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REVIEW

Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy

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This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
11 November 2016
Number of times this article has been viewed

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Abstract: Crohn's disease is characterized by a dysregulation of both innate and adaptive immunity responses. Interleukin-12/23 (IL-12/23) pathway has been found to be a major driver of inflammation in adaptive immune responses. Ustekinumab is a fully human immunoglobulin G1 kappa monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23 and prevents their interaction with their cell surface receptor and further cytokine activation. It is currently approved in the management of plaque psoriasis and psoriatic arthritis. Very promising data have emerged through phase II and phase III trials (UNITI-1, UNITI-2, and IM-UNITI) for both induction and maintenance of clinical response and remission in moderate-to-severe Crohn's disease, resulting in approval by the Food and Drug Administration for this condition. This article reviews the immunology of the IL-12/23 pathway, available data regarding the initial designing of ustekinumab, drug development through clinical trials including pharmacokinetics, efficacy, and safety, and its potential place in the treatment of Crohn's disease.

Keywords: ustekinumab, Crohn's disease, inflammatory bowel disease, interleukin-12/23 monoclonal antibody, interleukin-12, interleukin-23

Introduction

Crohn's disease is a chronic immune-mediated condition that is characterized by a relapsing nature and involvement of the gastrointestinal system from mouth to anus.[1] Although the pathophysiologic mechanisms have not been completely understood, the disease is likely a result of the interaction between commensal flora in the gut and host microbial defenses in a genetically predisposed individual.[2] These processes culminate in a dysregulated immune response. The microbial defenses include the mucosal barrier, the innate and adaptive immunity, that result in a transmural inflammatory response in Crohn's disease. The bowel inflammation results in symptoms such as diarrhea, abdominal pain, and fatigue, and a substantial minority may experience extra-intestinal manifestations. Over the long term, the transmural inflammatory response leads to the development of strictures and/or fistulae that require surgeries and/or hospitalizations.

Medical therapy in Crohn's disease has initially focused on nonspecific immunosuppressive therapies including thiopurines and methotrexate.[3,4] The treatment paradigm has since shifted toward targeting specific pathways of inflammation. Ustekinumab (Stelara; Janssen Biotech, Horsham, PA, USA) is a fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody that blocks interleukin-12 (IL-12) and IL-23 and has been previously approved for the treatment of moderate-to-severe plaque

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submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/DDDT.S102141

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psoriasis (2009) and active psoriatic arthritis (PsA; 2013).[5–11] The results of phase II and phase III trials for ustekinumab treatment of Crohn's disease appear very promising.[12–14] This has led to its approval by the Food and Drug Administration (FDA) for the treatment of moderately to severely active Crohn's disease in adults (≥18 years) who have failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed treatment with tumor necrosis factor (TNF) antagonists, or who failed or were intolerant to treatment with ≥1 TNF antagonists.[15] The approved dosing for induction regimen is weight based: 260 mg intravenous (IV) for <55 kg body weight, 390 mg IV for 55–85 kg, and 520 mg IV for >85 kg followed by maintenance with 90 mg subcutaneous (SC) every 8 weeks. This study reviews briefly the immunology of the interleukin-12/23 (IL-12/23) pathway, available data regarding the initial design of ustekinumab, drug development through clinical trials including the pharmacokinetics, efficacy, and safety, and its potential place in the treatment of Crohn's disease.

Design

Immunology of the IL-12/23 pathway

Crohn's disease is characterized by a dysregulation of both innate and adaptive immunity responses, with perturbations in adaptive immunity more likely driving the long-term tissue damage.[2] Adaptive immune responses are governed by a combination of resident and recruited cell populations, including mucosal B cells producing secretary IgA and IgG, a complex mixture of T cells dominated by a Th1, Th17, or Th2 phenotype, and regulatory T/B cells.[2] Crohn's disease has been shown to have a Th1 profile, unlike ulcerative colitis, which seems to exhibit a Th2-type-like cytokine profile.[2]

IL-12 and IL-23 are major drivers of the adaptive immune response. IL-12 is a cytokine that is primarily produced by phagocytic and dendritic cells in response to microbial stimulation and drives cell-mediated immunity by activating T-cell proliferation by Th1 cells.[16,17] Cytokines secreted from Th1 cells include IL-2, interferon γ (IFNγ), and TNF α and β. IFNγ further amplifies the inflammatory cascade, leading to expression of multiple cytokines (IL-7, IL-15, IL-18, and IL-21) that cause further proliferation of Th1 cells. The Th1 subset of T cells promotes cell-mediated immunity to intracellular pathogens, delayed-type hypersensitivity, and macrophage activation.[16] IL-12 is a heterodimer comprising covalently linked p40 and p35 protein subunits which then bind to a heterodimeric receptor complex consisting of IL-12 receptor (IL-12R)β1 and IL-12Rβ2 chains expressed on the surface of T cells or natural killer (NK) cells.[18]

In contrast, IL-23 plays a major role in the expansion of committed Th17 cells, which are fundamentally dependent on the transcription factor retinoid-related orphan.[19,20] Cytokines secreted from Th17 cells (IL-17A, IL-17F, IL-21, IL-22, IL-26, chemokine ligand 20, and IFNγ) exhibit increased tissue expression in Inflammatory bowel disease (IBD) and Crohn's disease (CD).[21] The IL-23 receptor is expressed on T cells, NK cells, and innate lymphoid cells, and also at low levels on monocytes, macrophages, and dendritic cells.[22,23] The ligand IL-23 is also a heterodimeric molecule, composed of a p40 and p19 chain, which are linked by a disulfide bond. The p40 chain is shared with IL-12, where it pairs with a p35 polypeptide.[24]

Neurath et al demonstrated that neutralization of the p40 protein was protective against the development of trinitrobenzene sulfonic acid (TNBS)-induced experimental colitis in mice.[25] This effect was ascribed to neutralization of IL-12. However, it was subsequently shown that CD40-induced colitis, but not wasting disease or serum proinflammatory cytokine production, depended on IL-23 p19 secretion, whereas IL-12 p35 secretion controlled wasting disease in this model.[26] Subsequent studies in LacZ knockin mice deficient of IL-23 p19 showed more severe colitis induced by TNBS than in wild-type mice, with amelioration of colitis with in vivo blockade of IL-12 p40.[27] These studies highlighted that both IL-12 and IL-23 might have a role in intestinal inflammation depending on the experimental mouse model.[28,29]

Mechanism of action

Ustekinumab is a monoclonal antibody with a human IgG1 heavy chain and a kappa light chain. It binds to the p40 subunit of IL-12 and IL-23 and prevents their interaction with the cell surface IL-12Rβ1 receptor, subsequently inhibiting IL-12- and IL-23-mediated cell signaling, activation, and cytokine production (Figure 1).

The binding epitope for ustekinumab is located in the D1 domain of the p40 subunit, which is spatially distant from IL-12p35 and IL-23p19.[24] Ustekinumab was shown to bind IL-12 and IL-23, equally neutralizing IL-12-mediated responses (intracellular phosphorylation of STAT4, cell surface marker expression, and IFNγ cytokine production) and IL-23-mediated responses (intracellular STAT3 phosphorylation and IL-17A, IL-17F, and IL-22 cytokine protein production).

Drug development

Pharmacokinetics

The pharmacokinetic properties of ustekinumab have mainly been defined in psoriasis. The characteristics of ustekinumab

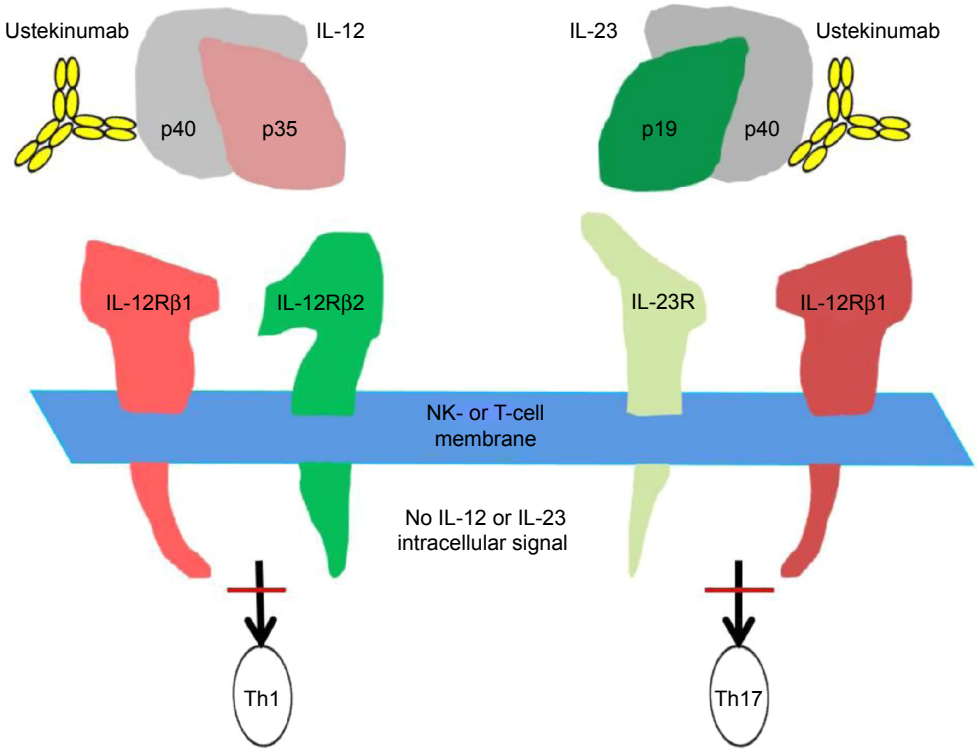

Figure 1 Ustekinumab binds to the p40 subunit of IL-12 and IL-23, preventing binding with the NK- or T-cell surface IL-12Rβ1, and inhibiting IL-12 signaling and further activation of Th1 subset of T cells as well as IL-23 signaling and further activation of Th17 subset of T cells.
Note: Image not drawn to scale; Adapted by permission from Macmillan Publishers Ltd: *Nat Biotechnol*. Benson JM, Sachs CW, Treacy G, et al. Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. 2011;29(7):615–624. Copyright (2011).[24]
Abbreviations: IL, interleukin; IL-12Rβ1, IL-12 receptor β1; NK, natural killer.

are similar to those of human endogenous IgG1 with IV and SC administration displaying an extended elimination half-life of ~3 weeks.[30] The extended elimination half-life is thought to be primarily due to the salvage effect of the neonatal Fc receptor that protects antibody proteins from lysosomal degradation.[30] In psoriasis patients, the median time to reach the maximum serum concentration after a single SC dose is dose-dependent, varying from 7 days (90 mg) to 13.5 days (45 mg).[31] The mean half-life ranged from 14.9 to 45.6 days across all psoriasis studies following IV and SC administration. The mean volume of distribution during the terminal phase following a single IV administration to patients with psoriasis ranged from 56.1 to 82.1 mL/kg. The mean systemic clearance of a single IV administration of ustekinumab to psoriasis patients ranged from 1.90 to 2.22 mL/day/kg. The estimated bioavailability following SC administration is ~57%.[31,32]

Interpatient variability related to differences in body mass index, serum albumin concentration, concomitant immunosuppressive use, severity of inflammation, and disease type has been described with monoclonal antibodies.[33] Using population pharmacokinetic modeling with serum ustekinumab concentration data across two phase III trials in patients with moderate-to-severe plaque psoriasis (PHOENIX 1 and PHOENIX 2), body weight, presence of diabetes mellitus, and antibodies to ustekinumab were the predominant determinants of drug clearance.[34] The potential effect of 28 concomitant medications, including amoxicillin and omeprazole, on the pharmacokinetics of ustekinumab was assessed, and none of these medications had a significant effect on the apparent clearance of ustekinumab.[35]

Efficacy

Data from psoriasis

PHOENIX 1 and PHOENIX 2 were phase III, multicenter, randomized, double-blind, placebo-controlled, parallel studies that were performed to evaluate the SC administration of ustekinumab in patients with moderate-to-severe psoriasis.[7,8] In PHOENIX 1, 766 patients were randomized to receive 45 mg ustekinumab (n=255) or 90 mg ustekinumab (n=256) at baseline and week 4, followed by every 12 weeks, or to receive placebo at week 0 and 4 (n=255), with crossover to receive either 45 or 90 mg ustekinumab at week 12.[7] The primary endpoint in this study was the percentage of patients achieving Psoriasis Area Severity Index (PASI) 75 at week 12, using an intention to treat analysis. At week 12, PASI 75 was achieved in 171 of those receiving 45 mg (67.1%), and 170 of those receiving 90 mg of ustekinumab

(66.4%) compared with 8 placebo-treated patients (3.1%). In PHOENIX 2, a total of 1,230 patients were similarly randomized to receive 45 or 90 mg ustekinumab or placebo at baseline, week 4, and then every 12 weeks or placebo at baseline and week 4, again with placebo crossover to receive 45 or 90 mg ustekinumab at week 12.[8] The primary endpoint was the proportion of patients achieving PASI 75 at week 12, and this was met in 273 patients receiving 45 mg ustekinumab (66.7%), and 311 receiving 90 mg ustekinumab (75.7%), compared with 15 receiving placebo (3.7%).

Based on the above studies, ustekinumab was approved for the treatment of chronic plaque psoriasis in the United States (October 2009), Canada (December 2008), and the European Union (January 2009).[6] The current licensed dosage regimen is 45 mg ustekinumab at baseline, 4 weeks, and every 12 weeks in those weighing ≤100 kg, and 90 mg ustekinumab at the same intervals for those >100 kg.

The comparative effectiveness of ustekinumab was tested head-to-head with etanercept in patients with moderate-to-severe psoriasis in a phase III trial.[36] The study design involved adaptive randomization with study investigators (but not the patient) blinded to treatment allocation. In this study, 903 patients were randomized to receive SC ustekinumab 45 or 90 mg at week 0 and 4, or etanercept 50 mg SC twice weekly for 12 weeks. The patients who were randomly assigned to ustekinumab received double injections (one injection of active treatment and one injection of placebo) to maintain blinding for the dose. The superiority of ustekinumab over etanercept was demonstrated at week 12 with those receiving ustekinumab 45 or 90 mg achieving PASI 75 in 67.5% and 73.8% of patients, respectively, compared with 56.8% of those receiving etanercept (P=0.01 and 0.001, respectively).

Data from PsA

PSUMMIT 1 and 2 were phase III, multicenter, double-blind, placebo-controlled trials performed to evaluate the SC administration of ustekinumab in patients with active PsA.[9,10] In PSUMMIT1, patients with active PsA were randomly assigned to 45 mg ustekinumab (N=205), 90 mg ustekinumab (N=204), or placebo (N=206) at week 0, 4, and every 12 weeks thereafter.[9] The primary endpoint was ≥20% improvement in the American College of Rheumatology (ACR20) criteria at week 24. A greater percentage of patients in both the 45 and 90 mg ustekinumab groups achieved ACR20 at week 24 compared to the placebo group (42.4%, 49.5%, and 22.8%, respectively, P<0.0001 for both comparisons) with responses maintained at week 52. PSUMMIT 2 comprised patients with active PsA despite treatment with conventional agents and/or TNF antagonists.[10] Patients were randomized to ustekinumab 45 or 90 mg at week 0, 4, and then every 12 weeks or placebo at week 0, 4, and 16 and then crossover to ustekinumab 45 mg at week 24, 28, and 40. The primary endpoint of ACR20 was achieved more often in the ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients at week 24 (P<0.001). Even among patients previously treated with ≥1 TNF antagonist, ACR20 response was higher in the ustekinumab-treated (35.6% combined) than placebo-treated patients (14.5%) at week 24 (P<0.01).

Data from Crohn's disease

A phase IIa trial was conducted in TNF antagonist-naïve and -experienced Crohn's disease patients (Table 1).[14] In the double-blind crossover component of this trial, 104 patients were randomized to four groups. Group 1 received SC placebo at weeks 0–3, followed by 90 mg ustekinumab at weeks 8–11; group 2 SC 90 mg ustekinumab at weeks 0–3, then placebo at weeks 8–11; group 3 IV placebo at week 0, followed by 4.5 mg/kg ustekinumab at week 8; and group 4 IV 4.5 mg/kg ustekinumab at week 0, then placebo at week 8. Clinical response (at week 8, primary endpoint) was defined as a 70-point decrement in the Crohn's disease activity index (CDAI) score and a minimum reduction of 25% from the baseline score. Clinical response in patients who received ustekinumab and placebo was 53% and 30% (P=0.02), respectively, at weeks 4 and 6, and 49% and 40% (P=0.34), respectively, at week 8. In a subgroup of patients who were previously given infliximab (neither primary nor secondary nonresponders), clinical response to ustekinumab was significantly greater than in the group given placebo (P<0.05) through week 8. In the open-label portion of the trial, a second population of 27 patients (primary and secondary nonresponders to infliximab) was randomized 1:1 to receive a single 4.5 mg/kg IV infusion or 4 weekly SC injections of 90 mg ustekinumab. At week 8, clinical response in the SC and IV ustekinumab groups was 43% and 54%, respectively. The clinical response observed with ustekinumab was paralleled by a decrease in the serum C-reactive protein (CRP) concentration, with higher baseline CRP values leading to larger treatment effects with ustekinumab, especially in infliximab-experienced patients.[37]

In a subsequent double-blind, placebo-controlled phase IIb trial of ustekinumab, 526 patients with moderate-to-severe CD who had previously failed ≥1 TNF antagonists were randomized to receive a single dose of 1, 3, or 6 mg/kg

Table 1 Summary of RCTs on ustekinumab in Crohn's disease

Name of the study	Type of RCT	Number of patients	Primary endpoint	Relevant secondary endpoints	Results	Serious adverse events[a]
Sandborn et al[14]	Phase IIa, (crossover), moderate-to-severe Crohn's	104	Clinical response at week 8		UST[b]: 49% PBO: 40%	UST[b]: 4%
				Clinical response at week 4 and 6	UST[b]: 53% PBO: 30%	PBO: 6%
		49 (subgroup: previous exposure to IFX)		Clinical response at week 8	UST[b]: 59% PBO: 26%	
CERTIFI[13]	Phase IIb, moderate-to-severe Crohn's: resistant to anti-TNF	526	Clinical response at week 6		UST: 39.7% (6 mg/kg dose IV) PBO: 23.5%	UST[c]: 5.8% PBO: 8.3%
		145 (subgroup: responders put on maintenance)		Clinical response at week 22	UST: 69.4% (90 mg SC) PBO: 42.5%	UST: 12.5%[d]
				Clinical remission at weeks 22	UST: 41.7% (90 mg SC) PBO: 27.4%	PBO:16.4%
UNITI-1[38,39]	Phase III, moderate-to-severe Crohn's: failed/ intolerant to anti-TNF	741	Clinical response at week 6		UST: 33.7% (6 mg/kg IV), 34.3% (130 mg IV) PBO: 21.5%	UST: 7.2% (6 mg/kg IV), 4.9% (130 mg IV) PBO: 6.1%
				Clinical remission at week 8	UST: 20.9% (6 mg/kg IV), 15.9% (130 mg IV) PBO: 7.3%	
				Clinical response at week 8	UST: 37.8% (6 mg/kg IV), 33.5% (130 mg IV) PBO: 20.2%	
UNITI-2[38,40]	Phase III, moderate-to-severe Crohn's	628	Clinical response at 6 weeks		UST: 55.5% (6 mg/kg IV), 51.7% (130 mg IV) PBO: 28.7%	UST: 2.9% (6 mg/kg IV), 4.7% (130 mg IV) PBO: 5.8%
				Clinical remission at week 8	UST: 40.2% (6 mg/kg IV), 30.6% (130 mg IV) PBO: 19.6%	
				Clinical response at week 8	UST: 57.9% (6 mg/kg IV), 47.4% (130 mg IV) PBO: 32.1%	
IM-UNITI[38,41]	Phase III maintenance, UNITI-1 and UNITI-2 responders	397	Clinical remission at week 44		UST: 53.1% (90 mg SC q8w), 48.8% (90 mg SC q12w) PBO: 35.9%	UST: 9.9% (q8w), 12.2% (q12w) PBO: 15.0%
				Clinical response at week 44	UST: 59.4% (90 mg SC q8w), 58.1% (90 mg SC q12w) PBO: 44.3%	
				Corticosteroid-free remission at week 44	UST: 46.9% (90 mg SC q8w), 42.6% (90 mg SC q12w) PBO: 29.8%	
				Continued remission at week 44 among those in remission at inclusion	UST: 66.7% (90 mg SC q8w), 56.4% (90 mg SC q12w) PBO: 45.6%	
				Clinical remission at 44 anti-TNF refractory/intolerant	UST: 41.1% (90 mg SC q8w), 38.6% (90 mg SC q12w) PBO: 26.2%	
				Clinical remission at 44 conventional therapy failures	UST: 62.5% (90 mg SC q8w), 56.9% (90 mg SC q12w) PBO: 44.2%	
				Clinical remission at 44 anti-TNF naïve	UST: 65.4% (90 mg SC q8w), 56.6% (90 mg SC q12w) PBO: 49.0%	

Notes: [a]Through week 8 unless specified. [b]Combined subcutaneous and intravenous group. [c]Combined data for 1, 3, and 6 mg/kg IV induction groups. [d]Through week 22.
Abbreviations: IFX, infliximab; PBO, placebo; TNF, tumor necrosis factor; UST, ustekinumab; RCTs, randomized control trials; IV, intravenous; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.

of IV ustekinumab or placebo.[13] At week 6, 36.6%, 34.1%, and 39.7% of patients in the 1, 3, and 6 mg/kg of ustekinumab groups, respectively, had a clinical response (defined as 100-point decrease in CDAI score from baseline) compared with 23.5% of patients in the placebo group (P=0.005 for the comparison with the 6 mg/kg group). In this study, responders to ustekinumab at week 6 were re-randomized to maintenance therapy with 90 mg of SC ustekinumab or placebo at weeks 8 and 16. In the maintenance phase of the study, ustekinumab was superior to placebo for both clinical remission, defined as CDAI score <150 points (41.7% vs 27.4%, P=0.03), and response (69.4% vs 42.5%, P<0.001) at 22 weeks.[13]

Following the promising results of the phase II trials, a couple of 8 week phase III induction trials (UNITI-1 and 2) and a 44 week phase III maintenance trial (IM-UNITI) have been conducted (Figure 2).[38–41] In UNITI-1, 741 patients with moderate-to-severely active Crohn's disease (CDAI score, 220–450) who previously failed or were intolerant to at least 1 TNF antagonist were randomized (1:1:1) at week 0 to a single dose of IV placebo, ustekinumab 130 mg, or weight-based tiered ustekinumab dosing approximating 6 mg/kg (260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], or 520 mg [weight >85 kg]).[39] The primary endpoint in UNITI-1 was clinical response at week 6, defined as reduction from baseline in the CDAI score of >100 points; patients with baseline CDAI score >220 to <248 points were considered in the clinical response if a CDAI score of <150 was present. Major secondary induction endpoints were clinical remission (CDAI score <150 points) at week 8, clinical response (CDAI 100-point response) at week 8, and ≥70-point CDAI decrease at week 3 and at week 6. At week 8, patients either transitioned to the IM-UNITI maintenance study or were followed to week 20. The primary endpoint (clinical response at week 6) was observed in 33.7% of those receiving weight-based dosing (6 mg/kg) and 34.3% of the 130 mg ustekinumab groups vs 21.5% in placebo (P=0.003 and 0.002, respectively). The secondary endpoint of clinical remission at week 8 was observed in 20.9% of the 6 mg/kg group and 15.9% of the 130 mg group vs 7.3% on placebo (P<0.001 and P=0.003, respectively). Clinical response at week 8 was seen in 37.8% of the 6 mg/kg and 33.5% of the 130 mg ustekinumab groups, vs 20.2% on placebo (each P≤0.001).

UNITI-2 (N=628) was another induction trial of ustekinumab specifically in moderately to severely active patients who had previously failed corticosteroids and/or immunomodulators and were either naïve to or had been exposed to TNF antagonists, but had not failed such biologic therapy.[40] These patients also had objective evidence of active Crohn's disease (ie, at least one of serum CRP concentration >3.0 mg/L, fecal calprotectin >250 mg/kg, or endoscopic ulcerations of ileum and/or colon). Patients participating in the phase III UNITI-2 study received ustekinumab or placebo at doses similar to UNITI-1 and were assessed with similar primary and secondary endpoints. In UNITI-2, greater proportions of patients

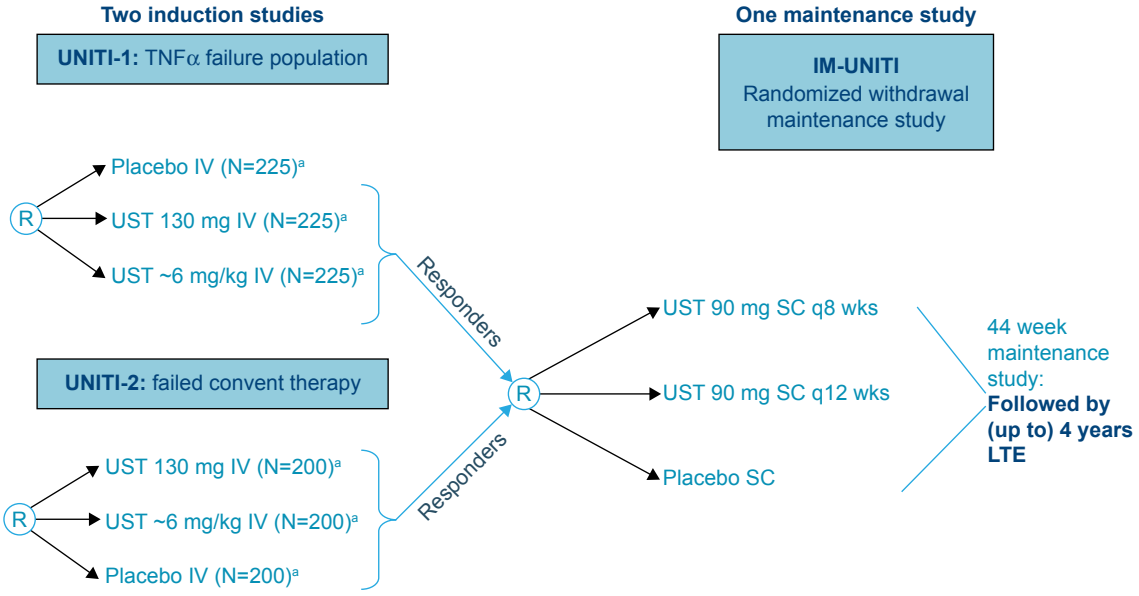

Figure 2 Overall structure of UNITI phase III program.
Note: [a]Subjects randomized to placebo and subjects who are non-responders to ustekinumab are eligible for non-randomized maintenance dosing after completion of the induction study.
Abbreviations: LTE, long-term extension; TNF, tumor necrosis factor; UST, ustekinumab; IV, intravenous; SC, subcutaneous; q8 wks, every 8 weeks; q12 wks, every 12 weeks.

who received ustekinumab 130 mg (51.7%) and 6 mg/kg (55.5%) demonstrated response at week 6 (primary endpoint) compared with 28.7% who received placebo ($P<0.001$ for both comparisons). At week 8, 30.6% and 40.2% of patients receiving ustekinumab 130 mg and ~6 mg/kg, respectively, achieved clinical remission, compared with 19.6% of patients receiving placebo ($P=0.009$ and $P<0.001$, respectively). In addition, 47.4% of patients receiving ustekinumab 130 mg and 57.9% of patients receiving ~6 mg/kg achieved clinical response at week 8, compared with 32.1% of patients receiving placebo ($P<0.001$ for both comparisons).

Induction trial completers participated in IM-UNITI, in which ustekinumab responders (N=397) were randomized to maintenance SC injections of 90 mg ustekinumab every 8 weeks (q8w) or 12 weeks (q12w), or placebo.[41] The primary endpoint for the maintenance trial was remission (CDAI <150) at week 44. Secondary endpoints at week 44 included clinical response, clinical remission among patients in clinical remission after ustekinumab induction, corticosteroid-free remission, and clinical remission in patients refractory or intolerant to TNF antagonists (UNITI-1 subgroup). Greater proportion of patients in the ustekinumab groups achieved clinical remission at week 44 compared with placebo (53.1% and 48.8% in the q8w and q12w groups vs 35.9% on placebo; $P=0.005$ and 0.040, respectively). Significantly greater proportions of patients also maintained clinical response at week 44 in the q8w (59.4%) and q12w (58.1%) ustekinumab groups vs placebo (44.3%; $P<0.05$ for both). The proportions of patients in clinical remission and not receiving concomitant corticosteroids at week 44 were significantly higher in the q8w group (46.9%) and numerically higher in the q12w group (42.6%) vs placebo (29.8%; $P=0.004$ and nominal $P=0.035$, respectively). The treatment effect difference for q8w versus placebo (17.2%, [95% confidence interval {CI}: 5.32%, 29.71%]) was numerically higher than that for q12w group (13.0%, [95% CI: 1.05%, 24.87%]). The q8w group had a significantly greater proportion of patients in remission at week 44 compared with placebo among patients who had failed conventional therapy (UNITI-2 subgroup). In the subset of patients refractory or intolerant to TNF antagonists (UNITI-1 subgroup), the proportion in clinical remission was numerically but not significantly greater than placebo for both dose groups.

Real-world experience

The open-label observational experience with ustekinumab prior to regulatory approval has been described in four studies (three published manuscripts and one abstract) from tertiary IBD centers in North America and Europe.[42–45] The experience from the IBD Mayo Clinic in Rochester, Minnesota (January 2008–August 2013) included 18 refractory Crohn's disease patients who had experienced failure of at least two TNF antagonists in 89% of patients, methotrexate in 83%, and thiopurines in 89%. Natalizumab had been used in 16.7% of patients prior to ustekinumab. Many of these patients had short bowel syndrome, were TPN-dependent, or had ostomies. The induction dose ranged from 45 to 270 mg SC at week 0 while the most common maintenance dose was 90 mg SC every 8 weeks. The cumulative probabilities of any response at 1, 2, and 6 months were 11.1%, 38.9%, and 44.4%, respectively. The cumulative probability of loss of response among patients with partial or complete response was 25% at 1, 3, and 6 months. Mucosal healing was observed in 3 of the 8 patients (37.5%) who had a repeat endoscopy.

The ustekinumab experience at McGill University, Montreal, Canada (March 2011–November 2013) included 38 Crohn's disease patients, all of whom had previously failed at least one TNF antagonist, and 95% had failed ≥2.[43] The induction dose varied from 45 mg (weeks 0 and 4) to 90 mg (weeks 0, 1, 2, or 0, 4), while maintenance doses varied between 45 mg every 12 weeks and 90 mg every 4, 8, or 12 weeks. Initial clinical response (at week 12 or first follow-up visit) was achieved in 73.7%, while maintenance of response was seen in 80% at 6 months, 88.9% at 12 months, and 71% at last follow-up. Dose escalation was required in 47.7% of the patients and was successful in 61.1% of them.

The ustekinumab experience (March 2011 to December 2014) across tertiary French and Swiss IBD centers that are part of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif included 122 consecutive CD patients all of whom had failed at least one, 92% failed two, 37% failed three, and 2% all four TNF antagonists.[44] Clinical benefit from ustekinumab was assessed within 3 months, defined as a significant improvement in CD-related clinical symptoms and laboratory tests, associated with complete weaning from steroids, without surgery, or new immunosuppressant introduction. This was seen in 65% of the patients within 3 months, with maintenance of clinical benefit for 6 and 12 months after introduction of ustekinumab in 93% and 68%, respectively. Additionally, concomitant immunosuppressant therapy at study inclusion increased the odds for a clinical benefit from ustekinumab (odds ratio, 5.43; 95% CI, 1.14–25.77; $P=0.03$).

The open-label experience across 42 Spanish tertiary IBD centers (March 2010 to December 2014) included 116

consecutive patients with Crohn's disease who failed at least one immunomodulator and one TNF antagonist and received treatment with ustekinumab for at least 2 months.[45] Clinical response (decrease in Harvey–Bradshaw index score by ≥3 points from the baseline) after induction dosing of ustekinumab was achieved in 84% of the patients. The clinical benefits at 6, 12 months and at the end of the follow-up were 76%, 64%, and 58%, respectively. Dose escalation was required in 10% of the patients and effective in the majority (73%) of those patients. Perianal disease also improved in 11 of 18 patients with active perianal disease (61%).

Endoscopic response as treatment endpoint

There are limited data on mucosal healing with ustekinumab. In the CERTIFI study, 8 of 41 patients in the ustekinumab group (19.5%) achieved mucosal healing compared to 1 in the placebo group.[13] In the study from McGill, endoscopic improvement was achieved in 10 of 13 cases (76.9%); mucosal healing was demonstrated in 2 of these patients.[43]

Immunogenicity and therapeutic drug monitoring

In the CERTIFI trial, only 3 of the 427 Crohn's disease patients with samples for analysis (0.7%) showed antibodies to ustekinumab through week 36.[13] Likewise, the incidence of antibodies to ustekinumab was low (0.2%) in the UNITI studies across both dose groups.[46] In IM-UNITI, the incidence of antibodies to ustekinumab through week 44 was similarly low (27/1,154 patients, 2.3%).[47] In a real-world experience at McGill University, none of the 49 patients tested had detectable antibodies to ustekinumab at >6 months usage.[48]

Across the three phase III trials, serum ustekinumab concentrations were dose-proportional and showed a positive association with clinical remission at week 8 (UNITI-1 and UNITI-2) and week 24 (IM-UNITI).[47] At the end of induction (week 8), median ustekinumab concentrations were 2.1 and 6.4 μg/mL for the 130 mg and 6 mg/kg dose groups, respectively. Additionally, the median steady-state trough serum ustekinumab concentrations over time in the q8w group (1.97–2.24 μg/mL) were 3-fold higher than in the q12w group (0.61–0.76 μg/mL). In a real-world analysis of 59 patients from McGill University, a serum ustekinumab level >4.5 μg/mL was associated with endoscopic response (72.2% sensitivity, 83.3% specificity; P=0.0006; area under curve, 0.782).[48] This level (compared to lower levels) was also associated with a composite outcome of steroid-free clinical remission and endoscopic response (50% vs 15%, P=0.024). Additionally, a ustekinumab level >5 μg/mL, compared to lower levels, was associated with normal serum CRP (63.6% vs 33%, P=0.024).

Adverse events (AEs)

Preclinical

The data for the risk of cancers in murine studies are conflicting because of the antitumor activity of IL-12 contrasting with the tumor promotion effect of IL-23.[49,50] However, preclinical toxicology testing conducted in cynomolgus monkeys did not show significant adverse effects with IV or SC ustekinumab administered biweekly at doses as high as 45 mg/kg for up to 6 months.[51]

Data from psoriasis

In PHOENIX 1, the most common AEs were reported as upper respiratory tract infections, nasopharyngitis, headache, and arthralgia.[7] AEs were reported in 54.5% of those receiving ustekinumab and 48.2% of those receiving placebo. Serious AEs occurred in 1.2% of the patients receiving ustekinumab and 0.8% of the patients receiving placebo. These were most common infections and cardiac events. No malignancies were reported during the placebo-controlled phase, although they were reported during the crossover phase (one case each of prostate cancer and thyroid cancer) and the withdrawal phase (one case of colon cancer).

In PHOENIX 2, during the placebo-controlled phase, AEs were similar in the 45 and 90 mg group and the placebo group.[8] The most common AEs were similar to PHOENIX 1 in addition to injection site erythema. Serious AEs were similar in type in all populations, with the most common events reported as infections and cardiac disorders. Through the three phases, one case each of basal cell skin cancer and squamous cell cancer of the tongue were reported in the ustekinumab group.

To evaluate a dose-dependent relationship with AEs and evaluate for cumulative exposure-dependent AEs, 3,117 patients from the four randomized, blinded, phase II and III ustekinumab studies in psoriasis were followed for up to 5 years.[52] At year 5, event rates per 100 patient years (45, 90 mg, respectively) were comparable for overall AEs (242.6, 225.3), serious AEs (7.0, 7.2), serious infections (SIs; 0.98, 1.19), nonmelanoma skin cancers (0.64, 0.44), other malignancies (0.59, 0.61), and major cardiovascular events (0.56, 0.36). In this study, the rates of other malignancies (excluding nonmelanoma skin cancers) were comparable with those expected in the general US population (standardized incidence ratio, 0.98; 95% CI, 0.74–1.29).

The risk of AEs was further evaluated in a real-world setting using the Psoriasis Longitudinal Assessment and Registry (PSOLAR) containing data on 4,364 patients who had received ustekinumab for psoriasis.[53] The cumulative incidence rates for malignancy, major cardiovascular events, SI, or mortality with ustekinumab were comparable to or lower than other biologics, and multivariate analyses did not show any association between these AEs and ustekinumab exposure. Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare, generally reversible neurological syndrome that can present with acute onset of headache, visual disturbances, altered mental status, and seizures.[54] Transient cerebral edema without infarction is usually seen on computed tomography or magnetic resonance images in the parietal and/or occipital lobes of the brain. The relationship of RPLS with ustekinumab is unclear, and a single case has been reported in a 65-year-old woman who developed RPLS after 12 doses over 2 years.[11,55]

Data from Crohn's disease

In the phase IIa study, the rate of serious AEs was similar between the ustekinumab and placebo groups.[14] Throughout the induction and maintenance phase, only 1 case of prostate cancer (with increased prostate-specific antigen levels before study entry) and 2 cases of SIs (viral gastroenteritis and disseminated histoplasmosis) were recorded in patients receiving ustekinumab.

In the phase IIb study, common non-gastrointestinal AEs included headache, arthralgia, and nasopharyngitis.[13] The rates of SIs were similar between the ustekinumab and placebo groups. These occurred in 6 patients (5 receiving ustekinumab 6 mg/kg and 1 in 1 mg/kg dose) during induction and 4 in the maintenance phase. These included *Clostridium difficile* infection, viral gastroenteritis, urinary tract infection, anal abscess, vaginal abscess, and a staphylococcal infection in a central catheter. Basal cell carcinoma developed in 1 patient receiving ustekinumab. No deaths, major cardiovascular events, tuberculosis (TB), or other serious opportunistic infections were reported.

In the UNITI-1 study, the proportion of patients with AEs, serious AEs, and infections were similar in the ustekinumab and placebo groups.[39] One significant opportunistic infection (*Listeria* meningitis) was reported in the group receiving 6 mg/kg ustekinumab. No malignancies, deaths, major adverse cardiovascular events, or TB occurred in ustekinumab-treated patients through week 20. Similar results were reported from the UNITI-2 study, with the proportion of patients with AEs, serious AEs, and infections (including SIs) similar to placebo.[40] No malignancies, deaths, opportunistic infections, or TB occurred.

In the 44 week IM-UNITI trial, similar proportions of patients with AEs were seen across treatment groups (81.7% and 80.3% for ustekinumab q8w and q12w, respectively, vs 83.5% placebo).[41] The proportions of patients with serious AEs were 9.9%, 12.2%, and 15.0% among the q8w, q12w, and placebo groups, respectively. SIs occurred in 2.3%, 5.3%, and 2.3% of patients in the q8w, q12w, and placebo groups, respectively. Among the randomized population, no deaths or major adverse cardiovascular events were reported, and 2 patients reported malignancies (1 basal cell carcinoma in each of the placebo and q8w groups). In the non-randomized population (those randomized to placebo in UNITI-1 or -2 or nonresponders to ustekinumab), a single case of active TB and a case of metastatic small bowel adenocarcinoma were reported.

The cumulative incidence rates of SIs (within 91 days of biologic administration) have also been evaluated among patients with self-reported IBD in the PSOLAR registry.[56] The cumulative incidence rates of SI (per 100 patient years) for patients with IBD were higher than the total PSOLAR population (1.38 vs 0.93) for ustekinumab exposure. However, patients treated with ustekinumab had numerically lower rates of SIs than patients receiving infliximab, other biologic, and systemic therapies (1.38 vs 5.75, 4.32, and 3.47, respectively) for psoriasis in the IBD subset. While concern has been raised for any major cardiac event with ustekinumab, a meta-analysis of randomized controlled clinical trials concluded that there was no significant difference in the rate of major cardiac events observed in patients receiving anti-IL-12/IL-23 antibodies or TNF antagonists.[57] Finally, there has been one case report of central demyelination diagnosed 1 year after ustekinumab treatment in a 63-year-old patient who was also previously treated with an immunomodulator and three other TNF antagonists.[58] There was no relationship between serum ustekinumab concentrations and the incidence of infections, SIs, or serious AEs following induction or maintenance treatment with ustekinumab in UNITI-1, UNITI-2, and IM-UNITI.[47]

Data in pregnancy

Ustekinumab is a US FDA class B medication, primarily based on animal studies in cynomolgus monkeys and with limited human data.[6,59,60] Evaluation of the 29 pregnancies reported with maternal use of ustekinumab (at least 1 dose) from 4 psoriasis studies demonstrated no congenital anomalies, a rate of spontaneous abortion comparable to the

general population (15%–20%), and no association between a longer duration of ustekinumab exposure before the reported pregnancy and adverse outcomes.[61] In the PIANO registry, ustekinumab (N=3) has been detected to cross the placenta and detected in the infant at birth at ratios (to maternal serum levels) similar to infliximab and adalimumab.[62] However, no association has been seen between detectable drug levels of biologics in the infant and the risk of infections, and breast-feeding is not contraindicated while on biologics.[62] It would appear prudent to avoid live-virus vaccines for the first 6 months in infants born to mothers exposed to ustekinumab given the detectable drug levels.[63]

Potential place in therapy

Current options for biologics with regulatory approval in the management of CD include TNF antagonists (infliximab, adalimumab, and certolizumab pegol) and the anti-integrins, vedolizumab, and natalizumab.[64] TNF antagonists are currently positioned as first-line biologics in the management of moderate-to-severe CD.[65] However, initial clinical response to TNF antagonists in trials has varied from 58% to 64%, with additional primary nonresponse in ~13%–40% of patients and a secondary loss of response estimated to occur at a rate of 13% per year.[66–68] This suggests the need for additional medications targeting other inflammatory pathways to treat patients who are primary nonresponders to TNF antagonists, are intolerant of the medications (due to AEs), or have a secondary nonresponse.

In the group of patients intolerant or refractory to TNF antagonists (UNITI-1), ustekinumab achieved clinical response (CDAI decrease ≥100 points) at week 6 in 33.7% (6 mg/kg) to 34.3% (130 mg) versus 21.5% in placebo (P=0.003 and 0.002, respectively).[39] The initial clinical response at week 6 is similar to that shown with vedolizumab (39.2% vs 22.3% with placebo, P=0.001) in GEMINI 3, which was an induction trial enriched with anti-TNF refractory patients.[69] Clinical remission (CDAI <150) at week 8 with ustekinumab (15.9%–20.9%) was also similar to the rates shown with vedolizumab at weeks 6 and 10 (15.2% and 26.6%) in this group of patients. During the maintenance phase of GEMINI 2 among initial responders to vedolizumab, 27.3% (every 4 week dosing) to 28% (every 8 week dosing) of the patients receiving vedolizumab were in clinical remission at week 52, in the group intolerant or refractory to TNF antagonists.[70] Ustekinumab demonstrated a higher rate of clinical remission at week 44 in this group of patients, ranging from 38.6% (90 mg q12w) to 41.1% (90 mg q8w), although IM-UNITI also demonstrated higher placebo remission rates than GEMINI-2 (26.2% vs 12.8%).[41] Ustekinumab also showed efficacy similar to vedolizumab in those who failed conventional therapy, factoring in the higher placebo response and remission rates in IM-UNITI.

The data from UNITI-1 and IM-UNITI demonstrate a clear role for ustekinumab among patients intolerant or refractory to TNF antagonists. The UNITI-2 data show that it may also potentially have a role among TNF antagonist naïve patients considering its favorable safety profile, potentially as a first-line biologic. However, this may be limited by cost considerations, especially with the introduction of biosimilars that are either FDA approved (infliximab biosimilar, CT-P13) or pending approval (adalimumab biosimilar, ABP 501).[71,72]

Specific subsets of Crohn's disease patients may be ideal candidates for ustekinumab therapy. These include patients with psoriasis and Crohn's disease as well as those who develop TNF-antagonist-induced psoriasis.[73] Paradoxical psoriasis induced by TNF antagonists has been described to involve 1.7%–10% of described cohorts, and identified risk factors include cigarette smoking status, female sex, and younger age of initiation of TNF antagonist in certain cohorts.[73–75] In a cohort of 434 IBD patients, 21 of whom developed psoriasis, all nine patients with Crohn's disease and severe psoriasiform lesions and/or TNF-antagonist-induced alopecia were successfully treated with ustekinumab. This study identified that IL-17A expression was significantly stronger in patients requiring ustekinumab than in patients responding to topical therapy (P=0.001).[73] Pyoderma gangrenosum (PG), including those recalcitrant to TNF antagonists and located in peristomal area, has been treated with ustekinumab.[76–78] In a case report, the tissue sample from the PG lesion in the lower extremity showed a highly elevated expression of IL-23, and this patient was successfully treated with ustekinumab.[78] Effects of the blockade of the IL-12/23 pathway on extra-intestinal manifestations are currently unknown, although studies have shown elevated serum IL-23 in Crohn's disease patients with associated arthritis and sacroiliitis.[79] An algorithm for the use of ustekinumab based on current available literature is proposed in Figure 3.

Specific IL-23 inhibition

Efficacy comparable to blocking of the IL-12/23 axis has been shown in mouse models of psoriasis and multiple sclerosis.[80] Available emerging data in psoriasis suggest that selective blockade of IL-23 may be critical in the pathogenesis of psoriasis more so than combined IL-12/23 blockade.[81] A phase II head-to-head psoriasis study showed

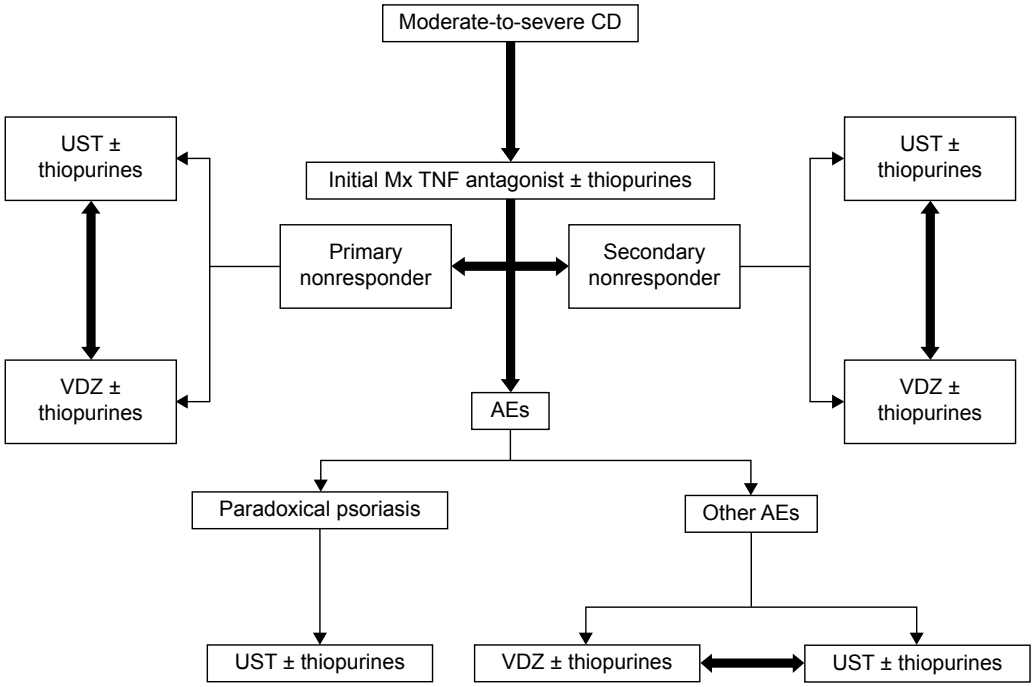

Figure 3 Proposed algorithm for use of UST in moderate-to-severe Crohn's disease.
Abbreviations: UST, ustekinumab; VDZ, vedolizumab; AEs, adverse events; TNF, tumor necrosis factor; CD, Crohn's disease.

superior efficacy of selective IL-23 blocker risankizumab (formerly investigational biologic compound BI 655066) over ustekinumab.[82,83] After 9 months, 69% of patients with moderate-to-severe plaque psoriasis maintained clear or almost clear skin (PASI 90) with risankizumab in the higher dose group compared to 30% of patients on ustekinumab. The NAVIGATE clinical trial comparing the relative efficacy of ustekinumab to guselkumab (another selective IL-23 blocker) in patients with moderate-to-severe plaque-type psoriasis has been completed and results are awaited.[84] Drugs specifically targeting the p19 subunit of IL-23 are being tested (risankizumab, MEDI2070) or will likely be tested (tildrakizumab and guselkumab) in CD, to potentially increase safety by allowing for normal IL-12-mediated Th1 response.[85–88]

Future directions

The effects of ustekinumab on healing of perianal disease and treating extra-intestinal manifestations are currently unknown. Additionally, development of predictive biomarkers for selecting patients likely to respond to ustekinumab may be the next step toward precision medicine in Crohn's disease, instead of a step-wise approach starting with TNF antagonists followed by ustekinumab or vedolizumab or vice versa. Serum soluble IL-2 receptor may be one such molecule.[89]

Author contributions

All authors contributed toward study conception, design, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Dr Loftus is a consultant for Janssen, Takeda, UCB, AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Mesoblast; research support from Janssen, Takeda, UCB, AbbVie, Genentech, Pfizer, Amgen, Robarts Clinical Trials, Gilead, Receptos, Seres, MedImmune. The authors report no other conflicts of interest in this work.

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