DOI:
10.1136/flgastro-2022-102168

Document Version
Peer reviewed version

Ustekinumab for the Treatment of Moderate to Severe Ulcerative Colitis: A Multicentre UK Cohort Study

Sailish Honap[1,2], Lulia Al-Hillawi[3], Samantha Baillie[4], Aaron S Bancil[5], Lawrence Matini[3], Rebecca Lau[4], Klaartje B Kok[5], Kamal V Patel[4], Alissa Walsh[3], Peter M Irving[1,2], Mark A Samaan[1]

[1]IBD Centre, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK

[2]School of Immunology and Microbial Sciences, King's College London, UK

[3]Translational Gastroenterology Unit, NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, OX3 9DU, UK

[4] Department of Gastroenterology, St George's University Hospitals NHS Foundation Trust, London, SW17 0QT, UK.

[5]Department of Gastroenterology, Royal London Hospital, Barts Health NHS Trust, London, E1 1FR, UK.

Corresponding author and requests for reprints: Dr Sailish Honap, IBD Centre, 1st Floor College House, South Wing, St. Thomas' Hospital, Westminster Bridge Rd, London SE1 7EH, UK. Emails: shonap@nhs.net, Tel: 020 7188 2497

WORD COUNT

2515 words

ABSTRACT

Objective

Ustekinumab is an IL-12/23 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 clinical 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 (interquartile (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 610mcg/g [IQR 333-1100] to 102mcg/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 3 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 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 a 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 anti-TNF 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.

KEY WORDS

Ustekinumab, interleukin-12/23, ulcerative colitis, real-world evidence, clinical effectiveness

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 or response and the risk of adverse events. Ustekinumab is an IgG1 kappa monoclonal antibody directed at the shared p40 subunit of interleukin-12 and -23, which activate Th1 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 (RCT) 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, amongst 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. Secondly, we aimed to assess predictors of clinical response.

METHODS

Study design and population

This was a multicentre, retrospective, observational cohort study across four tertiary 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 90mg 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 pre-designed 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) ≥5mg/L, and/or faecal

calprotectin ≥250µg/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] Adverse events (AE) during follow-up were also analysed. Serious adverse events (SAE) 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 interquartile range, or as mean with standard deviation, 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 timepoints 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 value of <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, version 9.3.1 for Mac, GraphPad Software, California.

Ethical considerations

Patients were not involved in the concept or design of this study, and in accordance with UK Health Research Authority guidelines, formal ethical approval for this real-world service evaluation was not required.[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% (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).

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/dl (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 score (n=37)*	2 (2-3)
Ustekinumab therapy	
Induction dose, n (%)	260mg, 7(6), 390mg, 76(69), 520mg, 27(25)
Total induction dose per kg	5.4

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 Hb, 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 2.5mg/dL [IQR 1.0-7.5], and faecal calprotectin to 102μg/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 GI 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). Post-induction endoscopy was available for 29% (32/110) of patients and performed at varying timepoints 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).

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
SCCAI	76	6 [4-8]	55	3 [1-5]	**0.0007**	49	3 [1-5]	**<0.0001**	39	3 [0-5]	**0.0007**
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

Regarding ustekinumab dosing regimens, all patients received a weight-based ustekinumab infusion as per product license. Six patients were maintained on 12-weekly dosing, 4 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 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 (Supplementary Table 1). On multivariate analyses only current smoking status was associated with treatment discontinuation, odds ratio 0.03 (95% CI 0.002-0.36, $p<0.01$) (Supplementary 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 (Supplementary 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 9 patients, of which 7 required a colectomy, and 2 required admission for intravenous corticosteroids and ustekinumab dose escalation. Other SAEs were comprised of hospitalisations deemed to be for non-drug- 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 sub-optimal 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 five 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. 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 timepoints, 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 a 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 to 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 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 to 76% in this UK cohort. This may be because the GETAID cohort was more treatment refractory; 85% had failed two classes of biologics compared to 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 IV induction dose and the first subcutaneous dose.[6] Therefore, those ceasing

treatment in the first eight 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.

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-tumour necrosis factor 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 IV 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 IV 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 program 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.

ACKNOWLEDGEMENTS

Nil

COMPETING INTERESTS

Sailish Honap has served as a speaker, a consultant, and/or advisory board member for Pfizer, Janssen, Abbvie, and Takeda, with research supported by Pfizer and Galápagos NV. Aaron S Bancil has received speaker fees from Takeda and meeting support fees from Abbvie, Dr Falk and Vifor Pharma. Klaartje Kok served as a speaker, a consultant, and/or advisory board member for Janssen, Takeda, PredictImmune, Galapagos, Ferring, and Amgen. Kamal Patel has received honoraria for educational meetings and speaker fees from Abbvie, Janssen, Takeda, DrFalk, PredictImmune and Ferring and has received advisory board fees from Abbvie, Galapagos and Janssen. Peter Irving has received lecture fees from Abbvie, Warner Chilcott, Ferring, Falk Pharma, Takeda, MSD, Johnson and Johnson, Shire, and Pfizer, financial support for research from MSD, Takeda, and Pfizer, advisory fees from Abbvie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, and Samsung Bioepis. Mark Samaan served as a speaker, a consultant, and/or an advisory board member for Sandoz, Janssen, Takeda, MSD, Falk, Abbvie, Bristol Myers Squibb, Galapagos, and Samsung Bioepis. LA, SB, LM, RL, AW report no conflicts of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1201–14.

2. Evidence-based recommendations on ustekinumab (Stelara) for treating moderately to severely active ulcerative colitis in adults [Internet]. NICE; [cited 2022 Jan 17]. Available from: https://www.nice.org.uk/guidance/TA633/chapter/1-Recommendations

3. Singh S, Murad MH, Fumery M, et al. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. Clin Gastroenterol Hepatol. 2020 Sep;18(10):2179-2191.e6.

4. Ha C, Ullman TA, Siegel CA, et al. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clinical Gastroenterology and Hepatology. 2012 Sep;10(9).

5. Chaparro M, Garre A, Iborra M, et al. Effectiveness and Safety of Ustekinumab in Ulcerative Colitis: Real-world Evidence from the ENEIDA Registry. J Crohns Colitis. 2021 Nov 8;15(11):1846–51.

6. Chiappetta MF, Viola A, Mastronardi M, et al. One-year effectiveness and safety of ustekinumab in ulcerative colitis: a multicenter real-world study from Italy. Expert Opin Biol Ther. 2021 Nov;21(11):1483–9.

7. Fumery M, Filippi J, Abitbol V, et al. Effectiveness and safety of ustekinumab maintenance therapy in 103 patients with ulcerative colitis: a GETAID cohort study. Aliment Pharmacol Ther. 2021 Oct;54(7):944–51.

8. Hong SJ, Krugliak Cleveland N, Akiyama S, et al. Real-World Effectiveness and Safety of Ustekinumab for Ulcerative Colitis From 2 Tertiary IBD Centers in the United States. Crohn's Colitis 360. 2021 Jan 1;3(1).

9. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut. 1998 Jul;43(1):29–32.

10. Higgins PDR, Schwartz M, Mapili J, et al. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005 Jun;54(6):782–8.

11. Peyrin-Biroulet L, Sandborn W, Sands B, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology [Internet]. 2015 Sep [cited 2022 Jan 29];110(9). Available from: https://pubmed.ncbi.nlm.nih.gov/26303131/

12. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021 Apr;160(5):1570–83.

13. NHS Health Research. NHS Health Research Authority - Service Evaluation [Internet]. 2017 [cited 2022 Jan 17]. Available from: http://www.hra-decisiontools.org.uk/research/docs/definingresearchtable_oct2017-1.pdf

14. Amiot A, Filippi J, Abitbol V, et al. Effectiveness and safety of ustekinumab induction therapy for 103 patients with ulcerative colitis: a GETAID multicentre real-world cohort study. Alimentary Pharmacology & Therapeutics. 2020 Jun;51(11).

15. Dalal RS, Esckilsen S, Barnes EL, et al. Predictors and Outcomes of Ustekinumab Dose Intensification in Ulcerative Colitis: A Multicenter Cohort Study. Clin Gastroenterol Hepatol. 2021 Mar 26;S1542-3565(21)00338-4.

16. Sandborn WJ, Feagan BG, Danese S, et al. Safety of Ustekinumab in Inflammatory Bowel Disease: Pooled Safety Analysis of Results from Phase 2/3 Studies. Inflamm Bowel Dis. 2021 Jun 15;27(7):994–1007.

17. Honap S, Meade S, Ibraheim H, et al. Effectiveness and Safety of Ustekinumab in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2021 Mar 16;

18. Badat Y, Meissner WG, Laharie D. Demyelination in a patient receiving ustekinumab for refractory Crohn's disease. Journal of Crohn's and Colitis. 2014 Sep 1;8(9):1138–9.

19. Osman G, Shah K, Khan MS, et al. Ustekinumab related CIDP in a patient with psoriatic arthritis (P2.451). Neurology [Internet]. 2018 Apr 10 [cited 2021 Nov 1];90(15 Supplement). Available from: https://n.neurology.org/content/90/15_Supplement/P2.451

20. Stübgen J-P. Tumor necrosis factor-alpha antagonists and neuropathy. Muscle Nerve. 2008 Mar;37(3):281–92.

21. Ghosh S, Gensler LS, Yang Z, et al. Ustekinumab Safety in Psoriasis, Psoriatic Arthritis, and Crohn's Disease: An Integrated Analysis of Phase II/III Clinical Development Programs. Drug Saf. 2019 Jun;42(6):751–68.

22. To N, Ford A, Gracie D. Systematic review with meta-analysis: the effect of tobacco smoking on the natural history of ulcerative colitis. Alimentary pharmacology & therapeutics. 2016 Jul;44(2).

23. Blackwell J, Saxena S, Alexakis C, et al. The impact of smoking and smoking cessation on disease outcomes in ulcerative colitis: a nationwide population-based study. Alimentary pharmacology & therapeutics. 2019 Sep;50(5).

24. Sandborn W, Rebuck R, Wang Y, et al. Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2021 Feb 19;

25. Yzet C, Diouf M, Singh S, et al. No Benefit of Concomitant Immunomodulator Therapy on Efficacy of Biologics That Are Not Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases: A Meta-analysis. Clin Gastroenterol Hepatol. 2021 Apr;19(4):668-679.e8.

TABLE LEGENDS

Table 1: Characteristics of the ustekinumab-treated cohort (n=110) including patient demographics, prior medication exposure, and baseline disease characteristics. Variables are presented as n (%), mean ± standard deviation, or median (interquartile range). Abbreviations: IQR, interquartile range; kg, kilogram; TNF; tumour necrosis factor-α; SCCAI, simple clinical colitis activity index; CRP, C-reactive protein; UCEIS, ulcerative colitis endoscopic index of severity. *Method of endoscopic scoring varied per study site.

Table 2: Clinical and biochemical parameters at baseline, weeks 8, 16, and 26 for patients with active disease at baseline (n=106). Paired values at various timepoints were compared to baseline using the Wilcoxon matched pairs signed rank test. Variables are presented as n (%), mean ± standard deviation, or median (interquartile range); p-values were obtained in paired data only. Abbreviations: N, number of patients; SCCAI, simple clinical colitis activity index; CRP, C-reactive protein; FCAL, faecal calprotectin; Hb, haemoglobin.

Supplementary Table 1: Univariate analysis of factors associated with ustekinumab discontinuation. Abbreviations: UST, ustekinumab; IQR, interquartile range; kg, kilogram; TNF; tumour necrosis factor-α; SCCAI, simple clinical colitis activity index; CRP, C-reactive protein

Supplementary Table 2: Multivariate analysis of factors associated with ustekinumab discontinuation

Supplementary Table 3: Univariate analysis of factors associated with clinical remission between weeks 14-16 following ustekinumab induction. Abbreviations: IQR, interquartile range; kg, kilogram; TNF; tumour necrosis factor-α; SCCAI, simple clinical colitis activity index; CRP, C-reactive protein.

FIGURE LEGENDS

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

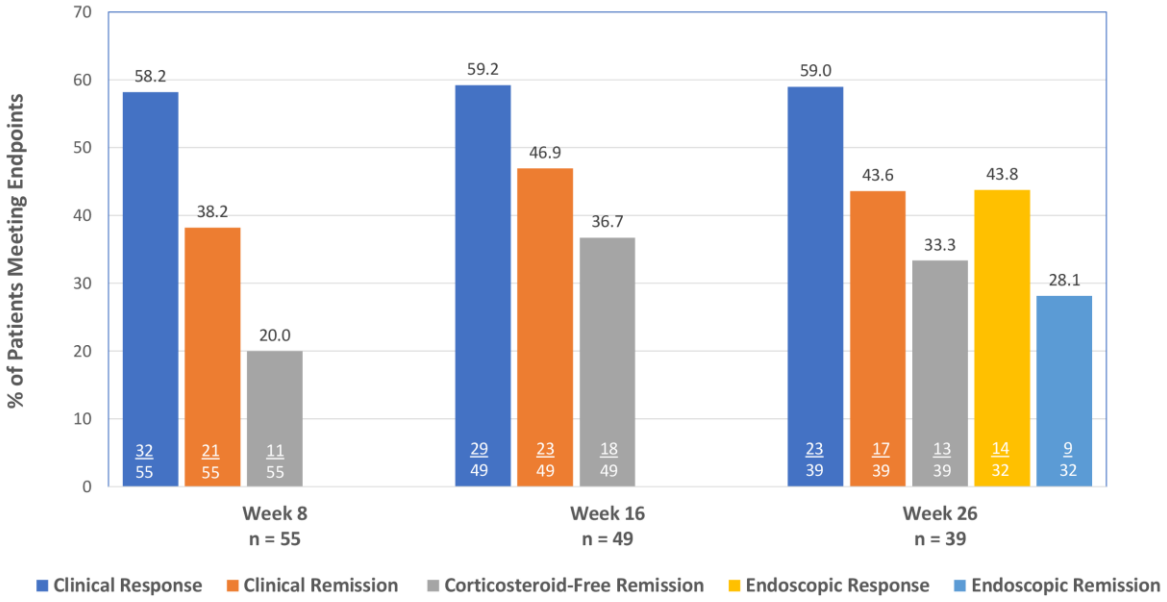
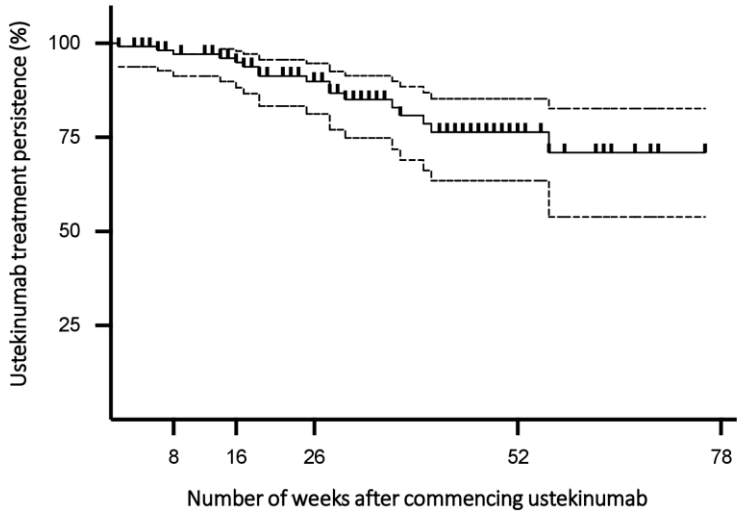


Figure 2: Survival curve of ustekinumab persistence in 110 patients with ulcerative colitis



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