The Role of IL-23 Inhibitors in Crohn’s Disease

Subjects: Gastroenterology & Hepatology

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Promoting a Th17 pathogenic response, the interleukin (IL)-23 pathway is crucial in the pathophysiology of inflammatory bowel disease (IBD). With a favorable safety profile, ustekinumab, a monoclonal antibody targeting the shared p40 component of IL-12/23, is currently approved for the treatment of IBD in patients with disease refractory to corticosteroids and biologic drugs. Risankizumab, mirikizumab, and guselkumab are specific IL-23p19 antagonists tested for the treatment of Crohn’s disease (CD). However, only risankizumab currently has been approved for its treatment. Trials with guselkumab and mirikizumab are currently ongoing, with promising preliminary efficacy and safety results.

Keywords: inflammatory bowel disease ; Crohn’s disease ; IL-23 inhibitors ; risankizumab ; guselkumab ; mirikizumab ; brazikumab

1. Risankizumab

1.1. Efficacy

Risankizumab is a humanized IgG1 monoclonal antibody already approved in 2019 for the treatment of moderate-to-severe plaque psoriasis [1].

It was initially studied for the treatment of moderate-to-severe CD in a phase II, proof of concept, multicenter, randomized, double-blind, placebo-controlled induction trial [2].

In this trial, 121 patients were enrolled; 93% of them had failed to respond to previous treatment with TNF-antagonists or vedolizumab and with moderate-to-severe CD defined by a Crohn’s disease endoscopic index of severity (CDEIS) ≥7 or ≥4 for isolated ileitis and a CDAI score between 220 and 450. These patients were randomized 1:1:1 to receive intravenous (IV) risankizumab (600 mg), risankizumab (200 mg), or a placebo once daily at week 0, 4, and 8 for an induction period of 12 weeks. The primary endpoint of clinical remission, defined by a CDAI < 150 at week 12, was achieved in 24% (200 mg group) and 37% (600 mg group) of patients treated with the drug compared with 15.4% in the placebo arm (p = 0.0489). Clinical response (CDAI < 150 or decrease of ≥100 points), endoscopic remission (CDEIS ≤ 4 or ≤2 for isolated ileitis), endoscopic response (decrease ≥50% of CDEIS), and deep remission (clinical plus endoscopic remission) were the secondary endpoints of the study. A higher rate of patients on risankizumab therapy achieved secondary endpoints: for clinical response: 31% in the pooled risankizumab dose groups vs. 15% of the placebo group (p = 0.0489); for endoscopic remission, 17% vs. 3% (p = 0.0015); for endoscopic response, 32% vs. 13% (p = 0.0104); while for deep remission, 7% vs. 0% of the placebo arm (p = 0.0107) [2].

In an open-label extension of the study, patients who did not achieve clinical remission and endoscopic remission at week 12 received open-label IV therapy with risankizumab (600 mg) every 4 weeks for 12 weeks, while those who did reach deep remission entered a 12-week washout phase. At week 26, 55% of patients in the placebo group, 59% in the 200 mg group, and 47% in the 600 mg group achieved clinical remission [3].

At week 26, 62 patients who were in clinical remission started maintenance therapy with a 180 mg SC dose of risankizumab. At week 52, 71% of the patients were in clinical remission, 35% achieved endoscopic response, and 29% were in deep remission [3].

Finally, in an open-label extension study, 65 patients (61 patients from maintenance study in therapy with risankizumab (180 mg SC q8w) and 4 patients who had lost response in the parent study and were first reinduced with risankizumab (600 mg) every 4 weeks) were enrolled to receive the same subcutaneous (SC) therapy for a median of 33 months. The proportions of patients with clinical and endoscopic remission remained stable at the end of the observation period of 112 weeks (>71% and >42%, respectively) [4].

In 2022, further findings on the effectiveness and safety of risankizumab in CD were disclosed from two phase III trials.

The ADVANCE trial was a double-blind, randomized, placebo-controlled trial. The aim of the study was to evaluate efficacy as induction therapy for moderate or severe CD in patients who had shown intolerance or ineffectiveness to one or more approved biologics or conventional therapy [5]. A total of 850 patients were enrolled and randomized 2:2:1 to receive a placebo or 1200 mg or 600 mg of risankizumab IV at week 0, 4 and 8. The coprimary endpoints were clinical remission (defined as a CDAI less than 150 in the USA and an average daily liquid or very soft stool frequency of 2.8 or less plus an average daily abdominal pain score of 1 or less, with both not worse than the baseline in non-USA countries) and endoscopic response (defined as a greater than 50% decrease in SES-CD from the baseline or (for isolated ileal disease and a baseline SES-CD of 4) at least a 2-point reduction from the baseline) at week 12. At week 12, at all primary endpoints, risankizumab was superior to the placebo. In particular, CDAI clinical remission was achieved in 45% of patients in the risankizumab 600 mg arm ($p < 0.0001$) and in 42% of patients in the 1200 mg arm ($p < 0.0001$) versus the placebo (25%). Similarly, clinical remission based on patient-reported stool frequency and abdominal pain was achieved in 43% of patients in the risankizumab 600 mg arm ($p < 0.0001$) and in 41% of patients in the 1200 mg arm ($p < 0.0001$) versus the placebo (22%). A considerably higher percentage of patients receiving 600 mg (40%; $p < 0.0001$) or 1200 mg (32%; $p < 0.0001$) of risankizumab also experienced an endoscopic response at week 12 compared to the placebo (12%). When examining the same endpoints within specific patient subgroups (those with prior biologic treatment and those without), similar patterns of higher response rates compared to the placebo were observed. Specifically, for CDAI-based clinical remission, the rates were 49% and 47% for patients without previous biologic treatment as opposed to 43% and 38% for patients with prior biologic treatment for the 600 mg and 1200 mg arms, respectively. Likewise, for clinical remission based on stool frequency and abdominal pain scores, there were rates of 48% (600 mg group) and 44% (1200 mg group) for patients without previous biologic treatment and 41% (600 mg arm) and 39% (1200 mg arm) for patients with prior biologic treatment. Finally, in patients without prior biologic treatment failure, the endoscopic response rates were 50% and 44% for the risankizumab 600 mg and 1200 mg groups, respectively. Conversely, in patients with a history of previous biologic treatment failure, the rates were 33% (600 mg group) and 24% (1200 mg group) [5].

In the MOTIVATE induction trial, which was a multicenter, double-masked, randomized study, the primary endpoints were clinical and endoscopic remission, but only patients with a history of prior biological treatment failure were included in the enrollment. A total of 569 patients were randomized 1:1:1 to receive 600 mg or 1200 mg or a placebo every 4 weeks. The rates of CDAI clinical remission (42% in the 600 mg group ($p < 0.0001$) and 40% in 1200 mg group ($p < 0.0001$)) and stool frequency and abdominal pain score clinical remission were significantly higher in risankizumab group (35% in the 600 mg arm ($p = 0.0007$) and 40% in 1200 mg arm ($p < 0.0001$)) compared to the placebo (20% and 19%, respectively). Similar results were obtained in achieving the endoscopic response at week 12 (29% with $p < 0.0001$ and 34% with $p < 0.0001$ versus 11% of the placebo group). No significant difference in efficacy was observed between two groups for any coprimary endpoints in the ADVANCE or MOTIVATE trials [6].

Additionally, a considerably larger proportion of treated patients evidenced mucosal healing (defined as an ulcerated surface subscore of 0 in subjects with a subscore of ≥1 at the baseline) and endoscopic remission (defined as SES-CD ≤ 4 and at least a 2-point reduction versus the baseline and no subscore greater than 1 in any individual variable) during the ADVANCE and MOTIVATE induction investigations. Patients who received risankizumab (600 mg IV) experienced mucosal healing at week 12 at 21% (ADVANCE) and 14% (MOTIVATE), respectively, as opposed to 8% and 4% of patients in the placebo arm. At week 12, achieving endoscopic remission was observed in 24% of patients in the ADVANCE trial and 19% in the MOTIVATE trial for those receiving the drug. This stands in contrast to 9% and 4% in the respective placebo groups [7].

In the phase III FORTIFY trial, a multicenter, randomized, double-blind, placebo-controlled, maintenance withdrawal study, patients who had achieved clinical remission in the previous two trials were enrolled and randomized 1:1:1 into three arms: subcutaneous (SC) risankizumab (180 mg), SC risankizumab (360 mg), or a placebo every 8 weeks. The primary endpoints were clinical remission and endoscopic response at week 52. At week 52, 55% ($p = 0.0031$) and 52% ($p = 0.0054$) of patients in 180 mg and 360 mg groups achieved CDAI clinical remission compared to the placebo (41%). In contrast, the endoscopic response rates were 47% in the two arms of patients receiving treatment with risankizumab ($p < 0.0001$) versus 22% in the placebo arm [8]. Mucosal healing and endoscopic remission were observed during the FORTIFY maintenance study in patients treated with risankizumab (360 mg SC). Mucosal healing was observed at week 52 in 31% in the drug-treated arm compared with 10% in the placebo-treated arm (nominal $p < 0.001$), while endoscopic remission was achieved in 39% of patients treated with the same drug dose compared with 13% of patients receiving the placebo (nominal $p < 0.001$) [7].

Given its valuable results, risankizumab was approved in 2022 by both the FDA and EMA for the treatment of moderate-to-severe CD [7][9].

The role of risankizumab in the treatment of CD was also compared with ustekinumab. The SEQUENCE study (NCT04524611), a phase III clinical trial, was designed as a direct comparison between risankizumab and ustekinumab in the treatment of CD in adults who have previously not responded to one or more TNF inhibitors [10]. The outcomes for the primary endpoint, which assessed clinical remission, defined as a Crohn's Disease Activity Index (CDAI) < 150 at week 24, demonstrated that risankizumab was non-inferior to ustekinumab, with a non-inferiority margin of 10%. Specifically, the remission rates were 59% in the risankizumab group and 40% in the ustekinumab group [11]. Regarding the second primary endpoint, which assessed endoscopic remission, defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≤4 with at least a 2-point reduction compared to the baseline and no subscore greater than 1 in any individual component) at week 48, the results indicated that risankizumab was superior to ustekinumab. The remission rates were 32% in the risankizumab group and 16% in the ustekinumab group, with a statistically significant difference ($p < 0.0001$) [11].

1.2. Safety

In the initial induction trial involving risankizumab for CD, the incidence of any AE was comparable across the three groups, with rates of 82% in the placebo group, 78% in the 200 mg group, and 76% in the 600 mg group [2].

In the open-label extension study, arthralgia (22% of patients), headache (20%), abdominal pain (18%), and nausea (16%) were the most common AEs, while severe adverse events (SAEs) (worsening of CD and intestinal obstruction) were observed in 11% of patients; serious infections were detected in 4% of patients [3].

The overall incidence of treatment-emergent AEs during and following the 12-week induction period in ADVANCE and MOTIVATE was comparable across all treatment groups. In the ADVANCE trial, the rates of incidence of AEs were 56%, 51%, and 56% for the 600 mg, 1200 mg, and placebo groups, respectively; and 48%, 59%, and 66% for the same group in the MOTIVATE trial. SAEs were detected in 7% and 4% vs. 15% and 5% and 4% vs. 13% in the ADVANCE and MOTIVATE trials. Only 1% of patients in every treatment group showed serious infections vs. 4% (ADVANCE trial) and 2% (MOTIVATE trial) of the placebo group. No cases of non-melanoma skin cancer, major adverse cardiovascular events (MACE), or death were recorded [5].

2. Brazikumab

2.1. Efficacy

Brazikumab (MEDI2070) is a human IgG2 monoclonal antibody that binds exclusively the p19 subunit of IL-23, inhibiting the binding of IL-23 to its receptor. It has been tested in the treatment of CD in patients that had a primary and secondary non-response to TNF antagonists in a phase II trial (NCT01714726) [12]. In this trial, 119 patients were enrolled and randomized 1:1 to receive 700 mg IV of brazikumab at the baseline and at week 4 or a placebo. A CDAI decrease of 100 points from the baseline (clinical response) or a CDAI < 150 (clinical remission) at week 8 were the primary outcomes. At week 8, clinical response was observed in 49.2% of the treated patients vs. 26.7% of the patients receiving a placebo ($p = 0.01$), while 27.1% of patients in the drug group compared to 15% of the placebo group achieved clinical remission at week 8 ($p = 0.10$). In contrast, a statistically significant difference ($p < 0.001$) was observed when the composite outcome consisting of clinical response and a reduction of at least 50% in fecal calprotectin or CRP was taken into consideration (42.4% vs. 10%) [12].

Week 12 through week 112 was the open-label period in which all patients received 210 mg SC of brazikumab every 4 weeks. At weeks 8 and 24, 42.3% of patients who received MEDI2070 during both trial periods experienced a persistent clinical response compared to 23.1% of patients who received a placebo during the double-blind phase; prolonged clinical remission occurred in 23.1% and 11.5% of patients, respectively. Unfortunately, the study did not include endoscopic or instrumental outcomes [12].

At week 8 and 12 of the double-blind period, significantly greater reductions in fecal calprotectin (least squares mean difference of −105.6 and −124.6 with respective *p*-values of 0.027 and 0.034) and CRP concentrations (least squares mean difference of −17.6 and −10.8 with respective *p*-values of 0.007 and 0.008) were shown in patients treated with brazikumab compared with those receiving a placebo. Patients who continued taking the medication throughout the open-label period maintained these reductions, but those who took a placebo during the double-blind period experienced significant drops in fecal calprotectin ($p = 0.001$) and CRP concentrations ($p = 0.002$) from weeks 12 to 24 [12].

Another phase IIb/III study (INTREPID) and its respective open-label extension study were developed to evaluate brazikumab versus a placebo and an active comparator (adalimumab) for CD [13].

However, in June 2023, Astrazeneca announced that the brazikumab development program for the treatment of CD was discontinued. Astrazeneca's decision was associated with the drug's development timeline and was not secondary to safety concerns [14].

2.2. Safety

At week 12, AEs occurred in 40 of 59 patients in the brazikumab group (67.8%) compared to 41 of 60 patients (68.3%) in the placebo group. SAEs were observed in 8% of patients in both the drug and placebo arms [12]. Clinically significant infections were reported in 4 patients in the drug arm vs. 11 patients in the placebo arm. In both research periods, 67.3% of patients receiving brazikumab experienced treatment-emergent AEs in the open-label phase (up to week 24) compared to 65.4% of patients receiving a placebo [12]. In the double-blind period, SAEs occurred in 7.7% of patients receiving a placebo and in 15.4% of patients receiving the drug during both study periods [12].

3. Guselkumab

3.1. Efficacy

Guselkumab is an all-human monoclonal antibody (IgG1-lambda) already approved for the treatment of psoriatic arthritis [15][16].

The phase II trial GALAXI-1 investigated the potential of guselkumab as a treatment for patients with moderately to severely active CD who had either not responded well or were intolerant to conventional or biologic therapies [17]. The study aimed to assess both the effectiveness and safety of guselkumab in this patient population. In this trial the patients were randomized 1:1:1:1:1 to receive guselkumab at 200 mg, 600 mg, or 1200 mg IV; a placebo at weeks 0, 4, and 8; or ustekinumab at 6 mg/kg IV at week 0 and SC at 90 mg at week 8 (reference arm) [17]. The primary endpoint was a change from the baseline in the CDAI score at week 12 assessed by using the difference in the least squares means (LSMs). It was achieved in the entire guselkumab group (−160.4 in the 200 mg arm, −138.9 in the 600 mg arm, and −144.9 in the 1200 mg arm) compared with the placebo (−36.2) ($p < 0.05$ for all comparisons). Excellent results also were achieved at the secondary endpoints [17]. Clinical remission (CDAI < 150) at week 12 was observed in 54%, 58%, and 50% of patients, respectively, in the 200 mg, 600 mg, and 1200 mg groups vs. 16.5% of the placebo group (nominal $p < 0.05$), while a clinical response (a CDAI decrease of at least 100 points) was observed at week 12 in 70.5% (200 mg), 66.7% (600 mg), and 60.7% (1200 mg) compared to the placebo group (24.6% with nominal $p < 0.05$) [17]. Also, the rates of endoscopic response were significantly higher in patients treated with guselkumab (37.7%, 36.5%, and 32.8%) vs. the placebo (11.5%, nominal $p < 0.05$) [17].

In contrast, the study design did not include a direct comparison between the efficacy of ustekinumab and guselkumab, since ustekinumab was a reference arm. No long-term maintenance data are available [17].

In addition, GALAXI 2 and GALAXI 3 are two ongoing 48-week phase III confirmatory studies [18].

On the contrary, DUET-CD (NCT05242471) represents a phase II clinical trial designed to assess the effectiveness and safety of a combined treatment approach (specifically, the use of guselkumab and golimumab) in managing CD. However, no data are available yet [19].

3.2. Safety

In the GALAXY1 trial, 60% of patients in the placebo arm, 43.8% in the 200 mg arm, 50.7% in the 600 mg arm, and 42.5% in the 1200 mg arm showed one or more AEs, while SAEs occurred in 5.7% (placebo group), 4.1% (200 mg group), 5.5% (600 mg group), and 1.4% (1200 mg group) [17]. The rates of infection were 21.4% in the placebo group and 12.3%, 17.8%, and 15.1% in the other groups. Finally, serum sickness or anaphylaxis were not experienced as severe hypersensitivity events. In addition, no opportunistic infections, deaths, or cases of active tuberculosis were documented through week 12 [17].

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