Research Paper

Study of the Effects of Risankizumab in Moderate to Severe Crohn's Disease

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To study the effect of risankizumab in moderate to severe Crohn's disease. In the trial, 80 patients with moderate-to-severe Crohn's disease who were hospitalized to our hospital between January 2021 and January 2022 were randomly assigned to the risankizumab group (n=40, with risankizumab added to conventional treatment) or the placebo group (n=40, with placebo added to conventional treatment) to compare the clinical efficacy, inflammatory indexes, incidence of adverse effects and quality of life of the two groups scores. The clinical remission rate and endoscopic remission rate were both higher in the risankizumab group than in the placebo group ($p<0.05$). After therapy, the risankizumab group had lower levels of C-reactive protein, platelet count, erythrocyte sedimentation rate, all quality of life scores, and the frequency of adverse reactions than the placebo group, while the mean platelet volume was higher than the placebo group ($p<0.05$). Risankizumab is effective in treating moderate to severe Crohn's disease, relieving the inflammatory state of the body, reducing the occurrence of adverse effects and improving quality of life.

Key words: Risankizumab, Crohn's disease, clinical remission, endoscopic remission, inflammatory response, quality of life

A chronic Inflammatory Bowel Disease (IBD) marked by ulceration and transmural inflammation is called Crohn's Disease (CD)[1], which can involve the entire GI tract and organs other than the GI tract such as joints, skin and eyes. The cause of CD is currently unknown and the pathogenesis may be related to a dysregulated immune response due to a complex interaction of genetic susceptibility, the environment and altered intestinal flora[2]. Patient's health and even lives are in grave danger if CD is not treated quickly and efficiently since it can result in problems such intestinal blockage, digestive tract perforation, gastrointestinal hemorrhage, and even malignancy. Traditional drugs are unable to interrupt the underlying inflammatory development of CD, let alone achieve the goal of targeted therapy[3]. Biological agents, on the other hand, can act on specific targets to control the inflammatory response in the body, thus significantly improving clinical symptoms. Since they were the first biologics used to treat IBD, anti-Tumor Necrosis Factor Alpha (TNF) medications have demonstrated efficacy in causing and maintaining remission in CD and ulcerative colitis[4,5]. However, relevant studies have shown that approximately 20 %-30 % of patients do not respond to anti-TNF-alpha (α) therapy and that secondary loss of response occurs in 15 %-20 % of patients each year[6]. At the same time, anti-TNF-α therapy increases the risk of local or acute infusion reactions, opportunistic infections and malignancies[7,8]. As a result, new drugs are being sought to address the unmet therapeutic needs of patients with CD.

Relevant basic research has highlighted the key role of impaired innate and adaptive immune responses in the pathogenesis of intestinal injury diseases, with Interleukin (IL)-12 and IL-23 being the main drivers of adaptive immune responses, particularly in CD. IL12/23 blockers or specific IL-23 blockers have emerged as a new therapeutic option for CD options. An IL-12/23 blocker, has beneficial effects on both IL-12 and IL-23 inhibition, and its effect size of inducing clinical remission can be as high as 9 %-18 % in patients who have failed previous TNF-α therapy[9,10]. However, it is not clear which cytokine

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inhibition of IL-12 and IL-23 drives the efficacy of the drug and its efficacy needs to be referenced with caution.

Basic studies have shown that blockade of IL-23 alone inhibits T cell-mediated reduction of inflammatory responses in colitis compared to blockade of IL-12 alone[11,12]. Additionally, genetic investigations have demonstrated an association between CD and polymorphisms in the human IL-23 receptor[13]. Thus, while targeting the IL-23 pathway represents an important opportunity for CD drug development. Genetic polymorphisms in IL-23 are associated with CD susceptibility and are key regulators of T helper and type 3 innate lymphocyte pathways that play a major role in inflammatory cell production and tissue inflammation formation[14,15]. A humanized Immunoglobulin G (IgG) monoclonal antibody called risankizumab binds to and neutralizes the IL-23 p19 subunit, inhibiting the activation of IL-23 receptors and disabling the IL-23/Th17 axis, which is crucial in reducing CD inflammation[16,17]. The US Food and Drug Administration (FDA) approved risankizumab in June 2022 for the treatment of moderately to severely active CD, and numerous trials have demonstrated its therapeutic efficacy. However, due to geographical differences, the effect of Risankizumab in Chinese patients with CD has not been observed; also, risankizumab has only recently been approved for the treatment of CD, and further research is required to determine whether it is effective.

On the basis of this, we carried out a randomized double-blind controlled experiment in a tertiary care hospital in China with the intention of examining the impact of risankizumab in the treatment of moderate to severe CD and offering a quick reference for clinical CD.

MATERIALS AND METHODS

Experimental design:

Eighty moderate-to-severe CD patients who were hospitalized to our hospital between January 2021 and January 2022 were included in the trial, and they were randomly assigned to either the risankizumab group (n=40, with risankizumab added to conventional treatment) or the placebo group (n=40, with placebo added to conventional treatment), as shown in fig. 1. All study subjects signed an informed consent form and the study was approved by the medical ethics committee of our hospital.

Inclusion and exclusion criteria:

Inclusion criteria: The study included patients who fit the following criteria; age 18 y-75 y; diagnosed with CD for ≥3 mo; moderate to severe disease severity: CD Activity Index (CDAI) of 220-450, ileal or (and) colonic mucosal ulcers, CD Internal Diameter Severity index (CDESI) ≥7; and complete treatment at our institution after diagnosis.

Exclusion criteria: Patients previously treated with national ustekinumab; patients treated with other biologics within 8 w prior to study entry, patients with combined cardiac, hepatic or renal dysfunction, patients with combined autoimmune or other inflammatory diseases, patients with combined malignancies, and women who are pregnant or breastfeeding.

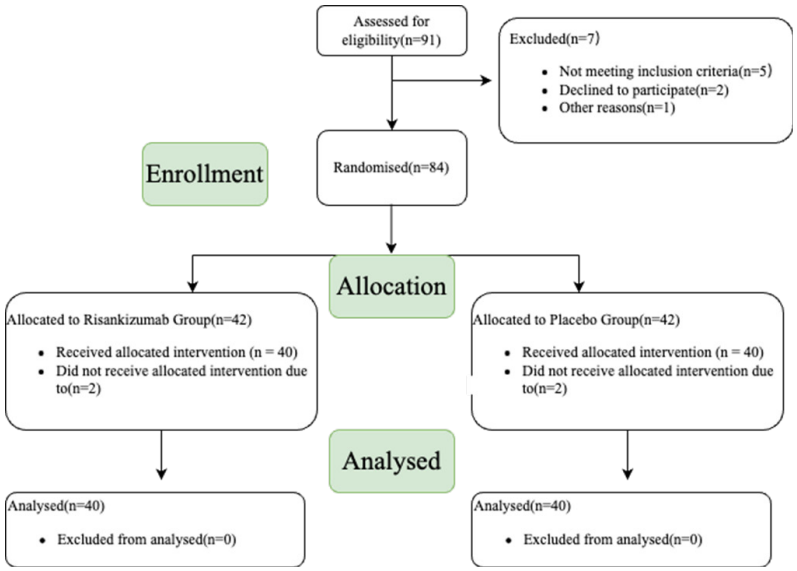

Fig. 1: Study subject inclusion process

Treatment methods:

At 0, 4 and 8 w before the start of the study, risankizumab or placebo 600 mg was given intravenously for induction treatment in both groups. At 12 w, risankizumab 360 mg or placebo was administered subcutaneously for maintenance treatment every 8 w. A total of 52 w of treatment was given.

Primary outcome measures:

Clinical outcome: The effectiveness of the treatment is evaluated at its conclusion. Clinical remission is defined as CDAI 150 and endoscopic remission as a CDESI score 4 (or 2 in patients with isolated ileitis). These two conditions are combined to form profound remission.

Inflammatory indicators: Before and after therapy, blood samples from patients were taken, and C-Reactive Protein (CRP) levels were determined using the immunoturbidimetric technique, Platelet (PLT) count and Mean Platelet Volume (MPV) were measured using the hemocytometer and Erythrocyte Sedimentation Rate (ESR) was measured using the Weil's method. Determine the incidence of adverse responses in both groups while tracking their occurrence during therapy.

Secondary outcome measures:

Quality of life score: The EuroQol 5-Dimension 5-Level (EQ-5D-5L)19 measures a patient's quality of life on five dimensions; mobility, self-care, daily activities, pain/discomfort and anxiety/depression, on a scale from "no problem" to "extreme problem," with higher scores indicating lower quality of life.

Safe endpoints: Safety endpoints are Adverse Events (AEs), AEs are coded using the medical dictionary for regulatory activities version 21.1 and severity is graded according to the common Toxicity Criteria in Rheumatology version 4.0.

Statistical processing:

The analysis software was Statistical Package for the Social Sciences (SPSS) 21.0 and the plotting software was GraphPad Prism 9.0. Differences were indicated as statistically significant at $p<0.05$. Measurement data were expressed as ($\bar{x}\pm s$) and compared using t-test, Analysis of Variance (ANOVA), and Least Significant Difference (LSD) test; count data were expressed as [n (%)] and compared using the Chi-square (χ^2) test. At $p<0.05$, differences were declared statistically significant.

RESULTS AND DISCUSSION

No patients in either group discontinued the study due to AEs. Between the two groups, there were no variations in the demographic and baseline data ($p>0.05$, Table 1). In comparison to the placebo group, the risankizumab group saw more deep remissions ($p<0.05$, Table 2).

Prior to therapy, there was no difference between the two groups' CRP, PLT, MPV and ESR levels ($p>0.05$). After treatment, MPV grew in both groups, but the risankizumab group was higher than the placebo group ($p<0.05$, fig. 2A), and CRP, PLT and ESR levels fell in both groups, with the risankizumab group having lower levels than the placebo group ($p<0.05$, fig. 2B-fig. 2D).

There was no distinction between the two groups in the frequency of unfavorable reactions ($p>0.05$, Table 3). Before treatment, there was no difference in all EQ-5D-5L scores between the two groups ($p>0.05$). After treatment, all scores decreased in both groups, with the risankizumab group being even lower than the placebo group ($p<0.05$, fig. 3).

Data show that nearly 300 people in Europe suffer from CD for every 1 00 000 people[18,19], and the incidence is increasing. The incidence of CD is increasing and has exceeded the mortality rate[20]. While 20 %-30 % of CD patients do not respond to anti-TNF-α therapy, the majority of CD patients experience relapses and >50 % require surgery within 10 y of their initial diagnosis[21]. Therefore, finding new therapeutic targets and creating potent medications are crucial for the treatment of CD. This study investigated the role of risankizumab, a humanized IgG monoclonal antibody against IL-23p1[22], when dealing with moderate to severe CD. The results showed that the clinical and endoscopic remission rates for CD patients treated with risankizumab were 80.00 % and 85.00 % respectively, higher than the placebo group, suggesting that patients with moderate to severe CD may benefit from treatment with risankizumab, which is consistent with previous studies. The study by Feagan *et al.*[23] conducted induction therapy in CD patients for 12 w, with maintenance treatment starting after 12 w. The entire course of treatment continued until 52 w and their assessment of efficacy at 12 w showed that the induction effect of risankizumab was significant as endoscopic remission rates and clinical remission rates were higher in CD patients treated with risankizumab than in those receiving placebo.

In this trial, individuals with moderate to severe CD received 12 w of induction therapy followed by 52 w of maintenance therapy. According to the study's findings, risankizumab has a good maintenance impact since both the clinical and endoscopic remission rates were greater. Taken together, it is clear that both induction and maintenance treatment with risankizumab are highly effective in treating moderate to severe CD, with no decline in efficacy with longer treatment duration, and that the efficacy is durable and good. This study also showed that risankizumab therapy did not increase the frequency of AEs, demonstrating the drug's safety.

Since CD is an inflammatory disease, inflammatory markers like CRP and WBC in patients play a role

TABLE 1: DEMOGRAPHICS AND BASELINE INFORMATION

	Risankizumab group (n=40)	Placebo group (n=40)	χ^2 or t	p
Age (years)	37.13±13.42	37.22±13.21	0.03	0.976
Sex			0.051	0.822
Female, n (%)	23 (57.50)	22 (55.00)		
Male, n (%)	17 (42.50)	18 (45.00)		
CD duration (years)	7.24±1.11	7.28±1.21		
CD location	0.028	0.028	0.028	0.028
Ileal, n (%)	6 (15.00)	5 (12.50)	0.105	0.745
Colonic, n (%)	18 (45.00)	18 (45.00)	0.000	1.000
Ileal-colonic, n (%)	16 (40.00)	17 (42.50)	0.052	0.82
CDAI scores	295.49±14.39	296.08±14.41	0.183	0.855
CDESI scores	11.19±2.17	11.23±2.21	0.082	0.935

TABLE 2: CLINICAL OUTCOMES [n (%)]

	Risankizumab group (n=40)	Placebo group (n=40)	χ^2	p
Clinical remission	32 (80.00)	23 (57.50)	4.713	0.03
Endoscopic remission	34 (85.00)	26 (65.00)	4.267	0.039
Deep remission	66/80 (82.50)	49/80 (62.25)	8.935	0.003

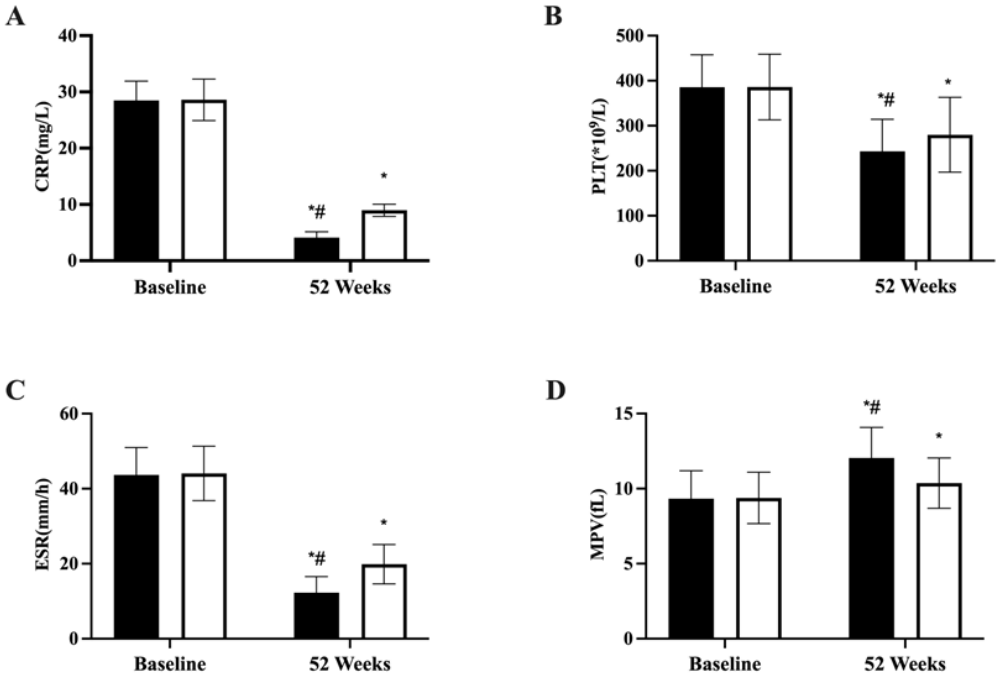

Fig. 2: Comparison of inflammatory parameters between the two groups, (A): Comparison of CRP; (B): Comparison of PLT; (C): Comparison of ESR and (D): Comparison of MPV
Note: (▬): Risankizumab group and (▭): Placebo group

TABLE 3: ADVERSE REACTIONS [n (%)]

	Risankizumab group (n=40)	Placebo group (n=40)	χ^2	p
Nausea	1 (2.50)	1 (2.50)	-	-
Worsening of Crohn's disease	0 (0.00)	1 (2.50)	-	-
Abdominal pain	1 (2.50)	1 (2.50)	-	-
Arthralgia	1 (2.50)	1 (2.50)	-	-
Anemia	1 (2.50)	1 (2.50)	-	-
Headache	1 (2.50)	2 (5.00)	-	-
Total	5 (12.50)	7 (17.50)	0.392	0.531

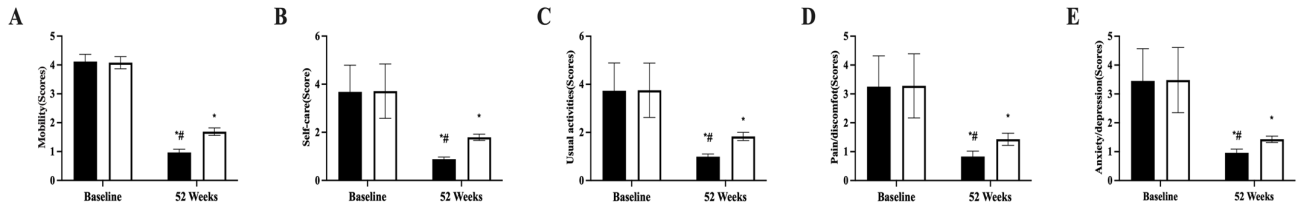

Fig. 3: Quality of life scores, (A): Molility comparison; (B): Self-care comparison; (C): Usual activities comparison; (D): Pain/discomfort comparison and (E): Anxiety/depression comparison
Note: (▬): Risankizumab group and (▭): Placebo group

in the onset and evolution of the condition and are crucial signs of CD activity[24]. And the reduction of inflammatory factor expression in the blood of CD patients is consistent with the blockade of IL-23 mediated intestinal inflammation[25]. Inflammatory markers like CRP were significantly lower in patients with moderate to severe CD who received risankizumab compared to those who received a placebo. According to our study, confirming that risankizumab is effective in downregulating inflammatory pathways associated with the IL-23 axis, thus achieving the desired effect of alleviating the inflammatory response of the organism in patients with CD.

A meta-analysis showed that 47 % of people with IBD have fatigue, up to 72 % in active IBD, and that >50 % of people in remission still have fatigue[14,26]. The burdensome symptom of debilitating fatigue has a detrimental effect on quality of life. Also, studies have shown that there is a greater financial burden for people with CD, which may be related to the cost of treatment required for chronic comorbidities or co-morbidities. This may lead to negative emotions such as anxiety and depression, which are detrimental to quality of life[27]. Our results show that patients treated with risankizumab have a higher quality of life after treatment, which may be related to the significant and sustained efficacy and higher safety profile as reflected by the low incidence of AEs. The improved quality of life suggests that risankizumab may provide additional benefits to patients with moderate to severe CD.

Firstly, the small number of subjects in this study will lead to a degree of statistical calculation chance and may reduce the credibility and generalizability of the conclusions. Secondly, the treatment period of 52 w is long and this study did not assess the efficacy of the patients and monitor laboratory indicators, etc. during the course of treatment and did not obtain dynamic changes in the indicators assessed. Third, the observational indicators in this study were not rich enough to fully explain the important role of risankizumab in moderate to severe CD and the benefit to patients. In future studies, the above limitations will be focused on and addressed.

Risankizumab is one of the new options for patients with moderate to severe CD as it can effectively induce and maintain clinical remission, endoscopic remission, reduce inflammatory response and improve quality of life in patients with CD with a high safety profile. However, it still suffers from a relatively short period of clinical application and insufficient clinical experience. This conclusion needs to be supported by more clinical studies and real-world follow-up data.

Author's contributions:

Yuan Fang and Jipeng Li have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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