Title: Real-world clinical effectiveness of ustekinumab in the treatment of Crohn's disease in the East Midlands UK

Short running title: UK real-world experience of ustekinumab in CD

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Abstract

Objectives: To evaluate the effectiveness of ustekinumab in treating CD in a UK real-world setting.

Design: This was a multicentre, retrospective observational study of patients (aged ≥18 years) with CD or inflammatory bowel disease of unclassified type (IBDU) starting ustekinumab between 11th November 2016 and 1st August 2020 across eight English hospitals. The primary objective was to determine the proportion of patients achieving corticosteroid-free remission at week 52 for patients with CD/IBDU following initiation with ustekinumab. Corticosteroid-free remission was defined as achieving a clinical Harvey-Bradshaw Index (HBI) score of ≤4 and corticosteroid-free status.

Results: The analysis included 422 patients with CD/IBDU. Corticosteroid-free remission was 41% (68/166) at week 16, 41% (47/115) at week 30, and 48% (38/80) at week 52. Clinical remission was 51% (85/166) at week 16 and 50% (40/80) at week 52. Clinical response was 34% (43/125) at week 16 and 32% (17/53) at week 52. Objective remission was 40% (4/10) at week 16 and 70% (7/10) at week 52. Corticosteroid-free remission at week 52 was achieved in patients with previous exposure to 1–2 biologics and/or small oral molecules (56%; 35/63), those without surgical history (64%; 16/25), and those without penetrating disease (54%; 29/54). Patients who achieved clinical remission at week 16 were more likely to achieve corticosteroid-free remission at week 52 (70%; 14/20) versus those who did not (20%; 4/20). In total, 37 adverse events occurred in 21 patients.

Conclusion: This multicentre study provides real-world experience of ustekinumab in patients with CD/IBDU in England.

Keywords

Crohn's disease, effectiveness, inflammatory bowel disease, ustekinumab, real-world data

Word count: 2,645 words

Key messages

What is already known on this topic?

- Ustekinumab is currently licensed for the treatment of adult patients with moderate-to-severe Crohn's disease (CD), with efficacy and safety demonstrated in clinical trials.
- However, there is limited multicentre real-world evidence on the effectiveness of ustekinumab in patients with CD in the UK.

What this study adds?

- This multicentre study provides real-world effectiveness data on ustekinumab in patients with CD or inflammatory bowel disease of unclassified type (IBDU) in the East Midlands.
- The results demonstrated that patients who had achieved clinical remission at week 16 were more likely to achieve corticosteroid-free remission at week 52, in line with the product licence which states that treatment discontinuation should be considered in patients who show no evidence of therapeutic benefit of ustekinumab after 16 weeks from the induction dose.
- Effectiveness outcomes differed according to patients' demographic and clinical characteristics, although differences were not statistically significant.

How this study might affect research, practice or policy?

- These findings confirmed the real-world clinical effectiveness of ustekinumab in a large cohort with CD constituting over half of patients with isolated ileal disease, and future research investigating the impact of disease phenotype on biologic treatment response is warranted.
- This study provides a better understanding of the clinical experience of ustekinumab which may support future practice, service provision, and optimal patient management in the UK.

Introduction

Crohn's disease (CD) is one of the two principal forms of inflammatory bowel disease (IBD), involving chronic immune-mediated inflammation of the gastrointestinal tract (1). The inflammatory and symptomatic burden of CD is heterogeneous between patients and within individuals over time (1). The humanistic and economic burden of CD is significant due to the relapsing and recurrent nature of disease (2,3).

In recent decades, the introduction of targeted biologic therapies has revolutionised the treatment of CD, providing clinical benefits including better disease control, decreased complications, and improved quality of life (4,5). Ustekinumab is an anti-interleukin (IL)-12/IL-23 human monoclonal antibody licensed for treating adult patients with moderately-to-severely active CD who have had an inadequate response with, lost response to, or were intolerant or have medical contraindications to conventional therapy or a tumour necrosis factor-alpha (TNF-α) inhibitor (6).

Efficacy and safety of ustekinumab for inducing and maintaining clinical remission in patients with moderate-to-severe CD has been demonstrated in clinical trials, including the UNITI-1 and UNITI-2 induction trials as well as the UNITI maintenance trial (7). Clinical effectiveness and safety of ustekinumab in the short (week 8, 12, 16, 24) and long (week 48, 52, 104) term have also been reported in real-world multicentre studies across Europe (8–12). However, there are limited real-world studies in the UK (5,11,13).

This study aims to describe the demographic and clinical characteristics, and clinical outcomes of patients with CD treated with ustekinumab across eight hospitals in the East Midlands.

Materials and methods

Study population and design

A multicentre retrospective observational study was conducted with patients initiated on ustekinumab across eight hospitals in the East Midlands. Participating centres are outlined in **Supplementary Materials**. The study was designed and conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (14) and in compliance with Good Pharmacoepidemiology Practices (15). Approval from the Health Research Authority and Health and Care Research Wales was obtained prior to the commencement of the study (REC reference: 21/HRA/5280). As this was a retrospective non-interventional study, there was no additional risk to patients since all data were collected from existing medical records by members of the direct care team. No personally identifiable information on any patient was collected or removed from the participating centres, and patients had no direct involvement in the study. As a result, ethical approval and patient consent were not required for this study.

Eligibility criteria

Patients were included if they were aged ≥18 years at the time of initiation of ustekinumab, had clinically confirmed CD or inflammatory bowel disease of unclassified type (IBDU), had received a minimum of one dose of ustekinumab between 11th November 2016 (drug licence date) and 1st August 2020, and had a minimum of 12 months follow-up. A clinically confirmed CD was defined as per standard endoscopic, radiological and histological criteria (1). Due to a small number of patients, IBDU cases were pooled and analysed with the CD data set.

Data collection

Anonymised patient data were extracted from secondary care hospital medical records and prescriptions from each hospital by the direct care team. Patients were identified using a prospectively maintained register of CD/IBDU patients on biologics/immunosuppressants that each hospital had for clinical, audit and governance purposes. Patient demographics prior to starting ustekinumab and clinical characteristics before and during each clinical visit for the entire treatment duration were recorded. The coordinating site, Nottingham University Hospitals coordinated data collection with each participating hospital. Data quality checks were conducted by sites before analysis.

Outcome measures and definitions

The primary objective was to determine the proportion of patients achieving corticosteroid-free remission at week 52 (±6 weeks) for patients with CD/IBDU following initiation with ustekinumab. The subgroup analyses were conducted according to whether patients were previously on biologics and/or small oral molecules use, whether patients had surgery history, and the disease behaviour.

Secondary outcomes included the proportion of patients achieving clinical remission, clinical response, corticosteroid-free remission, and objective remission at week 16 (±6 weeks), week 30 (±6 weeks) and week 52 (±6 weeks). These time points selected for the outcome measures were reflective of standard care practice and to capture additional outcomes dependent on clinical needs.

Corticosteroid-free remission was defined as clinical Harvey-Bradshaw Index (HBI) score ≤4 and corticosteroid-free status. Corticosteroid-free status was defined as achievement of clinical remission with no recorded use of budesonide, hydrocortisone, or prednisolone as documented on the medical records. All patients were included irrespective of corticosteroid use at baseline. Clinical remission was defined as HBI score ≤4. Clinical response was assessed as a >3-point decrease from baseline in HBI score for patients with CD/IBDU. Objective remission was defined as an absence of ulcers and inflammatory lesions (granularity, erythema or friability) assessed by endoscopy or small bowel magnetic resonance enterography (MRE) or a Simple Endoscopic Score for Crohn's disease (SES-CD) of 0–2.

Additional outcomes were to describe patient demographic and clinical characteristics at baseline; to evaluate the median time to effectiveness outcomes; to describe adverse events (AEs) recorded during the observation period; to describe drug survival and treatment discontinuation. Definitions for additional outcomes are described in **Supplementary Materials**.

Statistical analysis

As there was no hypothesis testing involved in the study, a descriptive analysis was performed. Parametric variables were presented as mean with standard deviations (SD) and non-parametric continuous variables as medians with interquartile ranges (IQR). Categorical variables were described as frequencies with percentages. Time to treatment discontinuation was evaluated using Kaplan–Meier (KM) methods. Patients who discontinued ustekinumab were censored at the time of discontinuation; patients remaining on treatment were censored at the last date of follow-up, 30th November 2020, or death, whichever occurred first.

Additionally, sensitivity analyses were performed according to whether patients had achieved clinical remission at week 16.

The available-case analysis was performed to address missing data, restricting the analysis to individuals with no missing data in different subsets of the data. Full details on missing data handling are described in **Supplementary Materials**; details on missing data for each variable of interest are presented in **Figure S1** and **S2**.

Data were analysed using R statistical software (version 4.2.2).

Results

Patient demographic and clinical characteristics

In total, 422 patients with CD/IBDU were included in the analysis. Of this cohort, 417/422 (99%) patients had clinically confirmed CD and 5/422 (1%) patients had IBDU. **Table 1** summarises patient demographics and disease characteristics. Mean (SD) age at diagnosis was 30.4 (15.5) years, and 56% (237/422) of patients were female. Mean (SD) age at initiation of ustekinumab was 41.9 (15.6) years. The most common indications for initiating ustekinumab were endoscopic or radiological evidence of active disease (36%; 150/422) or loss of response to prior treatment (31%; 132/422). At the initiation of ustekinumab, the median (IQR) HBI score of the overall cohort was 7.0 (4.0–9.0) (**Table S1**), and 68.3% (177/259) of the patients had an HBI score of ≥5 indicative of an active disease.

Most patients had ileal CD (L1) (59%; 246/419). For disease behaviour, 46% (188/411) of patients had non-stricturing/non-penetrating or inflammatory disease plus perianal (B1) while 27% (110/411) of patients were documented with a stricturing (B2) phenotype and 18% (74/411) with a penetrating (B3) phenotype. Perianal involvement was present in 18% (74/411) of patients (B1P–B3P).

Just over half of patients had a history of surgical treatment for IBD (54%; 227/422). Prior to initiation of ustekinumab, the medication history was recorded: biologics (95%; 399/422), corticosteroids (93%; 392/422), and immunosuppressants (82%; 344/422) were commonly prescribed. At the initiation of ustekinumab, the most commonly prescribed biologics were adalimumab (74%; 314/422), infliximab (60%; 252/422), and vedolizumab (23%; 96/422) (**Table 1**).

235 Table 1. Patient demographic and clinical characteristics

Variables	
Patients (N)	422
CD	417 (99%)
IBDU	5 (1%)
Indication of initiation of ustekinumab[a] (n, % n=421)	
Endoscopic or radiological evidence of active disease	150 (36%)
Corticosteroid dependency	16 (4%)
Intolerance to immunosuppressants or TNF inhibitors	65 (15%)
Loss of response to TNF inhibitors	132 (31%)
Non-response to TNF inhibitors	73 (17%)
Not known	2 (0%)
Age at initiation of ustekinumab (years, mean [SD]) (n=419)	41.9 (15.6)
Age at time of death (if deceased, years, mean [SD]) (n=4)	41.5 (17.2)
Age at last follow-up (if alive, years) (n=418)	43.2 (15.7)
Age at diagnosis (years, mean [SD]) (n=404)	30.4 (15.5)
0 to 16 years (n, % n)	67 (17%)
17 to 39 years (n, % n)	239 (59%)
≥40 years (n, % n)	98 (24%)
Sex (n, % n=422)	
Male	185 (44%)
Female	237 (56%)
Body mass index (kg/m^2, median [IQR]) (n=194)	25.5 (21.3–29.2)
Tobacco use (n, % n=403)	
Never smoked	268 (67%)
Current smoker	53 (13%)
Ex-smoker	82 (20%)
Have history of any malignancy (n, % n=420)	17 (4%)
Have drug history at baseline (n, % n=407)	401 (99%)
Class of drug history[a]	
Biologics/small oral molecules (n, % n=422)	399 (95%)
Adalimumab	314 (74%)
Infliximab	252 (60%)
Vedolizumab	96 (23%)
Golimumab	4 (1%)
Certolizumab	4 (1%)
Tofacitinib	2 (0%)
Corticosteroids (n, % n=422)	392 (93%)
Immunosuppressants (n, % n=422)	344 (82%)
Aminosalicylates (n, % n=419)	156 (37%)
Number of each type of concomitant medications use	
Number of types of aminosalicylates (mean [SD]) (n=179)	0.0 (0.0)
0 (n, % n)	179 (100%)
1 (n, % n)	0 (0%)
Number of types of corticosteroids (mean [SD]) (n=198)	0.3 (0.5)
0 (n, % n)	150 (76%)
1 (n, % n)	46 (23%)
2 (n, % n)	2 (1%)
Number of types of immunomodulators (mean [SD]) (n=263)	0.2 (0.4)
0 (n, % n)	221 (84%)
1 (n, % n)	42 (16%)

236

237 Table 1 (continued). Patient demographic and clinical characteristics

Variables	
Baseline stool frequency per 24 hours (median [IQR]) (n=369)	4.0 (3.0–6.0)
Have family history of IBD (n, % n=379)	25 (7%)
Have history of surgery (n, % n=422)	227 (54%)
IBD-related admission frequency at baseline (median [IQR]) (n=419)	6.0 (3.0–11.0)
The Montreal classification of Crohn's disease[b] (n, % n=419)	
Disease location	
L1 (ileal)	246 (59%)
L2 (colonic)	32 (8%)
L3 (ileocolonic)	113 (27%)
L4 (isolated upper disease/upper gastrointestinal tract)	29 (7%)
L1 + L4	22 (5%)
L2 + L4	0 (0%)
L1 + L4	5 (1%)
Disease behaviour (n, % n=411)	
B1 (non-stricturing, non-penetrating)	188 (46%)
B2 (stricturing)	110 (27%)
B3 (penetrating)	74 (18%)
B1P (non-stricturing, non-penetrating plus perianal)	30 (7%)
B2P (stricturing plus perianal)	10 (2%)
B3P (penetrating plus perianal)	34 (8%)
Faecal calprotectin levels at baseline (µg/g, mean [SD]) (n=38)	871.6 (843.3)
C-reactive protein levels at baseline (mg/L, mean [SD]) (n=162)	17.0 (25.2)

238 Data were analysed based on patients without missing data.
239 [a] Categories are not mutually exclusive. [b] Montreal classification system as defined by Silverberg et al. (2005) (16).
240 CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease of unclassified type; IQR, interquartile range;
241 SD, standard deviation
242

Overall effectiveness outcomes

The proportion of patients achieving corticosteroid-free remission was 41% (68/166) at week 16, 41% (47/115) at week 30, and 48% (38/80) at week 52 (**Figure 1**). Clinical remission rates were 51% (85/166) at week 16, 50% (57/115) at week 30 and 50% (40/80) at week 52 (**Figure 1**). Clinical response was achieved by 34% (43/125) of patients at week 16, 39% (33/84) of patients at week 30, and 32% (17/53) of patients at week 52 (**Figure 1**). Objective remission was observed in 40% (4/10) of patients at week 16, 50% (5/10) of patients at week 30, and 70% (7/10) of patients at week 52 (**Figure 1**).

The median (95% CI) time to achieve corticosteroid-free remission was 354 (290–426) days; the median (95% CI) time to achieve clinical remission was 126 (112–161) days (**Table S2**).

Effectiveness outcomes at week 52 by subgroup

Corticosteroid-free remission at week 52 was achieved in 49% (95% CI: 38%–60%) of patients who had previous exposure to biologics and/or small oral molecules (**Figure 2**). Amongst patients who had previous exposure to biologics and/or small oral molecules, corticosteroid-free remission at week 52 was achieved in 56% (95% CI: 43%–68%) of those who previously used 1–2 biologics/small oral molecules and in 20% (95% CI: 4%–48%) of those who previously used >2 biologics/small oral molecules (**Figure 2**).

For patients without a history of surgery, 64% (95% CI: 45%–83%) achieved corticosteroid-free remission at week 52, while for patients with a history of surgery 40% (95% CI: 27%–53%) achieved corticosteroid-free remission at week 52 (**Figure 2**).

Additionally, corticosteroid-free remission at week 52 was achieved in 48% (95% CI: 30%–66%) of patients with stricturing disease and in 46% (95% CI: 32%–60%) of patients without stricturing disease (**Figure 2**). Corticosteroid-free remission at week 52 was also achieved in 54% (95% CI: 40%–67%) of patients without penetrating disease and in 29% (95% CI: 11%–47%) of patients with penetrating disease (**Figure 2**).

Sensitivity analysis

The rates of achieving corticosteroid-free remission at week 52 were 70% (95% CI: 50%–90%) in patients who had achieved clinical remission at week 16 and 20% (95% CI: 6%–44%) in patients who had not achieved clinical remission at week 16 (**Table S3**).

Adverse events

Through the 52-week study period, 5% (21/399) of patients experienced at least one AE following initiation of ustekinumab. In total, 37 AEs were recorded, including sepsis (19%; 7/37), allergic reaction (16%; 6/37) and intolerance (11%; 4/37) (**Table S4**). There were no unexpected AEs or serious adverse events such as hospitalisation or death observed during the study period.

Treatment discontinuation

During the study period, 43% (95% CI: 38%–49%; n=182/422) of patients discontinued ustekinumab; the most commonly reported reasons for treatment discontinuation were primary non-response (36%; 39/108) and surgery (31%; 34/108). **Figure 3** shows the KM plot of drug survival for time to treatment discontinuation. The median time to discontinuation of ustekinumab was 365 days.

Discussion

This is the largest UK multicentre real-world observational study with a substantial cohort of patients with CD/IBDU treated with ustekinumab. Clinical effectiveness was achieved at week 16 and sustained through week 30 and week 52. At week 52, corticosteroid-free remission was 48%, clinical remission was 50%, and clinical response was 32%. These findings, except for clinical response, are generally consistent with the IM-UNITI trial (in patients receiving maintenance ustekinumab dosing every 8 or 12 weeks, glucocorticoid-free remission was 46.9% and 42.6%, clinical remission was 53.1% and 48.8% at week 44, and clinical response was 59.4% and 58.1% at week 44 respectively) (7).

Clinical response to ustekinumab has been reported in other UK real-world studies. In the multicentre Cross Pennine study II, clinical response/remission rates evaluated by the Physician Global Assessment (PGA) were 70.9% at week 14 and 62.5% at week 52 (5). In a UK single centre real-world study, the 1-year clinical response and remission (assessed by PGA) rates were 71% and 14% respectively, and the 1-year corticosteroid-free response was 65% (13). Furthermore, a Scottish real-world study reported that the 1-year cumulative rates of clinical remission and deep remission (defined as achieving clinical remission plus mucosal healing) were 32% and 19.3% respectively (17). However, comparisons of effectiveness should be made with caution as clinical evaluation and study design differed across studies.

Patient characteristics of this cohort were similar to those in the clinical trial and real-world studies (5,7,13), particularly mean age, gender distribution, proportion of patients with a surgical history, and medication history (use ≥1 medications). Collectively, with the existing literature (5,13), the results provided an overview of the type of patients who may be considered for ustekinumab, i.e., those who have failed previous biologics (e.g. infliximab, adalimumab), those with ileal or ileocolonic involvement and non-stricturing/non-penetrating or inflammatory disease.

Notably, patients who had one previous exposure to biologics and/or small oral molecules (rather than two or more), patients without a surgical history, or patients without penetrating disease were more likely to achieve corticosteroid-free remission at week 52, however differences were not statistically significant. These results highlight the possible impact of patient characteristics and disease phenotype on biologic treatment responses, in support of the literature (5,18).

Clinical outcomes and the results from sensitivity analyses confirmed that patients who had a response and remission at week 16 following initiation of ustekinumab were more likely to achieve a sustained response and corticosteroid-free remission at week 52. These findings are in line with the product licence which indicates that discontinuing treatment should be considered in patients who show no evidence of therapeutic benefit after 16 weeks (19).

Lastly, in this cohort, 43% discontinued ustekinumab with primary non-response being the most common reason for discontinuation, in line with the literature (5,13). The median time to discontinuation in this cohort appeared longer than other UK real-world cohort (365 versus 256 days) (13). Ustekinumab exhibited more favourable treatment persistence in this cohort.

A key limitation to this study was the retrospective study design, with quality of results being dependent on the completeness/quality of the medical records and accuracy during the audit process. Thereby, not all patients had data available, and the results for these endpoints might not be representative of the entire sample of patients included in this study. Furthermore, using HBI score alone for determining clinical remission may be insufficient. Although only available for a limited number of patients, other clinical parameters (e.g. endoscopy, biomarkers) were collected alongside HBI to ensure a rigorous assessment as per other clinical trials (1,20) and to fulfil the standardised outcome set for real-world data in IBD (21). Although desirable, data on endoscopic scores, histological/radiological outcomes and biomarkers are often scarce in the real-world setting due to limited use in daily practice (21). As with other real-world studies, missing data, a lack of opportunity to query and review medical records during the study and the descriptive analysis may hinder data interpretation. Moreover, the inclusion of patients with IBDU (1%; 5/422) and the use of tools designed to evaluate severity for CD on the IBDU cases are also limitations of this study.

Notwithstanding these limitations, an important strength was that ustekinumab remained effective in this study cohort containing a large number of patients with more complex or difficult-to-treat CD, i.e., 95% (399/422) were biologic-experienced and 59% (246/419) had isolated ileal disease which is considered to be more difficult-to-treat compared with colonic disease (22,23). As observed in this cohort, perianal disease response and/or remission following ustekinumab was evaluated, and 5/5 (100%) patients with available data did not achieve such effectiveness outcomes at week 16 (**Table S8**). Nevertheless, this observation was based on a small sample. Future research on effectiveness of ustekinumab in a cohort with isolated ileal disease is warranted. Additionally, 94/162 (58%) patients with low baseline C-reactive protein levels (0–10 mg/L) had isolated ileal disease (**Table S6**), reflecting the common characteristic of an active ileal disease or a post-surgical outcome. These results also imply that CRP level may not be a strong predictive marker for disease activity in patients with isolated ileal disease or those who underwent surgery, in line with the literature (24,25).

In conclusion, these findings confirmed the effectiveness of ustekinumab in this real-world cohort of patients with CD. This study provides a better understanding of the clinical experience of ustekinumab which may support future practice, service provision, and optimal patient management in the UK.

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Figures

Figure 1. Overall clinical effectiveness outcomes at week 16, 30 and 52

Figure 2. Proportion of patients achieving corticosteroid-free remission at week 52, by subgroup

Proportion of patients achieving corticosteroid-free remission at week 52 was evaluated by whether patients had previous exposure to biologic and/or small oral molecule, by the number of previous biologic and/or small oral molecule used, by whether patients had a history of surgery, and by disease behaviour including structuring and penetrating disease. Data are presented in percentages (indicated as black line in boxes) with 95% lower/upper confidence limit (represented by shaded boxes).
*Confidence interval is calculated based on binomial approximation.
SOM, small oral molecule

Figure 3. KM plot of time to treatment discontinuation

Patients are censored at 365 days if the treatment period is more than 1 year.
CI, confidence interval

Disclosures

Janssen-Cilag contributed to interpretation of data; in writing, reviewing, and approval of the final version. JR White is an employee of Nottingham University Hospital NHS Trust. S Ahmad, F Ashraf, and S Foley are employees of Kings Mill Hospital. S Din, R Das, and NM Charles are employees of Royal Derby Hospital. R Das has received educational funding from Takeda. J Pinheiro and A Palejwala are employees of Queens Hospital Burton NHS Trust. PB Wright was an employee of Janssen-Cilag Ltd and may hold shares in Janssen Ltd. M Andiappan and M Alexander were employees of OPEN Health. B Uddin, D Hoshen, and D Elphick are employees of Chesterfield Royal Hospital NHS Foundation Trust. T Qamar, N Rezwan, MV Hamza, J Glover, and R Robinson are employees of Leicester General Hospital. V Gopakumar is an employee of Lincoln County Hospital. A Sajjad and M Shahzad are employees of Kettering General Hospital NHS Foundation Trust. GW Moran is in receipt of research funding from Alimentiv, Astra Zeneca, Janssen and Bristol Myers Squibb. GW Moran has consulted on advisory boards from Abbvie and Pfizer, and works as a consultant for Alimentiv.

Data availability statement

Data are available upon reasonable request.

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