Ustekinumab for the treatment of Crohn's disease: can it find its niche?

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***Abstract*:** Crohn's disease is an immune-mediated disease that results in panenteric chronic inflammation in genetically predisposed individuals exposed to an appropriate environment. The past two decades have witnessed the emergence of an important class of drugs known as anti-tumour necrosis factor (TNF) agents in the treatment of Crohn's disease. Unfortunately, the utility of these agents have been hampered by primary and secondary nonresponse in a significant proportion of patients. Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin (IL) 12 and 23, is a novel pharmacotherapy for this patient cohort that offers an out-of-class option. It is approved for use in psoriasis and psoriatic arthritis, and has now been evaluated in phase II trials for moderate-to-severe Crohn's disease. We here review the published literature and describe a potential clinical role for its use in this disease cohort.

Keywords: anti-TNF agents, Crohn's disease, ustekinumab

Introduction

Crohn's disease is a chronic immune-mediated inflammatory disease that can potentially involve any segment of the gastrointestinal tract and is influenced by various host genetic and environmental factors. Since 1932 when the disease was first described by B.B. Crohn and colleagues at Mount Sinai Hospital in New York, much has been unravelled about its immunopathogenesis and genetic predisposition but a potential cure has remained elusive [Crohn *et al.* 2000].

For many years, Crohn's disease was managed by a stepup approach using steroids, mesalamine compounds, immunomodulators and antibiotics. In 1997, Targan and colleagues reported their experience in the first randomized control trial (RCT) using the anti-tumour necrosis factor (TNF) agent infliximab [Targan *et al.* 1997]. Infliximab is a chimeric (75% human and 25% mouse) immunoglobulin (Ig) G1 monoclonal antibody directed against both soluble and cell-bound TNF-α which helps limit the chronic inflammatory process associated with Crohn's disease. Over time, infliximab as well as other anti-TNF agents like adalimumab and certolizumab pegol have been shown to be effective in inducing and maintaining remission in Crohn's disease [Colombel *et al.* 2007; Ford *et al.* 2011; Hanauer *et al.* 2002, 2006; Present *et al.* 1999; Sandborn *et al.* 2007a; Sands *et al.* 2004; Schreiber *et al.* 2007]. Despite their financial cost, anti-TNF agents have created a paradigm shift in the management of this chronic and often progressive disease [Dignass *et al.* 2010].

Approximately one-third of patients prescribed an anti-TNF agent are primary nonresponders. Among the primary responders, subsequent loss of response may vary between 10 and 50% per year (secondary nonresponse) [Colombel *et al.* 2007; Hanauer *et al.* 2002, 2006; Sandborn *et al.* 2007a; Schreiber *et al.* 2007]. Failure of anti-TNF therapy has been classified into three main scenarios. Immunogenicity failures are characterized by low/absent drugs plasma levels in the presence of anti-drug antibodies (ADA). This is mainly seen in secondary nonresponders and is managed by switching to another anti-TNF agent [Afif *et al.* 2010; Baert *et al.* 2015; Roblin *et al.* 2014]. The anti-TNF response rates among secondary nonresponders who switch within class are generally lower than those observed in patients naïve to anti-TNF therapy [Allez *et al.* 2010; Colombel *et al.* 2007; de Silva *et al.* 2012; Sandborn *et al.* 2007b].

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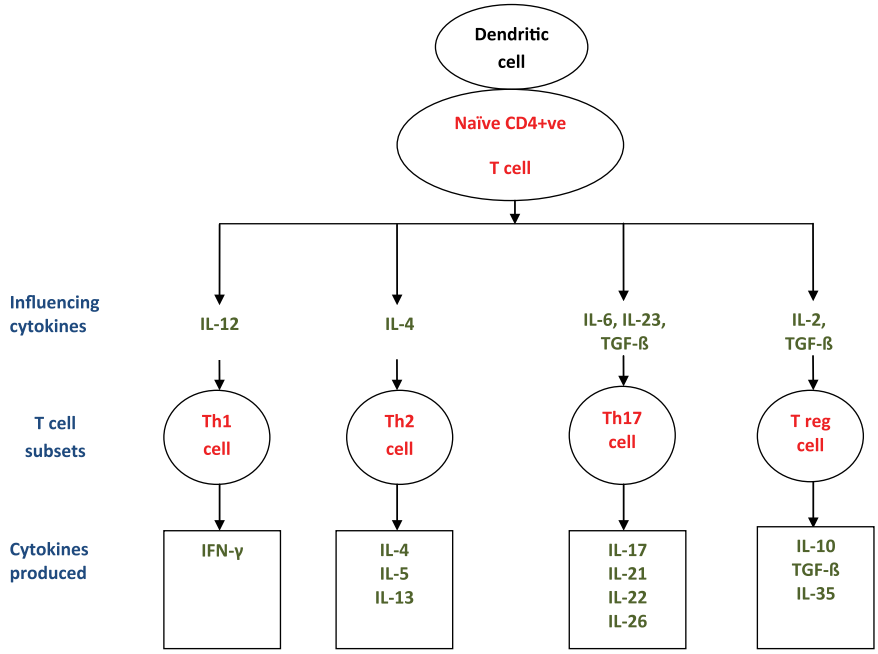

Figure 1. Differentiation of a CD4+ve T cell into different subsets.
IFN-γ, interferon-γ; IL, interleukin; TGF, transforming growth factor; Th, T helper; T reg, regulatory T cell.

In pharmacokinetic failures, where a low/absent drugs level is seen in the absence of ADA, dose optimization is needed [van de Casteele *et al.* 2015]. This is managed by increasing the dose escalation or shortening of the dose intervals of the anti-TNF agent [Katz *et al.* 2012]. Pharmacodynamic failures are characterized by adequate drugs plasma levels with absent ADA and seen in primary nonresponders. This scenario is usually managed by switching outside the anti-TNF class to another biological agent [Afif *et al.* 2010]. Therapeutic options targeting other inflammatory pathways are needed in moderate-to-severe Crohn's disease to allow clinicians to switch out of class. Ustekinumab (Stelara®, Janssen Biotech Inc., Horsham, PA, USA), an antibody to the p40 subunit of interleukin (IL) 12 and 23 offers such a promise. It has shown clinical efficacy in psoriasis, psoriatic arthritis and moderate-to-severe Crohn's disease [Gottlieb *et al.* 2009; Griffiths *et al.* 2010; Krueger *et al.* 2007; Leonardi *et al.* 2008; McInnes *et al.* 2013; Papp *et al.* 2008; Ritchlin *et al.* 2014; Sandborn *et al.* 2008, 2012].

IL-12 and IL-23 pathway

One of the key events in adaptive immunity involves the differentiation of a naïve CD4+ T cell into four main subsets: Th (helper) 1, Th2, Th17 and regulatory T (T reg) cells (Figure 1). In the presence of IL-12 and absence of IL-4, an activated CD4+ T cell differentiates into a Th1 cell; in the presence of IL-4, the CD4+ T cell differentiates into a Th2 subtype. CD4+ve T cells activated in the presence of IL-6, transforming growth factor (TGF) ß and IL-23 acquire a Th17 phenotype [Weaver *et al.* 2006]. In the presence of IL-2 and TGF ß, the CD4+ve T cell can differentiate into a T reg cell. Each of the newly formed Th cell subtypes can produce their own cytokine signature. Activated Th-1 cells increase interferon (IFN) γ production, enabling cell mediated immunity to control intracellular pathogens. Activated Th-2 cells produce IL-4, IL-5 and IL-13, activated Th-17 cells produce IL-17, IL-21, IL-22 and IL-26, and activated T reg cells produce IL-10, TGF-ß and IL-35. Dysregulation of immune cells and their cytokines may lead to chronic inflammation and autoimmune diseases. Immunophenotyping may help in identifying different clinical phenotypes of immune mediated diseases as well as in deciding more specific forms of therapy. Such a personalized strategy has been studied in the treatment of asthma [Hollams *et al.* 2009].

Ustekinumab

Preclinical studies have linked IL-12 and IL-23 to the pathogenesis of Crohn's disease with IL-12 found to be overexpressed and actively released

by intestinal lamina propria mononuclear cells [Strober *et al.* 2010]. Genome-wide association studies have found a significant association between Crohn's disease and a gene that encodes a subunit for the receptor of IL-23 [Duerr *et al.* 2006; Wang *et al.* 2009]. Structurally, IL-12 cytokine consists of the heterodimer of p35 and p40 which are covalently bound, while IL-23 cytokine is made up of p19 and p40 subunits. The IL-12 receptor is made up of IL-12Rß1 and IL-12Rß2, while the IL-23 receptor is composed of IL-12Rß1 and IL-23R subunits.

Monoclonal antibody-mediated neutralization of IL 12/23 by targeting the p40 shared subunit has been shown to be effective in murine models of colitis [Becker *et al.* 2006; Neurath *et al.* 1995; Yen *et al.* 2006]. Ustekinumab is a fully humanized IgG1κ monoclonal antibody (approximate molecular weight of 148,600 Daltons) that binds to p40 shared unit of unbound IL-12 and Il-23. This prevents IL-12/23 cytokine binding with IL-12Rß1 receptor, thereby reducing immune cell activation.

The median halflife of ustekinumab is approximately 3 weeks (ranging from 15 to 32 days), whereas the median time to reach maximum serum concentration (Tmax) after a single 90 mg subcutaneous (SC) injection in healthy subjects is 8.5 days. Ustekinumab can be given subcutaneously or intravenously, and is available as 45 mg/0.5ml and 90 mg/1 ml doses. It currently has US Food and Drug Administration (FDA) approval in the management of plaque psoriasis and psoriatic arthritis [Janssen Inc., 2015]. The recommended route and doses of ustekinumab in these conditions are SC 45 mg at 0 and 4 weeks, and every 12 weeks thereafter for patients with psoriatic arthritis and in patients with plaque psoriasis with a body weight of less than 100 kg. The approved dose is doubled to SC 90 mg in patients with plaque psoriasis with a body weight in excess of 100 kg.

It is unclear why the ustekinumab dose approved in psoriasis is lower than that prescribed in recent Crohn's disease trials [Gottlieb *et al.* 2009; Griffiths *et al.* 2010; Leonardi *et al.* 2008; Papp *et al.* 2008] [ClinicalTrials.gov identifier: NCT01369329, NCT01369342]. A possible explanation could be that psoriasis is a classic T-cell mediated organ-specific disease where IL-23 plays a central role in the disease pathogenesis by promoting the formation of Th17 cells [Blauvelt, 2008]. The inflammatory response in Crohn's disease is less clear and hence other cytokine regulatory pathways might play a role. The emergence of other out-of-class medication such as vedolizumab (Takeda Pharmaceuticals, Tokyo, Japan) [Sandborn *et al.* 2013] provides an indication that, in Crohn's disease, parallel inflammatory downstream signalling pathways might take place in the disease pathogenesis.

Efficacy in Crohn's disease

Clinical trials

Ustekinumab was first investigated in a phase IIa induction trial in moderate-to-severe Crohn's [Sandborn *et al.* 2008]. Adults who had moderate-to-severe Crohn's disease of at least 6 weeks duration and with Crohn's Disease Activity Index (CDAI) score of 220–450 points were included. Exclusion criteria included subjects positive for the tuberculin skin test, those with short bowel syndrome, an ostomy, strictures with obstructive symptoms, opportunistic infection or abscess, cancer and recent treatment with an anti-TNF agent or an investigational agent within the past 16 weeks.

The study design consisted of two populations. The first consisted of 104 patients who were randomized to a double-blind, placebo-controlled, parallel group study into 4 groups with crossover to the alternate therapy occurring at week 8. Patients were randomly assigned (1:1:1:1) to 1 of 4 groups: SC placebo at weeks 0, 1, 2 and 3 followed by SC 90 mg ustekinumab at weeks 8, 9, 10 and 11; SC 90 mg ustekinumab at weeks 0, 1, 2 and 3 followed by SC placebo at weeks 8, 9, 10, and 11; intravenous (IV) placebo at week 0 followed by IV 4.5 mg/kg ustekinumab at week 8; or IV 4.5 mg/kg ustekinumab at week 0 followed by IV placebo at week 8. The second population, consisting of 27 patients, was studied in an open-label fashion. Here the patients were assigned randomly (1:1) to either SC 90 mg ustekinumab at weeks 0, 1, 2 and 3, or IV 4.5 mg/kg ustekinumab at week 0. No additional treatment was administered after week 8.

Clinical response was defined as a reduction of at least 25% and 70 points in the CDAI score from week 0, while clinical remission was defined as an absolute CDAI score <150 points [Sandborn *et al.* 2002]. The primary endpoint was clinical response at week 8. Secondary endpoints included

clinical response at weeks 4 and 6, and clinical remission at weeks 4, 6 and 8. Mucosal healing by endoscopy was not assessed in this study.

In population 1, the clinical response rates for the combined groups were 49% (for ustekinumab) and 40% (for placebo) at week 8, which was not statistically significant ($p = 0.34$). However, the clinical response rates for the combined groups were significantly different ($p = 0.02$) between both the groups: 53% (ustekinumab) and 30% (placebo) at both weeks 4 and 6. In patients with prior but not recent infliximab exposure, the clinical response to ustekinumab was significantly better compared with placebo across all time points between weeks 2 and 8. A higher baseline CDAI score and a lower baseline body weight were associated with a better clinical response rate to ustekinumab compared with placebo at 8 weeks. The median C-reactive protein (CRP) levels decreased at 8 weeks in patients exposed to ustekinumab (either IV or SC).

In population 2, the clinical responses at week 8 to SC ustekinumab and IV ustekinumab were 43% and 54% respectively.

A phase IIb, double-blind, placebo-controlled trial was later conducted over 153 centres in 12 countries among patients with moderate-to-severe Crohn's disease resistant to anti-TNF agents [Sandborn *et al.* 2012]. All 526 patients were randomly assigned to receive either IV ustekinumab(at a dose of 1, 3 or 6 mg/kg body weight) or placebo at week 0. The primary endpoint was clinical response (defined as $\geqslant$100 point decrease in baseline CDAI score) at week 6. There were 145 patients who achieved a response to ustekinumab by 6 weeks. These were again randomly assigned to receive SC 90 mg ustekinumab or placebo at weeks 8 and 16.

A significant proportion of patients (36.6%, 34.1% and 39.7% of patients in the 1, 3 and 6 mg/kg of ustekinumab, respectively) achieved clinical response at 6 weeks (primary endpoint) compared with 23.5% in the placebo group ($p = 0.005$for the 6 mg group *versus* placebo). Clinical remission rates did not significantly differ between the ustekinumab and placebo treated cohorts at week 6, but clinical response (69.4% *versus* 42.5%, $p < 0.001$) as well as clinical remission (41.7% *versus* 27.4%, $p = 0.03$) rates were significantly higher in ustekinumab-treated patients at 22 weeks. Moreover, sustained clinical response, i.e. clinical response at all visits during the maintenance phase (55.6% *versus* 32.9%, $p = 0.005$) and glucocorticoid-free remission rates were significantly higher in ustekinumab-exposed patients at 22 weeks irrespective of the use of glucocorticoids at baseline (30.6% *versus* 17.8%, $p = 0.048$). No significant difference in the mucosal healing rates was noted between the 2 groups ($n = 50$, 19.5% in combined ustekinumab *versus* 11.1% in placebo, $p = 1$).

Based on the success of these phase II studies, three phase III trials have been completed or are underway.

UNITI-1 [ClinicalTrials.gov identifier: NCT01369329] is a multicentre, double-blind, placebo-controlled study investigating the safety and efficacy of ustekinumab in moderate-to-severe Crohn's disease in patients who have failed or are intolerant to anti-TNF agents. A total of 769 patients were enrolled and randomized to receive IV 130 mg ustekinumab, IV ustekinumab at 6 mg/kg or placebo. and followed up for a total of 8 weeks. The primary endpoint was clinical response at week 6.

UNITI-2 [ClinicalTrials.gov identifier: NCT01369342] is a multicentre, double-blind, placebo-controlled study investigating the safety and efficacy of ustekinumab in moderate-to-severe Crohn's disease in patients without previous failure or intolerance to anti-TNF agents. A total of 642 patients were enrolled and randomized to receive IV 130 mg ustekinumab, IV ustekinumab at 6 mg/kg or placebo. The primary endpoint was clinical response at 6 weeks.

IM-UNITI [ClinicalTrials.gov identifier: NCT01369355], open-label maintenance study, will recruit patients who have shown a clinical response to IV ustekinumab in UNITI 1 and UNITI-2. An estimated 1310 patients will be randomized to receive SC 90 mg ustekinumab every 8 weeks, every 12 weeks or placebo. Patients who are in the placebo or ustekinumab every 12 weeks arm will be allowed to cross over to the 8-weekly treatment arm if they lose response. The primary endpoint is clinical remission at 44 weeks.

UNITI-1 and UNITI-2 have been completed but the results are awaited. IM-UNITI is still enrolling patients and is expected to be completed by November 2018 [ClinicalTrials.gov identifier: NCT01369355]. Confirmative data from these studies on optimal dosing of ustekinumab in Crohn's disease are eagerly awaited.

Open-label clinical experience

Ginard and colleagues conducted a retrospective study involving 15 Spanish centres to assess the utility of ustekinumab in patients who had multi-drug-refractory Crohn's disease [Ginard *et al.* 2012]. Within the patient cohort, 66.7% had previously failed at least two immunosuppressants and 78.8% had previously failed at least two anti-TNF agents. In total, 33 patients (of which 20 were females) with a mean age of 38.1 ± 14.9 years were followed up for 184 ± 143 days. The majority (65.4%) received SC 90 mg ustekinumab for 4 weeks as induction schedule and 73.1% were given SC 90 mg in an 8-weekly maintenance schedule. After induction, 26.9%, 57.7% and15.4% had achieved clinical remission, response or failed therapy (all based on Harvey–Bradshaw index and medical judgment), respectively, while at the end of follow up, 45.5%, 30.3% and 24.2% were in clinical remission, response or failed therapy, respectively. Among the eight patients who failed treatment, two required surgery. Four subjects experienced non-severe adverse events (AEs).

Retrospective multicentre data from 97 patients (27 males, mean age 35.1 ± 11.6 years) who received at least one injection of SC ustekinumab after failing or being intolerant to immunomodulator therapy and at least one anti-TNF agent have shown a clinical benefit at 3 months [Wils *et al.* 2015] The mean cumulative dose of ustekinumab used as induction between weeks 0 and 4 was 148.5 ± 65 mg. The median follow up reported was 39.2 ± 32.8 weeks. In 71% of the total population and in 88.8% of those with perianal Crohn's, a clinical benefit (defined by physician's global assessment and corticosteroid-free remission) was observed. Among those who responded, 78% and 86% showed a clinical benefit at 6 and 12 months, respectively. There were no serious SAEs reported in relation to ustekinumab.

In a single centre Spanish study, the outcomes on compassionate use of ustekinumab were evaluated in eight patients with Crohn's disease refractory to conventional therapy (including two anti-TNF agents) [Herrara *et al.* 2015]. Six of the patients were female, median age was 39 and half were smokers. The induction dose was SC 3 mg/kg followed by 90 mg 8 weekly as maintenance (4 patients received an extra dose of 90 mg at week 4). From a baseline of 301 (range: 224–404), the median CDAI score declined to 167 (range: 35–262) at week 8 following induction and thereafter to 90 (range: 0–133) at end of follow up. At week 8, 37.5% had clinical remission while all but one had a clinical response. At 42 weeks' follow up, 75% were still in clinical remission. Two patients reported arthralgia as a possible AE.

The McGill group reported their retrospective open label study in which they studied the clinical response (defined by a combination of physician global assessment and the decision to continue treatment) to ustekinumab in 38 patients (18 males, median age 35.5 years) with Crohn's disease resistant to anti-TNF agents at 3, 6, 12 months and at last follow up [Kopylov *et al.* 2014]. The most frequent loading schedule (73.7%) was 90 mg at weeks 0, 1 and 2, while 73.7% were treated with maintenance regimen of 90 mg every 8 weeks. The majority of patients (73.7%) had an initial clinical response, of whom 80% had sustained response at 6 months. Among the patients who showed a response at 6 months, 88.9% continued to maintain a clinical response at 12 months. At their last follow up (7.9 ± 5.2 months); 71% maintained response while 73.3% were in corticosteroid-free remission. There was a need for dose escalation (n = 18) (mostly by interval reduction in 17 out of 18 patients) in 47.7% and this was successful in a majority (61.1%) of them. This would suggest that further dose optimization of ustekinumab may be needed in Crohn's disease.

Safety issues

Based on data from more than 3000 patients who have been recruited to ustekinumab trials for various immune-mediated diseases, we now have a better understanding of the potential clinical risk imposed by this novel pharmacotherapy [Croxtall, 2011; Scherl *et al.* 2010; Toussirot *et al.* 2013]. Most of the available safety data have emerged from the psoriasis trials and these are available up to a follow up of 76 weeks (PHOENIX 1). In this study, ustekinumab at doses 45 or 90 mg was prescribed [Leonardi *et al.* 2008].

Papp and colleagues have published the long-term safety experience in psoriasis over a 5 year follow up by pooling data from four RCTs [Papp *et al.* 2013]. A total of 3117 patients were included with a total follow up of 8998 patient-years. Approximately half (1569 patients) had at least 3 years' treatment duration. At the fifth year of

follow up, the event rate (per 100 patient-years) reported for 45 and 90 mg doses were: overall adverse events (242.6 and 225.3, respectively, for both doses used); serious AEs (SAEs) (7 and 7.2, respectively); serious infections (0.98 and 1.19, respectively); nonmelanoma skin cancers (0.64 and 0.44, respectively); other cancers (0.59 and 0.61,respectively); and major adverse cardiovascular events (MACE) i.e. cardiovascular death, myocardial infarction or stroke (0.56 and 0.36, respectively). The most commonly reported infections were nasopharyngitis and upper respiratory tract infection, while the serious infections were diverticulitis, cellulitis and pneumonia. Other commonly reported AEs were headache, arthralgia, sinusitis, back pain and influenza. The occurrence of overall mortality and other malignancies were similar to the general population. The study concluded that there was no dose-related or cumulative toxicity with long term use [Papp *et al.* 2013].

Reversible posterior leukoencephalopathy and a lymphomatoid drug eruption have been reported in two separate case reports [Gratton *et al.* 2011; Jung *et al.* 2011].

Although ustekinumab is approved in psoriatic arthritis, there has been a concern whether psoriatic arthritis will worsen in certain individuals following treatment as was reported in a case series [Stamell *et al.* 2013]. It might not be possible to transfer these risks from psoriatic patients to subjects with Crohn's due to the difference in pharmacokinetics and pharmacodynamics in these two distinct diseases. Moreover, ustekinumab has been predominantly used as monotherapy in psoriasis. Data on the added risk of concomitant immunosuppression in Crohn's are not yet available.

Experience from clinical trials in Crohn's disease (Table1)

In a phase IIa RCT [Sandborn *et al.* 2008], patients were followed up for safety through to week 28. On follow up of only the population 1 patients through week 8, there was no significant increase in the occurrence of AEs or SAEs in those patients exposed to ustekinumab compared with placebo. SAEs were predominantly related to Crohn's disease in the placebo and ustekinumab-exposed patients. In the placebo group, 3 patients (6%) had SAEs (small bowel stenosis and nonsteroidal anti-inflammatory drug related gastrointestinal ulceration, worsening of Crohn's and erythema nodosum, worsening Crohn's and small bowel obstruction), while two patients (4%) in the ustekinumab cohort developed SAEs (small intestinal obstruction and ischemic heart disease). More patients in the placebo cohort suffered from infectious complications compared with the ustekinumab cohort (23% *versus* 15%). However, neither the ustekinumab or placebo cohort reported serious infections or cancers. Mild AEs occurring within 1 hour of parenteral injection were more commonly observed in the IV ustekinumab group than the IV placebo group (19% *versus* 0%).

On follow up of both populations (1 and 2) through to week 28, 6 patients (6%) in population 1 had SAEs [worsening Crohn's (n = 2), colonic stenosis and pneumothorax (n = 1), small intestinal obstruction (n = 2) and prostate cancer (n = 1)] while 4 (15%) in population 2 had SAEs (viral gastroenteritis (n = 1), nephrolithiasis (n = 1), worsening Crohn's (n = 1), worsening Crohn's, syncope and disseminated histoplasmosis (n = 1). Two patients in population 2 developed serious infections (disseminated histoplasmosis and viral gastroenteritis). Two in population 1 developed cancers (prostate cancer and basal cell cum squamous cell cancers).

In a phase IIb RCT [Sandborn *et al.* 2012], the safety parameters were assessed up to 36 weeks. On follow up during the induction phase, the occurrence of at least one AE and the overall infection rate were similar in both ustekinumab and placebo cohorts. Serious infections were reported in six patients in the ustekinumab cohort (*Clostridium difficile* infection, viral gastroenteritis, urinary tract infection, perianal abscess, vaginal abscess and Staphylococcal infection), while a perianal abscess was seen in a patient recruited in the placebo cohort. Infusion reactions were mild and were similar in both cohorts (4.3% *versus* 4.5%).

On follow up of patients who had initial response to induction therapy, the rates of AEs and SAEs were similar in the ustekinumab and placebo cohorts. There were no reports of mortality, significant cardiovascular morbidity and mortality, tuberculosis or opportunistic infections. One patient exposed to ustekinumab reported basal cell carcinoma.

Experience from open-label studies in Crohn's disease

Among the open label studies, Ginard and colleagues reported four non-SAEs [Ginard *et al.*

Table 1. Summary of randomized control trials (RCTs) on ustekinumab in Crohn's disease.

Name of the study	Type of RCT	Number of patients	Primary endpoint	Secondary endpoints	Results	Serious adverse events (through week 8)
Sandborn *et al.* [2008]	Phase IIa, (crossover), moderate-to-severe Crohn's	104	Clinical response at week 8		Ustekinumab: 49% Placebo:40%	Ustekinumab: 4% Placebo:6%
		104		Clinical response at week 6	Ustekinumab: 53% Placebo:30% ($p = 0.02$)*	
		49 (subgroup: previous exposure to IFX)		Clinical response at weeks 8	Ustekinumab: 59% Placebo:26% ($p = 0.022$)*	
Sandborn *et al.* [2012]	Phase IIb, moderate-to-severe Crohn's: resistant to anti-TNF	526	Clinical response at week 6		Ustekinumab: 39.7% (6 mg/kg dose) Placebo:23.5% ($p = 0.005$)*	Ustekinumab: 5.8% Placebo:8.3%
		145 (subgroup: responders put on maintenance)		Clinical response at week 22	Ustekinumab: 69.4% Placebo:42.5% ($p < 0.001$)*	
		145 (subgroup: responders put on maintenance)		Clinical remission at weeks 22	Ustekinumab: 41.7% Placebo:27.4% ($p = 0.03$)*	
UNITI-1 (completed)	Phase III, moderate-to-severe Crohn's: resistant to anti-TNF	769	Clinical response at week 6		Awaited	Awaited
UNITI-2 (completed)	Phase III, moderate-to-severe Crohn's	642	Clinical response at 6 weeks		Awaited	Awaited
IM-UNITI (recruiting)	Phase III open-label maintenance, UNITI-1 and UNITI-2 responders	1310	Clinical response at 6 weeks		Awaited	Awaited

*Statistically significant.
IFX, infliximab; TNF, tumour necrosis factor.

2012], while two other studies did not observe any serious AEs. Only one patient exposed to ustekinumab in the McGill series developed a *C. difficile* infection [Kopylov *et al.* 2014].

There have been case reports of central demyelination and malignant melanoma in Crohn's patients exposed to ustekinumab [Badat *et al.* 2014; Ehmann *et al.* 2012]. There is also a special alert for healthcare providers on the risk of development of exfoliative dermatitis and erythrodermic psoriasis [Janssen Inc., 2014].

Anti-ustekinumab antibodies

The frequency of antibodies to ustekinumab in the psoriasis trials ranged from 3.8 to 5.4% [Papp *et al.* 2013]. In the Crohn's disease phase IIa RCT, samples were available from 99 patients recruited to this study. None developed anti-ustekinumab antibodies [Sandborn *et al.* 2008]. In the phase IIb RCT, out of the 427 available samples of patients who were exposed to ustekinumab, anti-ustekinumab antibodies were seen in only 3 subjects (0.7%) [Sandborn *et al.* 2012].

Pregnancy and lactation

No evidence of teratogenicity has been shown from animal studies conducted in cynomolgus monkeys [Enright *et al.* 2012; Martin *et al.* 2010]. The drug manufacturer advises giving the drug in pregnant women only if the benefit outweighs the risk [Janssen Inc., 2015].

It is not known whether the drug is secreted in human milk. The drug manufacturer advises choosing between discontinuation of nursing or discontinuation of the drug [Janssen Inc., 2015].

Patient-related perspectives

No data on the effect on quality of life (QOL) in ustekinumab-exposed patients are available for Crohn's disease. The results from the phase III RCT are eagerly awaited. In RCTs related to psoriasis and psoriatic arthritis, several patient related perspectives such as health-related QOL, work productivity, number of work days missed, anxiety, depression and sexual difficulties were observed to have significantly improved in those treated with ustekinumab [Gottlieb *et al.* 2009; Guenther *et al.* 2011; Langley *et al.* 2010; Leonardi *et al.* 2008; Papp *et al.* 2008; Reich *et al.* 2011].

Conclusion

Biological agents like ustekinumab targeting the IL-12/23 pathway may have a role in the armamentarium of various therapies that can be utilized in the management of refractory Crohn's disease. Phase II studies show that, in comparison with placebo, induction with ustekinumab is associated with a significant clinical response in patients who have had prior experience with anti-TNF therapy. In the same patient group, there is again significant clinical response as well as clinical remission in those prescribed maintenance ustekinumab. Patients not showing a response to induction ustekinumab are unlikely to benefit from maintenance therapy. The enhanced response in patients previously exposed to anti-TNF therapy suggests that inhibiting a parallel inflammatory pathway such as the IL-12/23 cytokine pathway might be beneficial in such a cohort. It is important to point out that these patients may have a higher disease burden and may respond suboptimally to downstream pharmacotherapy. It might be possible to speculate that patients who experience a pharmacodynamic failure to anti-TNF therapy should be offered an out-of-class option like ustekinumab. In pharmacokinetic and immunogenicity failures, further optimization within class may be suggested. Further concrete evidence will be available after the completion of the UNITI trials.

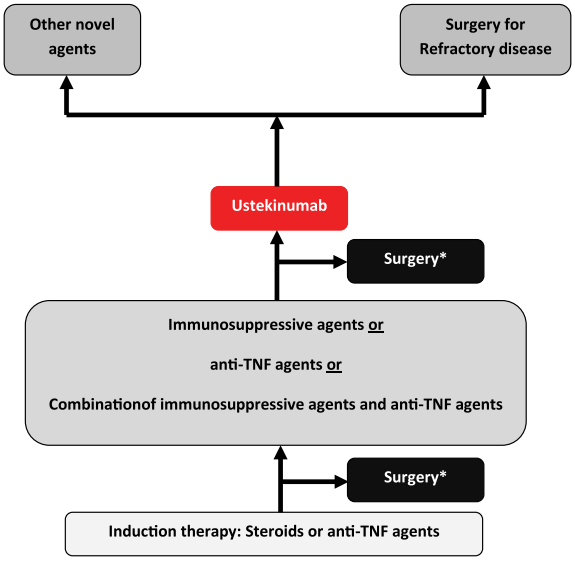

Figure 2. Hypothetical stepup approach utilizing ustekinumab in anti-TNF refractory Crohn's disease.
*Surgery to be considered in cases of complicated disease or if otherwise clinically indicated.
TNF, tumour necrosis factor.

There is no higher risk of SAEs and the development of antibodies to ustekinumab appears to be relatively nonsignificant in these short-term studies. However, there was no improved mucosal healing in comparison with placebo, while data on the QOL are not yet available. Based on immunophenotyping, there is a suggestion that ustekinumab may have a role to play in late Crohn's disease when there is increased Th17 activity [Veny *et al.* 2010]. Results from the three phase III RCTs should hopefully provide more information regarding the role of ustekinumab for Crohn's disease in the days to come. Data to date indicate that ustekinumab will be a clinically effective drug to use in refractory Crohn's disease especially as a second line agent after anti-TNF therapy (Figure 2).

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Conflict of interest statement

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