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IL12/23 or selective IL23 inhibition for the management of moderate-to-severe Crohn's disease?

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ABSTRACT

The interleukin (IL)-12 family of cytokines, including IL12 and IL 23, play an important role in driving aberrant Th1 and Th17 immune responses in patients with Crohn's disease (CD). Targeting this pathway has opened new avenues for therapeutic intervention. The approval of ustekinumab, a monoclonal antibody blocking the common p40 subunit of IL12 and IL23, marked an important evolution in medical management for CD: this novel class of biologic therapy demonstrated efficacy in both patients naïve to biologics as well as in patients experiencing inadequate response or loss of response to TNF antagonists. However, as our understanding of the IL12/23 pathway has evolved, specific targeting of IL23 through its unique p19 subunit has become a focus for novel therapeutic development. IL23p19 antagonists have been shown in head-to-head trials to have superior efficacy to ustekinumab for other immune-mediated conditions such as psoriasis. In CD, phase II trials of monoclonal antibodies targeting IL23, including risankizumab and brazikumab, have shown promising results, with multiple agents now entering phase II or phase III studies. In this review, we summarize the current evidence for both anti-IL12/23p40 and anti-IL23p19 monoclonal antibodies in CD.

Introduction

The introduction of monoclonal antibodies targeting tumor necrosis factor (TNF) alpha changed the landscape of medical management for Crohn's disease (CD). Rapid onset, high efficacy rates, relative safety compared to thiopurines, methotrexate, and corticosteroids, and the ability to induce and maintain long term mucosal healing established TNF antagonists as a mainstay treatment for patients with moderate-to-severe CD [1]. However, it has been recognized that over 30% of patients are primary non-responders to TNF antagonists and up to half will lose response in long-term follow-up [2,3]. Hence, the need for alternative treatments that are safe, effective, and well-tolerated for CD has driven the development of a rich pipeline of investigational compounds with different mechanisms of action [4].

Targeting interleukin (IL)-12/23 cytokines has become a key focus of investigation in CD [5]. The IL12 family of cytokines plays an important role in mediating adaptive immunity, particularly in differentiating T-helper (Th)-1 and −17 responses [6]. IL12 induces a predominantly Th1 response whereas IL23 induces a Th17 phenotype [7]. IL23 receptor activation results in downstream triggering of Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways, with regulation of gene expression to promote inflammatory cytokine expression including TNFα,

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Abbreviations

CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CRP	C-reactive protein
FCP	fecal calprotectin
FDA	Food and Drug Administration
IFN	interferon
IL	interleukin
IL23R	IL23 receptor
ILC	innate lymphoid cell
IV	intravenous
JAK	Janus kinase
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SNP	single nucleotide polymorphism
STAT	signal transducer and activator of transcription
Th	T-helper
TNF	tumor necrosis factor
UC	ulcerative colitis
UNITI	A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately-to-Severely Active Crohn's Disease

IL17, and interferon (IFN)-γ [8]. Additionally, IL23 stimulation results in functional $CD8^+$ T cells and natural killer cell responses, induction of innate lymphoid cells (ILC), and ILC-mediated changes in the intestinal microbiome [9,10]. These changes culminate in disruption of the normal gut homeostatic balance between immunity and pathological intestinal inflammation.

IL23 is a heterodimer consisting of covalently bonded p40 and p19 protein subunits: the p40 subunit is shared with IL12 whereas p19 is specific to IL23 [11]. Loss-of-function coding variants in the IL23 receptor (IL23R) are associated with protective effects against the development of intestinal inflammation, and in animal models, suppressing IL23 inhibits development of T-cell mediated colitis [12]. In 2016, ustekinumab, a monoclonal antibody targeting the common p40 subunit of IL12/23 was approved by the United States Food and Drug Administration (FDA) for the management of moderate-to-severe CD, informed by the pivotal phase III UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately-to-Severely Active Crohn's Disease) trials [13]. Ustekinumab has since been widely adopted in clinical practice and substantial real-world data has further supported efficacy in patients with CD [14–17]. More recently, ustekinumab has also demonstrated efficacy for the induction and maintenance of remission in patients with moderate-to-severe ulcerative colitis (UC) [18].

More recently, interest has shifted from targeting IL12/23p40 to IL23p19-specific immunosuppression. More precise targeting of IL23p19 allows sparing of IL12-mediated pathways, including Th1 responses that have been shown to be important for host immunity and malignancy surveillance [19–21]. Furthermore, IL23p19 may be a more important driver of inflammatory pathogenesis: in murine models, suppressing IL23 inhibits T-cell mediated colitis to a greater extent than blockade of IL12 [22,23]. In human studies of other immune-mediated disorders, particularly psoriasis, targeting IL23p19 has resulted in improved treatment efficacy compared to IL12/23p40. In a head-to-head phase II randomized trial, Papp et al. reported that treatment with risankizumab (an IL23p19 specific monoclonal antibody) resulted in a substantially greater proportion of patients achieving 90% reductions in the Psoriasis Area and Severity Index (PASI) score compared to ustekinumab (77% vs. 40%, $p < 0.001$) [24]. Subsequently, two double-blind phase III trials have confirmed the superiority of risankizumab compared to ustekinumab for psoriasis: at week 16, PASI-90 was achieved by 75.3% (229/304) and 74.8% (220/294) of patients receiving risankizumab compared to 42.0% (42/100) and 47.5% (47/99) of patients receiving ustekinumab in the UltIMMa-1 and UltIMMa-2 trials, respectively ($p < 0.0001$ for both comparisons) [25].

These observations collectively suggest that targeting IL23p19 may be potentially more effective than IL12/23p40 antagonism. Hence, multiple monoclonal antibodies blocking IL23p19 are currently being investigated, with several agents in late phase development [5]. In this review, we summarize the clinical trial data supporting the efficacy and safety of IL12/23p40 and IL23p19 antagonists in CD. We also discuss where these agents will be integrated into future treatment paradigms for CD in the future.

Efficacy and safety of IL-12/23 inhibition in CROHN'S disease

Ustekinumab

Ustekinumab (Stelara®, formerly CNTO1275; Janssen Biotech, Inc. Pennsylvania, United States) is an $IgG_{1\kappa}$ monoclonal antibody blocking IL12/23p40. The efficacy and safety of ustekinumab in patients with moderate-to-severe CD was evaluated in the phase III UNITI trial program, which was comprised of two identical 6-week induction studies: UNITI-1 (enrolling patients with non-response, loss of response, or intolerance to TNF antagonists) and UNITI-2 (enrolling patients failing conventional therapy with immunosuppressants or corticosteroids) [13]. Responders to ustekinumab induction were re-randomized in IM-UNITI, a 44-week maintenance study. Eligible patients with moderate-to-severe CD, defined by a Crohn's Disease Activity Index (CDAI) 220–450, with objective inflammation (as evidenced by a C-reactive protein [CRP] concentration >3.0 mg/L, fecal calprotectin [FCP] >250 mg/kg, or endoscopic ulcerations of the ileum or colon) were randomized 1:1:1 to receive either single dose ustekinumab 130 mg intravenously (IV), ustekinumab ~6 mg/kg IV (three doses by weight), or placebo in induction. During maintenance, patients were re-randomized 1:1:1 to either ustekinumab 90 mg subcutaneously (SC) every 8 weeks, every 12 weeks, or to placebo. The primary endpoint in the UNITI-1 and UNITI-2 trials was induction of clinical response, defined by a CDAI reduction ≥100 points compared to baseline at week 6. Clinical remission defined by a CDAI<150 was a secondary endpoint in induction and the primary outcome at week 44 in maintenance.

At week 6, a significantly higher proportion of patients randomized to either ustekinumab 130 mg IV or 6 mg/kg IV achieved clinical response and clinical remission as compared to placebo. Clinical response was achieved by 34.3% (84/245) of patients receiving ustekinumab 130 mg IV, 33.7% (84/249) of patients receiving ustekinumab 6 mg/kg IV, as compared to 21.5% (53/247) of patients receiving placebo ($p = 0.002$ and $p = 0.003$, respectively) in UNITI-1. In comparison, higher clinical response rates with ustekinumab were observed in the UNITI-2 trial (51.7%–55.5%, both significantly higher compared to the placebo response rate of 28.7%). These findings suggest that ustekinumab may be more effective when used in biologic-naïve patients compared to patients with disease refractory to TNF-antagonists. In both UNITI-1

and UNITI-2, patients receiving ustekinumab experienced significant reductions in CRP and FCP as early as week 3 after induction.

A total of 397 patients were randomized in the IM-UNITI trial. At week 44, clinical remission was achieved by 48.8% (63/129) of patients receiving ustekinumab q12 weeks and 53.1% (68/128) of patients receiving ustekinumab q8 weeks, compared to 35.9% (47/131) of patients receiving placebo ($p = 0.04$ and 0.005, respectively). A significantly higher proportion of patients receiving ustekinumab q8 weeks also achieved clinical response, sustained remission (remission at week 0 and 44 of maintenance treatment), and glucocorticoid remission compared to placebo. When considering the influence of previous TNF antagonist failure, patients receiving ustekinumab in UNITI-1 had non-significantly higher rates of remission at week 44 compared to placebo (38.6%–41.1% vs. 26.2%, $p = 0.10–0.14$). In contrast, patients naïve to biologic therapy in UNITI-2 and receiving ustekinumab 90 mg q8 weeks had significantly higher rates of clinical remission compared to placebo (62.5% vs. 44.3%, $p = 0.02$). In the maintenance phase, patients who met criteria for loss of response were allowed to undergo dose adjustment: patients receiving placebo who subsequently started on ustekinumab 90 mg SC every 8 weeks demonstrated 70.6% response and 39.2% remission q16 weeks after therapeutic escalation.

A subset of patients enrolled in the UNITI trial program underwent endoscopic evaluation [26]. At week 8, endoscopic response (defined by a Simple Endoscopic Score for CD SES-CD reduction $\geq$50% from baseline) was achieved by 20.6% (32/155) of patients treated with ustekinumab compared to 13.4% (13/97) of patients receiving placebo ($p = 0.144$). Similarly, nominal differences in endoscopic remission (SES-CD $\leq$2, 7.7% vs. 4.1%, $p = 0.252$) and mucosal healing (complete absence of ulcerations, 9.0% vs. 4.1%, $p = 0.141$) were observed with ustekinumab. In the maintenance component, a higher proportion of patients receiving ustekinumab 90 mg q8 weeks achieved endoscopic response compared to placebo (24.1% vs. 4.2%, $p = 0.043$).

In both UNITI-1 and UNITI-2, adverse events (AEs) occurred with similar frequency in patients treated with ustekinumab (50.0%–65.9%) as compared to placebo (54.3%–64.9%). Serious AEs also occurred with similar frequency between patients receiving ustekinumab (1.4%–4.5%) as compared to placebo (2.0%–2.9%). During maintenance, 81.7% of patients receiving ustekinumab q8 weeks and 83.5% of patients receiving placebo experienced an AE. Rates of serious infections were low (2.3%–5.3%) and were similar between treatment groups. In IM-UNITI, 2.3% (27/1154) of patients developed anti-drug antibodies in long-term follow-up, which is considerably lower compared to the immunogenicity profile of TNF antagonists.

In summary, results from the phase III UNITI development program confirmed the efficacy and safety of ustekinumab as both an induction and maintenance therapy in CD. These trials were pivotal in the regulatory approval of ustekinumab for CD.

Briakinumab

The efficacy and safety of briakinumab (ABT-874; Abbott Laboratories, Illinois, United States) in patients with CD was evaluated in a multicenter phase IIb placebo-controlled trial (NCT00562887) [27]. Patients with moderate-to-severe CD (CDAI 220–450) were eligible for inclusion and initially randomized 1:1:1:3 to placebo or 200 mg, 400 mg, or 700 mg IV briakinumab every 4 weeks. A subsequent protocol amendment dropped the 200 mg IV dose due to poor recruitment. The original study design was 115 weeks, including a 12-week induction phase, 12-week maintenance phase, and subsequent enrolment into either monitored withdrawal or open-label extension (OLE) phases. At week 12, patients in the placebo and 400 mg briakinumab arms achieving clinical response ($\geq$70-point decrease in CDAI compared to baseline) continued the same treatment assignment and dose whereas patients receiving 700 mg briakinumab achieving clinical response were re-randomized 1:1:1 to placebo, 200 mg or 700 mg briakinumab. The primary endpoint was clinical remission at week 6, defined by CDAI <150.

After a pre-specified interim analysis, the study was terminated early by the sponsor due to lack of efficacy. The primary endpoint of clinical remission at week 6 was not met, although a nominally higher proportion of patients receiving briakinumab 400 mg (13%) and 700 mg (17%) achieved clinical remission compared to placebo (9%) ($p = 0.455$ and 0.157, respectively). It was postulated that a prolonged induction phase may be required to observe efficacy with briakinumab: at week 12, a significantly higher proportion of patients receiving briakinumab 400 mg achieved remission compared to placebo (29% vs. 11%, $p = 0.030$), although a linear dose-response relationship was not observed with briakinumab 700 mg compared to placebo (22% vs. 11%, $p = 0.087$). At week 24, a higher proportion of patients receiving continuous briakinumab 400 mg (48%) or 700 mg (57%) were in clinical remission as compared to placebo (29%) (p-values not reported). However, no significant differences in remission were observed amongst patients initially treated with briakinumab 700 mg and then re-randomized to placebo at week 12, potentially due to residual carryover effects from briakinumab exposure during induction. The proportion of patients experiencing any AE, serious or severe AEs, and infectious AEs were similar in both induction and maintenance phases between patients receiving briakinumab or placebo and the drug was overall, well-tolerated. One patient experienced a fatal AE of acute respiratory distress secondary to acute pancreatitis.

In summary, results from this phase IIb trial demonstrated potential efficacy signals supporting IL12/23 blockade in CD although the primary efficacy endpoint was not achieved. Briakinumab has not continued in clinical development in CD.

Selective IL23p19 antagonists in clinical development

Risankizumab

Risankizumab (BI655066, ABBV066; AbbVie Inc., Illinois, United States) is a monoclonal IgG1 antibody targeting IL23p19. Its efficacy as an induction agent in CD was evaluated in a multicenter, randomized placebo-controlled phase II trial (NCT00562887), designed as a three-part study: an initial 12-week double-blinded IV induction, followed by 14-week open-label IV re-induction or washout, and finally 26-week SC maintenance therapy [28]. In induction, patients were randomized 1:1:1 to placebo or risankizumab 200 mg or 600 mg IV at weeks 0, 4, and 8. Importantly patients enrolled in this trial required a qualifying endoscopy scored by a blinded central reader with a Crohn's Disease Endoscopic Index of Severity (CDEIS) $\geq$7 or CDEIS $\geq$4 for isolated ileitis, in addition to a CDAI score of 220–450 for enrolment. The primary outcome was defined as clinical remission (CDAI <150) at week 12. Endoscopic remission (CDEIS $\leq$4 or $\leq$2 for isolated ileitis), endoscopic response (CDEIS reduction >50% from baseline), mucosal healing (absence of ulcerations), and deep remission (combined endoscopic and clinical remission) were assessed as secondary outcomes. Endoscopic endpoints were also adjudicated by blinded central readers.

A total of 121 patients were randomized (39 to placebo, 41 to each risankizumab group). Most patients (93.4%, 113/121) had previously been treated with a TNF antagonist and nearly 70% had failed multiple biologics. Pooling both risankizumab treatment arms, a significantly higher proportion of patients treated with risankizumab achieved clinical remission (31% vs. 15%, $p = 0.0489$), clinical

response (39% vs. 21%, $p = 0.0273$), endoscopic remission (17% vs. 3%, $p = 0.0015$), endoscopic response (32% vs. 13%, $p = 0.0104$), and deep remission (7% vs. 0%, $p = 0.0107$) compared to placebo. A linear dose-response was observed in this study with numerically higher proportions of patients receiving 600 mg risankizumab achieving all clinical and endoscopic outcomes compared to patients receiving 200 mg risankizumab. However, a dose-response plateau was not achieved, suggesting that potentially greater efficacy could still be observed with doses higher than 600 mg.

Results from the open-label extension and maintenance phases to week 52 were recently reported by Feagan et al. [29] Patients completing 12-week induction were included in the OLE. Patients not achieving combined clinical and endoscopic remission after induction received open-label IV 600 mg risankizumab ever 4 weeks for 12 weeks whereas patients in deep clinical and endoscopic remission washed out for 12 weeks. At week 26, patients with a CDAI <150 were enrolled in the maintenance phase and received risankizumab 180 mg SC every 8 weeks. At week 26, 53% (54/101) patients treated with 600 mg risankizumab in the OLE achieved clinical remission. A higher proportion of patients were in clinical remission at week 26 compared to week 12 irrespective of induction treatment assignment (55% vs. 18% amongst patients randomized to placebo, 59% vs. 21% in the original 200 mg risankizumab group, and 47% vs. 26% in the original 600 mg risankizumab group). Results from the OLE study suggest that extended induction treatment with risankizumab is effective in optimizing response. A total of 62 patients were treated with SC risankizumab as maintenance therapy. At week 52, clinical remission was maintained in 71% of patients, endoscopic remission in 35% of patients, and mucosal healing in 24% of patients. Arthralgia occurred in 22% (25/115) of patients, although no significant differences in serious adverse events were identified.

Overall, results from this phase II study are promising and identify a potential efficacy signal for risankizumab for the treatment of moderate-to-severe CD, with a comparable safety profile to placebo. Importantly, this trial enrolled heavily treatment-experienced patients yet demonstrated a magnitude of effect similar to trials of TNF antagonists in biologic-naïve patients. Secondly, benefits with risankizumab persisted across both clinical endpoints as well as objective, blindly adjudicated endoscopic outcomes. Based on these findings, a large phase III placebo-controlled trial of risankizumab for moderate-to-severe CD is now enrolling (NCT03105128).

Brazikumab

Brazikumab (MEDI2070, formerly AMG139; Allergan plc, Dublin, Republic of Ireland) is an IgG_2 monoclonal antibody specifically targeting IL23p19. The efficacy and safety of brazikimab was evaluated in a phase IIa double-blind placebo-controlled trial (NCT01714726) involving 121 CD patients by Sands et al. [30]. Patients were randomized 1:1 to receive either placebo or brazikumab 700 mg IV at weeks 0 and 4. Enrolment in this trial required previous primary non-response, secondary loss of response, or intolerance to at least one TNF antagonist, as well as objective demonstration of inflammation by biomarkers (CRP ≥5 mg/L, FCP >250 μg/g) or endoscopy (≥3 non-anastomotic ulcers, each >0.5 cm in diameter or ≥10 aphthous ulcers involving ≥10 cm of contiguous intestine). After the 12-week double-blind induction period, patients received brazikumab 210 mg SC every 4 weeks through a 100-week OLE. A composite outcome of clinical response (CDAI decrease ≥100 from baseline) or remission (CDAI <150) at week 8 was assessed. Endoscopy was not reported as a primary endpoint in this trial, although a composite endpoint of response based on 50% reductions in either FCP or CRP from baseline in combination with CDAI decrease ≥100 or CDAI <150 was evaluated.

A modified intent-to-treat analysis based upon data from 119 patients randomly assigned to placebo or brazikumab induction therapy was reported. Clinical response was achieved by 49.2% (29/59) of patients treated with brazikumab at week 8 compared to 26.7% (16/60) of patients receiving placebo ($p = 0.01$). When the composite endpoint of clinical response in combination with FCP or CRP reduction was evaluated, 42.4% (25/59) of patients treated with brazikumab achieved the composite outcome compared to 10.0% (6/60) of patients receiving placebo ($p < 0.001$). Similar treatment effects were observed at week 12 (37.3% [22/59] vs. 8.3% [5/60], $p < 0.0001$), although the rate of clinical remission was not significantly different between patients receiving brazikumab (20.3%) and placebo (13.3%, $p = 0.31$). Higher rates of sustained clinical response (42.3% vs. 23.1%) and clinical remission (23.1% vs. 11.5%) at both weeks 8 and 24 were achieved by patients treated with continuous brazikumab through week 24; however, patients initially randomized to placebo and then subsequently treated with brazikumab in the open-label period were able to achieve similar response, remission, and combined clinical/biomarker response rates compared to patients treated with continuous brazikumab. Serum IL22 levels were identified as a potential companion biomarker that predicted clinical response. Patients with serum IL22 concentrations ≥15.6 pg/mL had an increased likelihood of clinical response and remission after induction at week 8. This finding may help personalize the decision to use brazikumab in clinical practice, although it requires reproduction in larger trials.

Long-term safety of brazikumab 210 mg SC in the 100-week OLE has been reported in abstract form [31]. 104 patients (52 treated with placebo to brazikumab, 52 treated with brazikumab throughout) were enrolled in the OLE. A total of 12 patients (11.5%) experienced a treatment emergent AE resulting in drug discontinuation and 20 patients (19.2%) experienced a SAE, half of which were related to CD. No opportunistic infections occurred, and the overall AE profile was similar to patients completing the 12-week induction therapy with either placebo or brazikumab. AEs were reported in 67.8% of patients treated with brazikumab and 68.3% of patients treated with placebo at week 12. At week 24, 67.3% of patients treated with brazikumab and 65.4% of patients initially treated with placebo developed AEs. A total of three patients (2.5%) developed antidrug antibodies.

Overall, results from this phase II study suggest brazikumab may be another effective therapy for CD, particularly in patients with previous TNF antagonist exposure. The predictive power of serum IL22 for response requires independent validation and the dose-response relationship remains unclear.

Other IL23p19 antagonists

Guselkumab (CNTO1959; Janssen Biotech, Inc., Pennsylvania, United States) is a monoclonal $IgG_{1\lambda}$ antibody also targeting IL23p19 [32]. The GALAXI trial program (NCT03466411) is a large integrated phase II/III placebo- and ustekinumab-controlled study, aiming to enroll 2000 participants randomized to five different guselkumab treatment arms. This will be one of the first head-to-head trials of different biologic agents and will provide crucial insights into the comparative efficacy of agents blocking IL12/23p40 vs. those that are IL23p19-specific. Mirikizumab (LY3074828; Eli Lilly & Co., Indiana, United States) is another IL23p19 specific monoclonal antibody [33]. Data from a phase II trial of mirikizumab in UC have been reported [33] and a phase II trial of mirikizumab in CD (SERENITY, NCT02891226) is now recruiting. This 104-week trial aims to evaluate 180 patients with CD randomized to mirikizumab or placebo, with a primary endoscopic endpoint of 50% reduction in baseline SES-CD.

The future of IL23 inhibition in CROHN'S disease

While the treatment options for moderate-to-severe CD have expanded in the past five years with the addition of vedolizumab and ustekinumab to a stable of TNF antagonists, currently available biologic therapies are not effective for all patients. Risankizumab and brazikumab represent the first two novel IL23p19 antagonists to have completed phase II induction and open-label maintenance trials with encouraging results. Several other agents are in various stages of clinical development. Rates of clinical response and remission with IL23p19 antagonists in CD are similar in magnitude to those observed with early trials of infliximab [34–36] and adalimumab [37,38], even after enrolling a more difficult-to-treat patient population of patients who had previously failed TNF antagonists. The positive symptomatic, endoscopic, and biomarker outcomes achieved with IL23p19 antagonists in phase II studies collectively suggest that this mechanism of action may be appreciably more effective for the treatment of CD than existing therapies. Furthermore, the safety profile of these agents appears to be highly favorable, with similar AE rates compared to placebo and infrequent serious AEs or infections. The lack of appreciable safety signal has allowed for higher doses to be explored in the pivotal phase III trials, the results of which are eagerly awaited (NCT03105128; NCT03104413).

Despite promising early data, several unanswered questions remain. First, the optimal positioning of IL12/23p40 and IL23p19 antagonists in the treatment algorithm for CD is not defined. Although the UNITI data suggests that ustekinumab is more effective as a first-line biologic therapy in patients who are TNF-antagonist naïve, no head-to-head trials exists to evaluate the comparative efficacy of TNF antagonists against ustekinumab. A network meta-analysis by Singh et al. has suggested that infliximab and adalimumab ranked highest for induction of clinical remission in biologic-naïve patients, although ustekinumab had the lowest rate of serious AEs [39]. This question is currently being evaluated in a head-to-head phase IIIb 52-week trial of CD patients randomized to either adalimumab or ustekinumab (Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year SEAVUE Study, NCT03464136). No current IL23p19 trials have evaluated a primarily biologic-naïve patient population. Rather, some data suggests that patients who are refractory to TNF antagonists have upregulated mucosal IL23R and IL17A that may be particularly responsive to an IL23p19 antagonist. Schmitt et al. recently identified expansion of apoptosis-resistant intestinal TNFR2+IL23R + T cells that were associated with TNF antagonist resistance, providing a biologic basis for blocking IL23p19 as a molecular target in CD patients failing infliximab or adalimumab [40].

The relative positioning of IL12/23p40 and IL23p19 antagonists will be further challenged by the simultaneous development of several classes of novel oral small molecules. These agents overcome many of the pitfalls of currently available biologic therapies, including oral bioavailability and lack of immunogenicity. Tofacitinib, a JAK1/3 inhibitor, has recently been approved for UC [41], and although tofacitinib will not enter phase III trial programs in CD after negative phase II studies [42,43], several other JAK inhibitors including filgotinib and upadacitinib have reported encouraging results in phase II CD trials [44,45]. Sphingosine-1-phosphate receptor agonists, including ozanimod and etrasimod are also in clinical development programs [46]. Conceivably, more than six classes of biologic or small molecule therapies for CD management may become available within the next decade. A personalized approach to choosing between these different options will be required and likely be informed by either direct or indirect comparative studies of both efficacy and safety. Accurately determining a patient's pretest probability of treatment response will allow more efficient treatment decision-making: hence, the identification of predictive factors such as serum IL22 levels for brazikumab response require further investigation.

Both ustekinumab and agents blocking IL23p19 appear to have excellent safety profiles. An integrated safety analysis of all phase II and III trials of ustekinumab in psoriasis, psoriatic arthritis, and CD demonstrated lower AE rates for patients receiving ustekinumab compared to placebo (420.39–423.45 events/100 patient-years vs. 534.80–570.44 events/100 patient-years) [47]. Similarly, rates of AEs and serious AEs in both the psoriasis literature and in the phase II trials of risankizumab and brazikumab appear similar to placebo. Combined with evidence to support the efficacy of this mechanism of action after failure of TNF antagonists, monoclonal antibodies targeting the IL12/23 pathway appear to be attractive for potential use in combination therapy. Combination therapy with vedolizumab may be a particularly prudent combination given the favorable safety profile of both agents. As existing remission rates with monotherapy are less than 40%, even with IL23p19 antagonists or novel oral small molecules, a 'top-down' combination approach with multiple safe and effective therapies may be required to achieve optimal long-term outcomes in CD patients with poor prognostic features or highly refractory disease.

Conclusions

Targeting the IL12/23 pathway has opened new therapeutic avenues for the treatment of patients with moderate-to-severe CD. Although ustekinumab has been firmly established in the therapeutic armamentarium for CD, the development of targeted IL23p19 antagonists offer the possibility of a potentially even more effective mechanism of action. At this stage in development, phase II trials of risankizumab and brazikumab have demonstrated promising efficacy and safety results that require confirmation in phase III studies. Additional data is also needed to identify the optimal dosing strategies for these agents and to clarify their efficacy in specific subgroups of patients with fistulizing disease or extraintestinal manifestations. Nevertheless, these agents are the forefront of an exciting pipeline of potential new therapies for CD.

Practice points

- Ustekinumab is a safe and effective therapy for the treatment of moderate-to-severe Crohn's disease
- Ustekinumab is effective in patients naïve to biologic therapy and in patients previously exposed to TNF antagonists
- Risankizumab and brazikumab are IL23p19-specific antagonists that have shown efficacy in phase II randomized controlled trials of patients with moderate-to-severe Crohn's disease

Research agenda

- The comparative efficacy of IL23p19 antagonists with IL12/23p40 antagonists for Crohn's disease has yet to be established
- The comparative efficacy of IL23p19 antagonists with novel oral small molecule therapies for Crohn's disease has yet to be established
- Future studies should determine factors predictive of response to IL23p19 antagonists

Author contributions

CM, VJ, and BGF: drafting of the manuscript; all authors: critical revision of the manuscript for important intellectual content.

Conflicts of interest

C.M. has no conflicts of interest to declare.

R.P. has received scientific advisory board fees from Abbott/AbbVie, Amgen, Janssen, Merck, Pfizer.

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