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# Long-term Clinical Effectiveness of Ustekinumab in Patients with Crohn's Disease Who Failed Biologic Therapies: A National Cohort Study

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## Abstract

**Background:** Ustekinumab [UST] was recently approved in Europe for the treatment of moderate to severe Crohn's disease [CD]. Long-term real-world data are currently scarce for CD patients previously exposed to several biologics.

**Methods:** This is an observational, national, retrospective multicentre study. Patients received intravenous UST ~6 mg/kg at baseline, with 90 mg subcutaneously thereafter every 8 weeks. Response and remission rates were assessed at Weeks 8, 16, and 52.

**Results:** Data from 152 patients were analysed. All patients were exposed to at least one anti-TNFα agent, with 69.7% were exposed to even two anti-TNFα and vedolizumab. After 1 year, 42.1% and 25.7% of patients had experienced clinical response and clinical remission, respectively, and

**Abbreviations:** AS, ankylosing spondylarthritis; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; IQR, interquartile range; IV, intravenous; LOR, loss of response; ORs, odds ratios; VAS, visual analogue scale; UST, ustekinumab.

38.8% and 24.3% had achieved steroid-free clinical response and remission, respectively; 38.8% of patients discontinued therapy during the 12 months of follow-up. Colonic location was predictive of clinical response at 1 year, and low body mass index [BMI] at baseline was a negative predictor of clinical remission. Resolution of arthralgia was associated with clinical response over time. De novo arthralgia was reported by 17.9% of patients at Week 8 and 13.5% of patients at Week 52. No impact of UST on arthralgia was observed in patients with concomitant ankylosing spondylitis [*n* = 17]. Others adverse events were reported in 7.2% of patients.

**Conclusions:** This real-world cohort study confirms the effectiveness of UST in CD patients previously exposed to several biologics. Ustekinumab was well tolerated with respect to adverse events.

**Podcast:** This article has an associated podcast which can be accessed at https://academic.oup.com/ecco-jcc/pages/podcast

**Key Words:** Clinical effectiveness; ustekinumab; real-life cohort; Crohn's disease

## 1. Introduction

Over the past two decades, the therapeutic armamentarium for treating inflammatory bowel disease [IBD] has been rapidly expanding with the development of anti-TNF and anti-integrin agents, which have dramatically improved the outcomes of Crohn's disease [CD].[1,2] Despite their efficacy, primary non-response to anti-TNF agents is observed in approximately one-third of patients, and secondary loss of response [LOR] in 10–50% of patients.[1,3] Primary non-response and LOR present a major challenge in daily practice, which indicates a need for novel therapies.

Ustekinumab [UST], a fully humanized IgG1 monoclonal antibody, targets the p40 subunit of IL-23 and IL-12, and represents a valid therapeutic option in treating Crohn's disease.[4,5] Moreover, its fully humanized structure could partially alleviate issues encountered with chimeric biologics, such as hypersensitivity and immunogenicity.[6,7]

Two randomized controlled trials[7,8] showed a benefit of UST with respect to short-term clinical response in CD. In the Phase IIb study CERTIFY,[7] patients receiving UST who had had a prior failure to anti-TNFα were more likely to have a clinical response than those receiving placebo. Based on these preliminary results, three Phase III studies have been conducted[9]: UNITI-1 evaluated patients who had failed or were intolerant to anti-TNFα, with clinical response at Week 6 as the primary end point. UNITI-2 had the same primary end point as UNITI-1 but evaluated patients naive to anti-TNFα. Finally, IM-UNITI was a maintenance study that included patients from UNITI-1 and UNITI-2 who had shown a clinical response to UST at induction.[10] A number of observational and retrospective studies have confirmed the effectiveness of UST in CD patients with previous failure to anti-TNFα, although most did not include an intravenous [IV] induction scheme.[11–13]

The objective of this present study was to report real-world experience of UST in a large national CD cohort in Belgium of patients with prior exposure to biologics, including anti-TNFα agents and vedolizumab.

## 2. Methods

### 2.1. Study design and population

Data from 174 patients starting UST between September 2016 and the end of August 2017 were retrospectively collected in 14 Belgian medical centres.

The study protocol for this retrospective analysis was developed by the Belgian IBD Research and Development [BIRD] group, and approved by the Ethics Committee of the Erasme hospital [EC P2017/484: approval date November 14, 2017; amendment for study extension received October 9, 2018].

### 2.2. Data collection and serum samples

Baseline data included gender, age, weight, smoking status, disease duration, disease phenotype at inclusion [according to Montreal Classification], history of CD surgery, extra-intestinal manifestations or associated immune-mediated inflammatory disease, previous and current CD treatments [including immunomodulators, anti-TNFα therapy, other biologics], clinical and serologic measures of disease activity at UST induction (C-reactive protein, Harvey–Bradshaw Index [HBI]). Follow-up data collected included use of concomitant medications [steroids and immunomodulators], HBI, C-reactive protein [CRP], and albumin at Weeks 8, 16 and 52. Following UST approval in Europe, the national IBD study group BIRD recommended to its members that they document arthralgia in IBD patients as accurately as possible, including the use of a visual analogue scale [VAS]. Completed VASs were then retrospectively collected and integrated into the present study. The entire cohort was treated uniformly during induction, with a baseline intravenous infusion based on weight ranges: <55 kg: 260 mg, 55–85 kg: 390 mg, >85 kg: 520 mg. During maintenance, UST 90 mg was subcutaneously administered every 8 weeks. Treatment intensification, with a new IV infusion and/or interval shortening [injections every 4 weeks], could be performed from Week 16 onwards in patients with initial response and subsequent loss of clinical response at the discretion of the treating physician [in some centres only].

Serum UST samples were prospectively collected at Week 8 in 82 patients [47.1%] in four centres [UZ Leuven, Erasme Hospital, CHU Liege, and AZ Delta]. Ustekinumab serum concentrations were determined by use of an in-house-developed sandwich-type enzyme-linked immunosorbent assay [ELISA] allowing the detection of UST concentrations ranging from 0.25 µg/mL to 64.0 µg/mL. This in-house-developed UST assay has been shown to be comparable with the UST assay of Janssen R&D in terms of specificity, selectivity, accuracy, and precision.[14]

### 2.3. Outcomes and parameters

Baseline patient and disease characteristics were recorded. Outcomes were evaluated at Weeks 8, 16, and 52. Clinical disease activity was assessed with the HBI, and clinical response and remission were

defined as a reduction in the HBI of ≥3 and a HBI of ≤4, respectively. Biological response was defined as a 50% decrease in CRP and/or CRP of ≤5 mg/L, and biological remission as CRP ≤ 5 mg/L, if CRP was >5 mg/L at baseline. Steroid-free clinical response and remission were defined as achievement of clinical response and remission without use of concomitant systemic or oral controlled-release steroids.

Primary non-response was defined as the absence of clinical improvement within 8 weeks and further drug discontinuation, whereas loss of response was defined as drug discontinuation due to secondary loss of response after response to the drug during induction.

First, clinical response and remission rates were assessed after IV induction [at Week 8], during early maintenance [at Week 16], and after 1 year of follow-up [at Week 52]. Second, biological response, proportion of steroid weaning, and the proportion of CD patients with improvement/resolution of arthralgia across follow-up were assessed. Adverse events through Week 52 were collected. Ustekinumab trough levels at Week 8 were correlated with different outcomes and at time points [Weeks 8–16–52].

### 2.4. Statistical methods

The Wilcoxon test was used for non-parametric, paired, continuous variables. Results were therefore expressed as the median with interquartile range [IQR]. The Pearson $\chi 2$ test was used to compare categorical variables. Predictable variables were assessed by uni- and multivariate analyses using logistic regression. Results were expressed as odds ratios [ORs] and their 95% confidence intervals [CIs]. Significant difference between outcomes was set as a *p*-value lower than 0.05. The Kaplan–Meier method was used to assess UST drug continuation over time. Analyses were performed on intent-to-treat basis, and any end of treatment with UST for any reasons, including adverse events, loss of response, or loss of follow-up, was considered as treatment failure from that time forward. The analyses were performed with SPSS version 20.0 [SPSS Inc., Chicago, IL, USA].

## 3. Results

### 3.1. Study population

A total of 174 CD patients were included in the study. After exclusion of 11 patients due to presence of an ostomy or ileo–anal pouch, and 11 patients with HBI ≤ 4 at baseline, data from 152 CD patients were subsequently analysed [Figure 1]. The clinical and demographic characteristics of the overall population are summarized in Table 1. All but one patient, due to a history of cancer, had been exposed to one anti-TNFα agent; 82% of the cohort had been exposed to two anti-TNFα agents; and 69.7% had been exposed to two anti-TNFα agents and vedolizumab. At baseline, concomitant steroids (70.1% systemic steroids [methylprednisolone] and 29.9% oral controlled-release formulation [beclomethasone or budesonide]) were used in 44.7% of patients.

### 3.2. Clinical response and remission to ustekinumab

At Week 8, 59.2% of patients [*n* = 90] had experienced a clinical response, including 28.2% [*n* = 44] with clinical remission; 38.2% [*n* = 58] and 19.7% [*n* = 30] of the population had achieved a steroid-free clinical response and remission, respectively. At Week 16, 51.9% [*n* = 79] experienced a clinical response, including 30.9% [*n* = 47] with clinical remission; 45.4% [*n* = 69] and 26.9% [*n* = 41] of the population had obtained a steroid-free clinical response and remission, respectively. Of 62 patients without clinical response at Week 8, 24.2% [*n* = 15] experienced a late clinical response at Week 16. By 1 year of follow-up, 42.1% [*n* = 64] had experienced a clinical response, including 25.7% [*n* = 39] with clinical remission. Of the population, 38.8% [*n* = 59] and 24.3% [*n* = 37] obtained a steroid-free clinical

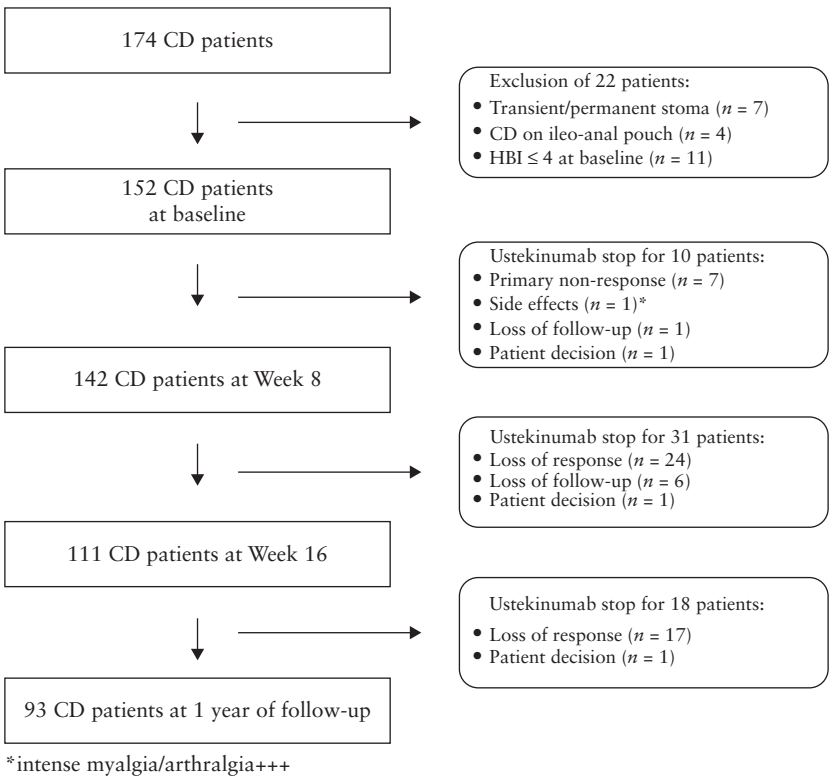


**Figure 1.** Flow chart of the overall population.

**Table 1.** Baseline demographics and characteristics of the overall population

| | | | Patients at baseline | | |
|---|---|---|---|---|---|
| | | | [*n* = 152] [105 females [69.1%]] | | |
| **Age,** years [min–max] | | | 41 [19–74] | | |
| **Disease features** *n*, [%] | | | | | |
| Age at diagnosis, years [min–max] | | | 23 [6–66] | | |
| A1 [<17 years] | L1 | B1 | 5 [3.3] | 24 [15.8] | 67 [44.1] |
| A2 [17–40 years] | L2 | B2 | 103 [67.8] | 30 [19.7] | 45 [29.6] |
| A3 [>40 years] | L3 | B3 | 42 [27.7] | 98 [64.5] | 39 [25.6] |
| Unknown | +L4 | Unknown | 2 [1.2] | 14 [9.2] | 1 [0.7] |
| Peri-anal disease | | | 62 [40.8] | | |
| **Concomitant conditions** *n*, [%] | | | | | |
| Primary sclerosing cholangitis | | | 4 [2.4] | | |
| Rheumatoid arthritis | | | 1 [0.6] | | |
| Psoriatic arthritis | | | 2 [1.2] | | |
| Ankylosing spondylitis | | | 17 [11.2] | | |
| Psoriasis | | | 7 [4.2] | | |
| Uveitis/episcleritis | | | 10 [5.9] | | |
| **Past history of CD surgery** *n*, [%] | | | 94 [59.2] | | |
| **Smoking status** *n*, [%] | | | | | |
| Current | | | 46 [30.3] | | |
| Never | | | 65 [42.8] | | |
| Former | | | 36 [23.7] | | |
| Unknown | | | 5 [3.3] | | |
| **Prior exposure to biologic** *n*, [%] | | | | | |
| 1 anti-TNF# | | | 151 [99.4] | | |
| 2 anti-TNF | | | 125 [82.2] | | |
| 2 anti-TNF + vedolizumab | | | 106 [69.7] | | |
| **Concomitant medications at baseline** *n*, [%] | | | | | |
| Steroids | | | 68 [44.7] | | |
| Azathioprine/ 6 MP | | | 16 [10.5] | | |
| Methotrexate | | | 9 [5.4] | | |
| None | | | 73 [48] | | |
| **Clinical and biological data at baseline** median [IQR 25–75] | | | | | |
| Harvey–Bradshaw index | | | 10 [7–14] | | |
| C-reactive protein [mg/L] [*n* = 140; *n* ≤ 5 mg/L = 28] | | | 16.2 [10.6–28.8] | | |

#One patient had a contraindication for anti-TNF therapy due to neoplasia.

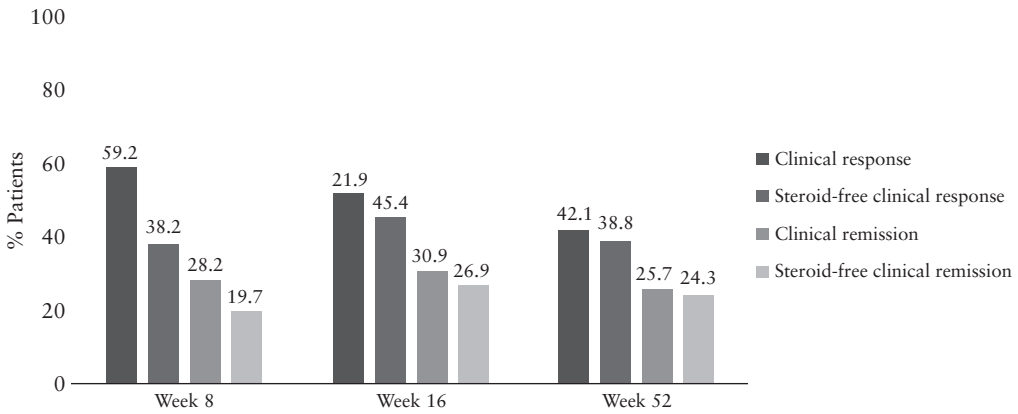


**Figure 2.** Clinical effectiveness at Weeks 8–16–52. Percentages of response and remission in 152 Crohn's disease patients treated with ustekinumab at Weeks 8–16 and 52. Analyses were performed with intention-to-treat.

response and remission, respectively [Figure 2]. Among the 59 patients with steroid-free clinical response at 1 year, steroid withdrawal was reported from Week 8 onwards in 76.3% [*n* = 45] and from Week 16 onwards in 91.5% [*n* = 54]. Among 37 patients with steroid-free clinical remission at 1 year, steroid withdrawal was reported from Week 8 in 81% [*n* = 30] and from Week 16 in 97.3% [*n* = 36].

Looking at the steroid-free clinical response and remission in the subpopulation of patients concomitantly treated with steroids at baseline [*n* = 68], 22.1% [*n* = 15] and 14.7% [*n* = 10] of the subpopulation had achieved a steroid-free clinical response and remission at Week 8, respectively. At Week 16, 32.4% [*n* = 22] and 27.9% [*n* = 19] of the subpopulation had achieved a steroid-free clinical response and

remission, respectively. By 1 year of follow-up, 27.9% [*n* = 19] and 17.6% [*n* = 12] of the subpopulation had achieved a steroid-free clinical response and remission, respectively [Supplementary Figure 1].

Among 105 patients without clinical remission at Week 16, 11.4% [*n* = 12] were in clinical remission at 1 year. Of the patients in clinical remission at Week 16, 55.3% [*n* = 26] experienced a sustained clinical remission after 1 year. By 1 year of follow-up, a progressive steroid weaning was observed: 44.7% were on steroid therapy at baseline [*n* = 68], 34.2% at Week 8 [*n* = 52], 17.1% at Week 16 [*n* = 26], and 11.2% at Week 52 [*n* = 17].

The cumulative probabilities for maintained UST treatment at 8 weeks, 16 weeks, and 12 months were 93.4% [SE ± 0.02], 73% [SE ± 0.04], and 61.2% [SE ± 0.04], respectively [Figure 3]. Ustekinumab treatment was stopped in 38.8% of patients [*n* = 59] over the 12 months of follow-up. The reasons for UST discontinuation were primary non-response [*n* = 7], loss of response [*n* = 41], side effects [intense myalgia and arthralgia] [*n* = 1], patient decision [*n* = 3], and loss to follow-up [*n* = 7]. A treatment intensification was reported in 6.6% [*n* = 10] of patients: two patients received a new IV infusion; an interval reduction at 4 weeks was applied for 8 patients, and 1 patient received both new a IV infusion and interval reduction. After optimization, all patients continued treatment with UST.

### 3.3. Evolution of biomarkers

Baseline CRP was available for 140 patients, of which 112 [80%] had CRP > 5 mg/L. CRP significantly decreased from baseline [16.1 mg/L, IQR 10.6–28.8] to 8.5 mg/L at Week 8 [IQR 3.9–14, $p < 0.0001$], 9.1 mg/L at Week 16 [IQR 4–16, $p < 0.0001$], and 6.6 mg/L at Week 52 [IQR 6.6–15.1, $p < 0.0001$] [Supplementary Figure 2]. Considering the relative drop in CRP levels according to patients with clinical response versus non-response, and patients with clinical remission versus non-remission at Week 8, a trend was observed; however, this was not significant when comparing clinical non-responders and responders (median drop of 41% [0–74.5] versus 62% [11.7–84], respectively, $p = 0.59$); in addition, the drop in CRP levels did not significantly differ between remitters and non-remitters (median drop of 45% [10–78] and 68.5% [37–85.5], respectively, $p = 0.12$). At Week 8, biological response was observed in 41.1% of patients [*n* = 46] and at Week 16, 34.8% [*n* = 39]. Additionally, 17.2% of patients without biological response at Week 8 obtained one at Week 16 [*n* = 11]. At Week 52, a 50% drop was observed in 33% [*n* = 37].

### 3.4. Predictors of clinical response and clinical remission at 1 year of follow-up

Clinical factors associated with clinical response and remission at 1 year are summarized in Tables 2 and 3. In univariate analysis, patients with colonic disease (OR: 2.5 [95% CI: 1.08–5.8]) were more likely to have clinical response 1 year after UST initiation, whereas an albumin level of <40 g/L at baseline (OR: 0.4 [95% CI: 0.18–0.87]) was a negative predictor of obtaining a clinical response 1 year after UST initiation. In multivariate analysis, only colonic disease (OR: 3.5 [95% CI: 1.34–9.41]) remained a positive predictor of clinical response.

In univariate analysis, patients with CRP > 10 mg/dL at baseline (OR: 2.4 [95% CI: 1.03–5.4]) were more likely to have clinical remission 1 year after UST initiation, whereas patients with body mass index [BMI] < 18 (OR: 0.28 [95% CI: 0.09–0.87]) and an albumin level of <40 g/L at baseline (OR: 0.29 [95% CI: 0.11–0.78]) were negative predictors of obtaining clinical remission. In multivariate analysis, only low BMI (<18) at baseline remained a negative predictor of clinical remission.

### 3.5. Pharmacokinetics

Ustekinumab trough levels at Week 8 were analysed in a subgroup of 82 patients, with a median UST level of 7.1 µg/mL [IQR 3.8–9.9]. An inverse weak correlation was observed between CRP level at Week 8 and UST trough level at Week 8 [rho spearman = –0.3, $p = 0.001$] [Supplementary Figure 3], whereas a positive moderate correlation was observed between albumin and UST trough level at Week 8 [rho spearman = 0.5, $p < 0.0001$]. In contrast, no association was found between UST trough levels at Week 8 and clinical response and remission at any time point [Weeks 8, 16, or 52]. Also, when dividing the overall population into quartiles, no tendency was observed. Similarly, no significant association between UST trough levels at Week 8 and biological response was observed at any time point [Weeks 8, 16, or 52].

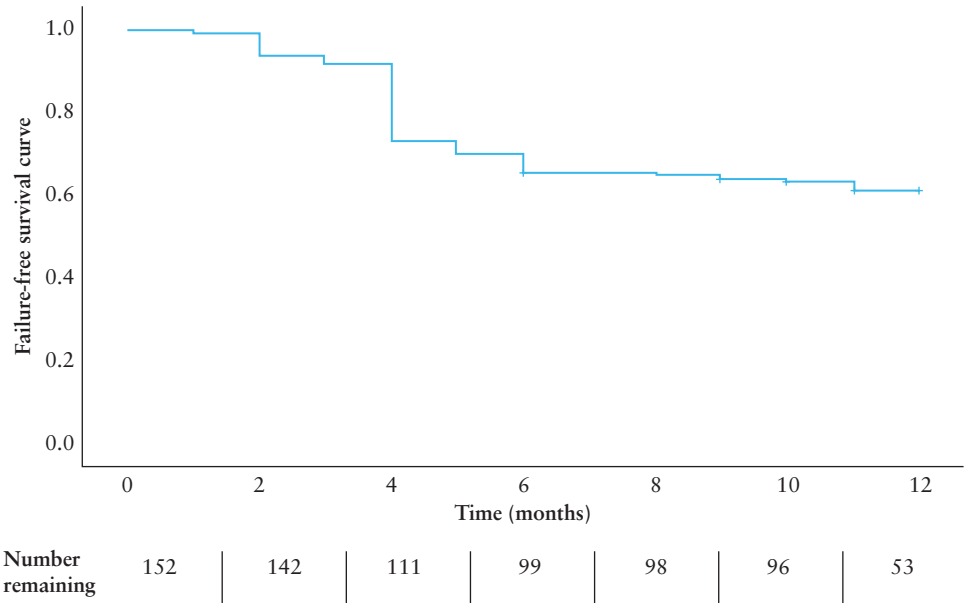


**Figure 3.** Kaplan–Meier curve showing the failure-free survival of ustekinumab therapy by 1 year of follow-up. The cumulative probabilities for maintained ustekinumab treatment at 8 weeks, 16 weeks, and 12 months were 93.4% [SE ± 0.02], 73% [SE ± 0.04], and 61.2% [SE ± 0.04], respectively.

**Table 2.** A Variables associated with ustekinumab response at 1 year of follow-up

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | *p*-value | OR | 95% CI | *p*-value | OR | 95% CI |
| Age | 0.3 | 0.9 | 0.96–1.01 | | | |
| Sex | 0.52 | 0.8 | 0.39–1.61 | | | |
| Age at diagnosis | 0.9 | 0.99 | 0.97–1.03 | | | |
| Perianal disease | 0.6 | 1.2 | 0.62–2.3 | | | |
| Ileal disease [L1] | 0.9 | 1.05 | 0.43–2.58 | | | |
| Colonic disease [L2] | **0.03** | 2.5 | 1.08–5.80 | **0.01** | 3.55 | 1.34–9.41 |
| Ileo-colonic disease [L3] | 0.06 | 0.5 | 0.26–1.03 | | | |
| Inflammatory behaviour [B1] | 0.7 | 0.88 | 0.46–1.7 | | | |
| Stricturing behaviour [B2] | 0.43 | 0.75 | 0.37–1.53 | | | |
| Penetrating behaviour [B3] | 0.21 | 1.6 | 0.77- 3.34 | | | |
| No history of CD surgery | 0.84 | 0.94 | 0.48–1.8 | | | |
| Smoking status | 0.8 | 0.9 | 0.45–1.85 | | | |
| BMI < 18 | 0.08 | 0.37 | 0.12–1.15 | | | |
| Steroids at baseline | 0.06 | 0.54 | 0.27–1.04 | | | |
| IMM at baseline | 0.8 | 0.9 | 0.38–2.2 | | | |
| CRP > 10 mg/L at baseline | 0.06 | 1.03 | 1.007–1.05 | | | |
| Albumin < 40 g/L at baseline | **0.02** | 0.4 | 0.18–0.87 | | | |
| USK trough level at Week 8 | 0.34 | 0.9 | 0.86–1.05 | | | |

**Table 3.** Variables associated with ustekinumab remission at 1 year of follow-up

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | *p*-value | OR | 95% CI | *p*-value | OR | 95% CI |
| Age | 0.3 | 0.9 | 0.96–1.01 | | | |
| Sex | 0.41 | 0.71 | 0.31–1.61 | | | |
| Age at diagnosis | 0.52 | 0.99 | 0.95–1.02 | | | |
| Perianal disease | 0.4 | 1.4 | 0.66–2.88 | | | |
| Ileal disease [L1] | 0.6 | 0.77 | 0.26–2.23 | | | |
| Colonic disease [L2] | 0.19 | 1.8 | 0.74–4.33 | | | |
| Ileo-colonic disease [L3] | 0.47 | 0.76 | 0.35–1.62 | | | |
| Inflammatory behaviour [B1] | 0.24 | 0.64 | 0.3–1.35 | | | |
| Stricturing behaviour [B2] | 0.78 | 0.89 | 0.39–1.99 | | | |
| Penetrating behaviour [B3] | 0.1 | 1.93 | 0.87- 4.25 | | | |
| History of CD surgery | 0.4 | 0.74 | 0.35–1.54 | | | |
| Smoking status | 0.4 | 1.4 | 0.65–3.05 | | | |
| BMI < 18 | **0.03** | 0.28 | 0.09–0.87 | **0.008** | 0.18 | 0.05–0.64 |
| Steroids at baseline | 0.06 | 0.54 | 0.27–1.04 | | | |
| IMM at baseline | 0.8 | 0.9 | 0.38–2.2 | | | |
| CRP > 10 mg/L at baseline | **0.04** | 2.4 | 1.03–5.4 | | | |
| Albumin < 40 g/L at baseline | **0.01** | 0.29 | 0.11–0.78 | | | |
| USK trough level at Week 8 | 0.57 | 0.96 | 0.85–1.09 | | | |

### 3.6. Evolution of arthralgia with ustekinumab treatment

Of our population of CD patients, 11.2% had a concomitant diagnosis of ankylosing spondylitis at baseline [*n* = 17], and 30.3% [*n* = 46] reported arthralgia at UST initiation. Of the patients with concomitant ankylosing spondylitis, 70.6% [*n* = 12] did not report any impact of UST on the intensity of their symptoms, based on VAS. Of patients with arthralgia at the start of UST [*n* = 46], a gradual resolution in symptoms [VAS = 0] was observed, with 63% of patients still experiencing symptoms at Week 8 [*n* = 29], 45.6% at Week 16 [*n* = 21], and 17.4% at Week 52 [*n* = 8]. Arthralgia resolution was also significantly associated with clinical response at the various time points [*p* = 0.03 at Week 8, *p* = 0.03 at Week 16, and *p* = 0.04 at Week 52]. Among patients with persistent arthralgia across follow-up, no reduction in intensity was reported, based on VAS. Surprisingly, 17.9% of patients developed de novo arthralgia at Week 8 [*n* = 16/89], 19.1% at Week 16 [*n* = 17/89], and 13.5% at Week 52 [*n* = 12/89].

### 3.7. Adverse events

During the 12 months of follow-up, 11 adverse events, other than the aforementioned de novo arthralgia, were reported; these are listed in Table 4. One patient discontinued therapy due to intense myalgia/arthralgia. No malignancy or deaths were reported. Of the overall population, 10% [*n* = 17] underwent surgery due to CD complications during the follow-up.

## 4. Discussion

In this real-world experience of CD patients with previous failure to several biologics, UST-induced clinical response and remission were observed in 59.2% and 28.2% of patients at Week 8, respectively. At

**Table 4.** Adverse events and surgery

| Total numbers of adverse events, *n* | 11 |
|---|---|
| Allergic reaction IV ustekinumab infusion | 1 |
| Intense arthralgia | 2 |
| Deep venous thrombosis | 1 |
| Spontaneous abortion | 1 |
| Infections | 5 |
| Gastroenteritis | 3 |
| Pyelonephritis | 1 |
| Pneunomia | 1 |
| Abdominal abscess | 1 |
| **Total numbers of CD surgery, *n*** | **17** |
| Fistula surgery | 4 |
| Colostomia | 1 |
| Definitive ileostomia | 2 |
| Resection | 6 |
| Not described | 3 |

1 year of follow-up, clinical response and remission were achieved in 42.1% and 35.7% of patients, respectively [5.3% were lost to follow-up]. Ustekinumab trough levels at Week 8 were correlated with level of albumin, and inversely correlated with CRP.

In UNITI-1,[10] the short- [Week 8] and long-term [Week 52] clinical remission rates of 20.9% and 41.1%, respectively, were slightly different from those obtained in the present study, which could be explained by the different study design and clinical scoring system used. Other real-life cohorts reported so far have quite similar clinical response and remission rates to ours, with the following limitations[11,12,15]: the dosage, treatment regimen, and administration route varied significantly across and within studies, which hampers the comparison of the therapeutic effectiveness of UST between these studies. In contrast, our study is much more homogenous in the treatment regimen, with weight-based IV induction, and maintenance every 8 weeks with subcutaneous 90 mg injections for all patients [10 patients had treatment intensification]. Importantly, 70% of the current cohort had previously exposed to two anti-TNFα agents and vedolizumab, which was not the case in the above-mentioned studies, in which very few patients had received vedolizumab previously. In our study, 24% of patients without clinical response at Week 8 achieved a clinical response at Week 16. This is somewhat lower than the 50% delayed response that was observed in the UNITI studies.

Two predictive markers of UST effectiveness were identified. Colonic disease [L2] was identified as a favourable predictive marker of a clinical response at 1 year. The predictive value of colonic disease has already been described in previous studies on UST, but with low evidence.[11,16] However, this association has also been found with anti-TNF therapy.[17] The genetic background associated with colonic CD could be an explanation.[18] In contrast, low BMI at baseline was identified as a negative predictive marker of clinical remission at 1 year. This observation could be related to the severity of the underlined CD.

The safety profile of UST has already largely been studied in psoriasis, with reassuring long-term data from the PSOLAR registry.[19] However, we should keep in mind that dosage and therapeutic schedules are different in psoriasis patients. In several real-world CD cohorts,[11,12,20] including our cohort, no safety issues were identified.

Although UST has been approved for the treatment of psoriatic arthritis,[21,22] arthralgia is frequently reported as a side effect in both pivotal and real-life studies on CD,[7,8,10–12,20] and even reported as not being efficacious in axial spondyloarthritis.[23] In the present study, we confirmed that UST was ineffective for CD patients with active AS. In CD patients without ankylosing spondylitis, two groups were observed to have opposite trends in response: a significant proportion of patients with arthralgia at baseline experienced a complete resolution of symptoms in correlation with clinical response, but some patients without arthralgia at baseline developed arthralgia during the follow-up period. These results need to be interpreted with caution because data were based on VAS, the location of the arthralgia [peripheral/axial] was not available, and none of these patients were evaluated by a rheumatologist. Nevertheless, de novo arthralgia has also been reported during anti-TNF therapy and during vedolizumab therapy.[24]

The trough-level distribution observed at Week 8 was similar to that observed in UNITI-I using the same method.[10] The trough levels we observed at Week 8 did not show correlation with clinical outcomes, in contrast with the findings of others.[25,26] This may be for two possible reasons: First, trough levels were performed in our study in a subgroup of 82 patients, which may impact the statistical power. Second, in Battat et al.'s and Adedokun et al.'s studies, UST trough levels were better correlated to objective end points such as CRP or endoscopy than clinical end points.[25,27] We actually found an inverse correlation with CRP.

This study has some limitations. First, its retrospective nature could induce an underestimation of adverse events, especially mild adverse events. However, we had little missing data. Second, due to the high percentage of previous use of biologics in this cohort, UST was probably maintained in some patients without clinical response due to absence of other therapeutic options. Hence, it was difficult to pinpoint primary non-responders. This difficulty could to some extent explain why no pharmacokinetics trend was observed. Third, endoscopic data were not available for assessment of mucosal healing. Moreover, although the collection of faecal calprotectin was available in >50% of the overall cohort, analyses were difficult to manage due to different cut-offs and variability in methods of measurement between the 14 centres.

In conclusion, this study confirms the effectiveness of UST in CD patients previously exposed to both anti-TNFα and vedolizumab in real-world experience. Ustekinumab was well tolerated and few adverse events were observed.

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## Conflict of Interest

CL, PVH, JD, MN, HP, CVK, WVM, and EH have nothing to declare.

FB has received research grants from AbbVie, Chiesi, Ipsen, MSD, Roche, and Ipsen; and speaker and consultancy fees from AbbVie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Celgene.

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## Author Contributions

CL, BV, FB, DF, and SV developed the study design. CL managed the Ethics Committee submission. CVK, EM, MDV, WVM, JFR, PB, JD, EH, DS, HP, PVH, EL, DF, FB, and SV recruited patients. CL, MN, BV, and CVK helped with collection of data. AG performed ustekinumab measurements, CL analysed data, and CL and DF wrote the draft. All co-authors have reviewed and corrected the draft.

## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

## Podcast

This article has an associated podcast which can be accessed at https://academic.oup.com/ecco-jcc/pages/podcast

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