Original research

Ustekinumab for the treatment of moderate to severe ulcerative colitis: a multicentre UK cohort study

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ABSTRACT

Objective Ustekinumab is an interleukin-12/interleukin-23 receptor antagonist licensed for the treatment of ulcerative colitis (UC). Clinical trial data were promising; however, real-world data are limited. We assessed the safety and effectiveness of ustekinumab in UC in a real-world setting.

Design/method This was a multicentre, retrospective, observational cohort study between February 2020 and January 2022. Disease activity was assessed using the Simple Clinical Colitis Activity Index (SCCAI). Clinical remission was defined as a SCCAI≤2. The primary endpoints were rates of corticosteroid-free remission (CSFR) at week 16 and at week 26. Objective outcomes, including faecal calprotectin (FCAL), were also collected.

Results 110 patients with UC (65% male; median age 40 (IQR range 29–59); 96% with prior biologic and/or tofacitinib exposure) had a median follow-up of 28 weeks (IQR 17–47). CSFR was 36% (18/50) at week 16% and 33% (13/39) at week 26, corresponding with a significant fall in SCCAI from 6 (IQR 4–8) at baseline to 3 (IQR 0–5) at week 26, p<0.001. By week 16, there was improvement of median FCAL measurements, which fell from a baseline of 610 µg/g (IQR 333–1100) to 102 µg/g (IQR 54–674) at week 16. At the end of follow-up, 15% (17/110) had discontinued treatment; 13 patients due to primary non-response or loss of response, and 1 patient for family planning. Treatment was discontinued in three patients due to adverse events.

Conclusion In the largest real-world study to date, ustekinumab was effective with a reassuring safety profile in a refractory cohort of patients.

Significance of this study

What is already known on this topic

⇒ Failure rates of existing medical therapies for ulcerative colitis (UC) are high and there remains an unmet need for patients, particularly those with refractory disease.
⇒ The safety and efficacy of ustekinumab, an antagonist of the p40 subunit of interleukin-12 and interleukin-23, were demonstrated in the UNIFI clinical trials.
⇒ Many patients are ineligible to enrol into randomised controlled trials, thus, external validity is suboptimal. Real-world data for ustekinumab in UC are needed.

What this study adds

⇒ This comparatively large multicentre UK study demonstrates that ustekinumab leads to corticosteroid-free clinical remission in one-third of patients at weeks 16 and 26 in a treatment-refractory cohort, with improvement in objective measures of inflammation including faecal calprotectin and endoscopy.

How this study might affect clinical practice?

⇒ Ustekinumab should be considered in patients with UC to induce and maintain remission where antitumour necrosis factor therapy is contraindicated, has failed or limited by side effects.
⇒ While a proportion of patients have a beneficial effect by week 8, some patients show a delayed response, highlighting the importance of treatment persistence and administering the second dose.

INTRODUCTION

Despite the increasing number of therapies available in this rapidly evolving therapeutic setting, currently licensed treatments for ulcerative colitis (UC) remain limited by primary and secondary loss of response and the risk of adverse events (AEs). Ustekinumab is an IgG1 kappa monoclonal antibody directed at the shared p40 subunit of interleukin-12 and interleukin-23, which activate Th1

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and Th17-mediated immune responses, respectively. Ustekinumab has proven efficacy for the treatment of moderate to severe UC as demonstrated by the UNIFI phase III clinical trials.[1] In June 2020, based on these findings, the National Institute for Health and Care Excellence in the UK recommended its use in UC following tumour necrosis factor (TNF)-α inhibitor failure, intolerance or if anti-TNF-α was deemed unsuitable.[2]

A network meta-analysis of randomised controlled trials (RCTs) found that ustekinumab was ranked highest for the induction of remission and endoscopic improvement in UC following anti-TNF-α failure.[3] However, RCTs may not be suitable for effectiveness research due to poor external validity, a consequence of, among other things, strict inclusion criteria.[4] Therefore, real-life data of ustekinumab in UC are needed, and remain very limited.[5–8] The aim of this study was to supplement the body of observational research by describing the effectiveness and safety of ustekinumab in UC patients in everyday clinical practice. Second, we aimed to assess predictors of ustekinumab response and persistence.

METHODS

Study design and population

This was a multicentre, retrospective, observational cohort study across four tertiary inflammatory bowel disease (IBD) referral units in the UK: Guy's and St Thomas' NHS Foundation Trust, Oxford University Hospitals NHS Foundation Trust, St George's University Hospitals NHS Foundation Trust and Barts Health NHS Trust. The study included consecutive patients who received an intravenous ustekinumab induction infusion between February 2020 and January 2022 at each site. Patients were excluded if <18 years of age, diagnosed with Crohn's disease or IBD unclassified or those with a prior colectomy. For all patients, ustekinumab was prescribed as per product license and administered intravenously at an approximate dose of 6 mg/kg at baseline, followed by 90 mg injected subcutaneously at week 8, and then every 8–12 weeks according to clinical assessment. Some patients were escalated to 4-weekly therapy.

Data collection and outcome measures

A predesigned data capture form was sent to study investigators at participating centres to record patient demographics and clinical characteristics together with clinical, laboratory, and endoscopic outcomes as close to weeks 8, 16 and 26 as possible. Clinical disease activity was assessed using the SCCAI and clinical response and remission were defined as a reduction in SCCAI ≥3 points and achievement of SCCAI ≤2, respectively.[9 10] Corticosteroid-free remission (CSFR) was defined as remission without steroid use at that time point, regardless of steroid use at baseline. Patients with active disease at baseline were used to determine the effectiveness outcomes whereas all enrolled patients were used to determine safety outcomes. Active disease at baseline was defined as SCCAI ≥4, and/or C reactive protein (CRP) ≥5 mg/L, and/or faecal calprotectin ≥250 µg/g, and/or endoscopically active disease; Mayo endoscopic subscore (MES) ≥2, Ulcerative Colitis Endoscopic Index of Severity (UCEIS) ≥3. Outcomes at weeks 8, 16 and 26 were analysed based on patients with available follow-up at those time points.

The primary endpoints of this study were to assess rates of CSFR at week 16, and at week 26 after ustekinumab induction. Secondary endpoints included clinical response and remission, and endoscopic response and remission, at weeks 8, 16 and 26. We defined endoscopic response as any improvement in MES or UCEIS, and remission as MES≤1 or UCEIS ≤1.[11 12] AEs during follow-up were also analysed. Serious AEs (SAEs) were defined as those that were life-threatening, resulted in persistent/permanent or significant disability/incapacity, or that led to hospitalisation.

Statistical analysis

This study was designed as a service evaluation and therefore a priori power calculations were not required. Descriptive statistics were used for continuous variables and stated as median with IQR, or as mean with SD, depending on distribution. Categorical or discrete variables were recorded as numbers and percentages. Baseline and paired symptom scores, laboratory indices, and endoscopy outcomes, at various time points during treatment, were analysed using the Wilcoxon signed-rank test. Univariable analyses were performed using Fisher's exact test for categorical data and Mann-Whitney U test for continuous, non-parametric data to identify baseline clinical variables and biomarkers associated with primary non-response at week 16 and ustekinumab discontinuation. Variables with a $p<0.2$ in the univariable analysis were selected for the multivariable analysis. A two-sided p value of 0.05 or less was considered statistically significant. All analyses were performed using GraphPad Prism, V.9.3.1 for Mac, GraphPad Software, California, USA.[13]

RESULTS

Patient characteristics

In total, 110 patients were treated with ustekinumab during the study period: 25% (27/110) were treated and followed up at Guy's and St Thomas' NHS Foundation Trust, 40% (44/110) at Oxford University Hospitals NHS Foundation Trust, 22% (24/110) at St George's University Hospitals NHS Foundation Trust and 14% (15/110) at Barts Health NHS Trust. The median duration of follow-up was 28 weeks (IQR 17–47). Overall, 59% (65/110) were male, and the median age at initiation was 40 (range 18–89). Median disease duration was 7 years (IQR 3–13) and 96%

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Table 1 Characteristics of the ustekinumab-treated cohort

Characteristics	Median (IQR) or n (%) Total n=110
Sex: male	65 (59)
Age at drug initiation, years	40 (29–59)
Age at diagnosis, years	30 (21–45)
Weight, kg	75 (66–88)
Disease duration, years	7 (3–13)
Disease extent, Montreal	
E1: Proctitis	4 (4)
E2: Left-sided colitis	47 (43)
E3: Extensive colitis	59 (54)
Current smoker	5 (5)
Prior immunomodulator	
Thiopurine	60 (55)
Methotrexate	16 (15)
Tacrolimus	6 (5)
≥2 immunomodulators	19 (17)
None	12 (11)
Prior biologic/small molecules	
Bio naïve	4 (4)
≥1 anti-TNF agent	71 (65); IFX 43, ADA 47, GOL 2
≥2 anti-TNF agents	21 (19)
Vedolizumab	59 (54)
Tofacitinib	35 (32)
Anti-TNF + vedolizumab	36 (33)
Anti-TNF + vedolizumab + tofacitinib	19 (17)
Corticosteroids at induction	65 (59)
Immunosuppressant at induction	13 (12)
Clinical and biochemical disease activity	
SCCAI (n=80)	6 (4–7)
Haemoglobin g/L (n=106)	128.4±15.9
Serum albumin, g/L (n=103)	37.8±5.5
CRP, mg/L (n=105)	3 (1–9)
Faecal calprotectin, µg/g (n=60)	601 (325–984)
Baseline endoscopic assessment (n=67)	
UCEIS (n=55)*	5 (4–5)
Mayo endoscopic subscore (n=37)*	2 (2–3)
Ustekinumab therapy	
Induction dose, n (%)	260 mg, 7 (6), 390 mg, 76(69), 520 mg, 27(25)
Total induction dose per kg	5.4

*Method of endoscopic scoring varied per study site.
ADA, adalimumab; CRP, C reactive protein; GOL, golimumab; IFX, infliximab; IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index ; TNF, tumour necrosis factor; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

(106/110) had prior exposure to a biologic or tofacitinib. At baseline, 59% (65/110) were being treated with corticosteroids and 12% (13/110) were on a concomitant immunomodulator. Table 1 shows the characteristics of the cohort. Most patients (n=106) satisfied the aforementioned criteria for active UC at ustekinumab induction (table 2).

Clinical, biochemical and endoscopic outcomes

At week 8, 50% (55/110) had data available for assessment of clinical outcomes with 38% (21/55) and 20% (11/55) achieving clinical remission and CSFR, respectively (figure 1). Median SCCAI fell significantly from 6 (IQR 4–8) to 3 (IQR 1–5), p=<0.01. While there was no significant change in the paired faecal calprotectin measurements from baseline, there was a marginal but significant improvement in other laboratory markers of disease activity, including haemoglobin, platelets, CRP and serum albumin (table 2).

At week 16, data for 45% (49/110) patients were available. There was an increase in the proportion of patients in remission 47% (23/49) and CSFR 37% (18/49). Median SCCAI fell fell significantly to 3 (IQR 1–5), p=<0.01, with a non-significant fall in CRP to 2.5 mg/dL (IQR 1.0–7.5) and faecal calprotectin to 102 µg/g (IQR 54–674]). At week 26, 35% (39/110) patients were eligible for assessment and rates of remission (44%) 17/39 and CSFR (33%) 13/39 remained largely unchanged.

Lower gastrointestinal endoscopic examination was undertaken in a total of 60% (66/110) of patients at baseline. The method of endoscopic disease activity assessment varied by study site between using MES, UCEIS or both. Where both were recorded, the more commonly used MES was used. Of those examined endoscopically, 97% (64/66) of patients had active disease at baseline; median MES was 2 (n=36) and median UCEIS was 5 (n=54). Postinduction endoscopy was available for 29% (32/110) of patients and performed at varying time points with a median time of 25 weeks (IQR 16–34). Of these, 44% (14/32) had endoscopic improvement and 28% (9/32) achieved endoscopic remission (figure 1).

Regarding ustekinumab dosing regimens, all patients received a weight-based ustekinumab infusion as per product license. Six patients were maintained on 12-weekly dosing, four patients were escalated to 4-weekly dosing, and the remaining patients were treated at 8-weekly intervals during maintenance therapy. Due to small numbers, it was not possible to determine the effect of dosing frequency on effectiveness outcomes.

Ustekinumab persistence and predictors of ustekinumab remission

At the end of follow-up, 15% (17/110) of patients had discontinued treatment over a median follow-up of 28 weeks (IQR 17–47). Ustekinumab was stopped in four patients due to primary non-response, in nine due to loss of response, in three due to AEs, and one patient chose to discontinue for family planning. Figure 2 shows the survival curve of ustekinumab persistence. The probability of remaining on

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Table 2 Clinical and biochemical parameters at baseline, weeks 8, 16 and 26

Parameter	N	Baseline	N	Week 8	P value	N	Week 16	P value	N	Week 26	P value
CRP	102	3.5 (1.0–9.3)	49	3.0 (1.0–6.0)	**0.02**	40	2.5 (1.0–7.5)	0.5664	26	3.0 (1.0–9.3)	0.8565
FCAL	59	610 (333–1100)	26	369 (130-644)	0.1375	19	102 (54-674)	0.3755	17	188 (86-767)	0.2676
Hb	103	128±16	53	130±17	**0.0006**	49	129±14	0.0861	28	125±22	0.2766
Platelets	103	332±107	53	307±94	**0.0326**	47	315±101	**0.0346**	29	336±113	0.8096
Albumin	100	37.7±5.5	51	40.0±4.9	**<0.0001**	46	39.7±4.8	**0.0024**	28	40.1±4.3	0.4001

Bold denotes statistical significance.
CRP, C reactive protein; FCAL, faecal calprotectin; Hb, haemoglobin; SCCAI, Simple Clinical Colitis Activity Index.

ustekinumab was 97% at 8 weeks, 95% at 16 weeks, 90% at 26 weeks and 76% at 52 weeks. Univariate analyses identified that current smokers and those with prior advanced therapy failures, except prior anti-TNF alone, were associated with ustekinumab discontinuation (online supplemental table 1). On multivariate analyses, only current smoking status was associated with treatment discontinuation, OR 0.03 (95% CI 0.002 to 0.36, p<0.01) (online supplemental table 2).

While univariate analyses identified that an older age at the time of ustekinumab induction and those naïve to both anti-TNF and anti-integrin were associated with remission at week 16, no clinical predictors of remission were identified on multivariate analyses (online supplemental table 3).

Ustekinumab safety

SAEs and AEs were recorded in 12% (13/110) and 18% (20/110) of the study cohort, respectively. Hospitalisation for disease progression was the most common SAE affecting nine patients, of which seven required a colectomy, and two required admission for intravenous corticosteroids and ustekinumab dose escalation. Other SAEs were composed of hospitalisations deemed to be for non-drug-related or non-IBD-related reasons, including appendicitis requiring an appendicectomy, and an ectopic pregnancy requiring a salpingectomy. The most frequent AEs were arthralgia (n=3) and worsening diarrhoea, likely reflecting suboptimal disease control (n=7). Three patients had AEs that required treatment discontinuation. One patient had a non-anaphylactic infusion reaction, and another developed a widespread urticarial rash 24 hours post infusion. One patient, a 47-year-old female, developed a marked inflammatory demyelinating polyneuropathy 5 days after ustekinumab induction, substantiated by compatible changes on electromyography. Following neurology review, ustekinumab was discontinued and the patient was treated with intravenous immunoglobulin, which led to complete symptom resolution and return of neurological function.

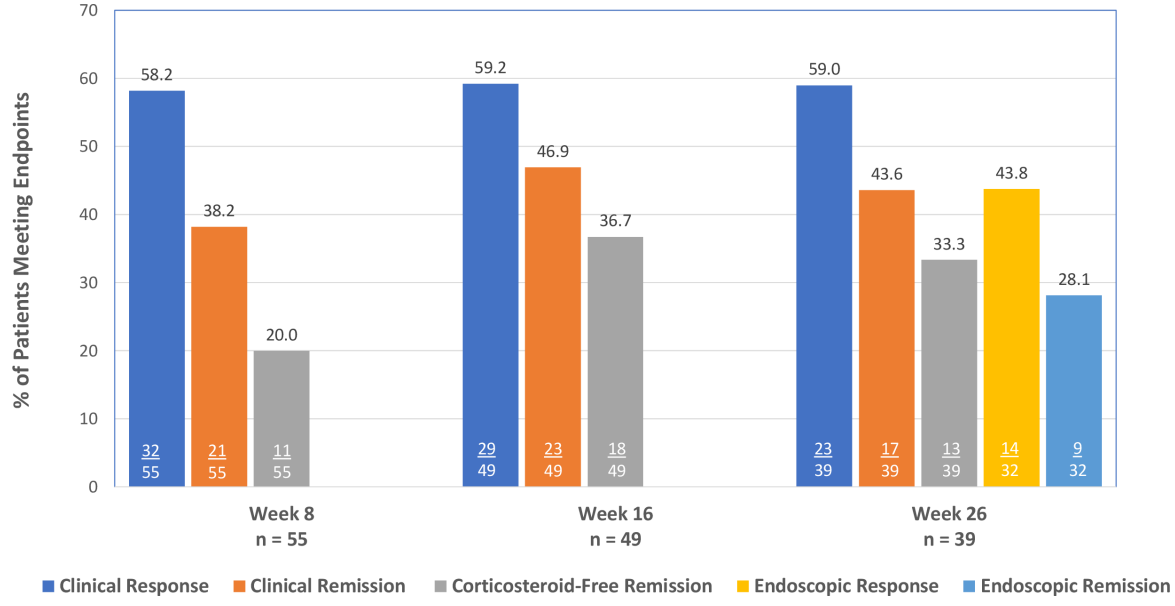

Figure 1 Proportion of ustekinumab-treated patients reaching clinical and endoscopic endpoints.

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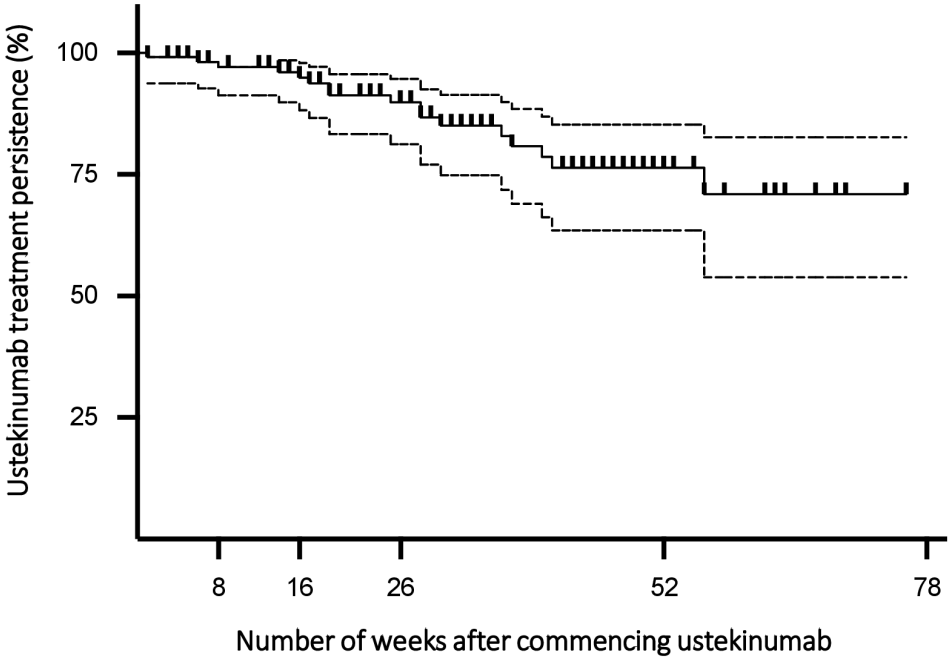

Follow up after ustekinumab (weeks)	0	8	16	26	52
Ustekinumab treatment persistence (%)	100.0	97.1	94.9	89.8	76.4
Number of patients at risk	110	97	85	61	19

Figure 2 Survival curve of ustekinumab persistence in 110 patients with ulcerative colitis

Notwithstanding the above, overall, ustekinumab had a favourable side effect profile in our cohort.

DISCUSSION

This study presents the largest cohort assessing effectiveness and safety of ustekinumab in UC. Of those patients with available data, one third met the primary endpoints of CSFR at week 16 and week 26, with 23% of patients achieving endoscopic remission. For those that had assessments at all time points, 60% of patients had a clinical response. This was a refractory group of patients, who were almost exclusively biologic and/or tofacitinib experienced. Patients had a median disease duration of 7 years and nearly all (96%) had either left sided or extensive colitis.

The finding that one-third of our patients were in CSFR following induction is consistent with recently published real world studies, though we acknowledge missing clinical data.[5–8 14] Chaparro *et al* evaluated 95 patients from the Spanish ENEIDA registry and found CSFR rates of 30% and 32% at weeks 24 and 52, respectively.[5] Similarly, the French GETAID study of 103 patients demonstrated CSFR rates of 35% between weeks 12–16% and 32% at 12 months.[7 14] Two smaller cohorts from Italy and the USA had similar outcomes, with a higher 12-month CSFR rate of 53% in the latter.[6 8] It is worth noting that due to prescribing restrictions, only 3.6% (n=4) of our cohort were escalated to 4-weekly therapy, compared with 63% and 44% of the respective GETAID and US cohorts who received 4-weekly ustekinumab.[7 8] This is likely to have influenced CSFR rates as ustekinumab dose intensification in UC has been shown to be effective in those failing 8-weekly treatment.[15]

Ustekinumab treatment persistence at week 52, either actual or estimated (for cohorts with a shorter follow-up), varied between 58% to 87% across real-world studies, including our own.[5–8] The variability in persistence, which is often used as a proxy for assessing sustained effectiveness, may reflect the heterogeneity of included cohorts, varying treatment regimens, and study designs. For example, the probability of ustekinumab persistence at month 12 in the GETAID cohort was 58% compared with 76% in this UK cohort. This may be because the GETAID cohort was more treatment refractory; 85% had failed two classes of biologics compared with only 33% in this cohort who had failed both anti-TNF and anti-integrin therapy.[7] The Italian cohort had the highest persistence rates at week 52, however, the study only included patients receiving both the intravenous induction dose and the first subcutaneous dose.[6] Therefore, those ceasing treatment in the first 8 weeks due to treatment failure or AEs, would not have been included. Despite this variability, reasons for discontinuation were consistent among the cohorts and this was primarily due to primary non-response or secondary loss of response; ustekinumab was curtailed in less than 5% in all studies for AEs/SAEs.

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We show that overall, ustekinumab's safety profile is consistent with previously reported clinical trial and real world data in IBD.[16 17] Most AEs and SAEs were due to disease progression and treatment failure. However, we report the third known case of ustekinumab-induced demyelination in a patient with active UC.[18 19] Although anti-TNF agents are associated with central and peripheral nervous system demyelination, neurological complications of ustekinumab are exceptionally rare.[20] In pooled analyses of 12 ustekinumab registrational trials with 5884 patients and 4521 patient-years follow-up, there were no cases of demyelinating disorders.[21] However, most of these patients were treated for plaque psoriasis and psoriatic arthritis where lower ustekinumab doses are used with no intravenous induction. Subsequent safety analyses of 2574 IBD clinical trial patients with 1733 patient-years follow-up identified a case of non-serious progression of multiple sclerosis in patient with known relapsing-remitting disease.[16] There was also a case of possible demyelination in a patient who received the intravenous induction followed by the week 8 dose. However, imaging revealed small vessel disease and no demyelination. For our patient, ustekinumab discontinuation and treatment with intravenous immunoglobulin led to a complete recovery.

We found a weakly negative correlation between current smokers and ustekinumab discontinuation-free survival. It is difficult to extrapolate on this tenuous link, particularly as the evidence for effects of cigarette smoking on UC disease course has been contradictory; in contrast to previous studies, recent data have shown no significant difference between smokers and non-smokers with regard to disease exacerbation, corticosteroid dependency, hospitalisation and colectomy.[22 23]

It is likely that our results are applicable to other patients with moderate-to-severely active UC. Ustekinumab has several potential advantages over current advanced therapies including its lack of immunogenicity, the infrequent dosing regimen and its encouraging safety profile. Data from the IM-UNITI programme in Crohn's disease demonstrate low rates of immunogenicity with ustekinumab serum concentrations being maintained throughout the long-term extension trial.[24] In a meta-analysis of data from RCTs and observational cohorts, combining ustekinumab with an immunomodulator was no more effective than monotherapy in induction or maintenance of remission.[25] In our cohort, concomitant immunomodulator use at baseline was not associated with short-term remission or with a reduction in ustekinumab persistence.

We acknowledge the limitations associated with this study. Inherent to our retrospective study design, our results are potentially subject to interpretation bias and bias resulting from missing data, particularly post-treatment endoscopic outcomes. In part, this may be explained by the severe disruption caused by the coronavirus pandemic with delays in clinical assessments and endoscopic evaluation. However, it may also reflect real-world clinical practice of using other outcome measures to gauge treatment response, particularly for patients showing a clinical improvement. Therefore, our primary endpoint was restricted to a clinical outcome (CSFR) rather than a composite endpoint including endoscopy and histology data. Another limitation was that the follow-up duration of our cohort was short, hindering long-term effectiveness conclusions. Despite these limitations, our study provides relevant findings to further strengthen the body of observational effectiveness data in this field.

CONCLUSION

In this multicentre UK study, we demonstrate that ustekinumab is effective in a refractory group of UC patient with a favourable safety profile and good persistence.

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Contributors SH and MAS: conception and study design. SH, LA-H, SB, AB, RL and LM data collection. SH data analysis, data interpretation, writing the manuscript and guarantor. All authors critically reviewed the manuscript before submission.

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