, Risankizumab exhibits a linear dose–response with repeated administration. It requires three intravenous induction doses (600 mg at weeks 0, 4, and 8), followed by subcutaneous maintenance dosing every 8 weeks, with doses of either 180 or 360 mg starting from week 12. Steady-state concentrations are achieved by week 16.[25] Our regression analysis revealed a dose-dependent relationship, with higher doses of Risankizumab correlating with greater efficacy. This aligns with

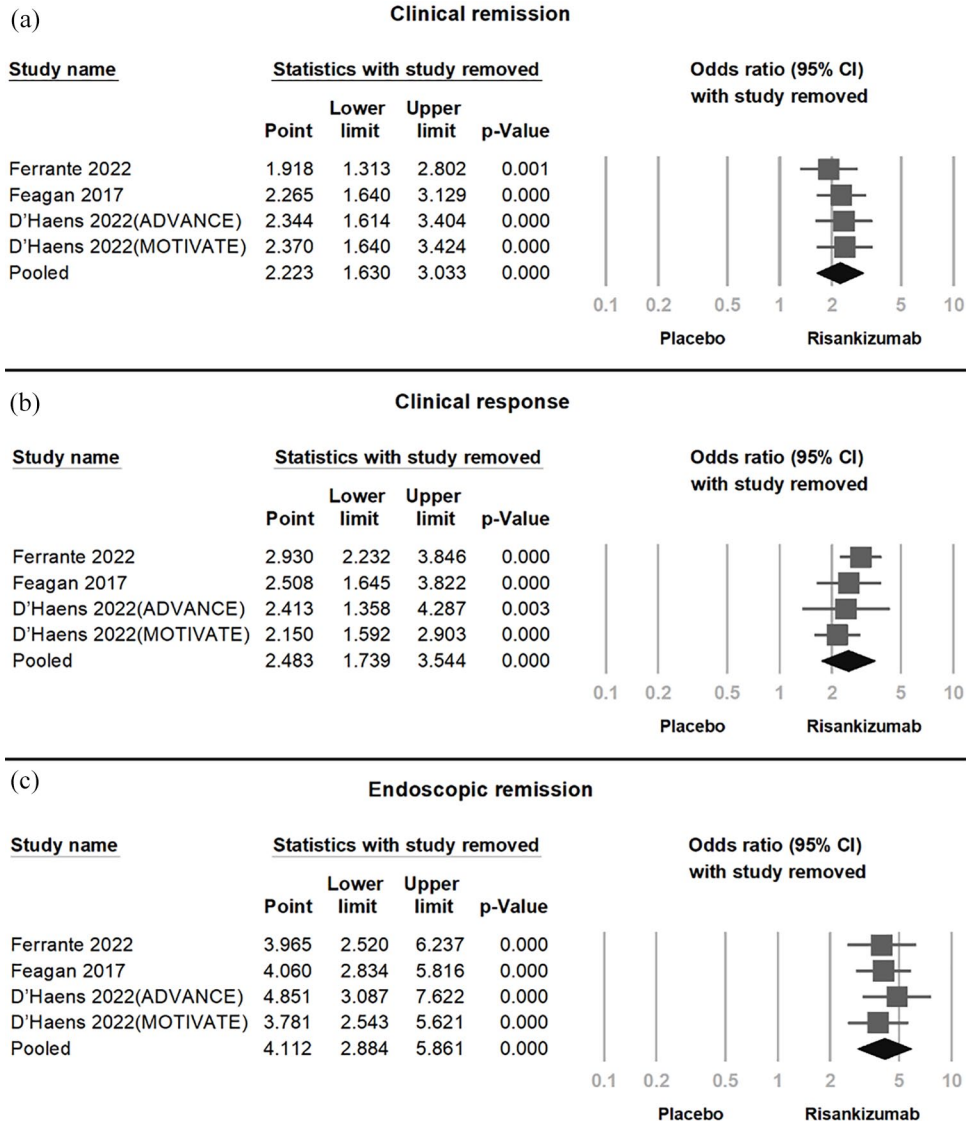

Figure 4. Sensitivity analysis confirming consistent Risankizumab effects on (a) clinical remission, (b) clinical response, and (c) endoscopic remission, with significance maintained across all study removals.

findings from prior reviews exploring the dose-dependent effects of Risankizumab.[26] When treatment duration was considered, only clinical remission showed significant improvement, likely because it reflects sustained and comprehensive patient recovery. In contrast, clinical response captures initial disease activity reduction without indicating long-term stability, and endoscopic remission depends on factors such as baseline mucosal damage and local tissue responses.

Risankizumab demonstrates significant efficacy in Crohn's disease, regardless of disease duration or prior biologic exposure. The subgroup analysis shows that patients with shorter disease duration (<10 years) had slightly higher ORs for clinical remission and response, suggesting better outcomes with earlier intervention. However, patients with longer disease duration (>10 years) experienced more pronounced endoscopic remission, indicating Risankizumab's ability to induce mucosal healing even in refractory cases. Both bio-naïve and biologic-exposed patients benefited from the treatment, with strong improvements in clinical and endoscopic outcomes. These findings support Risankizumab's use as an effective option for both early and long-standing disease, as well as for patients with prior biologic failure.

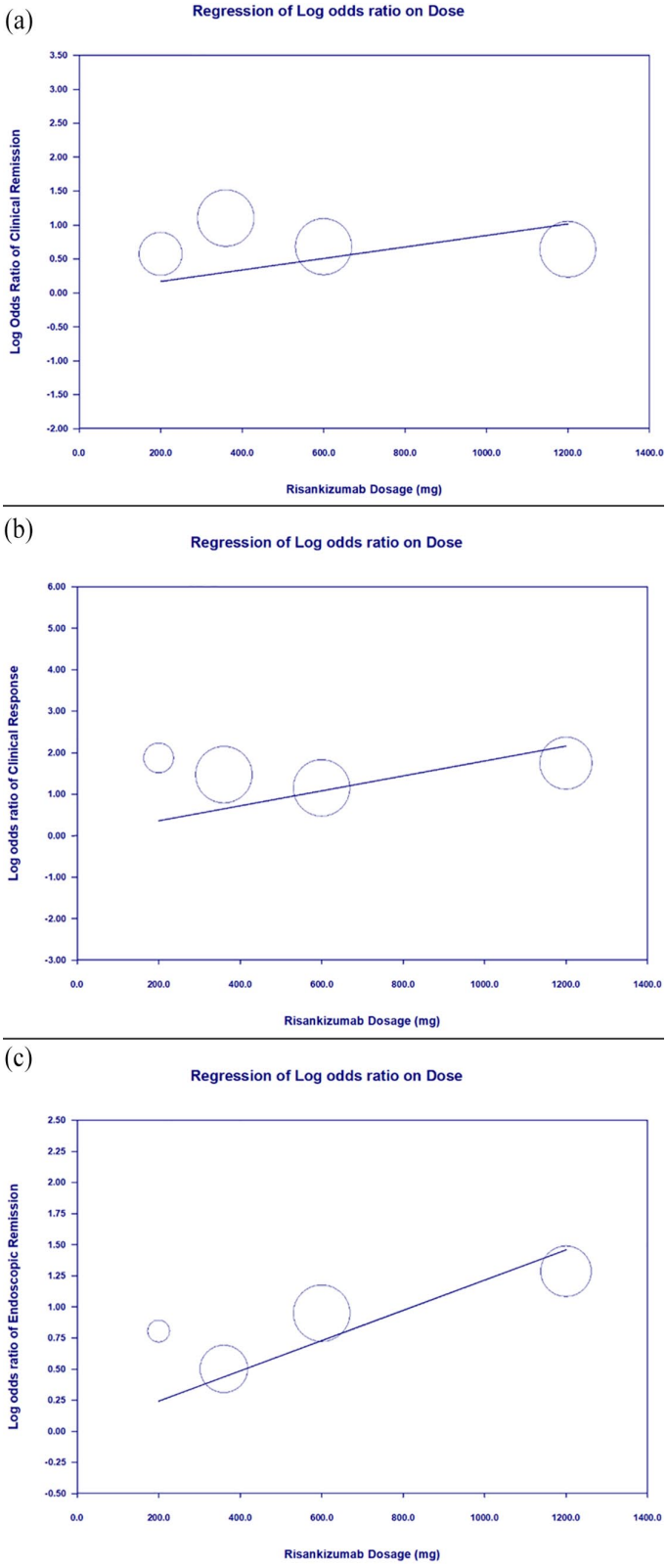

Figure 5. Meta-regression showing the correlation between treatment dosage and outcome. (a) Clinical remission (coefficient = 0.0008 per mg, $p = 0.0491$). (b) Clinical response (coefficient = 0.0018 per mg, $p = 0.0004$). (c) Endoscopic remission (coefficient = 0.0012 per mg, $p = 0.0001$).

The baseline conditions of participants, all of whom had moderate-to-severe Crohn's disease, did not significantly affect Risankizumab's clinical response. Some trials included patients intolerant to previous therapies, highlighting its potential role in refractory cases.[12] However, moderate heterogeneity in clinical response may be influenced by baseline disease severity (mean disease duration: 8.8 years in ADVANCE vs 11.7 years in MOTIVATE), previous biologic failure (ranging from 47% to 73% across trials), and trial duration (12-week induction vs 52-week maintenance). Sensitivity analyses confirmed the robustness of these findings. Previous meta-analyses have established Risankizumab's efficacy in conditions like psoriatic arthritis.[9] Network meta-analyses also suggest Risankizumab offers the highest probability of early remission induction and superior clinical responses in biologic-exposed patients compared to other Crohn's disease treatments.[27] Our findings are consistent, showing that Risankizumab produces mild-to-large improvements in clinical outcomes, depending on the assessment used.

The included RCTs showed no significant differences in adverse event rates between Risankizumab and placebo groups. Common adverse events included headache and nasopharyngitis. Serious infections (e.g., opportunistic infections, herpes zoster, and COVID-19) were rare and observed across all groups. Hepatic events were infrequent, occurring in less than 4% of participants, primarily as mild liver enzyme elevations.[28] Given the relatively short duration of the included trials (4–52 weeks), long-term safety remains a concern. However, no serious adverse effects, such as opportunistic infections, active tuberculosis, or herpes zoster, were observed. Nonetheless, long-term rates of infection and malignancy are still under investigation. While adverse events associated with Risankizumab are manageable, its significant efficacy in inducing clinical remission and response, particularly in biologic-exposed or refractory cases, underlines its potential as a promising therapeutic option for moderate-to-severe Crohn's disease.

Insights for Clinical Practice Risankizumab, a humanized monoclonal antibody targeting the p19 subunit of IL-23, is approved for moderate-to-severe Crohn's disease in adults. By inhibiting the IL-23/Th17 axis, Risankizumab reduces gene expression related to inflammation, biomarkers like FCP and high-sensitivity C-reactive protein

(hs-CRP), and Th17 cells in the gut.[5,25] Our study highlights Risankizumab as a promising therapeutic option. However, treatment outcomes can be influenced by several factors, including disease duration, prior bowel resection, extraintestinal manifestations (EIMs), previous biologic exposure, number of prior therapies, and patient-specific variables such as age, gender, and smoking status.

Patient-reported outcomes, including AP and stool frequency (SF), were assessed at baseline and weeks 24 and 52. Clinical remission was defined as an average daily SF ⩽2.8 and an AP score ⩽1, while clinical response was defined as a ⩾30% reduction in average daily AP and/or SF. In the two induction RCTs, ADVANCE (42% bio-naïve) and MOTIVATE (47% with only one prior biologic exposure), 37.6% of patients achieved steroid-free clinical remission at week 12. In the FORTIFY trial, subcutaneous risankizumab maintenance therapy, following induction with ADVANCE and MOTIVATE, led to approximately 60% of patients achieving steroid-free clinical remission at week 52 (51.8% in the 360 mg arm and 46.5% in the 180 mg arm). These findings suggest that durable clinical remission is correlated with subcutaneous risankizumab maintenance therapy.[12,29] In a Belgian multicentric cohort study focusing on multirefractory Crohn's disease (85.5% of patients exposed to at least four advanced therapies and 98.6% to ustekinumab, with 14 having an ostomy), clinical outcomes were assessed at weeks 24 and 52. Among patients without an ostomy, 61.8% (34/55) achieved a steroid-free clinical response, while 18.2% (10/55) attained remission at week 24. By week 52, these rates were 58.2% (32/55) and 27.3% (15/55), respectively. Outcomes for patients with an ostomy were comparable, with 42.9% achieving a steroid-free clinical response and 14.3% achieving remission.[29] These findings support the efficacy of risankizumab in treating multirefractory Crohn's disease patients.

The STRIDE-II and SPIRIT initiatives outline treatment goals for Crohn's disease, starting with clinical response, followed by clinical remission to ensure symptom control and biomarker reduction. Long-term objectives include endoscopic healing and improved quality of life.[30,31] An open-label extension study by Ferrante et al.[14] demonstrated that median reductions were noted at week 0 (FCP ⩽250 mg/kg; hs-CRP ⩽5 mg/L)

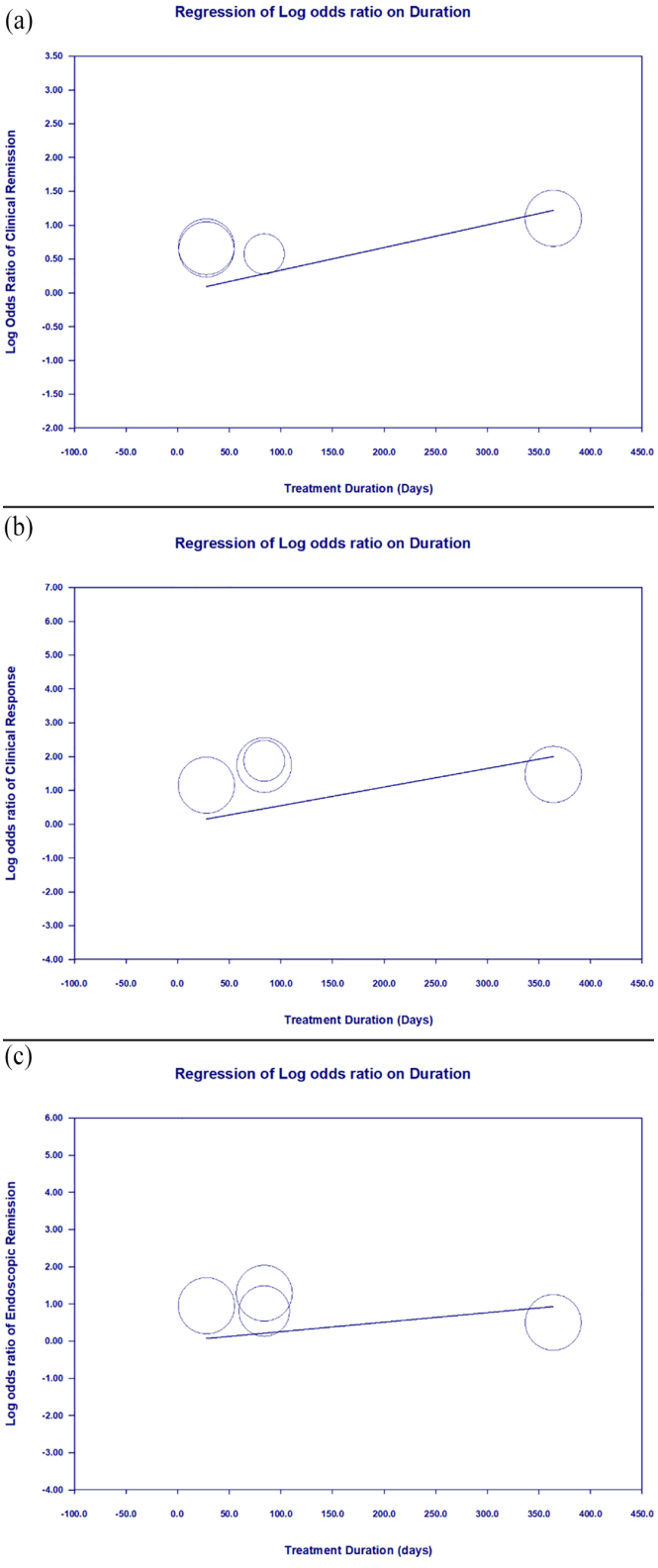

Figure 6. Meta-regression showing the correlation between treatment duration and outcome. (a) Clinical remission (coefficient = 0.0034 per day, $p = 0.0158$), achieved statistical significance. (b) Clinical response without statistical significance (coefficient = 0.0055 per day, $p = 0.0670$). (c) Endoscopic remission without statistical significance (coefficient = 0.0026 per day, $p = 0.3171$).

and sustained through week 52, reinforcing Risankizumab's efficacy.

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated, widely used disease-specific tool that assesses IBD across four dimensions: bowel symptoms, systemic symptoms, social functioning, and emotional well-being.[32] Among patients treated with Risankizumab, the percentage who achieved an IBDQ response and remission following 12 weeks of induction treatment was sustained through 52 weeks of maintenance therapy. Furthermore, a greater proportion of patients achieved IBDQ response and remission after 52 weeks of maintenance treatment with risankizumab.[33]

EIMs, including skin, joint, and systemic organ involvement, are common challenges in Crohn's disease. IL-23 plays a critical role in Th17-mediated inflammation, contributing to these manifestations. Meta-analyses have shown significant associations between psoriasis and IBD, with higher risk in Crohn's disease (risk ratio, 2.53, 95% CI: 1.65–3.89).[34,35] Risankizumab, a humanized monoclonal antibody targeting IL-23, has shown significant efficacy in treating moderate-to-severe plaque psoriasis, as demonstrated in head-to-head efficacy comparisons.[36] The 2024 ECCO guidelines on EIMs in Crohn's disease recommend humanized monoclonal antibodies, such as Risankizumab, for refractory or severe skin conditions like pyoderma gangrenosum. However, TNF-α antagonists, commonly used in IBD, are associated with complications such as paradoxical psoriasis, psoriasiform eczema, and palmoplantar pustulosis.[37] These complications may result from a shift from Th1 to Th2 responses, inhibiting macrophage apoptosis and promoting abnormal T-cell activation. A case report highlighted the efficacy of Risankizumab in a Crohn's disease patient with concurrent IgA nephropathy and guttate psoriasis. IgA nephropathy is marked by elevated Th2 and Th17 cell levels and reduced Th1 activity. IL-23 inhibition effectively downregulated Th17-mediated pathways, achieving promising disease control.[38] Spondyloarthritis (SpA) is another common EIM in IBD. Shared genetic loci between SpA and IBD, particularly within the IL-12/23 pathway, underscore their interconnected pathophysiology. The 2024 ECCO guidelines also highlight the effectiveness of ustekinumab in treating non-axial spondyloarthropathy, including psoriatic arthropathy and arthralgia, in Crohn's disease patients.[39]

Crohn's disease is influenced by various factors, with smoking behavior serving as a significant genetic and environmental contributor. The interleukin-23 receptor (IL23R) has been identified as a critical determinant of disease susceptibility in independent patient cohorts. Database analyses suggest a potential mechanism linking IL23R variants, smoking behavior, and Crohn's disease-associated genes, such as NOD2 and ATG16L1. IL-23, a key cytokine, plays a central role in orchestrating innate and T-cell-mediated immune responses during intestinal inflammation.[40,41] Clinically, smoking exacerbates disease severity, increasing the frequency of flare-ups, penetrating complications, and the likelihood of requiring surgical intervention compared to non-smokers. Moreover, therapeutic responses may differ across subgroups, underscoring the importance of personalized treatment approaches. Notably, a strong additive interaction exists between IL23R single nucleotide polymorphisms and smoking behavior, significantly elevating disease risk in specific genetic backgrounds.[42]

The analyzed RCTs primarily included relatively young participants, with limited subgroup analyses addressing elderly patients. The efficacy and safety of biological agents, including Risankizumab, can vary with age. While some studies report similar outcomes between elderly and younger individuals, others indicate reduced efficacy or an increased risk of adverse events in older populations.[40] However, evidence on the use of Risankizumab in elderly patients remains scarce.[43] Future research should focus on biologic-naïve populations, age-specific effects, long-term follow-up, and large-scale RCTs to comprehensively evaluate the efficacy and safety of Risankizumab in Crohn's disease.

Strengths and limitations

The strengths of this review include a robust and comprehensive search strategy, the inclusion of studies with diverse populations and Risankizumab treatment protocols, and the utilization of standardized outcome measures to ensure consistency and reliability. However, limitations include the relatively small number of studies analyzed and the heterogeneity in reporting corticosteroid use across trials, which

precluded a formal subgroup analysis based on this variable. Furthermore, the overlap in patient cohorts across some included studies may introduce a degree of dependency, potentially influencing effect estimates. Additional research is needed to confirm these findings and further explore the long-term efficacy of risankizumab across different patient subgroups.

Relation to prior work

A prior systematic review assessed the efficacy and safety of selective IL-23p19 and IL-12/23p40 inhibitors in patients with moderate-to-severe Crohn's disease, establishing the role of IL-23 antagonists in clinical care. However, registry-based data for IL-23p19 antagonists in Crohn's disease are still needed.[44] Our study extends this body of work by identifying dose-dependent efficacy trends and emphasizing the potential benefits of prolonged treatment for achieving clinical remission. By employing a one-study-removed sensitivity analysis and ORs for statistical evaluation, we present evidence of moderate efficacy in improving clinical outcomes for patients with Crohn's disease.

Conclusion

This systematic review and meta-analysis assessed the effects of Risankizumab on clinical outcomes in Crohn's disease, synthesizing data from four RCTs. The results demonstrate that Risankizumab significantly enhances clinical remission, clinical response, and endoscopic remission, with efficacy showing a clear dose-dependent trend. The safety profile of Risankizumab is favorable, with manageable adverse events and no significant differences observed compared to placebo. Mechanistically, Risankizumab targets the IL-23/Th17 pathway, effectively mitigating inflammation associated with Crohn's disease. However, the small number of studies may impact the reliability of these findings. Additional large-scale RCTs are required to confirm its long-term effectiveness, safety in elderly populations, and efficacy in biologic-naïve patients.

Declarations

Ethics approval and consent to participate

This study is a meta-analysis that exclusively utilizes data extracted from previously published trials, all of which have obtained ethical approval and informed consent from participants as per their respective study protocols. No new patient data were collected, and no direct patient interaction was involved. Therefore, additional informed consent was not required for this study. Regarding Institutional Review Board (IRB) approval, we applied to the Tri-Service General Hospital IRB under application number 62689, and it was classified as an exempt study.

Consent for publication

Not applicable.

Author contributions

Po-Feng Huang: Conceptualization; Investigation; Methodology; Writing – original draft.

Tien-Yu Huang: Conceptualization; Resources.

Yi-Chiao Cheng: Formal analysis; Software.

Peng-Jen Chen: Investigation; Writing – review & editing.

Wei-Kuo Chang: Funding acquisition; Validation; Visualization; Writing – review & editing.

Chao-Feng Chang: Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are publicly available since this is a systematic review of published literature.

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Supplemental material

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