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Long-term benefit of ustekinumab in ulcerative colitis in clinical practice: ULISES study

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Summary

Background: Ustekinumab is approved for ulcerative colitis (UC).

Aims: To assess the durability of ustekinumab in patients with UC and its short-term effectiveness, durability and tolerability in clinical practice.

Methods: Retrospective, multicentre study of patients who had received their first ustekinumab dose at least 16 weeks before inclusion. Patients were followed until treatment discontinuation or last visit. Only patients with active disease at the start of ustekinumab treatment were considered in the effectiveness analysis. Patients who stopped ustekinumab before their last visit were considered not to be in subsequent remission.

Results: We included 620 patients; 155 (25%) discontinued ustekinumab during follow-up (median 12 months). Rate of discontinuation was 20% per patient-year of follow-up. Anaemia at baseline (hazard ratio, HR 1.5; 95% confidence interval [CI] 1.1–2.1), steroids at baseline (HR 1.5; 95% CI 1.06–2.08) and more severe clinical activity at baseline (HR 1.5; 95% CI 1.09–2.06) were associated with higher risk of discontinuation. At the end of induction, 226 (40%) patients were in steroid-free clinical remission. Moderate–severe vs mild disease activity at baseline (odds ratio [OR] 0.3; 95% CI 0.2–0.5), male sex (OR 0.5; 95% CI 0.4–0.8), and increased number of previous biologics (OR 0.6; 95% CI 0.6–0.8) were associated with lower likelihood of steroid-free clinical remission at week 16. One hundred and seventy-six patients (28%) had at least one adverse event. We observed no negative impact of ustekinumab on extraintestinal manifestations and/or immune-mediated diseases.

Conclusions: Ustekinumab durability in UC was relatively high, and treatment was effective in highly refractory patients. The safety profile was consistent with previous studies.

1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing–remitting, inflammatory bowel disease that causes continuous mucosal inflammation of the colon, leading to organ damage and impaired quality of life. In the last two decades, biologic therapies have increased the probability of achieving and maintaining remission thereby changing the natural history of UC; nevertheless, these therapies still fail in a considerable percentage of patients.[1–7] Hence, there is a constant need to find new therapeutic strategies and novel drugs to control this chronic debilitating disease.[8,9]

Ustekinumab is a fully human immunoglobulin G1 kappa monoclonal antibody to human IL-12/23 that binds with high affinity to the p40 subunit shared by human IL-12 and IL-23. By inhibiting interaction of these cytokines with the cell surface IL-12Rβ1 receptor, ustekinumab effectively neutralises all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses.[10] Ustekinumab is effective in inducing and maintaining remission in Crohn's disease patients and has also been recently approved for the treatment of UC in patients who fail or are intolerant to conventional therapy or biologics.

The UNIFI trial demonstrated the superiority of ustekinumab over placebo in inducing and maintaining remission in patients with active UC, not only in naïve patients but also in those refractory to previous biological agents, with a good safety profile.[11–14] These promising results in the pivotal phase III trial should be confirmed in clinical practice.

The use of drugs in clinical trials differs from that in routine clinical practice in several aspects, such as patient characteristics (patients are frequently more refractory to treatments and have more comorbidities in real-life practice). These differences limit the generalisation of clinical trial results. In this respect, real-world studies are crucial to assess the real benefit of drugs and provide information complementary to clinical trials on the effectiveness and safety of treatments in real clinical practice settings. However, evidence from studies assessing both effectiveness and safety of ustekinumab for UC treatment in clinical practice is still limited.[15–22] Most of the studies conducted to date on the benefit of ustekinumab in UC in clinical practice have involved a limited number of patients, with relatively short follow-up, which precludes providing definitive answers regarding some beneficial aspects of ustekinumab treatment for UC

in clinical practice. Some studies based on administrative data have been performed[23–27]; this kind of studies have several limitations also, such as the lack detailed clinical information, which can limit the ability to adjust for confounding factors.

The aim of our study was to perform a comprehensive analysis of the benefit of ustekinumab treatment for UC in a large, multicentre cohort of UC patients. The specific aims of this analysis included: assessing the durability of ustekinumab treatment in UC as a global indicator of ustekinumab benefit, characterising the short-term response and the long-term effectiveness, finding predictive factors of response, describing the schedules of ustekinumab administration in real-life and the need for dose adjustments, colectomy rate and hospitalizations during ustekinumab treatment, and finally, assessing the safety of ustekinumab in clinical practice. We can anticipate that this study will help clinicians to position ustekinumab in UC therapy in clinical practice.

2 | METHODS

2.1 | Study design

We performed a retrospective, multicentre, non-interventional study to assess the durability of ustekinumab treatment in patients with UC. This study included patients diagnosed with UC in follow-up in the hospital setting, whose management and monitoring were mainly conducted by gastroenterologists. Participation was offered to all eligible patients in each centre to avoid inclusion bias and to ensure obtaining a sample as representative as possible. A total of 67 centres in Spain participated and recruited patients from December 2022 to June 2023. The study protocol was approved by the Ethics Committee of Research with Medicines of Hospital Universitario de La Princesa (Madrid), which was the referral committee.

2.2 | Study population

The study population consisted of adult patients who received at least one dose of ustekinumab for UC at least 16 weeks before entering the study. Patients who had received treatment with ustekinumab for any indication other than UC, those with a history of previous colectomy or those who had participated in a clinical trial involving ustekinumab were excluded.

2.3 | Data collection

The following variables were collected in this study: sex, age, smoking habit, age at diagnosis, disease extent, extraintestinal manifestations (EIMs), concomitant use of steroids and immunomodulators at the beginning and during follow-up, previous treatments for UC, reasons for discontinuation of previous treatments for UC (immunomodulators, biologic agents and tofacitinib); start date of ustekinumab therapy, response to ustekinumab, clinical activity at baseline and during follow-up, concomitant medication for UC, date of discontinuation (when appropriate), reason for discontinuation (lack of primary response, secondary loss of response, patient choice, adverse event, surgery for UC worsening; others; unknown reason), dosing regimen during maintenance, treatment after loss of response to ustekinumab (if any), dose increase (if any), dose decrease (if any), response after dose optimization, evolution of EIMs and immunomediated inflammatory diseases (IMIDs), surgery for UC, hospitalizations (due to UC or for other reasons) and adverse events. Additional information, such as endoscopic evaluation or biological markers (C-reactive protein and faecal calprotectin concentration), were requested from clinicians responsible for patients' treatment, when available.

Data were collected and managed using REDCap electronic data capture tool hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es). AEG is a non-profit Scientific and Medical Society focused on Gastroenterology, and it provides this service free of charge, with the sole aim of promoting independent investigator driven research.[28] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for importing data from external sources.

2.4 | Study outcomes

2.4.1 | Durability

The main outcome of the study was ustekinumab treatment durability. It was calculated considering the entire period under ustekinumab treatment as the elapsed time from the first dose to the last dose. In addition, time to loss of efficacy was also calculated.

2.4.2 | Effectiveness outcomes

Patients included in this study received ustekinumab for the UC. Some patients received the treatment while being in clinical remission, due to intolerance or contraindication to other drugs. Only patients with active disease at the start of ustekinumab (Partial Mayo Score [PMS] >2) were considered in the analysis of short-term effectiveness.

2.5 | Active disease

Active disease was defined as a PMS >2. When endoscopy was available, endoscopic severity was graded by local investigators as quiescent, mild, moderate or severe. The severity of clinical activity was rated based on the PMS.

2.6 | Evaluation of effectiveness

The primary effectiveness endpoint was steroid-free clinical remission, which was defined as clinical remission in the absence of steroid treatment at a certain time point. Clinical remission was defined as a PMS ≤2. Clinical response was defined as reduction in PMS ≥3 points and a decrease of at least 30% from baseline, with a decrease of ≥1 point on the rectal bleeding subscale (absolute score 0–1) without reaching clinical remission.

To evaluate response to induction, clinical remission/response was evaluated through PMS assessment at the beginning and at weeks 4, 8 and 16. If PMS data were not available at these time points, data available within the period between 2 weeks before an 2 weeks after those time points were considered. Patients discontinuing ustekinumab for any reason before last visit were considered failures (absence of clinical remission) in subsequent visits (negative imputation).

Loss of efficacy was defined as a worsening in the patient's symptoms together with endoscopic, radiographic or serological evidence of activity (elevated C-reactive protein or faecal calprotectin concentration) leading to treatment dose escalation, addition of another medication for UC control, switch to another treatment, or surgery. Loss of efficacy was assessed in patients who had active disease at baseline and were in steroid-free clinical remission at the end of the induction treatment (week 16).

2.7 | Evolution of EIMs and IMIDs

The evolution of previous EIMs and IMIDs was evaluated based on clinicians' judgement. New-onset EIMs and IMIDs under ustekinumab treatment were recorded.

2.7.1 | Safety assessments

All the adverse events occurring during ustekinumab treatment were registered and their relationship with ustekinumab administration was evaluated according to investigator's criteria (based on the International Conference on Harmonization [ICH]) and recorded.

2.8 | Statistical analysis

Categorical variables were expressed as percentages (with their 95% confidence intervals [CI]) and quantitative variables as means and standard deviations (SD), or medians and interquartile ranges (IQR), depending on whether they were normally distributed or not. In the univariate analysis, categorical variables were compared using chi-squared test and quantitative variables using the appropriate test. For short-term effectiveness evaluation, only patients with PMS >2 at baseline were considered. Short-term effectiveness was evaluated at weeks 4, 8 and 16. Variables associated with the likelihood of treatment response after the induction treatment (week 16) were identified using a logistic regression model. Negative imputation was used to impute missing data for effectiveness analysis.

The Kaplan–Meier method was used to evaluate the long-term durability of ustekinumab treatment (main outcome). Patients who discontinued ustekinumab for any reason were rightly censored at the time of discontinuation. In addition, we analysed the cumulative incidence of loss of response in patients who reached steroid-free clinical remission at week 16. Differences between survival curves were evaluated with the log-rank test. Stepwise multivariate analysis using the Cox model was performed to identify factors associated with ustekinumab discontinuation or loss of response over time. In the log-rank test and in the multivariate analysis, statistical significance was considered when $p < 0.05$.

3 | RESULTS

3.1 | Study population

A total of 620 patients from 67 Spanish centres were included. The main characteristics of the study population are summarised in Table 1. Of note, 354 (57%) patients had extensive colitis, 561 (90%) had active disease (PMS >2) at baseline, 435 (70%) patients had a moderate–severe flare and 179 (30%) patients had anaemia. A total of 590 (95%) patients had been previously exposed to biologics and 158 (25%) to tofacitinib. Mean number of previous biologics was two. With respect to concomitant treatments at baseline, 160 (26%) patients were treated with systemic steroids, 350 (56%) with mesalamine and 48 (8%) with thiopurines.

For induction treatment, 613 (99%) received the approved ustekinumab dose (6 mg/kg intravenously [iv]) at baseline, 499 (80%) received a second dose of 90 mg subcutaneously (sc) at week 8 and 17 (3.4%) of the patients received an extra dose of 90 mg sc at week 12. The starting dose of the maintenance phase was quite heterogeneous: while about 467 (78%) of patients started with the approved dosages of 90 mg every 8 and 20 (3.3%) every 12 weeks sc, 19% of patients started on an off-label dosage (Table S1.).

3.2 | Durability of ustekinumab treatment

The treatment was interrupted in 155 (25%) patients (median time 12 months, IQR = 6.4–20 months). The main characteristics of the patients according to whether they discontinued ustekinumab or not are summarised in Table 2. The proportion of patients maintaining ustekinumab treatment at different times is shown in Figure 1: 78% at 12 months, 68% at 24 months and 61% at 36 months. The incidence rate of ustekinumab discontinuation was 20% per patient-year of follow-up. The reasons for ustekinumab discontinuation were as follows: primary non-response in 60 (39%) patients, loss of response in 55 (35%) patients, medical decision in 20 (13%) patients, adverse events in 11 patients (7%) and partial response in 9 (5.8%) patients.

TABLE 1 Characteristics of the study population.

Variable	*N* = 620
Age at diagnosis (years), median (IQR)	39 (26–52)
Age at ustekinumab start (years), median (IQR)	51 (38–62)
Median CRP at baseline (mg/dL), median (IQR)	0.9 (0.3–2)
Faecal calprotectin at baseline (mg/g), median (IQR)	1231 (543–2880)
Exposure time (months), median (IQR)	12 (6.4–20)
Number of previous biologics, mean (SD)	1.9 (0.9)
Follow-up time (months), median (IQR)	16 (11–26)
PMS at baseline, median (IQR)	6 (4–7)
Male sex, *n* (%)	328 (53)
Smokers, *n* (%)	32 (5.1)
Comorbidities, *n* (%)	207 (33)
Ulcerative colitis extension, *n* (%)	
Extensive colitis	354 (57)
Left-sided colitis	240 (39)
Proctitis	26 (4)
Extraintestinal manifestations, *n* (%)	211 (34)
Previous biologics/JAK inhibitors, *n* (%)	
Adalimumab	321 (52)
Infliximab	391 (63)
Golimumab	100 (16)
Vedolizumab	399 (64)
Tofacitinib	158 (25)
Anti-TNF	549 (89)
Anti-TNF and vedolizumab	358 (58)
Anti-TNF, vedolizumab and tofacitinib	137 (22)
Anaemia at baseline, *n* (%)	179 (30)
Endoscopic activity at baseline[a], *n* (%)	
Inactive	6 (1.5)
Mild	17 (4.4)
Moderate	145 (38)
Severe	214 (56)
Active disease at baseline (PMS>2), *n* (%)	561 (90)
Thiopurines at baseline, *n* (%)	48 (7.7)
Mesalamine at baseline, *n* (%)	350 (56)
Steroids at baseline, *n* (%)	160 (26)
Clinical severity at baseline, *n* (%)	
Remission	59 (10)
Mild	126 (20)
Moderate–severe	435 (70)

Abbreviations: Anti-TNF, anti-tumour necrosis factor; CRP, C-reactive protein; IQR, intrequartille range; JAK, Janus kinase; PMS, Partial Mayo Score; SD, standard deviation.

[a]382 patients had endoscopy assessment at baseline.

After ustekinumab discontinuation, most patients received another medical treatment—39 (25%) tofacitinib, 29 (19%) anti-TNF, 19 (12%) vedolizumab, 16 (10%) upadacitinib, 7 (4.5%) filgotinib and 17 (11%) other medical options—whereas 28 (18%) patients underwent colectomy.

In the multivariate analysis, disease severity at baseline was associated with lower ustekinumab durability, as shown in Table 3.

3.3 | Ustekinumab effectiveness

A total of 561 patients had active disease (PMS>2) at baseline and were therefore considered in the effectiveness analysis. A total of 114 (20%) patients were in steroid-free clinical remission at week 4, 191 (34%) patients at week 8 and 226 (40%) at the end of induction (week 16). The proportions of patients in steroid-free clinical remission, and in clinical response during follow-up are shown in Figure 2. The main characteristics of patients based on whether they achieved steroid-free clinical remission or not at week 16 are summarised in Table 4.

In the multivariate analysis, male sex, moderate–severe clinical activity at baseline (vs. mild), and number of previous biologics were associated with lower likelihood of achieving steroid-free clinical remission at week 16, as it is shown in Table 5.

3.4 | Durability of effectiveness

A total of 226 patients were in steroid-free clinical remission at week 16. Among them, 57 (25%) lost response during follow-up. The main characteristics of patients based on whether they experienced a loss of efficacy or not are summarised in Table S2. The proportion of patients maintaining steroid-free clinical remission was 75% at 12 months and 57% at 24 months (Figure 3). None of the factors analysed were associated with risk of loss of response.

Among patients who lost response, ustekinumab dosage was escalated in 41 (72%) patients and 3 (5.2%) patients received a re-induction. After dose escalation, 27 (66%) patients regained remission, 6 (15%) responded and 8 (19%) remained non-responsive. None of the patients studied responded to the re-induction dose.

3.5 | Ustekinumab effectiveness in hospitalised patients

Twenty-nine patients started ustekinumab during hospital admission. Nineteen (66%) patients had extensive colitis and 10 (34%) left-sided colitis. In total, 28 (97%) patients had been previously exposed to anti-TNF, and 15 (52%) to both anti-TNF and vedolizumab. Twenty-four (83%) patients underwent an endoscopy before starting ustekinumab: 16 (67%) had severe activity and 8 (33%) moderate activity. Sixteen (55%) patients were under concomitant systemic steroids at ustekinumab start.

Two (6.9%) patients exhibited steroid-free clinical remission at week 4, 4 (14%) at week 8, and 6 (21%) at week 16. At the last visit, ustekinumab treatment was maintained in a total of 13 (45%) patients, while it was discontinued in 16 (55%), mainly due to primary failure (*n* = 9, 56%).

TABLE 2 Characteristics of the study population according to ustekinumab discontinuation.

Variable	Discontinuation (*N* = 155)	No discontinuation (*N* = 465)	*p*-value
Age at diagnosis (years), median (IQR)	35 (26–52)	40 (26–53)	>0.05
Age at ustekinumab start (years), median (IQR)	45 (33–60)	52 (40–63)	<0.05
CRP at baseline (mg/dL), median IQR	1.1 (0.4–2.2)	0.9 (0.3–2)	>0.05
Calprotectin at baseline (mg/g), median (IQR)	1151 (700–2812)	1250 (516–2880)	>0.05
PMS at baseline, median (IQR)	6 (5–7)	5 (4–7)	<0.01
Number of previous biologics, mean (SD)	2 (0.8)	1.9 (0.9)	<0.05
Male sex, *n* (%)	81 (52)	247 (53)	>0.05
Smokers, *n* (%)	10 (6.5)	22 (4.8)	>0.05
Comorbidities, *n* (%)	50 (32)	157 (34)	>0.05
Colitis extension, *n* (%)			
Proctitis	4 (2.6)	22 (4.7)	
Left-sided colitis	54 (35)	186 (40)	>0.05
Extensive colitis	97 (63)	257 (55)	
Extraintestinal manifestations, *n* (%)	54 (35)	157 (34)	>0.05
Previous biologics/JAK inhibitors, *n* (%)			
Adalimumab	70 (45)	251 (54)	>0.05
Infliximab	112 (72)	279 (60)	<0.01
Golimumab	124 (80)	396 (85)	>0.05
Vedolizumab	43 (28)	178 (38)	<0.05
Tofacitinib	105 (68)	357 (77)	<0.05
Anti-TNF	144 (93)	405 (87)	<0.05
Anti-TNF and vedolizumab	105 (68)	253 (54)	<0.01
Anti-TNF, vedolizumab and tofacitinib	46 (30)	91 (20)	<0.001
Active disease at baseline (PMS > 2), *n* (%)	147 (95)	414 (89)	<0.05
Endoscopic activity at baseline, n (%)			
Inactive	1 (1)	5 (1.8)	
Mild	8 (8)	9 (3.2)	
Moderate	41 (39)	104 (37)	>0.05
Severe	54 (52)	160 (58)	
Concomitant treatments at baseline, *n* (%)			
Mesalamine	74 (48)	276 (59)	<0.05
Thiopurines at baseline	11 (7)	37 (8)	>0.05
Steroids at baseline	52 (33)	108 (23)	<0.05
Anaemia at baseline, *n* (%)	61 (40)	118 (40)	<0.05
Hospitalisation due to the flare, *n* (%)	16 (10)	13 (2.8)	<0.01

Abbreviations: Anti-TNF, anti-tumour necrosis factor; CRP, C-reactive protein; IQR, interquartile range; JAK, Janus kinase; PMS, Partial Mayo Score; SD, standard deviation.

3.6 | Impact on EIMs and IMIDs

Data on the impact of ustekinumab treatment on EIMs and IMIDs that were inactive prior to ustekinumab treatment, on those that became active at the start of ustekinumab treatment, and on those that developed after ustekinumab initiation (new-onset) are presented in Tables S3 and S4, and Table 6, respectively. It is noteworthy that most of the EIMs and IMIDs that were inactive at the beginning of ustekinumab treatment remained inactive, while some EIMs and IMIDs that are related to disease activity or can be treated with ustekinumab showed improvement. Only a few EIMs and IMIDs developed after ustekinumab initiation.

3.7 | Safety

One hundred seventy-six (28%) patients had at least one adverse event under ustekinumab treatment. Parameters such as the

FIGURE 1 Survival curve of ustekinumab treatment in ulcerative colitis.

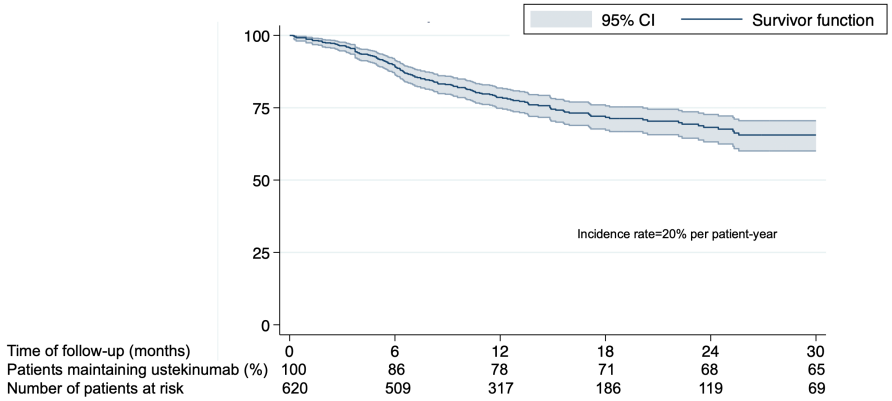

TABLE 3 Variables associated with ustekinumab discontinuation.

	Hazard ratio	95% confidence interval
Anaemia at baseline	1.5	1.1–2.1
Clinical severity at baseline[a]	1.5	1.09–2.06
Systemic steroids at baseline	1.48	1.06–2.08

[a]Categorised as remission, mild and moderate–severe.

proportion of each adverse event, the proportion of serious adverse events, the proportion of adverse events related to ustekinumab, and the resultant change to ustekinumab treatment are summarised in Table 7. Of note, only a minority of adverse events were related to ustekinumab treatment, and only in very few cases they led to ustekinumab discontinuation.

4 | DISCUSSION

To our knowledge, this is the study with the largest number of patients and longest follow-up time evaluating the benefit of ustekinumab treatment for UC in clinical practice; the high number of patients together with the long follow-up has allowed us to thoroughly investigate the role of ustekinumab in UC treatment in clinical practice. Our results provide a series of crucial insights to maximise the benefit of this drug in real-life settings. First, we were able to assess the durability of ustekinumab, the main reasons for discontinuations and predictive factors of drug discontinuation. Second, we could assess both short and long-term effectiveness. Third, we identified predictive factors of response. Fourth, we could evaluate the frequency and the success of drug optimization in patients losing response. Fifth, we assessed the safety of ustekinumab in a large cohort of patients. Finally, we were able to study the impact of ustekinumab treatment for UC on IMIDs and EIMs which, to our knowledge, had never been studied before in UC patients.

Drug survival is of great importance in clinical practice, as it considers not only the effectiveness of the treatment but also the tolerance and preferences of both the physician and the patient. In this respect, we reported an incidence rate of ustekinumab discontinuation of 20% per-patient year of follow-up. Even though our cohort included highly refractory patients, this figure is in the same range of discontinuation rates reported for other biologics and small molecules.[7,29,30] The long-term efficacy and safety of ustekinumab in UC was evaluated in the long-term extension (LTE) of the UNIFI trial.[14] UC patients who responded to an 8-week induction treatment with ustekinumab (either 130 mg or 6 mg/kg iv at baseline) and completed a 44-week subcutaneous maintenance therapy (90 mg every 8 or 12 weeks or placebo) in the UNIFI trial[11] were offered to continue their maintenance treatment in the LTE study. Starting at week 56, patients could receive dose adjustment to 90 mg every 8 weeks.[14] Patients were followed-up through 4 years. Of the patients randomised in the maintenance trial who continued ustekinumab treatment in the LTE, 29.8% (42/141) in the 90 mg sc every 12 weeks group and 29.4% (42/143) in the 90 mg sc every 8 weeks group discontinued treatment. Patients with previous failure of biologics were more likely to discontinue treatment (42.7%, 53/124) than biologics-naïve patients (18.8%; 28/149).[14] The cumulative incidence of ustekinumab discontinuation was therefore lower than that in our study. However, these results should be interpreted with caution, as patients who did not respond to ustekinumab at week 16 in the UNIFI trial did not enter the maintenance phase and did not count as treatment discontinuation in the long term. Moreover, although all responsive patients were considered for inclusion in the LTE study, only those patients who accepted were enrolled. This could be a potential bias towards higher treatment durability because it suggests that in these cases both the physician and the patient perceived benefit from ustekinumab treatment.

To date, data reported on ustekinumab discontinuation in UC in real life are limited; however, the discontinuation rates found in these studies are similar to the value obtained in our study.[15] Only disease severity (higher clinical activity, anaemia, steroid use) at baseline was associated with an increased risk of long-term treatment discontinuation in our study. Concurrent treatment with immunosuppressants or mesalamine at treatment initiation was not associated with a higher likelihood of drug maintenance; therefore, these agents should not be added only to increase ustekinumab survival. In our study, the main reasons for ustekinumab discontinuation

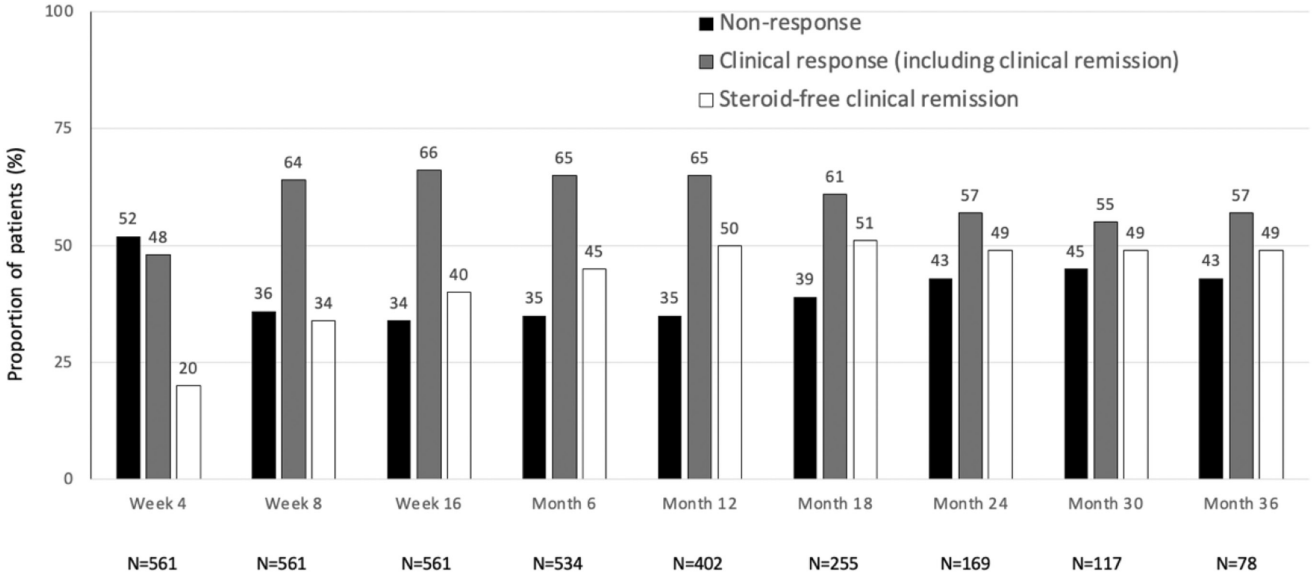

FIGURE 2 Short and long-term effectiveness of ustekinumab in ulcerative colitis.

were lack of effectiveness and loss of response, but not safety issues, in accordance with other real-world studies.[15]

Regarding effectiveness, at week 16, 40% of the patients in our study were in steroid-free remission, whereas the proportion of patients in symptomatic remission (with or without steroids) in the UNIFI trial was 58.4% in patients treated with ustekinumab 130 mg iv and 53.1% in those treated with 6 mg/kg iv.[31] There are some differences between our study and the UNIFI trial. First, despite the heterogeneity of real-world data, most of the patients in our cohort received ustekinumab 6 mg/kg iv at baseline and ustekinumab 90 mg sc at week 8, while in the UNIFI trial, only patients with lack of response to ustekinumab iv received ustekinumab 90 mg sc at week 8. Second, the proportion of patients previously exposed to biologic agents in the UNIFI trial was approximately 50%, whereas in our cohort virtually all patients were exposed to anti-TNF agents. Finally, our main effectiveness endpoint was steroid-free clinical remission, while patients of the UNIFI trial could be under steroid treatment at the time of evaluation (and they had to maintain steroids at stable doses during the induction if they were under steroid treatment at baseline).

The effectiveness of ustekinumab in UC in clinical practice was evaluated in a recent meta-analysis published by Gisbert et al.[15] The proportion of patients in steroid-free remission after 4–16 weeks was evaluated in 6 studies and ranged from 14% to 67%, reflecting the heterogeneity of definitions used in clinical practice. Of note, we only included in the effectiveness analysis patients with active disease at baseline and we used negative imputation in patients discontinuing ustekinumab for any reason, thus, our analysis was very conservative. In the multivariate analysis, we found that disease severity and the number of previous biologic agents were associated with lower probability of steroid free-remission after induction. In the UNIFI trial, although ustekinumab was effective both in patients exposed to anti-TNF and in naïve patients, the proportion of patients in symptomatic remission at each time point was greater in biologics-naïve patients than in those with previous failure of biologics. Among observational studies, only one demonstrated a negative effect of primary failure to anti-TNF on clinical remission in response to ustekinumab.[31] In fact, most of the observational studies on this therapy have been unable to identify predictive factors of ustekinumab effectiveness, probably due to limited sample size.

The UNIFI trial showed early response to ustekinumab in UC; a significantly greater proportion of patients achieved symptomatic remission at week 2 in the ustekinumab 130 mg group (20%) and ustekinumab 6 mg/kg group (20.2%) compared to placebo (12.9%). In addition, significant changes from baseline were observed in daily stool number as early as day 7 in response to treatment.[32] Similarly, a significant proportion of patients achieved early response to ustekinumab in our study; we observed that 20% of our patients were in steroid-free clinical remission already at week 4, despite the highly refractory characteristics of our cohort.

On the other hand, the question arises as to how long we can consider a patient to respond to induction before treatment interruption. Although in most real-world clinical practice studies, induction is considered as the first iv dose followed by the sc dose at week 8, as extrapolated from the pivotal trials in Crohn's disease. In the UNIFI study, patients received an iv dose at baseline, and only those who had not responded to this dose received a sc dose at week 8.[11] In this regard, among patients who had not responded at week 8 and received ustekinumab 90 mg sc, 59.7% responded at week 16 (delayed responders).[11] In a post-hoc analysis, compared with early ustekinumab responders, delayed responders had greater inflammatory burden at baseline, but both early and late responders had similar 1-year outcome.[33] In our cohort, the proportion of patients with steroid-free remission increased from 20% at week 4, to 34% at week 8 and 40% at week 16. Based on these results, it could be suggested that, whenever possible, the sc dose be administered at

TABLE 4 Characteristics of the study population according to steroid-free clinical remission at week 16.

Variable	Steroid-free clinical remission (*N* = 226)	No steroid-free clinical remission (*N* = 335)	*p*
Age at diagnosis (years), median (IQR)	39 (25–51)	39 (28–53)	>0.05
Age at ustekinumab start (years), median (IQR)	51 (35–61)	51 (38–63)	>0.05
CRP at baseline (mg/dL), median (IQR)	0.7 (0.2–1.9)	1.1 (0.4–2.1)	<0.05
Faecal calprotectin at baseline (mg/g), median (IQR)	1306 (559–2703)	1250 (591–3000)	>0.05
PMS at baseline, median (IQR)	6 (4–7)	6 (5–7)	<0.01
Number of previous biologics, mean (SD)	5.3 (1.6)	6 (1.5)	<0.01
Male sex, *n* (%)	107 (47)	198 (59)	<0.01
Smokers, *n* (%)	16 (7.1)	14 (4.2)	<0.05
Comorbidities, *n* (%)	144 (64)	230 (69)	>0.05
Colitis extension, *n* (%)			
Proctitis	9 (4)	15 (4.5)	
Left-sided colitis	95 (42)	123 (37)	>0.05
Extensive colitis	122 (54)	197 (59)	
Previous biologics/JAK inhibitors, *n* (%)			
Adalimumab	127 (56)	161 (48)	>0.05
Infliximab	130 (57)	222 (68)	<0.05
Golimumab	33 (15)	60 (18)	>0.05
Vedolizumab	119 (53)	248 (74)	<0.01
Tofacitinib	42 (19)	103 (31)	<0.01
Anti-TNF	199 (88)	301 (90)	>0.05
Anti-TNF and vedolizumab	106 (47)	225 (67)	<0.01
Anti-TNF, vedolizumab and tofacitinib	35 (15)	91 (27)	<0.01
Anaemia at baseline, *n* (%)	61 (28)	111 (34)	>0.05
Clinical severity at baseline			
Mild	74 (33)	5 (16)	<0.01
Moderate–severe	152 (67)	283 (85)	<0.01
Endoscopic activity at baseline, *n* (%)			
Inactive	0 (0)	1 (0.5)	
Mild	5 (3.6)	10 (4.7)	
Moderate	64 (46)	70 (33)	>0.05
Severe	71 (51)	133 (62)	
Concomitant treatments at baseline, *n* (%)			
Mesalamine	126 (56)	189 (56)	>0.05
Systemic steroids	36 (16)	116 (35)	<0.01
Thiopurines	17 (7.5)	23 (6.9)	>0.05
Hospitalisation due to disease flare, *n* (%)	6 (2.7)	23 (6.9)	>0.05

Abbreviations: Anti-TNF, anti-tumour necrosis factor; CRP, C-reactive protein; IQR, interquartile range; JAK, Janus kinase; PMS, Partial Mayo Score; SD, standard deviation.

TABLE 5 Variables associated with steroid-free clinical remission at week 16 under ustekinumab treatment.

	Odds ratio	95% confidence interval
Male gender	0.5	0.4–0.8
Severity at baseline (moderate–severe vs. mild)	0.3	0.2–0.5
Number of previous biologics	0.6	0.5–0.8

week 8 to obtain the maximum benefit of ustekinumab during induction therapy.

In our study, the incidence rate of loss of response among patients who had active disease at baseline and reached steroid-free remission at week 16 was 27% per patient-year of follow-up, which is consistent with other biologic agents.[7] Although the immunogenicity of ustekinumab is described as low, it is not surprising that there is loss of response through other mechanisms, such as the activation of inflammatory pathways independent of IL-12 and

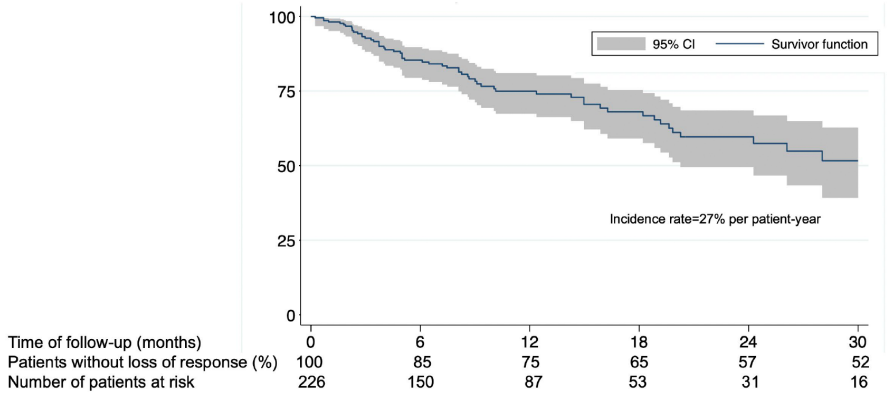

FIGURE 3 Survival curve of ustekinumab steroid-free remission in ulcerative colitis.

TABLE 6 New-onset extraintestinal manifestations and immune-mediated inflammatory diseases after ustekinumab start.

	N (%)	Treatment change after disease onset	Outcome after treatment change
Peripheral arthropathy	7 (1.1)	No change: 6; withdrawal: 1	Remission: 1
Primary sclerosing cholangitis	2 (0.3)	No change: 2	
Episcleritis	1 (0.1)	No change: 1	
Erythema nodosum	2 (0.3)	No change: 2	
Axial spondylarthritis	1 (0.1)	No change: 1	
Aphthous stomatitis	1 (0.1)	No change: 1	
Autoimmune hepatitis	1 (0.1)	No change: 1	
Pyoderma gangrenosum	1 (0.1)	No change: 1	
Psoriasis	1 (0.1)	No change: 1	
Uveitis	1 (0.1)	Withdrawal: 1	Remission: 1
Vasculitis	1 (0.1)	No change: 1	
Others	4 (0.65)	No change: 4	

TABLE 7 Adverse events in ulcerative colitis patients treated with ustekinumab.

Type	Adverse events	Serious adverse events	Attributed to ustekinumab	Attitude with ustekinumab treatment
Anaemia, *n* (%)	80 (13)	4 (5)	1 (1.2)	Dose escalation: 2 (3); no change: 78 (97)
MACE, *n* (%)	3 (0.4)	2 (67)	0 (0)	No change: 2 (67); withdrawal: 1 (33)
Herpes zoster, *n* (%)	5 (0.8)	0 (0)	4 (80)	No change: 5 (100)
Hypercholesterolemia, *n* (%)	2 (0.3)	0 (0)	1 (50)	No change: 2 (100)
Hypertriglyceridemia, *n* (%)	4 (0.6)	0 (0)	0 (0)	No change: 4 (100)
Infections, *n* (%)	66 (11)	19 (29)	12 (18)	No change: 58 (88); temporary discontinuation: 7 (11); withdrawal: 1 (1)
Lymphopenia, *n* (%)	1 (0.1)	0 (0)	0 (0)	No change: 1 (100)
Neoplasia, *n* (%)	5 (0.8)	4 (80)	0 (0)	No change: 3 (60); temporary discontinuation: 1 (20); withdrawal: 1 (20)
Pulmonary venous thromboembolism, *n* (%)	5 (0.8)	4 (80)	0 (0)	No change: 5 (100)
Peripheral venous thromboembolism, *n* (%)	4 (0.6)	2 (50)	0 (0)	No change: 4 (100)
Others, *n* (%)	52 (8.3)	16 (31)	7 (13)	No change: 43 (83); dose decrease: 1 (2); temporary discontinuation: 4 (7.5); withdrawal: 4 (7.5)

IL-23. The phenomenon of loss of response not associated with immunity has been described for all biological drugs. In the UNIFI trial, the proportion of patients treated with ustekinumab 90 mg every 8 weeks decreased 7% per year (from weeks 44 to 200) in patients with previous failure to biologics; however, these patients were stable and had showed benefit with ustekinumab for approximately the first year of treatment.[14] A commonly used rescue strategy in patients experiencing a loss of response to biologics is dose adjustment. However, the benefit of this strategy is, largely empirical and has been mainly used in or non-anti-TNF biologics different from anti-TNF. Therefore, its benefit in ustekinumab treatment needs to be probed. In this regard, in the UNIFI trial the benefit of dose adjustment was not clearly demonstrated.[13] There are certain limitations to consider when interpreting the results from the UNIFI trial: patients in the LTE study had the flexibility to change concomitant medications at any time, and the decision to adjust the dose was made based on the investigator's clinical judgement of a patient's disease activity, rather than on protocol-specified criteria. Therefore, the interpretability of these data is limited, particularly because many of the patients who underwent dose adjustment were in symptomatic remission at the time. Finally, the most commonly used dose adjustment in clinical practice, 90 mg every 4 weeks, was not evaluated in the UNIFI trial. In our study, among patients who lost response, ustekinumab dosage was escalated in 41 (72%) and approximately two-third of those patients responded.

Biological treatments for inflammatory bowel disease may exert an effect on concomitant EIMs or IMIDs in treated patients; they may also induce the appearance of these diseases as a paradoxical effect of the treatment. In our study, we observed an improvement in those EIMs typically associated with UC activity. In addition, few patients worsened from these conditions after ustekinumab and the number of new-onset EIMs/IMIDs was also very low. These results are aligned with the findings of a recently published systematic review and meta-analysis.[34] Regarding safety, our results showed that ustekinumab was safe for UC treatment in clinical practice, with no new safety signal in comparison with previous reports. It is worth highlighting that only a minority of our patients discontinued the treatment due to safety issues.

Our study has some limitations, mainly related to its retrospective nature. The main limitation was the lack of a pre-specified follow-up protocol, which had an impact on the availability of endoscopic data. In clinical practice, endoscopies are usually performed mainly in case of treatment failure and, therefore, endoscopic outcomes could not be assessed in most of the patients. However, to our knowledge and up to now, this is the largest study with the longest follow-up evaluating ustekinumab treatment for UC in clinical practice. Accordingly, our findings provide detailed information on the benefit and the way to manage ustekinumab treatment for UC in real life.

In conclusion, our study highlights the benefit of ustekinumab in UC in clinical practice, even in a cohort of highly refractory patients. The main reasons for discontinuation are primary failure and loss of response. However, ustekinumab has been demonstrated to be a well-tolerated therapy. The severity of the disease and the number of previous biologics, but not the concomitant use of thiopurines, have an impact on treatment effectiveness. Drug escalation is useful in patients losing response after remission. Ustekinumab treatment is safe, without safety signals regarding general adverse events or those related to preexisting or new-onset EIMs or IMIDs.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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