The Expanding Role of Anti–IL-12 and/or Anti–IL-23 Antibodies in the Treatment of Inflammatory Bowel Disease

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Abstract: The interleukin (IL)-12/IL-23 pathway is one of many proposed mechanistic pathways of intestinal inflammation. Earlier studies introduced IL-12 as a major cytokine in the pathogenesis of inflammatory bowel disease. However, the discovery of IL-23 drew attention toward this new cytokine. Overwhelming data indicated that antibodies against IL-12p40 rendered their anti-inflammatory effect primarily via inhibition of IL-23. This is because IL-12 and IL-23 have the subunit p40 in common. These cytokines have become an attractive target of treatment in patients with inflammatory bowel disease. Targeting IL-12 selectively was not found to be an efficacious treatment. Coblockade of IL-12 and IL-23 via targeting of p40, however, was found to be effective. More recently, selective IL-23 blockade has been extensively studied with promising preliminary results. To date, there are several ongoing randomized clinical trials investigating the safety and efficacy profiles of selective IL-23 inhibitors. Overall, the classes of anti–IL-12/IL-23 inhibitors and selective IL-23 inhibitors seem to be effective alternatives in patients who are nonresponders to anti–tumor necrosis factor-α agents, especially in a subgroup of secondary nonresponders. In addition, the immunogenicity and adverse event rates associated with antibodies against IL-12 and/or IL-23 seem to be very low. Considering all of this, these agents will be an important part of the treatment algorithm for patients with inflammatory bowel disease going forward.

Inflammatory bowel disease (IBD) comprises 2 distinct entities: ulcerative colitis (UC) and Crohn's disease (CD). The pathogenesis of IBD involves a complex network of immune cells such as T-helper (Th) cells, cytokines such as tumor necrosis factor (TNF)-α and interleukins (ILs), and their receptors. Research on intestinal inflammation revealed that the interplay between the members of this network propagates the inflammatory cascades in IBD. As a result, targeting the members of this network to modulate inflammation became a plausible therapeutic strategy.
It has been more than 2 decades since the first agent blocking TNF-α was approved for IBD.1 Subsequently, a number of TNF-α inhibitors became commercially available. However, targeting a sole inflammatory pathway was associated with a lack or loss of response to treatment in a substantial portion of patients.2 Moreover, adverse events (AEs) associated with blockade of TNF-α, although rare, remained a constant concern to patients and clinicians.3 Hence, it was inevitable to target different axes of inflammation. The IL-12/IL-23 axis is one of many proposed mechanistic pathways of intestinal inflammation.4 For years, IL-12 was advocated as a key cytokine in IBD pathogenesis.5 However, with the discovery of IL-23, subsequent studies revealed that IL-12 inhibitors, which resulted in amelioration of inflammation in animal models, provided this effect primarily through inhibition of IL-23.6,7 This was due to the molecular structure of IL-12 and IL-23 having a subunit (IL-12p40) in common as the target of neutralizing antibodies.8 Further investigations targeted IL-12, IL-23, or both as potential treatment options for IBD. To date, the only selective IL-12 inhibitor studied in IBD was discontinued in the early phases of investigation due to inefficacy.9 The only drug marketed in this class (ustekinumab [Stelara, Janssen]), approved for CD, was initially recognized as an IL-12 inhibitor. However, it was reclassified later as an IL-12/IL-23 inhibitor.10 In recent years, with growing data in support of IL-23 in IBD pathogenesis, selective IL-23 inhibitors have become other attractive topics of further exploration.4 This article aims to elaborate on the IL-12/IL-23 pathway in IBD pathogenesis and the treatment options targeting this pathway.

**Interleukin-12: Discovery, Biologic Function, and Role in Inflammatory Bowel Disease Pathogenesis**

In 1989, a study on the mechanism of natural killer (NK) cell activation resulted in the discovery of a novel cytokine promoting interferon (IFN)-γ production and enhancing NK cell–mediated cytoxicity.11 This was labeled NK cell stimulating factor (NKSF). Subsequently, due to its IL properties, NKSF was designated IL-12.12 IL-12 is a heterodimer consisting of 2 polypeptides with molecular masses of 40 (IL-12p40) and 35 (IL-12p35) kilodalton.11 Similarly, IL-12 receptor (IL-12R) is a heterodimeric protein comprising IL-12Rβ1 and IL-12Rβ2. IL-12, via coupling with IL-12R, induces activation of Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2), subsequently activating signal transducer and activator of transcription (STAT) 4. This is essential for induction of IFN-γ and Th1 differentiation (Figure).13,14 IL-12 is produced by monocytes and macrophages to modulate T and NK cells.15 Dendritic cells, via IL-12 secretion, drive the differentiation of naive T cells into IFN-γ–producing Th1 cells.16 Due to its part in Th1 differentiation, IL-12 was proposed as an important player in IBD pathogenesis.17 In a mouse model of chemically induced chronic colitis, administration of monoclonal antibody (mAb) against IL-12 resulted in the resolution of colitis.16 Isolated CD4+ T cells from the colonic lamina propria in the treated mice were unable to release IFN-γ.3 The results were replicated by different animal and human studies, which showed that anti–IL-12 antibodies led to the amelioration or prevention of colitis.18-20 A significant reduction in IL-12, IFN-γ, and TNF-α release within the colonic lamina propria suggested that targeting IL-12 modulates the downstream cytokines.20

**Interleukin-23: Discovery, Biologic Function, and Role in Inflammatory Bowel Disease Pathogenesis**

In 2000, computational sequence analysis of the IL-6 family identified a novel cytokine named p19.8 This molecule was structurally close to the IL-12p35 subunit. Although p19 coexpresses with other IL-6 family molecules, only its coexpression with IL-12p40, within the same cell, generates a bioactive heterodimer designated as IL-23.9 Monocytes, macrophages, and dendritic cells are the primary producers of IL-23 (Figure).8,21 IL-23 receptor (IL-23R) comprises 2 subunits: IL-23R and IL-12Rβ1.22 Binding of IL-23p19 to IL-23R results in a restructuring process of the IL-23p19 helical domain, which enables binding of IL-12p40 to IL-12Rβ1.23 This process activates JAK2 and TYK2, leading to STAT3 and STAT4 formation, which ultimately function as transcription factors.23,24 IL-23 is a key player in the late stage of differentiation of naive CD4+ T cells into Th17 cells.21,22,25 Being devoid of IL-23R, naïve T cells require other cytokines, such as transforming growth factor (TGF)-β and IL-6, to modulate the early stage of differentiation.10 These cytokines induce expression of retinoic acid receptor–related orphan receptor-γ as the transcription factor, which promotes expression of IL-23R.25,26 Immature Th17 cells induced by TGF-β and IL-6 require exposure to IL-23 to attain pathogenicity.26,27 Once matured, Th17 cells are capable of producing IL-17 and TNF-α.6,22

Additionally, IL-23 was held accountable as a mediator of an organ-specific inflammatory response. In an experimental autoimmune encephalomyelitis (EAE) model, a population of T cells promoted by IL-23, once transferred to naïve mice, invaded the central nervous system.28 In line with these findings, specific IL-23–deficient
Figure. A schematic illustration of the interleukin (IL)-12/IL-23 pathway. IL-12 and IL-23 are released from macrophages and dendritic cells. IL-12 via coupling of IL-12p40 with IL-12Rβ1, and IL-12p35 with IL-12Rβ2, induces activation of Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2). This leads to activation of signal transducer and activator of transcription (STAT) 4, which is essential for induction of interferon (IFN)-γ and T-helper (Th) 1 differentiation. Naive T cells lack IL-23 receptor (IL-23R). Transforming growth factor-β (TGF-β) and IL-6 induce expression of retinoic acid receptor–related orphan receptor-γt (RORγt), which, along with STAT3, promotes expression of IL-23R. Th17 cells induced by TGF-β and IL-6 are not mature; thus, exposure to IL-23 is required to promote their pathogenicity. Binding of IL-23 to its receptor activates JAK2 and TYK2, leading to STAT3 and STAT4 formation.

(ML-23p19 knockout) mice showed protective characteristics against EAE and collagen-induced arthritis. Surprisingly, in IL-10 knockout mice, which spontaneously develop intestinal inflammation, the IL-10/IL-23p19 double-knockout subgroup was resistant to spontaneous inflammation.

The role of IL-23 in immune-mediated inflammatory responses was also supported by genetic studies. Genome-wide association study (GWAS) linked IL-23R polymorphisms with predisposition to autoimmune conditions such as psoriasis and psoriatic arthritis, ankylosing spondylitis, and CD. An association between rs11209026, a single-nucleotide polymorphism (SNP) in the IL-23R gene, and CD has been established. This variant is shown to be protective against CD and UC. The protective characteristic of rs11209026 was confirmed in a meta-analysis that showed that carriage of this SNP variant reduced disease risk in a cohort of more than 75,000 cases and controls. This SNP variant, along with a few other coding variants of IL-23R, leads to a decrease in the expression of IL-23R, thus reducing the immune responses mediated through the IL-23 axis.
Interleukin-12 or Interleukin-23: Which One Is a Key Player in Inflammatory Bowel Disease Pathogenesis?

Data from mouse models showed that IL-12, via promoting IFN-γ-producing T cells, mediates intestinal inflammation. However, the role of the IL-12/IFN-γ pathway was undermined with subsequent studies. In a colitis model, treatment with mAb against IFN-γ in the early stage diminished disease severity but did not show any effect on established colitis. Subsequently, the randomized, controlled trial (RCT) of fontolizumab, a mAb against IFN-γ, failed to show any clinical response in CD patients despite producing improvement in inflammatory markers. In contrast, treatment with anti–IL-12p40 antibody in a colitis model improved inflammation. Studies confirmed that anti–IL-12p40 antibody, and not anti–IFN-γ antibody, resulted in the resolution of colitis. It was postulated that the part played by IL-12 in intestinal inflammation was likely independent of IFN-γ.

With the discovery of IL-23, further studies diluted the role of IL-12 in IBD pathogenesis. Reagents inhibiting IL-12 via targeting the IL-12p40 subunit showed the same effect on IL-23, which has IL-12p40 in common with IL-12. Moreover, data from several studies supported IL-23’s role in immune-mediated inflammatory responses. Thus, the conundrum was whether anti–IL-12p40 antibodies rendered their effects via inhibition of IL-12, IL-23, or both. Different animal models, strikingly, showed that IL-23, and not IL-12 deficiency, possesses a resistance to organ-specific inflammatory responses. In the EAE model, although IL-23–specific or IL-12/IL-23–deficient mice were resistant to the disease, mice with specific IL-12 deficiency (IL-12p35 knockout) were highly susceptible. Similar results were observed in intestinal inflammation models. IL-10/IL-23p19 double-knockout mice showed resistance, whereas IL-10/IL-12p35 double-knockout mice developed colitis early in life. In an anti-CD40–induced colitis model, administration of anti–IL-12p40 or anti–IL-23p19 antibodies inhibited the inflammatory process. In the same model, specific IL-12 deficiency showed susceptibility to colitis, but specific IL-23 deficiency was protective. Moreover, selective inhibition of IL-23R in chemically induced colitis leads to disease improvement. These data, collectively, supported the theory that immune responses formerly attributed to IL-12, indeed, were IL-23 responsibilities.

Targeting Interleukin-12 and Interleukin-23 as Treatment Options for Inflammatory Bowel Disease

The blockade of IL-12 was investigated with the development of the SMART anti–IL-12 antibody, an IL-12–specific inhibitor that recognized the heterodimeric structure (IL-12p35/IL-12p40) of IL-12. However, its production was discontinued, possibly due to ineffectness.

Interleukin-12 and Interleukin-23 Coblockade

It is now well known that antibodies against IL-12p40, initially recognized as anti–IL-12 antibodies, are anti–IL-12/IL-23 antibodies. Briakinumab (ABT-874, Abbott) and ustekinumab are both fully humanized immunoglobulin (Ig) G1 mAbs against the IL-12p40 molecule. Briakinumab was studied in multiple sclerosis, psoriasis, and CD. Ustekinumab was approved for the treatment of psoriasis in 2009, psoriatic arthritis in 2013, and CD in 2016. Although ustekinumab shares these clinical indications with TNF-α inhibitors, it did not achieve clinical success in the other clinical indications of TNF-α inhibitors, such as rheumatoid arthritis or ankylosing spondylitis.

Briakinumab in Moderate-to-Severe Crohn’s Disease

A phase 2a RCT examined patients receiving subcutaneous injections of briakinumab 1 or 3 mg/kg or placebo. Clinical response and remission rates were based on Crohn’s Disease Activity Index (CDAI) score (decrease in CDAI score ≥100 points and <150, respectively). The initial response rate was higher in the 3-mg/kg group than with placebo, but at the end of the 18-week follow-up, the difference was no longer significant. The remission rates were not different at any points of the study. In a phase 2b RCT, 225 patients were stratified into 3 intravenous induction regimens: placebo or 400 or 700 mg of briakinumab (3 doses every 4 weeks [q4w]). Then, responders entered the maintenance phase; those in the placebo and 400-mg groups continued the same regimen, whereas those in the 700-mg group were rerandomized to receive placebo or 200 or 700 mg of briakinumab for 3 additional doses at the same frequency. However, the primary endpoint, clinical remission at week 6, was not met.

Ustekinumab in Moderate-to-Severe Crohn’s Disease

A phase 2a RCT stratified patients to receive ustekinumab 90 mg subcutaneously, 4.5 mg/kg intravenously, or placebo. Although clinical response rates for the ustekinumab groups combined were higher than with placebo at weeks 4 and 6, this difference did not maintain through week 8. A phase 2b RCT (CERTIFI) comprised 8-week induction and 28-week maintenance phases. For the induction phase, 526 patients who experienced anti–TNF-α therapy were randomized to receive 1 dose of intravenous ustekinumab 1, 3, or 6 mg/kg or placebo. In the maintenance phase, 145 patients who responded at week 6, after second randomization, received
subcutaneous ustekinumab 90 mg or placebo at weeks 8 and 16. Clinical response at 6 weeks was significantly higher than with placebo only in the 6-mg/kg arm (23.5% vs 39.7%, respectively; \( P = .005 \)). Clinical remission rates did not significantly differ across the groups. However, in the maintenance phase, ustekinumab compared with placebo resulted in significantly increased rates of clinical response (69.4% vs 42.5%, respectively; \( P < .001 \)) and remission (41.7% vs 27.4%, respectively; \( P = .03 \)). Approval of ustekinumab for CD was based on the results of 3 RCTs, UNITI-1 and -2 (with 8-week induction phases) and IM-UNITI (with a 44-week maintenance phase). In the induction trials, patients received a single dose of ustekinumab (130 mg or ~6 mg/kg intravenously) or placebo. The ~6-mg/kg dose equated to 260 mg for no more than 55 kg of body weight, 390 mg for more than 55 but less than 85 kg, and 520 mg for at least 85 kg. UNITI-1 enrolled 741 patients who had experienced anti–TNF-\( \alpha \) therapy, and UNITI-2 enrolled 628 patients regardless of their anti–TNF-\( \alpha \) status. In IM-UNITI, 397 patients who met the endpoint of the induction phases were randomized to receive ustekinumab (90 mg/kg subcutaneously every 8 weeks [q8w] or every 12 weeks [q12w]) or placebo. One-time dose adjustment to q8w was allowed in patients randomized to q12w or placebo who lost response. The clinical response rates at week 6 in the 130-mg and ~6-mg/kg groups were higher than with placebo (UNITI-1: 34.3%, 33.7%, and 21.5%, respectively; \( P = .003 \) for both comparisons; UNITI-2: 51.7%, 55.5%, and 28.7%, respectively; \( P < .001 \) for both comparisons). In IM-UNITI, the ustekinumab q8w and q12w groups showed higher clinical remission rates at week 44 compared with placebo (53.1%, 48.8%, and 35.9%, respectively; \( P = .005 \) and \( P = .04 \), respectively). Patients from IM-UNITI (n=397) who completed the 44-week period of the study entered the long-term extension study. Clinical remission rates at weeks 44 and 92 were 77.4% and 72.6% in the q12w group, 84.1% and 74.4% in the q8w group, and 63.4% and 53.5% in the prior dose adjustment group. To evaluate endoscopic healing, a post-hoc analysis was conducted on 334 patients who completed 44 weeks of IM-UNITI. The primary endpoint was the variation of the Simplified Endoscopic Activity Score for Crohn’s Disease (SES-CD) at week 8. Patients in all ustekinumab groups combined had a higher reduction in SES-CD than the placebo group (2.8 vs 0.7 points, respectively; \( P = .012 \)). The SES-CD reduction correlated with the ustekinumab dose (~6-mg/kg group: 3 points; \( P = .009 \); 130-mg group: 2.5 points; \( P = .096 \); both compared with placebo). The SES-CD reduction from baseline was maintained in the combined ustekinumab groups through week 44, although the difference with placebo was not statistically significant (2.5 vs 1.9 points, respectively; \( P = .176 \)).

**Ustekinumab in Moderate-to-Severe Ulcerative Colitis**

Studies showed a higher IL-23 serum level in UC patients than in healthy controls, with a positive correlation between the serum level and the disease duration and severity. As in CD, GWAS highlighted the association between IL-23R SNPs and UC. Thus, inhibition of IL-23 in UC treatment was a justified target. UNIFI, a phase 3 RCT, evaluated the safety and efficacy of ustekinumab induction therapy in UC. A total of 961 patients (50% biologic-experienced) were randomized to receive a single dose of ustekinumab (as in the UNITI trials) or placebo. At week 8, study endpoints were evaluated in 941 patients who completed the study. Clinical response rates (decrease in Mayo score \( \geq 30\% \) and \( \geq 3 \), with either a decrease in the rectal bleeding subscore \( \geq 1 \) or a rectal bleeding subscore \( \leq 1 \) in the 130-mg and ~6-mg/kg groups were higher than with placebo (51.3%, 63.8%, and 31.3%, respectively; \( P = .001 \) for both comparisons). In addition, a significantly higher proportion of patients who received ustekinumab met all other study endpoints, compared with placebo.

**Interleukin-23–Specific Blockade**

Beside the fact that IL-23 and not IL-12 is the key player in IBD pathogenesis, selective IL-23 blockade may have other advantages. Data from animal models suggested a divergent role of IL-12 and IL-23 in colon cancer development with the former protective and the latter inducive. Selective anti–IL-23 mAbs in clinical investigation for IBD (Table) include brazikumab (MEDI2070, Allergan), risankizumab (BI 655066, Boehringer Ingelheim and ABBV-066, AbbVie), mirikizumab (LY3074828, Eli Lilly), and guselkumab (Tremfya, Janssen). These are fully humanized IgG2, IgG1, IgG4, or IgG1, respectively, mAbs. Of these, guselkumab is the only one that has been approved for a clinical indication (psoriasis). Another mechanism for blockade of the IL-23 pathway is through antagonizing IL-23R. PTG-200 (Protagonist Therapeutics in codevelopment with Janssen), a first-in-class selective IL-23R inhibitor, acts locally in the gut and has been shown to improve colitis in animal models. The manufacturers announced successful results from a phase 1 RCT and plan to study the drug in CD.

**Brazikumab in Moderate-to-Severe Crohn’s Disease**

A phase 2a RCT stratified 119 patients (anti–TNF-\( \alpha \) failures) to receive intravenous brazikumab (700 mg) or placebo at weeks 0 and 4. Thereafter, all patients received open-label, subcutaneous brazikumab (210 mg q4w) from weeks 12 to 112. Clinical response at week 8 was higher in the treatment group than with placebo (49.2% vs 26.7%, respectively; \( P = .01 \)). At week 24, clinical response rates in the treatment group (53.8%) and in patients who previously received placebo (57.7%) were
Table. Ongoing Clinical Trials on Selective Anti–Interleukin-23 Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Drug (Trial Sponsor)</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Clinical Indication</th>
<th>Active Comparator</th>
<th>Design</th>
<th>Primary Endpoint</th>
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<tr>
<td><strong>Guselkumab (Janssen)</strong></td>
<td>NCT03466411</td>
<td>CD</td>
<td>Ustekinumab</td>
<td>Phase 2/3, randomized, double-blind, placebo- and active-controlled, parallel-group studies: - 48-week, phase 2, dose-ranging study (GALAXI 1) - Two 48-week, phase 3 studies (GALAXI 2 and 3) - Long-term extension study: if phase 2 or 3 trials completed</td>
<td>Phase 2: Change from baseline in CDAI score at week 12 Phase 3: Clinical remission at week 12. CDAI score &lt;150</td>
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<td></td>
<td>NCT03662542</td>
<td>UC</td>
<td>Golimumab</td>
<td>Phase 2a, randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study: - Combination therapy: guselkumab and golimumab - Monotherapy: guselkumab or golimumab</td>
<td>Clinical response (as defined by Mayo score) at week 12</td>
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<td><strong>Risankizumab (AbbVie)</strong></td>
<td>NCT03105128</td>
<td>CD</td>
<td>None</td>
<td>Phase 3, randomized, double-blind, placebo-controlled induction study (M16-006)</td>
<td>Percentage of participants at week 12 with: - Endoscopic response - Clinical remission</td>
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<td></td>
<td>NCT03104413</td>
<td>CD</td>
<td>None</td>
<td>Phase 3, randomized, double-blind, placebo-controlled induction study (M15-991)</td>
<td>Percentage of participants at week 12 with: - Endoscopic response - Clinical remission</td>
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<td></td>
<td>NCT02513459</td>
<td>CD</td>
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<td>Open-label, single-group, long-term safety extension</td>
<td>Incidence of drug-related adverse events</td>
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<td></td>
<td>NCT03105102</td>
<td>CD</td>
<td>None</td>
<td>Subjects who responded to induction in M16-006 or M15-991: - Substudy 1: randomized, double-blind, placebo-controlled study; maintenance therapy - Substudy 2: randomized, exploratory maintenance study with 2 different doses Subjects who completed substudy 1 or 2 or the phase 2, open-label extension study: - Substudy 3: Open-label, long-term extension study</td>
<td>Percentage of participants at week 52 with: - Endoscopic response - Clinical remission</td>
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<td>Randomized, double-blind, placebo-controlled induction study</td>
<td>Percentage of participants at week 12 with: - Clinical remission (Mayo score)</td>
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<tr>
<td></td>
<td>NCT03398135</td>
<td>UC</td>
<td>None</td>
<td>Subjects who responded to induction: - Substudy 1: 52-week, randomized, double-blind, placebo-controlled maintenance study - Substudy 2: 52-week, randomized, exploratory maintenance study - Substudy 3: open-label, long-term extension study (completed substudy 1 or 2)</td>
<td>Percentage of participants at week 52 with: - Clinical remission (Mayo score)</td>
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**Table.** (Continued) Ongoing Clinical Trials on Selective Anti–Interleukin-23 Monoclonal Antibodies

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<td>NCT03616821</td>
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<td>Vedolizumab</td>
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<td><strong>Mirikizumab (Eli Lilly)</strong></td>
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<td>CD</td>
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<td>Phase 2, randomized, parallel-arm, placebo-controlled study (SERENITY)</td>
<td>Proportion of participants achieving 50% reduction from baseline on the SES-CD at week 12</td>
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<td>None</td>
<td>Phase 3, randomized, double-blind, parallel-arm, placebo-controlled induction study (LUCENT 1)</td>
<td>Percentage of participants at week 12 with:  – Clinical remission (modified Mayo score)</td>
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<td>NCT03524092</td>
<td>UC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None</td>
<td>Phase 3, randomized, double-blind, parallel-arm, placebo-controlled maintenance study (completed LUCENT 1)</td>
<td>Percentage of participants at week 40 with:  – Clinical remission (modified Mayo score)</td>
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<td>NCT03519945</td>
<td>UC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None</td>
<td>Phase 3, open-label extension study:  – Long-term efficacy and safety</td>
<td>Percentage of participants at week 52 with:  – Clinical remission (modified Mayo score)</td>
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</tbody>
</table>

<sup>a</sup>Patients with intolerance or inadequate response to biologic therapy; excluded were patients with prior exposure to p19 inhibitors.

<sup>b</sup>Patients with intolerance or inadequate response to biologic therapy.

<sup>c</sup>Patients with intolerance or inadequate response to biologic therapy; excluded were patients with prior exposure to p40 or p19 inhibitors.

CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; SES-CD, Simplified Endoscopic Activity Score for Crohn’s Disease; UC, ulcerative colitis.

Similar. This study also proposed the IL-22 serum level as a predictor of response to brazikumab. It has been shown that the serum level of IL-22, which is released from IL-23R–expressing Th17 cells, is correlated with CD activity. Treatment with brazikumab was associated with a decline in IL-22 serum level. Moreover, an IL-22 median serum level above 15.6 pg/mL was associated with a higher rate of clinical response and remission with brazikumab.55

**Risankizumab in Moderate-to-Severe Crohn’s Disease**

In a phase 2 RCT, 121 patients (93% with anti–TNF-α experience) were randomized to receive intravenous risankizumab 200 or 600 mg or placebo at weeks 0, 4, and 8. Clinical remission (CDAI <150) at week 12 was achieved in 36.6% of the 600-mg group compared with 15.4% of the placebo group ($P=.025$). Patients who completed the 12-week induction phase were included in this open-label extension study. If patients were not in deep remission (CDAI <150 and Crohn’s Disease Endoscopic Index of Severity ≤4, or ≤2 for patients with isolated ileitis), they received 600 mg of risankizumab q4w intravenously for 12 weeks. Patients in deep remission entered a 12-week washout phase. Patients in clinical remission at week 26 were enrolled in the maintenance phase to receive subcutaneous risankizumab (180 mg) q8w for 26 weeks. At week 26, 53% of patients treated with 600 mg of risankizumab were in clinical remission. At week 52, clinical and endoscopic remission were maintained in 71% and 35% of patients, respectively.
Mirikizumab in Moderate-to-Severe Ulcerative Colitis

In a phase 2 RCT, 249 patients (63% biologic-experienced) were randomized to receive placebo or intravenous mirikizumab (50 or 200 mg [with dose adjustment allowed, to a maximum 600-mg dose, based on the mirikizumab serum level at certain points] or a fixed 600-mg dose) at weeks 0, 4, and 8. Clinical response rates (9-point Mayo subscore decrease ≥2 points and more than 35% change from baseline) at week 12 were higher among all mirikizumab groups compared with placebo (20.6%, 41.3%, 59.7%, and 49.2% for placebo and all doses in numerical order, respectively; P < .05 for all comparisons). However, the clinical remission rate (9-point Mayo subscore for rectal bleeding ≤0, stool frequency ≤1 with ≥1-point decrease from baseline, and endoscopy ≤1) was higher than placebo only in the 200-mg mirikizumab group (4.8% vs 22.6%; P < .01). Endoscopic healing rates (Mayo endoscopic subscore ≤1) were higher for the 50- and 200-mg groups compared with placebo (23.8%, 30.6%, and 6.3%, respectively; P < .05 for both comparisons).

Safety Concerns Associated With Interleukin-12 and Interleukin-23 Blockade

The first safety signal of briakinumab was observed following a report on the pooled safety data from the psoriasis trials.60 Patients who received at least 1 dose were followed up to 45 days after the last dose. A total of 2520 patients with 4704 patient-years of drug exposure was included in the analysis. The AEs included serious infections (1.3%), malignancies (2.6%), and major adverse cardiovascular events (MACEs; 1%), with 5.6% leading to withdrawal. Strikingly, the incidence of MACEs was 0.57/100 patient-years.60 These results warranted safety monitoring for MACEs among moderate-to-severe psoriasis patients receiving anti–IL-12/IL-23 therapy. Despite briakinumab’s clinical efficacy in psoriasis,61 in 2011, Abbott announced the withdrawal of the licensing application for this clinical indication and the termination of ongoing trials, reportedly due to the increased AE rate.60,62 Thus, a possible association between anti–IL-12/IL-23 therapy and MACEs has become a concern. A paradoxical rise in IL-12p40 serum levels has been reported in the early course of ustekinumab therapy in psoriasis followed by a gradual decline to a level above the baseline.63 With IL-12 as a hypothetically proatherogenic cytokine,64 there is potential for an increased rate of MACEs in the context of anti–IL-12/IL-23 therapy.65 Although patients with MACEs from safety data of briakinumab had multiple cardiac risk factors, these risk factors existed in the placebo group with no MACEs.60 Thus, caution in anti–IL-12/IL-23 therapy among patients with cardiac risk factors may be indicated. To date, it is unclear whether MACEs in this setting are a drug effect (briakinumab) or a class effect (anti–IL-12/IL-23 therapy). Moreover, data on MACEs associated with anti–IL-12/IL-23 therapy are primarily derived from psoriasis research, which might not necessarily extrapolate to CD.66

The IM-UNITI extension is the only report on the long-term safety outcomes of ustekinumab in patients with CD.48 From weeks 0 to 96, placebo and all ustekinumab groups had a similar number of safety events per hundred patient-years (244.2 vs 1020.0 patient-years, respectively), including serious AEs (19.24 vs 18.82, respectively) and serious infections (4.09 vs 4.02, respectively). When calculated for weeks 44 to 96, the numbers were only numerically higher for the ustekinumab group compared with placebo (serious AEs: 24.27 vs 19.56; serious infections: 5.20 vs 3.73), without dose effect. Although MACEs were not reported, 2 deaths with presumable cardiovascular cause occurred in the ustekinumab group.48 Similar to MACEs, long-term safety data on ustekinumab are coming from psoriasis and psoriatic arthritis studies.67 Moreover, CD is conventionally treated with a higher dosage of the drug. Therefore, safety data from other clinical indications of ustekinumab might not be applicable to CD. In a report across all clinical indications of ustekinumab through year 1, the incidence of serious AEs in CD was higher, yet comparable to placebo, suggesting CD as the underlying cause of the higher serious AE rate and not the drug.67 Across RCTs of selective IL-23 inhibitors in IBD, the AE rates in the treatment groups were not higher than those with placebo.57,59,68 In the long-term (100 weeks) safety report of brazikumab in CD, the most stated AEs were headache (22.1%) and nasopharyngitis (22.1%), with a 19% discontinuation rate.68 Collectively, data on ustekinumab and selective IL-23 inhibitors support the favorable safety profiles of these drugs in patients with IBD.

Efficacy of Interleukin-12 and Interleukin-23 Blockade in Prior Biologic Failures

Downregulation of IL-23p19 is reported following anti–TNF-α therapy in patients with CD, even in nonresponders.69 These data suggest that in anti–TNF-α nonresponders, IL-23 is not the primary axis of inflammation, thus arguing against the advantage of IL-23 blockade. In contrast, upregulation of mucosal IL-23p19 and IL-23R has been shown in nonresponders to anti–TNF-α agents. Thus, a possible role for IL-23 inhibition in this context is advocated.70

In UNITI-1 (anti–TNF-α agent–experienced patients),47 clinical remission rates were higher in the
ustekinumab groups than with placebo. However, for the UNITI-I subgroup of IM-UNITI, the clinical remission rate was not maintained through week 44 (26.2%, 38.6%, and 41.1% for the placebo, q12w, and q8w groups, respectively; \( P = .14 \) and \( P = .10 \), compared with placebo, respectively).\(^{47}\) Thus, a question remains regarding the efficacy of ustekinumab in a large portion of patients who failed anti–TNF-\( \alpha \) therapy (thereafter referred to as primary and secondary nonresponders). In the CERTIFI trial, although clinical response to ustekinumab in primary nonresponders was not superior to placebo (27.8% vs 15.9%, respectively; odds ratio [OR], 2; \( P = .20 \)), it was significantly higher in secondary nonresponders compared to placebo (44.2% vs 19.8%, respectively; OR, 3.2; \( P < .001 \)).\(^{46}\) Similarly, in UNITI-I, in the subgroup of primary nonresponders, the clinical response rate in the ustekinumab group was not higher than with placebo (23.6% vs 23%, respectively; OR, 1.1; \( P = .816 \)).\(^{47}\) However, among secondary nonresponders, this rate was significantly higher than with placebo (36.8% vs 20%, respectively; OR, 2.3; \( P < .001 \)).\(^{47}\) Evaluation of endoscopic healing of patients from UNITI-I showed superiority of ustekinumab to placebo; however, data among primary vs secondary nonresponders were not reported.\(^{49}\) Similarly, RCTs of risankizumab and brazikumab in CD, in which more than 90% of the cohorts consisted of patients who had failed anti–TNF-\( \alpha \) therapy, showed the efficacy of the treatment groups compared with placebo.\(^{55,57}\)

In general, these data suggest that the response rate to ustekinumab in CD patients who had experienced anti–TNF-\( \alpha \) therapy is less than in those who were naive to it. However, when the comparison was made with respect to primary vs secondary nonresponse to anti–TNF-\( \alpha \) therapy, lower efficacy was deemed to be driven by poorer response among primary nonresponders. Meanwhile, studies on the selective IL-23 inhibitors primarily recruited patients who had experienced anti–TNF-\( \alpha \) therapy, so it is unclear if this class has a higher efficacy in patients naive to anti–TNF-\( \alpha \) agents.\(^{55,57,59}\) In addition, in these studies, data are lacking on the comparison between primary and secondary nonresponders.

**Anti-Interleukin-12/Interleukin-23 Serum Level and Immunogenicity**

Antidrug antibody (ADA) was reported in early research on mAb against IL-12/IL-23.\(^{44}\) In the long-term extension phase of IM-UNITI, the ADA rate was 4.2% among all randomized patients.\(^{48}\) This rate was 2.4% for patients who continued ustekinumab throughout IM-UNITI and 8.2% for patients who received placebo during IM-UNITI and switched to ustekinumab during the extension phase.\(^{48}\) The higher rate of ADA in the placebo arm was hypothesized to be secondary to the gap during IM-UNITI following induction with ustekinumab in the UNITI trials.\(^{46}\) In a study on the sera of 1154 patients who received at least 1 dose of ustekinumab during the UNITI trials and IM-UNITI, 2.3% were positive for ADA with the majority transiently positive.\(^{71}\) Neutralizing ADA was found in 1.5% of patients. The presence of ADA was associated with a lower drug serum level without increased risk of reaction to ustekinumab.\(^{71}\) The rate of ADA with concomitant use of immunomodulators (1.9%) was not lower than in monotherapy (2.6%).\(^{71}\) In addition, combination therapy was not found to increase the ustekinumab serum level or the remission rate.\(^{72}\) An association was reported between the ustekinumab serum level and clinical and endoscopic responses, with a level of 0.8 mg/mL (or even up to 1.4 mg/mL) linked to a higher proportion of patients in clinical remission.\(^{71}\) Similarly, ADA was reported at a low rate in the RCTs of brazikumab (2.5%) and risankizumab (4%) in IBD patients.\(^{57,68}\) No neutralizing ADA was found against risankizumab.\(^{57}\) Overall, ADA formation for ustekinumab appears to be at a much lower rate compared with anti–TNF-\( \alpha \) therapy. In a systematic review of the literature, the ADA rates for infliximab (Remicade, Janssen) and adalimumab (Humira, AbbVie) were as high as 65.3% and 38%, respectively.\(^{73}\)

**Summary**

Targeting the IL-12/IL-23 pathway is a safe and effective treatment approach in patients with IBD. Antibodies against IL-12/IL-23 show efficacy in patients who failed treatment with anti–TNF-\( \alpha \) agents; however, the efficacy is more pronounced among secondary nonresponders. There is a safety signal for MACEs, which is likely a drug effect more than a class effect phenomenon, but due to the lack of long-term safety data, risk stratification is deemed necessary. Although data are scarce, during treatment with mAbs against IL-12/IL-23, measurement of the drug’s serum level and dose intensification may be an appropriate strategy when clinical efficacy is not achieved. Interruption during the course of treatment with ustekinumab may increase the risk of ADA formation, and combination therapy with immunomodulators is not deemed to lower this risk.

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