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Long-Term Effectiveness and Safety of Ustekinumab in Crohn's Disease: Results from a Large Real-Life Cohort Study

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Abstract: Background: Ustekinumab (UST) is an interleukin-12/interleukin-23 receptor antagonist approved for the treatment of Crohn's disease (CD). Only limited real-life data on the long-term outcomes of CD patients treated with UST are available. This study assessed UST's long-term effectiveness and safety in a large population-based cohort of moderate to severe CD patients. **Methods:** This was a multicenter, retrospective, observational cohort study that included both naïve and biologic-experienced patients treated with UST who achieved clinical remission or clinical response after at least one year of treatment. Clinical activity was scored according to the Harvey–Bradshaw Index (HBI). The primary endpoints were the maintenance or achievement of clinical

remission after a further 12-month period of treatment, defined as an HBI of ≤5, and safety. Other endpoints included steroid-free remission, mucosal healing (MH), steroid discontinuation, and the need for treatment optimization during the follow-up. **Results:** Out of 562 CD patients, after an overall 24-month follow-up, clinical remission was present in 450 (80.0%) patients, and at 12 months, clinical remission was observed in 417/437 (95.4%) patients; 33/125 (26.4%) showed clinical response at 12 months ($p = 0.000$). A total of 38/103 (36.9%) patients achieved MH. Only 2.1% (12/562), 3% (17/562), and 1.1% (6/562) of patients required surgery, optimization, and re-induction, respectively. Adverse events occurred in eight patients (1.42%). According to a multivariate analysis, the only predictor of long-term remission was the presence of remission at the 12-month follow-up ($p = 0.000$). **Conclusions**: Long-term treatment with UST presents good efficacy and safety profiles in CD patients, especially for patients who achieve remission after one year.

Keywords: Crohn's disease; ustekinumab; remission; response; re-induction; safety

1. Introduction

Crohn's disease (CD) is a chronic, transmural, granulomatous inflammatory condition of the gastrointestinal (GI) tract of unknown etiology [1]. CD's global incidence and prevalence have increased along with an improved understanding of the disease's clinical presentation, diagnosis, and natural history [2–4]. A relapsing and remitting progression characterizes the clinical course of the disease, and an aggressive therapeutic approach is often required to prevent complications from occurring [5].

Following the discovery of the critical pathogenetic role of tumor necrosis factor-α (TNF-α) in inflammatory bowel disease (IBD), monoclonal anti-TNFα antibodies have been developed and successfully adopted in clinical practice [5]. However, many patients do not respond to anti-TNF treatment or experience a secondary loss of response or intolerance to treatment due to intolerance, immunogenicity, or mechanistic failure [6,7]. Furthermore, there is a risk of infectious complications attributable to non-specific TNF-mediated inhibition [8,9]. Thus, novel therapeutic agents targeting alternative pathogenetic pathways have been investigated and approved for IBD treatment.

Ustekinumab (UST) is a monoclonal antibody blocking the p40 subunit of the interleukin (IL) 12/23 [10] that was granted marketing authorization in November 2016 by the European Medicines Agency for the treatment of moderate-to-severe CD in adult patients with inadequate response, loss of response, or intolerance to either conventional therapies or biologics [11]. It is also currently approved for the treatment of psoriasis and ulcerative colitis [12,13]

The efficacy and safety of UST in CD over a one-year period has been previously established in UNITI-1 and UNITI-2 (8 weeks) and IM-UNITI (44 weeks) controlled studies [14,15]. In the 3-year extension of this trial, 38.0% of UST induction responders receiving the drug every 12 weeks, and 43.0% receiving the drug every eight weeks, were in remission at week 152 [16]. Finally, 34.4% of patients in the every-8-weeks group and 28.7% in the every-12-weeks group were in clinical remission at week 252 [17].

Several real-world cohort studies have assessed the effectiveness and safety outcomes up to 52 weeks, confirming its efficacy in daily practice [18–35]. However, long-term outcomes beyond 52 weeks have only been assessed in a few real-world studies, often constrained by small numbers of enrolled patients or other limitations such as monocentric enrollment or the lack of specific assessment [36–44].

The present study aimed to assess UST's long-term effectiveness and safety in a large cohort of adult patients with CD with a minimum follow-up time of twelve months. We also set out to identify clinical and laboratory parameters that may influence the response to UST in the long term.

2. Methods

We conducted a retrospective, observational, multicenter study that included both naïve and biologic-experienced CD outpatients (including those who experienced failed treatments with anti-TNFa antibodies and vedolizumab) treated with UST in 40 Italian IBD centers who were in clinical remission or showed clinical response after completing at least one year of treatment.

Men and women at least 18 years of age with a CD diagnosis established according to standard endoscopic and/or radiologic and/or histological criteria were considered eligible [45]. Exclusion criteria included patients presenting with a diagnosis of unclassified IBD, intestinal strictures or complications accompanied by surgical indications, a stoma, extensive bowel resection (≥2 bowel surgical resection and/or 50 cm of ileal resection) [46], intestinal failure, and those receiving dual biological therapy (i.e., simultaneously using UST plus another biologic agent or a small molecule drug).

A common database was created to collect demographic and clinical data. At baseline, we collected the following data: gender, age at diagnosis, current smoking status, presence of comorbidities, previous appendectomy, previous surgery for CD, the extension of the disease according to the Montreal classification, disease duration, previous immunosuppressive and biologic therapies (anti-TNFα and/or anti-integrin), concomitant medications, fecal calprotectin (FC), C-reactive protein (PCR), erythrocyte sedimentation rate (ESR), Harvey–Bradshaw Index (HBI), Simple Endoscopic Score for CD (SES-CD), and Rutgeerts score for endoscopy (for patients with previous surgery).

We conducted the study according to the clinical practice guidelines and following the principles of the Declaration of Helsinki. All patients provided written informed consent before undergoing endoscopy and UST treatment. The reference center (Brotzu Hospital, Cagliari, Italy, PROT. PG/2020/9414, 29 April 2020) obtained ethics committee approval for this retrospective study, and this approval was accepted by the other centers.

2.1. Study Treatment

All patients were treated uniformly during the induction phase with a baseline intravenous infusion adapted to the following weight ranges: <55 kg: 260 mg; 55–85 kg: 390 mg; >85 kg: 520 mg. After induction, subcutaneous UST 90 mg was administered every eight weeks to maintain remission.

This interval of administration for maintenance treatment was chosen by all the investigators, considering that most of the patients had experienced the failure of one or more biological agents.

The investigators were left to judge the need for treatment discontinuation or dose escalation during the every-4-week therapy. They were also left to judge concomitant medications, such as oral and topical aminosalicylates, steroids, and/or immunosuppressants.

2.2. Clinical Assessment at Baseline and During the Follow-Up

The Montreal classification [47] was used to assess disease extension, while the Harvey–Bradshaw Index (HBI) [48] score was used to evaluate the activity of the disease. All the patients included in the study expressed active disease at the time of UST enrollment, defined as an HBI score > 5 points [48], despite concomitant treatment. Patients were clinically evaluated at entry and then again after 2, 6, 12, 18, and 24 months and subsequently, every 12 months, or in the case of loss of clinical response. CRP and FC levels were obtained at baseline and then at 2, 6, 12, 18, 24 and after that, every twelve months or in case of loss of clinical response.

2.3. Endoscopy Assessment at Baseline and During the Follow-Up

All patients underwent a colonoscopy before starting UST treatment, per standard protocol, in the participating centers. After 1-year of follow-up or earlier, as well as later in the study, depending on the patient's clinical history and the clinician's discretion, an ileocolonoscopy, with biopsies, was offered to monitor disease activity or for cancer

surveillance. The Simple Endoscopic Score for CD (SES-CD) and Rutgeerts score (for patients with prior surgery) were used to assess endoscopic severity [49–51]. Central reading for the assessment of the endoscopic activity was not performed.

2.4. Outcomes

The primary outcome was to assess the effectiveness of UST in terms of the maintenance or achieving clinical remission in CD patients who, after 12 months of treatment with UST, were in clinical remission (HBI of $\leq$5) or presented a clinical response, with a mild clinical activity (HBI 6–8), respectively. The co-primary outcome was the safety of UST, defined as the absence of adverse events (AEs) during the follow-up. The AEs were subdivided into early events (during the infusions) and late events (at least one week after the infusion/injection) and graded as mild (which did not require treatment interruption) and severe (which instead required interruption of the treatment) [52].

In addition, this study provided several secondary outcomes:

- Mucosal healing, defined as SES-CD $\leq$ 2 in CD patients;
- Reduction of steroid use during the study (defined as the use of systemic or topic steroids);
- Maintenance of steroid-free remission during the study;
- Occurrence of any surgical procedure related to the disease in CD;
- UST optimization, defined as the reduction of the time between the injections from eight to four weeks) during follow-up;
- CRP, FC, and HBI variations during follow-up;
- Re-induction of remission, defined as re-induction with intravenous infusion of either ustekinumab 260, 390, or 520 mg, according to the weight per prescribing guidelines [53].

2.5. Statistical Analysis

The data are presented using descriptive statistics. Continuous variables are expressed as the median and interquartile range (IQR); dichotomous or ordinal variables are presented as the number (percentage) of patients.

Clinical remission was considered as the primary endpoint. The predictive value of the clinical parameters was evaluated using time-to-event methods for censored observations because of the varying length of follow-up. Follow-up times were calculated from the date of diagnosis to the date of event or censorship. The time-to-event analysis used Kaplan–Meier estimates to draw the cumulative incidence curves, which were compared using log-rank tests and univariate and multivariate Cox proportional hazards models of the prognostic variables. The hazard ratios are presented with the 95% confidence intervals and *p*-values. A ratio higher than unity implies that an event has a higher probability than that of the reference group. The Friedman test was used to investigate any change in CRP and FC levels during follow-up. *p*-values < 0.05 were considered to be statistically significant.

3. Results

3.1. Baseline Characteristics (At 12 Months After Beginning UST Treatment)

A total of 562 were included; the median follow-up was 12 (18–36) months. Table 1 shows the baseline characteristics of patients at one year of follow-up. CD was located in the ileal and ileocolonic tracts in most patients, and stricturing disease was the most common phenotype (47.5%). Of note, approximately one patient out of four was a current smoker, and more than half (55.5%) had undergone intestinal resections in the past.

Regarding concomitant therapies, most of the patients were taking mesalazine, whereas only 15.8% were on steroids.

Furthermore, a relevant proportion of patients experienced previous failure with one or more (86.9%) lines of therapy using anti-TNFs and/or anti-integrin.

Concerning disease activity, the median CRP was 3 (1–5) mg/dL and FC 148 (80–244) µg/g, while the median HBI was 4 (2–5), and the SES-CD was 5 (2–8).

At one year of follow-up, 437 (77.8%) patients had achieved clinical remission, while 125 (22.2%) had shown a clinical response and were still displaying mild clinical activity.

Table 1. Characteristics of the study group.

Male Sex	**312 (55.5)**
Median (IQR) age at diagnosis, years	45 (32–57)
Current smokers	150 (26.7)
Previous appendectomy	141 (25.1)
Previous surgery for CD	312 (55.5)
Montreal classification	
Age at diagnosis (years)	
17–39	225 (40.0)
≥40	337 (60.0)
Location	
Isolated ileal disease	199 (35.4)
Isolated colonic disease	81 (14.4)
Ileocolonic disease	282 (50.2)
Concomitant perianal disease	71 (12.6)
Behavior	
Non stricturing, non-penetrating	205 (36.5)
Stricturing	267 (47.5)
Penetrating	90 (16.0)
Median (IQR) disease duration, years	11 (7–19)
Failure of other biologics	488 (86.8)
Naïve	74 (13.2)
Steroid-free	519 (92.3)
Concomitant medications	
Mesalazine	316 (56.2)
Azathioprine	21 (3.7)
Median (IQR) fecal calprotectin (μg/g)	148 (80–244)
Median (IQR) CRP (mg/L)	3 (1–5)
Median (IRQ) HBI	4 (2–5)
Median (IRQ) SES-CD (130 pts)	5 (2–8)
Rutgeerts score (110 pts)	1 (1–2)
Clinical response	125 (22.2)
Clinical remission	437 (77.8)

Data are given as the number (percentage) of patients, unless otherwise indicated. IQR, interquartile range; CRP, C-reactive protein; HBI, Harvey–Bradshaw Index; SES-CD, Simple Endoscopic Score for Crohn's disease.

3.2. Primary Outcomes

After a median (IQR) of 12 (6–24) months from the enrollment (i.e., two years after the beginning of UST treatment), clinical remission was present in 450 (80.0%) patients (Figure 1), including 417 out of 437 (95.4%) patients who were in clinical remission at the 12-month follow-up, and 33 out of 125 (26.4%) patients showing clinical response at the 12-month follow-up ($p = 0.000$, Figure 2).

Optimization was performed in 17 (3.0%) patients (13 patients with clinical remission and 4 patients without clinical remission) and re-induction in 6 patients (5 patients with clinical remission and 1 patient without clinical remission).

According to multivariate analysis, it was determined that the only predictor of long-term remission was the presence of remission at the 12-month follow-up ($p = 0.000$; Table 2). In the 33 patients with a clinical response at enrollment, long-term clinical remission was achieved in 29 (87.9) non-smokers and 4 (12.9) active smokers ($p = 0.030$).

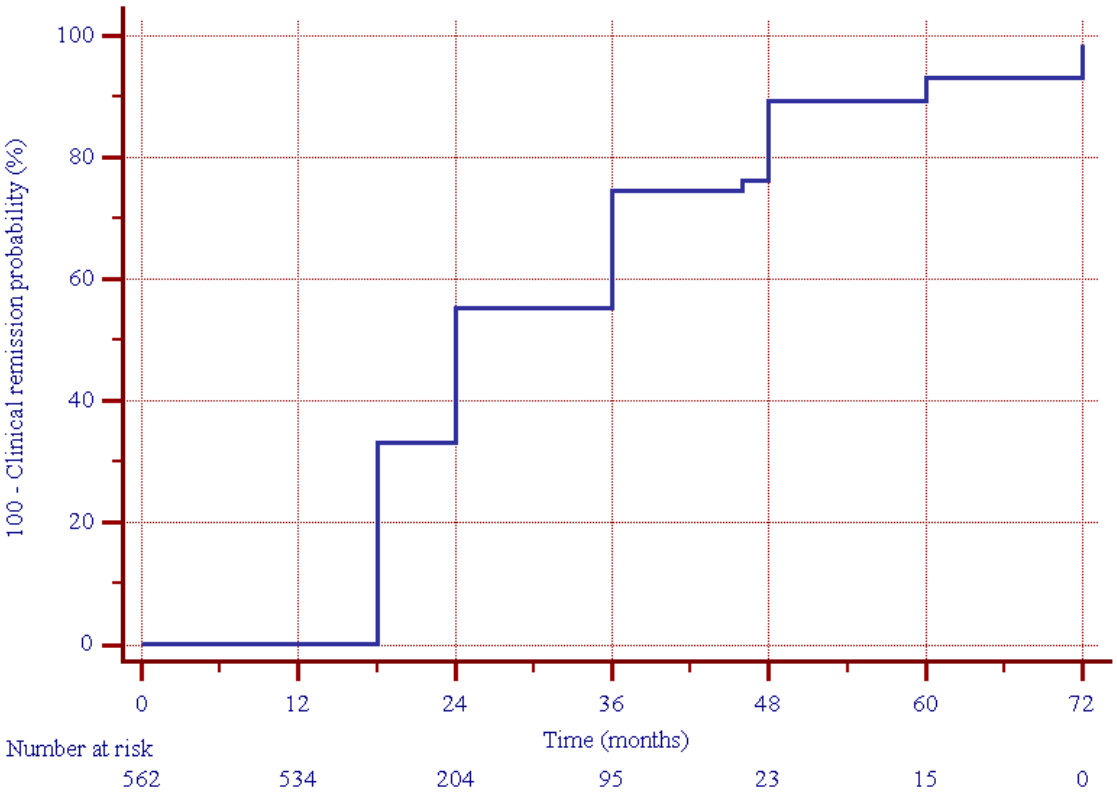


Figure 1. Estimated cumulative clinical remission probability during follow-up in the study group.

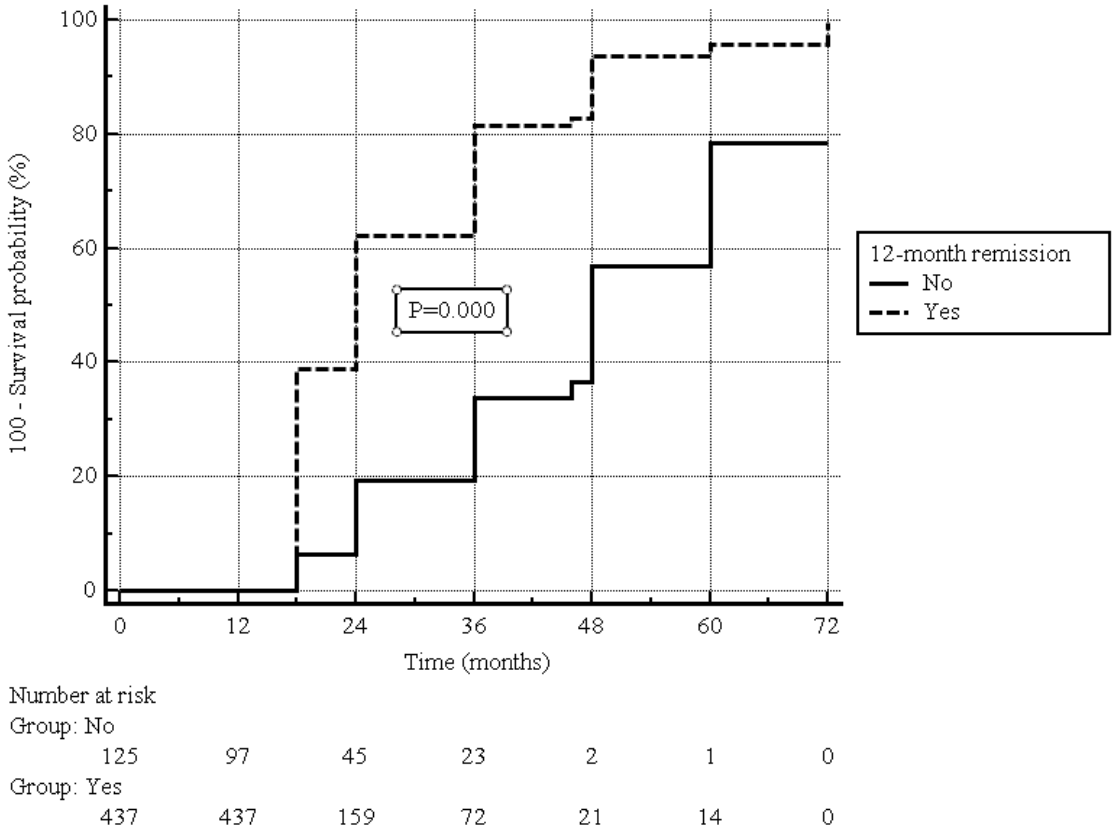


Figure 2. Estimated cumulative clinical remission probability during follow-up in patients with or without clinical remission at 12-month follow-up; log-rank test.

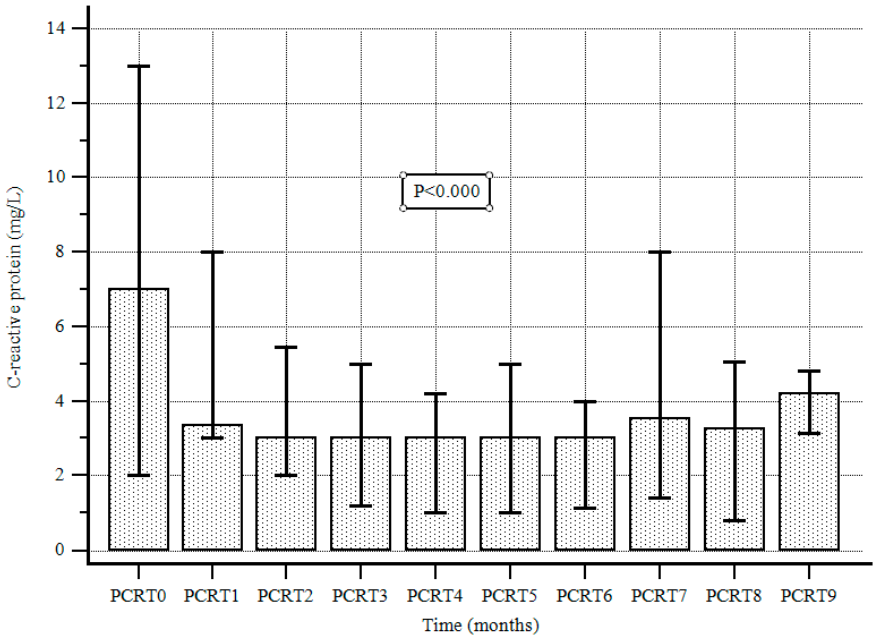
Table 2. Predictors of long-term clinical remission.

	Total	Remission	No Remission	Univariate Analysis				Multivariate Analysis		
Variable	**562**	**450 (80.1)**	**112 (19.9)**	**HR**	**95% CI**	***p***		**HR**	**95% CI**	***p***
Sex										
Female	250 (44.5)	198 (79.2)	52 (20.8)				Ref.			
Male	312 (55.5)	252 (80.8)	60 (19.2)	0.99	0.83–1.20	0.954		0.96	0.80–1.16	0.695
Current smokers										
No	412 (73.3)	332 (80.6)	80 (19.4)							
Yes	150 (26.7)	118 (78.7)	32 (21.3)	0.88	0.72–1.08	0.131		0.87	0.70–1.08	0.201
Previous surgery for CD										
No	250 (44.5)	201 (44.7)	49 (43.7)				Ref.			
Yes	312 (55.5)	249 (55.3)	63 (56.2)	0.98	0.82–1.18	0.860		1.05	0.87–1.27	0.622
Previous appendectomy										
No	421 (74.9)	348 (82.7)	73 (17.3)				Ref.			
Yes	141 (25.1)	102 (72.3)	39 (27.7)	0.94	0.76–1.17	0.499		0.90	0.85–1.46	0.087
Age										
18–39	225 (40.0)	185 (82.2)	40 (17.8)				Ref.			
≥40	337 (60.0)	256 (78.6)	72 (21.4)	0.88	0.73–1.07	0.100		0.86	0.71–1.04	0.129
Location										
Other	280 (49.8)	218 (77.9)	62 (22.1)				Ref.			
Ileocolonic	282 (50.2)	232 (82.3)	50 (17.7)	1.06	0.88–1.28	0.401		1.03	0.86–1.25	0.712
Behavior										
Non stricturing, non-penetrating	205 (36.5)	167 (81.5)	38 (18.5)				Ref.			
Stricturing/penetrating	357 (63.5)	283 (79.3)	74 (20.7)	0.92	0.75–1.11	0.258		0.91	0.75–1.11	0.362
Naïve to biologics										
No	488 (86.8)	397 (88.2)	91 (81,2)				Ref.			
Yes	74 (13.2)	53 (11.8)	21 (18.8)	0.98	0.73–1.31	0.873		0.94	0.71–1.401	0.241
Non-response to biologics										
No	229 (40.7)	183 (79.9)	46 (20.1)				Ref.			
Yes	333 (59.3)	267 (80.2)	66 (19.8)	1.15	0.95–1.38	0.067		1.27	1.03–1.56	0.028
Clinical response										
No	62 (11.0)	15 (3.3)	47 (42.0)				Ref.			
Yes	500 (89.0)	435 (96.7)	65 (58.0)	3.55	2.64–4.78	0.000		1.44	0.725–2.88	0.295
Clinical remission										
No	125 (22.2)	33 (7.3)	92 (82.1)				Ref.			
Yes	437 (77.8)	417 (92.7)	20 (17.9)	3.15	2.50–3.97	0.000		2.95	1.82–4.78	0.000

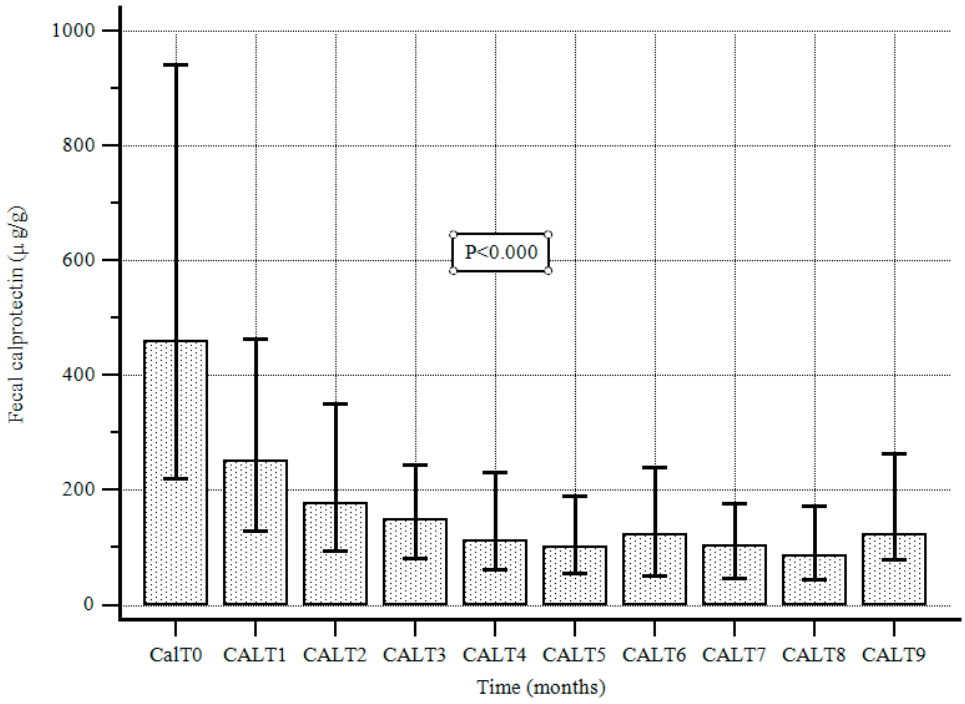
Data are given as the number (percentage) of patients, including HR, hazard ratio, and CI, confidence interval.

3.3. Secondary Outcomes

At the beginning of the treatment with UST, median FC and CRP values were 459 µg/g (220–942) and 7 mg/L (2–13), respectively. During the follow-up, the C-reactive protein and FC values were significantly reduced compared to the baseline and 1-year values (Figure 3A,B).



(**A**)



(**B**)

Figure 3. (**A**). C-reactive protein values at baseline and during follow-up. Data are expressed as the median and interquartile range (error bars), according to the Friedman test. (**B**). Fecal calprotectin values at baseline and during follow-up. Data are expressed as the median and interquartile range (error bars), according to the Friedman test.

The median (IQR) CRP level at the end of the follow-up was 4.4 mg/L (3.2–4.8), with a significant reduction compared to baseline values ($p < 0.000$). Moreover, the median (IQR) FC level was 85 µg/g (42.5–172.0), with a significant reduction compared to baseline values ($p < 0.000$).

Steroids were maintained in only 22 (4.9%) patients exhibiting clinical remission and 21 (18.8%) patients showing clinical response ($p = 0.000$).

An endoscopic assessment was performed in 103 patients 12 (6–24) months after enrollment (1 year after the beginning of UST treatment), and mucosal healing was achieved in 38 (36.9%) patients.

Overall, 17 (3%) patients requested dosage optimization, whereas 6 (1.1%) patients chose re-induction.

Finally, surgery occurred in 12 (2.1%) patients after a median of 12 (6–24) months from the enrollment (1 year after the beginning of UST treatment) (Table 2).

3.4. Safety Profile

Table 3 reports adverse events (AEs). During follow-up, AEs occurred in 8 (1.42%) patients.

Table 3. Adverse events.

	Group A (437/562)	Group B (125/562)	*p*-Value
Total Adverse Events (AE)	6 (1.4%)	2 (1.6%)	ns
Mild-Moderate AE			
- Allergy	1 (0.2%)	-	ns
- Erythema nodosum	1 (0.2%)	-	ns
- Herpes zoster	1 (0.2%)	-	ns
- Dermatitis	1 (0.2%)	-	ns
- Urinary tract Infection	-	1 (0.8%)	ns
- Orchitis	-	1 (0.8%)	ns
Severe AE			
- Tracheal stenosis	1 (0.2%)	-	ns

ns: not significant.

Adverse events were all mild to moderate, except for one tracheal stenosis that required treatment discontinuation. We recorded only one case of simplex herpes zoster (a single dermatome was involved, and the infection resolved within four weeks). This patient was not vaccinated against herpes zoster, as the large majority (>95%) of the population was enrolled before the recombinant vaccine became available in Italy in March 2021.

No differences were found between the patients with or without clinical remission at baseline.

4. Discussion

A growing body of evidence from RW data for UST provides credible evidence for its effectiveness and safety for treating moderately to severely active CD. Since the publication of the UNITI pivotal trials, several real-life studies from Europe, Asia, and North and South America have been conducted, confirming its efficacy in daily practice [14–16,18–35]. However, long-term data reflecting their use in real-life clinical practice are still being compiled [36–44]. To our knowledge, this multicenter real-world study is the largest assessing the effectiveness and safety of UST in a real-life long-term scenario. We showed that most patients reaching remission after one year of treatment can maintain remission for 12 months. Moreover, we found that about one-fourth of patients showing clinical response after one year of treatment can reach remission even after 12 months of treatment, and this late remission is easier for no-smoking patients to achieve.

It is essential to highlight the characteristics of our population at baseline to understand and interpret the results of our study. First, in a cohort of 562 patients, most of whom had already been treated with other biologics, 77% were in clinical remission at baseline. These results appear to be better not only than those of the pivotal studies UNITI-1 and

UNITI-2 [14,15] but also than those from a recent meta-analysis of real-life studies, in which a pooled remission rate of 40% was observed at 52 weeks [54]. A possible explanation could be the high proportion of patients who started UST to prevent post-operative recurrence (POR) rather than for the treatment of active CD.

Second, the primary endpoint, clinical remission over 12 months, was achieved in 80% of patients with a median follow-up of 24 months. Again, compared with the literature data, our results seem more favorable. The IM-UNITI trial found that 38.0% of UST induction responders receiving the drug every 12 weeks and 43.0% receiving the drug every eight weeks were in remission at week 152 [16]. Finally, 34.4% of patients in the every-8-weeks group and 28.7% in the every-12-weeks group were in clinical remission at week 252 [17]. Of course, our results could be explained by the 8-week regimen generally adopted in real life in Italy rather than, as previously reported, to the large proportion of patients treated for the prevention of POR [28,33].

The most robust data of our study are related to treatment persistence. Almost all (95%) of patients in remission 12 months after starting treatment maintained remission for at least another 12 months. In addition, a significant proportion (approximatively 25%) of "late remitters", i.e., patients not in remission at baseline, achieve remission during follow-up. This finding is relevant in practice and should encourage clinicians to continue maintenance therapy for 12 months. On the other hand, another therapeutic option should be considered in the absence of clinical signs of efficacy and with objective markers of disease activity.

We also analyzed factors that might predict long-term clinical remission with UST. We found that remission at the 12-month follow-up was the only predictor of long-term remission using multivariate analysis. Interestingly, confirming a finding already reported in our previous research regarding treating CD patients with UST [33], clinical remission seems to be independent of the number of different biological agents previously used, and this also applies to the subgroup of patients who achieve remission during follow-up. Overall, these data lead to two important considerations. The first is that UST is effective in obtaining remission even in patients already treated with more than one monoclonal antibody. This is confirmed by the very low number of patients requiring dose optimization or reinduction to reach or maintain remission (4.1%). This rate is too low to allow for an adequate sub-analysis, even if the recent POWER study identifies some parameters that are more likely to achieve a clinical response after reinduction [55]. The second is that UST may work better in CD patients after the first treatment with an anti-TNFα. In particular, with a view toward the rational sequencing of biological drugs, the evidence that non-responders to anti-TNF therapy show an increase in apoptosis-resistant, IL23-positive T cells, which promote inflammation, makes the IL 12/23 and IL 23 blockage particularly attractive [56].

Concerning the secondary end-points, we found that UST also exhibits a significant efficacy in reaching other important clinical outcomes. Both CRP and CF significantly dropped under treatment with UST, and MH was present in almost 40% of patients. This confirms that the clinical remission derived from UST is closely related to MH, even if the small number of endoscopic control patients limits these results. During follow-up, there was a reduction in steroid use, with more than 95% of patients in clinical remission also being steroid-free. Finally, overall, dosage optimization was requested in 17 (3%) patients, whereas re-induction was used in 6 (1.1%).

The safety profile of UST is very favorable according to pivotal trials and the IM-UNITI trial [14–16]. This favorable profile has also been confirmed in real life. In CD, the mean rate of the AEs is about 11%, with the large majority of them being mild and not requiring the discontinuation of treatment. This study confirms an excellent safety profile, since AEs occurred in only 8 (1.42%) patients.

Adverse events were mild to moderate, including only one case of simplex herpes zoster in an unvaccinated patient. There was only one case of serious AEs, a tracheal stenosis that required discontinuation of treatment.

This study has both strengths and limitations. The main strengths lie in the large number of patients enrolled, the reasonably good length of follow-up, and the use of clinical scores to evaluate the disease. An adjunctive strength is its long-term evaluation of drug safety. Finally, for the first time, we found that one-fourth of patients showing clinical response after one year of treatment can reach remission even after 12 months of treatment, and this late remission is easier for non-smoking patients to achieve. This means that in patients with a clinical response at one year, it seems appropriate to continue the therapy beyond one year since, especially for non-smokers [57], the chances of achieving delayed remission are significant.

The primary limitations lie in the retrospective nature of the study, which does not permit the enrollment of patients at the same time through the follow-up (for both clinical and endoscopic follow-up). The second limitation is that we mainly enrolled outpatients with less aggressive, or generally moderate rather than severe, disease behavior. This could explain the superior results of this study compared to those for the UNITI trial [17]. The third limitation is that, as this was a multicentric study involving 40 centers, it was impossible to guarantee that each patient received standardized management. For example, there is no clear indication of when to perform endoscopic control, which is generally reserved for patients who do not respond to the treatment, in real-life patients under treatment with biologics [58]. This could explain the lower rate (about 20%) of patients undergoing endoscopic follow-up recorded in this study.

5. Conclusions

The results of our real-world, multicenter study found that UST is effective and safe in managing outpatient CD during long-term follow-up. Interestingly, we identified some parameters that can help the physician predict the long-term efficacy of this drug. Further studies featuring large sample sizes and prospective designs are needed to confirm these findings.

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Data Availability Statement: Data from this study are available from the corresponding authors upon reasonable request.

Conflicts of Interest: G.M. (Giammarco Mocci) served as speaker for and/or received advisory board fees from AbbVie, Amgen, Aurora Biopharma, Biogen, Celltrion, Chiesi, Fenix Pharma, Ferring, Galápagos, Janssen, MSD, Omega Pharma, Sandoz, Takeda, and Vifor Pharma; A.T. has served as a

speaker and/or consultant for AbbVie, Bayer, Fenix Pharma, Galápagos, Janssen, Nalkein, Omega Pharma, and SILA; F.S. (Franco Scaldaferri) has served as a lecturer for AbbVie, Celltrion, Ferring, Janssen, Lilly, Pfizer, Sanofi, and Takeda; D.P. received speaker fees from AbbVie, MSD, Takeda, Janssen, and Pfizer; E.V.S. has served as a speaker for AbbVie, AGPharma, Alfasigma, Dr Falk, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, and Unifarco and has served aa s consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr Falk, Fresenius Kabi, Janssen, Merck & Co., Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, and Unifarco; G.M. (Giovanni Maconi) has served as a speaker for and/or has received advisory board fees from AlfaSigma, Arena, Janssen, Gilead, and Roche; A.P. (Alfredo Papa) received speaker fees from Janssen. The remaining authors declare no competing interests.

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