ORIGINAL PAPERS

Ustekinumab in Crohn's disease: real-world outcomes and predictors of response

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ABSTRACT

Background: ustekinumab is a monoclonal antibody that inhibits interleukins IL-12 and IL-23, and is approved for the treatment of Crohn's disease (CD) and, more recently, also ulcerative colitis (UC). The aim of this study was to evaluate the effectiveness and safety of ustekinumab, as well as to identify possible predictive factors of response in a real-life setting.

Methods: an observational, retrospective, multicenter study was carried out in 4 hospitals in Andalusia. Adult patients with a confirmed diagnosis of CD treated with ustekinumab from 2017 to 2019 were included. Clinical response was analyzed at 3, 6 and 12 months of treatment. Clinical disease activity was assessed with the Harvey-Bradshaw index (HBI) and the Crohn's Disease Activity Index (CDAI); biochemical response was assessed with lab parameters such as CRP and ESR. One-year ustekinumab drug-survival was analyzed.

Results: a total of 98 patients were analyzed (mean age, 43 years; 52 % were male); 56 % had failed with ≥ 2 previous biologicals therapies. At 3 months, 69 % of the patients were in response and 40.8 % in remission. At 6 months, 56 % were in clinical remission. At 12 months, 73.7 % were in clinical response and 60.5 % in remission. Corticosteroid-free remission was 32.4 %, 44 %, and 47.4 % at 3, 6, and 12 months, respectively. Cumulative survival after one year of treatment with ustekinumab was 85.3 %. Biochemical parameters such as CRP and ESR showed a statistically significant decrease between baseline and control levels at 3, 6, and 12 months. A lower HBI at baseline and female sex were predictors of corticosteroid-free clinical remission in a univariate analysis. In the multivariate analysis no variables were found as predictors of corticosteroid-free clinical remission.

Conclusion: ustekinumab therapy is safe and useful, inducing clinical response in more than 50 % of patients, including patients who failed with other biological therapies.

Keywords: Inflammatory bowel disease. Crohn's disease. Ustekinumab.

BACKGROUND

The therapeutic armamentarium available for Crohn's disease (CD) has evolved widely in recent years, especially with the introduction of anti-TNF drugs. However, despite their great efficacy, up to a third of patients exhibit a primary non-response to anti-TNFs (1), and a variable percentage have a secondary loss of response (2). This represents an important challenge in daily clinical practice, which evidences the need for newer therapies.

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Ustekinumab (UST) is a fully human monoclonal antibody targeting the p40 subunit of interleukin-12 and interleukin-23. It was approved by the European Medicines Agency (EMA) in 2016 (3) for the treatment of moderate to severe Crohn's disease in patients who have had an insufficient response or loss of response to anti-TNFα agents, or have intolerance or contraindication to their use.

Ustekinumab efficacy to induce and maintain clinical remission in moderate to severe CD was evaluated in the UNITI and IM-UNITI registration trials (4). However, clinical trials do not fully reflect routine care, and therefore real-world studies are needed. Data on ustekinumab effectiveness and safety in the real-life setting remain scarce (5). In Spain, the short- and long-term experience with this agent has been published, with good results in terms of efficacy and safety (6,7). The aim of this study was to evaluate the long-term efficacy and safety of ustekinumab in daily clinical practice in our Autonomous Community, Andalusia. Secondly, potential predictors of clinical response were evaluated.

METHODS

Study design

An observational, retrospective, multicenter study was carried out in Andalusia in 4 hospitals. All adult CD patients who received ustekinumab therapy from July 2017 to December 2019 were included. The induction regimen was a single intravenous dose of approximately 6 mg/kg (260 mg if < 55 kg; 390 mg if 55-85 kg, and 520 mg if over 80 kg), followed by subcutaneous administration of ustekinumab 90 mg at week 8 and every 8 (q8w) or 12 weeks (q12w) thereafter. The patients were followed for one year at their regular check-up visits. The medical records were exhaustively reviewed to gather information from the patients.

Variables

Demographic and clinical data were collected from the clinical records, including previous and concomitant treatments, previous surgeries, and luminal and perianal activity in order to analyze potential predictors of remission. The Harvey-Bradshaw index (HBI), the Crohn's Disease Activity Index (CDAI), and objective laboratory markers such as fecal calprotectin, C-reactive protein (CRP), and baseline erythrocyte sedimentation rate (ESR) were used to assess clinical response after 3 months, 6 months, and 12 months of treatment.

Definitions

Clinical response was defined as a decrease ≥ 3 points in HBI index score from baseline. Clinical remission was defined as an HBI score ≤ 4 points. For the effectiveness analysis, patients who were already in remission at the beginning of treatment (n = 11) or without HBI data (7) were excluded. Corticosteroid-free clinical remission was defined as clinical remission plus complete systemic corticosteroid discontinuation. Intensification was defined as any dose interval shorter than q8w.

Statistical analysis

For the descriptive analysis, absolute frequency (N) and relative frequency (%) were calculated for categorical variables. For continuous variables the results were presented as mean and standard deviation or median and interquartile range (IQR). For quantitative variables, normal distribution was evaluated with the Shapiro-Wilk test. Change from baseline in quantitative variables was assessed with a paired T-test or Wilcoxon's rank test for normally or non-normally distributed variables, respectively. The Kaplan-Meier method was used to analyze the probability of maintaining treatment or drug-survival.

Variables associated with corticosteroid-free clinical remission at 3, 6, or 12 months were investigated using univariate binary logistic regression. The odds ratio (OR) of the statistically significant variables in the model was calculated. Independent variables with a p-value < 0.2 in the univariate analysis were included in the multivariate analysis. This multivariate analysis used the backward elimination (conditional) method. A 95 % confidence level was taken into account, so the experimental p-value was compared with a significance level of 5 %. The statistical analysis was carried out using the statistical package IBM SPSS Statistics 22®.

Ethical considerations

The study was reviewed and approved by the ethics committees at the participating centers.

RESULTS

A total of 98 patients were included, and baseline characteristics and concomitant medications are detailed in table 1. Mean age at ustekinumab initiation was 43 years with a median disease duration of 10 years (IQR: 4-18); 52 % were male, the most frequent phenotype was inflammatory (50.4 %), and the most frequent location was ileocolic (52.6 %). Only 1 patient (1.1 %) was naïve to biological therapy, 42.8 % had previously failed one biologic and 56 % had failed two or more. The main reason for starting ustekinumab was clinical disease activity (72.5 %), with a median HBI of 8 (IQR: 6-10) and a median CDAI of 200 (IQR: 170-235). Previous intestinal resection was reported in 41 patients (41.8 %). The flow chart of patients reaching each follow-up visit is shown in figure 1.

Cumulative ustekinumab survival is shown in figure 2. Mean follow-up was 7.02 months, and maximum follow-up was 12 months. Of the 98 included patients, 12 (12.2 %) discontinued ustekinumab after a mean duration of 36 weeks. The probability of continuing with ustekinumab after one year of treatment was 85.3 % (Fig. 2A). In addition, the durability of the treatment was also analyzed according to the number of previous biological therapies, 0 or 1 vs 2 or more, and the comparison showed a non-significant difference in ustekinumab persistence between the two groups (Fig. 2B). Similarly, there was also a non-significant difference when comparing different treatment maintenance regimens, q8w or q12w (according to the summary of product characteristics) vs an interval shorter than q8w (Fig. 2C).

Table 1. *Baseline patient characteristics*

Patient characteristics	n
Number of patients	98
Age; median, IQR	41 (35-50)
Gender (M/F); n, %	51 (52 %)/47 (48 %)
BMI (kg/m²); median, IQR	24.6 (21.5-27.3)
Smoking status; n, %:	
Former smoker	12 (14.6 %)
Current smoker	23 (28 %)
Non-smoker	47 (57.3 %)
Median disease duration (years); median, IQR	10 (4-18)
Age at diagnostic; n, %:	
< 17 years (A1)	10 (10.3 %)
17-40 years (A2)	73 (75.3 %)
> 40 years (A3)	14 (14.4 %)
CD location; n, %:	
Ileal (L1)	31 (32 %)
Colonic (L2)	9 (9.3 %)
Ileocolonic (L3)	51 (52.6 %)
Upper gastrointestinal (L4)	6 (6.2 %)
Phenotype; n, %:	
Inflammatory (B1)	49 (50.4 %)
Stenosing (B2)	24 (24.7 %)
Penetrating (B3)	24 (24.7 %)
Perianal (p)	34 (35.8 %)
Extraintestinal manifestations; n, %:	51 (53 %)
Joint manifestations	39 (40.6 %)
Previous intestinal resections; n, %	41 (41.8 %)
Harvey-Bradshaw index; median, IQR	8 (6-10)
CDAI; median, IQR	200 (170-235)
CRP (mg/L); median, IQR	1 (0.4-3)
Fecal calprotectin (mg/kg); median, IQR	550 (332-1488)
Therapies	
Number of patients	98
Previous therapy; n, %:	
Mesalazine	61 (62 %)
Steroids	89 (91 %)
Thiopurines (AZA/6MP)	81 (82.6 %)
Methotrexate	48 (49 %)
Failure with previous biological therapies; n, %:	
Naïve	1 (1.1 %)
1 failure	42 (42.8 %)
2 failure	36 (36.7 %)
3 or more failures	19 (19.4 %)
Reason of initiation ustekinumab; n, %:	
Steroids refractory	3 (3 %)
Steroid dependency	43 (50 %)
Clinical activity	69 (72.5 %)
Extraintestinal manifestations	30 (31.6 %)
Perianal disease	12 (12.6 %)
Concomitant therapies; n, %:	
Mesalazine	21 (21.8 %)
Steroids	27 (27.5 %)
Thiopurines	13 (13.9 %)
Methotrexate	2 (2.0 %)
Harvey-Bradshaw index at baseline; n, %:	
Remission (HBI ≤ 4)	11 (11.2 %)
Mild disease (HBI: 5-7)	28 (28.6 %)
Moderate disease (HBI: 8-16)	48 (48.9 %)
Severe disease (HBI > 16)	4 (4.1 %)
ND	7 (7.1 %)

IQR: interquartile range; CRP: C-reactive protein; ND: no data.

Ustekinumab clinical effectiveness was assessed in patients with documented HBI and at least 3-month follow-up. Patients in clinical remission (HBI ≤ 4) at baseline (n = 11) were not included in the analysis. The proportion of patients with clinical response to ustekinumab was 69 % at 3 months, 82 % at 6 months, and 73.7 % at 12 months. The proportions of patients in clinical remission at 3, 6, and 12 months were 40.8 %, 56 %, and 60.5 %, respectively, whereas the percentages of patients achieving corticosteroid-free clinical remission at 3, 6, and 12 months were 32.4 %, 44 %, and 47.4 %, respectively (Fig. 3).

Clinical evolution according to the CDAI and HBI scores throughout follow-up visits are shown in figure 4 A and B, respectively. There was a progressive decrease in the median value of both clinical indices at 3, 6, and 12 months. A statistically significant decrease vs baseline was also observed for both CDAI and HBI.

Biochemical parameters were also recorded to objectively assess the degree of systemic inflammation. A statistically significant decrease vs baseline in mean C-reactive protein (CRP) concentration was observed at 3, 6, and 12 months (Fig. 5A). Similarly, mean erythrocyte sedimentation rate (ESR) decreased significantly from 6 months as compared to baseline levels (Fig. 5B).

A univariate and multivariate analysis was performed to identify predictive factors of corticosteroid-free clinical remission at 3, 6, and 12 months (Table 2). Patients in clinical remission (HBI ≤ 4) at baseline were excluded from the analysis. A multivariate analysis was performed only for variables with $p < 0.2$ in the univariate analysis. In the univariate analysis a lower HBI at baseline was associated with higher rates of corticosteroid-free remission at 3 (OR: 0.73; 95 % CI: 0.6-0.9) and 12 months (OR: 0.83; 95 % CI: 0.7-0.9). Female sex was also identified as a predictor of corticosteroid-free remission at 6 months (OR: 3.89; 95 % CI: 1.19-12.68). However, these factors did not reach statistical significance when assessed as multivariable predictors.

The safety profile of ustekinumab in all 98 patients was consistent with previous reports. During follow-up, 4 adverse events were recorded, most of them mild. One patient had a herpes zoster infection after 11 months with ustekinumab, and another patient had a mouth sore after 6 months of treatment. There was one infusion reaction to an intravenous dose that did not require treatment discontinuation. Finally, there was one case of thrombosis of the superior mesenteric and portal veins after abdominal surgery (colectomy) in a patient who had already suspended ustekinumab treatment. Although we reported this in the study, we consider it probably unrelated to ustekinumab therapy.

DISCUSSION

To date, the treatment of CD remains a challenge despite new available therapeutic options. We often observe adverse events, primary and secondary non-response, and contraindications to some therapies. It is paramount to assess the real-world effectiveness of novel therapies due to the limited therapeutic armamentarium that is available (8,9).

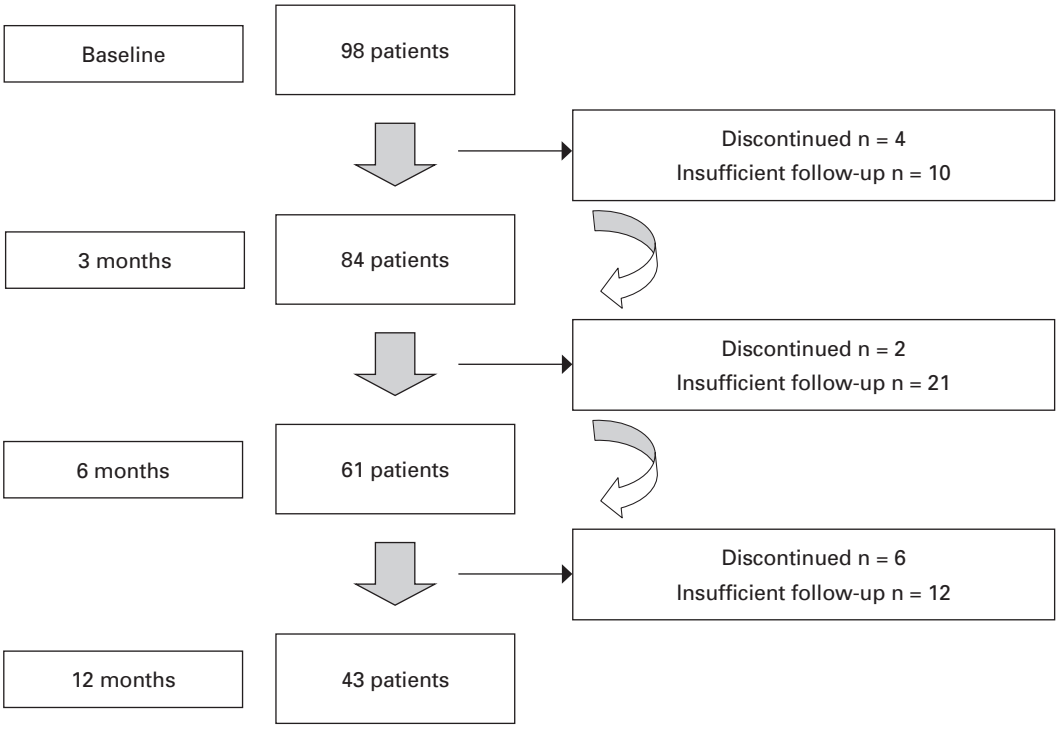

Fig. 1. *Flow chart of the patients included in the study.*

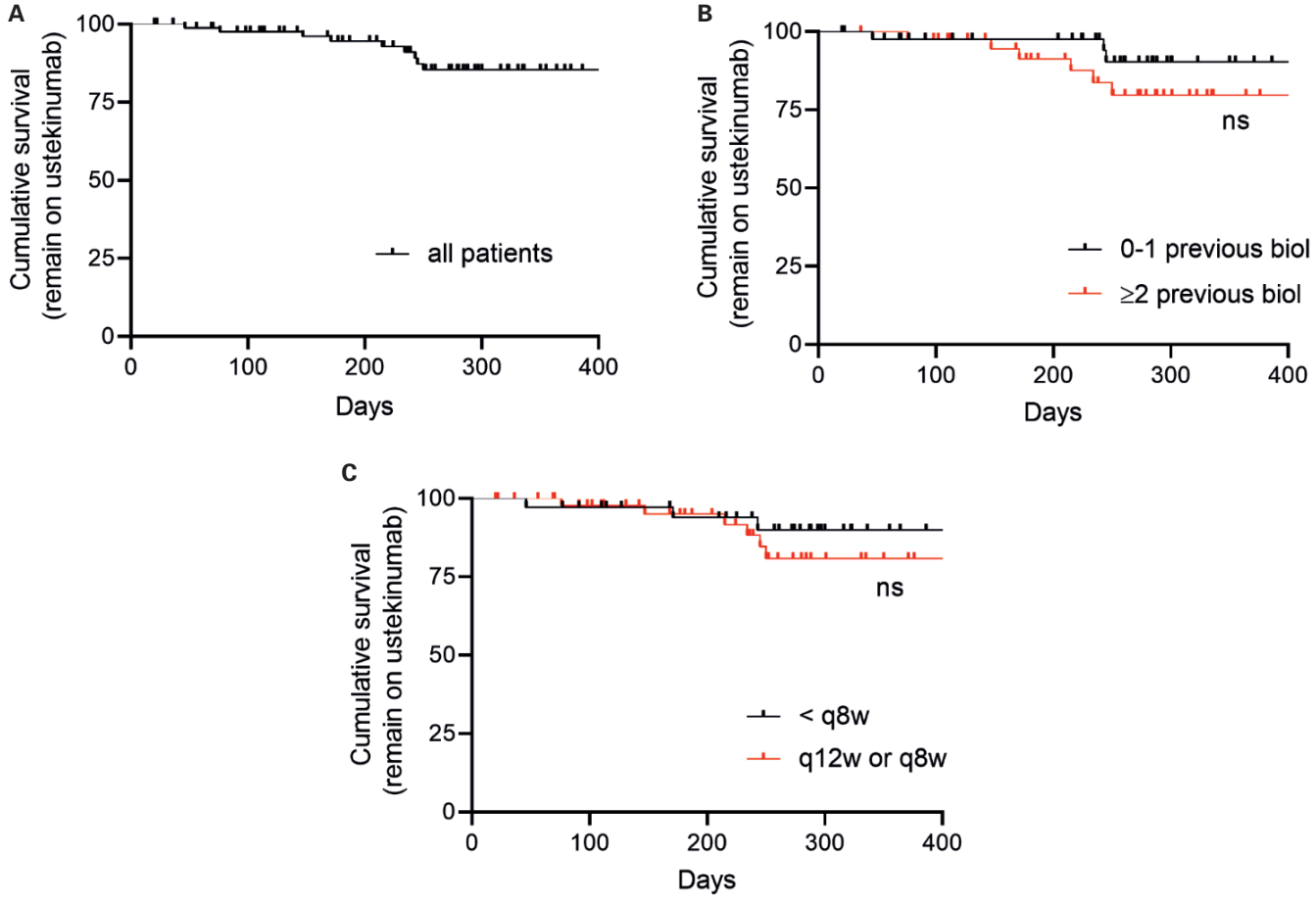

Fig. 2. *Kaplan-Meier survival curve for the probability of maintaining ustekinumab treatment at 12 months. Biol: biological treatment.*

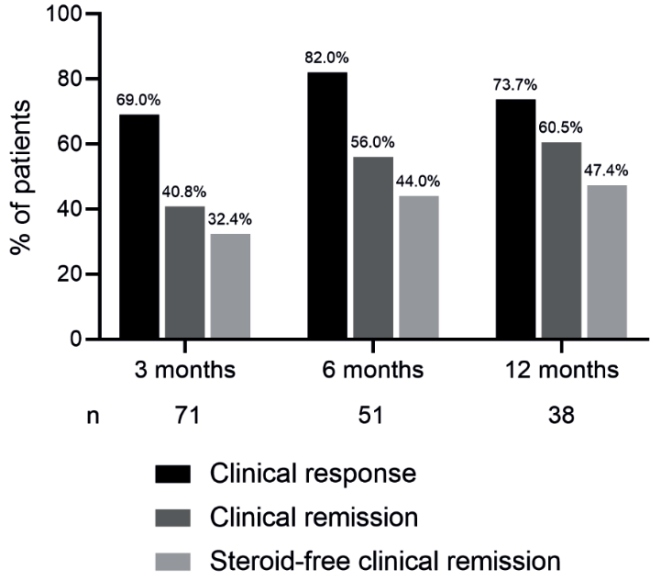

Fig. 3. *Proportion of patients in clinical response (reduction of at least 3 points in HBI from baseline), clinical remission (HBI ≤ 4) and steroid-free clinical remission. Patients in clinical remission at baseline were excluded from the analysis.*

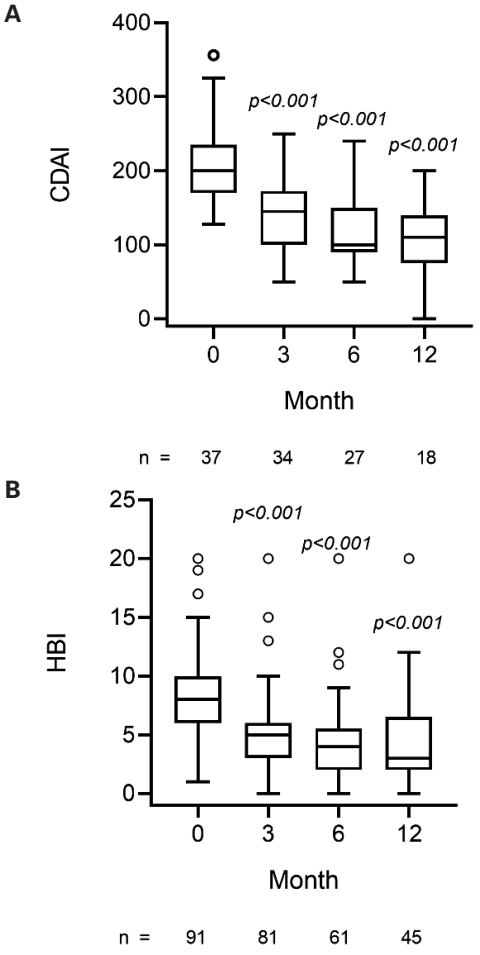

Fig. 4. *A. median CDAI. B. Median HBI. Boxes represent medians with interquartile 25th-75th range; whiskers show 10th-90th percentile ranges; dots show values beyond defined percentiles. For the statistical analysis follow-up visits were compared to baseline.*

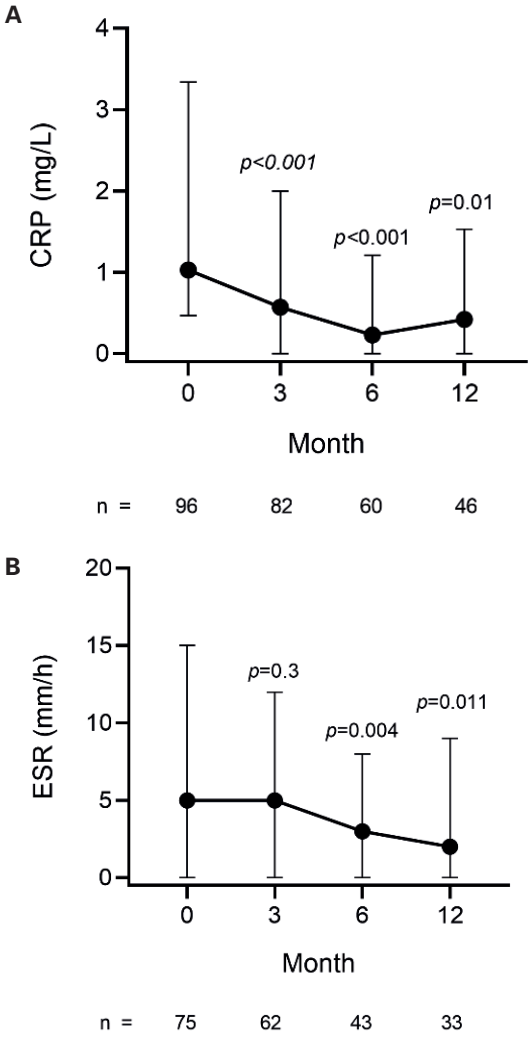

Fig. 5. *Mean concentration of C-reactive protein (CRP) and mean erythrocyte sedimentation rate (ESR). Error bars represent the standard deviation. For the statistical analysis follow-up visits were compared to baseline.*

Our cohort includes complex patients, 98.9 % were biological-experienced patients with long-standing Crohn's disease, and a median duration from diagnosis of 10 years. Furthermore, there was a significant prevalence of perianal disease (35.8 %) and up to 40 % of patients required abdominal surgery. Despite the refractory and complex nature of our cohort, 85.3 % of patients maintained ustekinumab therapy after one year. Moreover, corticosteroids-free clinical remission was achieved in 32.4 % of patients as early as 3 months, in 44 % at 6 months, and in 47.4 % at 12 months. Clinical remission was observed in 40.8 %, 56 %, and 60.5 % of patients at 3, 6, and 12 months, respectively, whereas clinical response was achieved by 69 %, 82 %, and 73.7 % of patients at 3, 6, and 12 months, respectively.

In comparison, the UNITI-1 induction registration trial evaluated the efficacy of ustekinumab in patients with one previous failure of biological therapy, similar to patients in our cohort. The proportion of patients in clinical response at week 8 in the 6 mg/kg arm was 37.8 %, while 20.9 % were in clinical remission (4). Other real-world observational

Table 2. *Univariate and multivariate analysis*

Corticosteroid-free clinical remission at 3 months	Univariate analysis		Multivariate analysis			
	OR	95 % CI	p-value	OR	95 % CI	*p-value*
Age	1.039	0.991-1.089	0.117	1.026	0.979-1.076	0.284
Sex:						
Male	Ref.			Ref.		
Female	0.688	0.241-1.964	0.484		-	-
Smoking status:						
Smoker	1.118	0.302-4.130	0.868	-	-	-
Nonsmoker and former smoker	Ref.			Ref.		
Harvey-Bradshaw index	0.731	0.596-0.896	0.003*	0.876	0.714-1.074	0.202
Fecal calprotectin (mg/kg)	1.000	0.998-1.001	0.521	-	-	-
Perianal disease	0.302	0.069-1.317	0.111	0.761	0.214-2.705	0.673
Corticosteroid-free clinical remission at 6 months	**Univariate analysis**		**Multivariate analysis**			
	OR	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**
Age	1.000	0.960-1.040	0.842	-	-	-
Sex:						
Male	Ref.			Ref.		
Female	3.89	1.19-12.68	0.025*	3.600	0.870-14.904	0.077
Smoking status:						
Smoker	1.538	0.359-6.599	0.562	-	-	-
Nonsmoker and former smoker	Ref.			Ref.		
Harvey-Bradshaw index	0.90	0.79-1.03	0.121	0.906	0.751-1.093	0.301
Fecal calprotectin (mg/kg)	1.00	1.00-1.00	0.401	-	-	-
Perianal disease	1.23	0.34-4.44	0.750	-	-	-
Corticosteroid-free clinical remission at 12 months	**Univariate analysis**		**Multivariate analysis**			
	OR	**95 % CI**	**p-value**	**OR**	**95 % CI**	***p-value***
Age	1.010	0.935-1.091	0.806	-	-	-
Sex:						
Male	Ref.			Ref.		
Female	1.286	0.292-5.567	0.740	-	-	-
Smoking status:						
Smoker	5.091	0.518-50.004	0.163	-	-	-
Nonsmoker and former smoker	Ref.			Ref.		
Harvey-Bradshaw index	0.829	0.691-0.994	0.043*	-	-	-
Fecal calprotectin (mg/kg)	0.999	0.997-1.000	0.149	-	-	-
Perianal disease	3.316	0.353-31.158	0.294	-	-	-

OR: Odds ratio; CI: confidence interval. *Statistically significant.

studies, such as the Spanish ENEIDA registry, have reported higher remission rates than the pivotal trials. Eight weeks after induction, 47.4 % of patients achieved clinical remission. The authors argue that this higher remission rate could be accounted for by the absence of washout periods between drugs in clinical practice, and the associated treatments that were not permitted in the clinical trial by Iborra et al. (7) or in the study by Miyazaki et al. (10).

In the long-term, the IM-UNITI maintenance registration trial reported clinical remission rates at week 44 of 53.1 % in the q8w arm and 48.8 % in the q12w arm. Corticosteroid-free clinical remission was achieved by 46.9 % of patients in the q8w arm and 42.6 % of patients in the q12w arm. These results are in line with the remission rates reported in our study. Real-world studies that assess long-term efficacy, such as the meta-analysis by Macaluso et al. (11), the German cohort by Kubesch et al. (12), and te research by Hoffmann et al. (13), Iborra et al. (6), and Biemans et al. (5) reported similar or even higher response rates compared to the pivotal trials. This may be explained by the associated treatments allowed in real-life studies, which might improve treatment response (5).

Biochemical markers of disease activity were also assessed. There was a significant decrease in inflammation markers (CRP and ESR) during follow-up, which has also been observed in the pivotal trials (4) and other observational studies (7). We attempted to identify predictive factors of response to ustekinumab, and predictors of response to biological treatment have been extensively studied (14,15). Knowing which patient will respond to a therapy and who will need other therapeutic approaches would avoid delays in starting an effective drug. Furthermore, it has been shown in multiple studies that patients with failure to previous biological therapies have a lower response rate than naïve patients. Previous studies have reported the use of concomitant immunomodulatory drugs, disease pattern, disease location, and clinical severity as predictors of response to ustekinumab (16,17). In our cohort, we found that a low HBI at baseline and female sex were associated with corticosteroid-free clinical remission in a univariate analysis.

Hoffman et al. also found a similar association between sex and responsiveness to ustekinumab; in their study, male sex was a predictor of non-response to ustekinumab therapy (17). However, further studies and larger cohorts are needed to evaluate this relationship.

Our study shows that ustekinumab is a safe therapeutic option for CD patients, and the rate of adverse events was low 0.04 (4/98), a majority of these being mild herpetic infections or skin reactions. These findings are similar to previous reports (5,18,19). However, our study has several limitations. First, the retrospective nature of the study, with the limitations that this entails, such as bias and quality of evidence. However, it is a multicentric study with an adequate number of patients. The primary endpoint of response to therapy was measured by clinical activity indexes. Another limitation is the lack of endoscopic results to assess mucosal healing; endoscopic examinations are not performed as frequently in clinical practice since they are invasive tests. Clinical activity was measured with the HBI and CDAI indices. However, CDAI values were available in less than half of the patients since it is a more labor-intensive index as well as less practical for daily use. Fecal calprotectin was recorded at baseline; however, it was not available for most follow-up visits and therefore no further analysis could be performed. In contrast to pivotal studies, only one patient in our cohort received ustekinumab as first-line treatment, therefore comparisons of our data to those of the pivotal studies should be performed with caution.

CONCLUSION

Our data suggest that ustekinumab is safe and efficacious at inducing a durable clinical response in more than 50 % of patients, including those who have failed with other biological therapies.

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