Ustekinumab for the Treatment of Refractory Crohn's Disease: The Spanish Experience in a Large Multicentre Open-label Cohort

Sam Khorrami, MD, Daniel Ginard, MD,* Ignacio Marín-Jiménez, MD,† María Chaparro, MD, PhD,‡ Mónica Sierra, MD,§ Mariam Aguas, MD, PhD,‖ Beatriz Sicilia, MD, PhD,¶ Valle García-Sánchez, MD, PhD,** Cristina Suarez, MD, PhD,†† Albert Villoria, MD,‡‡ Carlos Taxonera, MD, PhD,§§ Antonio Velasco-Guardado, MD, PhD,‖‖ Javier Martínez-González, MD,¶¶ and Javier P. Gisbert, MD, PhD‡on behalf of the USTEK Study Group*

Background: Ustekinumab is a fully human monoclonal antibody against IL-12/23. Ustekinumab induced clinical response and maintained higher rate of response than placebo in patients with Crohn's disease (CD). This study aims to assess the effectiveness and safety of ustekinumab in refractory patients with CD in real-life practice.

Methods: Consecutive patients with CD who were treated with subcutaneous ustekinumab between March 2010 and December 2014 were retrospectively included in a multicenter open-label study. Clinical response was defined by Harvey-Bradshaw index score and assessed after the loading doses, 6, 12 months, and last follow-up.

Results: One hundred sixteen patients were included, with a median follow-up of 10 months (interquartile range: 5–21). Clinical response after loading ustekinumab was achieved in 97/116 (84%) patients. The clinical benefit at 6, 12 months, and at the end of the follow-up was 76%, 64%, and 58%, respectively. Dose escalation was effective in 8 of 11 (73%) patients. Perianal disease also improved in 11 of 18 (61%) patients with active perianal fistulae. The initial response to ustekinumab and previous use of more than 2 immunosuppressant drugs were associated with a clinical response to ustekinumab maintenance therapy. In contrast, previous bowel resection predicted a long-term failure with ustekinumab. Adverse events were reported in 11 (9.5%) patients, but none required ustekinumab withdrawal.

Conclusions: Subcutaneous ustekinumab is effective and safe in a high proportion of patients with CD that were resistant to conventional immunosuppressant and antitumor necrosis factor drugs.

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Key Words: ustekinumab, IL-12, IL-23, Crohn's disease, inflammatory bowel disease, refractory

Crohn's disease (CD) is a chronic inflammatory disorder resulting in a progressive and irreversible damage to the intestines. In the last decade, monoclonal antibodies against tumor necrosis factor (anti-TNF) have been a breakthrough in the management of inflammatory bowel disease (IBD). It also changed the perception of the disease and introduced new therapeutic targets such as mucosal healing and deep remission.[1] However, one-third of patients are primary nonresponders to anti-TNF, and about 40% lose response during the therapy and require dose intensification or switch to other drugs.[2,3]

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From the *Servicio de Aparato Digestivo, Hospital Universitario Son Espases, Instituto de Investigación Sanitaria de Palma (IdISPa), Palma de Mallorca, Spain; †Servicio de Aparato Digestivo, Hospital Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain; ‡Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; §Servicio de Aparato Digestivo, Complejo Hospitalario de León, León, Spain; ‖Servicio de Aparato Digestivo, Hospital Universitario y Politécnico La Fe, CIBERehd, Valencia, Spain; ¶Servicio de Aparato Digestivo, Complejo Asistencial Universitario de Burgos, Burgos, Spain; **Servicio de Aparato Digestivo, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; ††Servicio de Aparato Digestivo, Hospital Universitario Puerta de Hierro, Madrid, Spain; ‡‡Servicio de Aparato Digestivo, Corporació Sanitària Universitària Parc Taulí, CIBERehd, Instituto de Salud Carlos III, Sabadell, Spain; §§Servicio de Aparato Digestivo, Hospital Clínico San Carlos, Instituto de Investigación del Hospital Clínico San Carlos (IdISSC), Madrid, Spain; ‖‖Servicio de Aparato Digestivo, Hospital Universitario de Salamanca, Salamanca, Spain; and ¶¶Servicio de Aparato Digestivo, Hospital Universitario Ramón y Cajal, Madrid, Spain.

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Reprints: Sam Khorrami, MD, Servicio de Aparato Digestivo Hospital Universitario Son Espases, Instituto de Investigación Sanitaria de Palma, Carretera de Valldemossa 79, Palma de Mallorca 07010, Spain (e-mail: sam.khorrami@ssib.es).

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Nevertheless, overall response in patients who receive a second or third anti-TNF is lower compared with naive patients.[4,5] Therefore, more drugs targeting different inflammatory pathways are clearly needed.

Interleukin (IL) 12 and IL-23 are pro-inflammatory cytokines implicated in the pathogenesis of CD. IL-12 stimulates the cellular immunity inducing the differentiation of $CD4^+$ T cells into T-helper (Th) 1 cells, whereas IL-23 induces the Th 17 pathway.[6,7] Moreover, genome-wide association studies have identified genes encoding IL-12/23 and IL-23 receptor as susceptibility loci for CD.[8]

Ustekinumab is a fully human IgG1 monoclonal antibody to the common p40 subunit of IL-12 and IL-23. Blocking the IL-12/IL-23 axis is proposed as a therapeutic target in several inflammatory disorders.[9,10] Treatment with ustekinumab has been mostly investigated for moderate-to-severe psoriasis and psoriatic arthritis.[11–13] The potential beneficial effect of ustekinumab for other autoimmune disease such as multiple sclerosis is less consistent and continues to be investigated.[14] In IBD, 2 phase II trials had shown that ustekinumab is more effective than placebo for induction and maintenance of clinical response in moderate-to-severe infliximab-refractory CD.[15,16] Currently, ustekinumab is approved for the treatment of psoriasis and psoriatic arthritis. In Europe, only subcutaneous vials are available. Although, ustekinumab has been proven in refractory CD for compassionate use in clinical practice, data are still very limited. The best induction regimen and maintenance schedule are also unclear. The aim of this study was to describe the real-life experience with ustekinumab in Spain, and assess the effectiveness and safety of this drug in a large multicenter open-label cohort of patients with refractory CD.

METHODS

Patients and Study Design

We included consecutive patients with CD that were treated with subcutaneous ustekinumab between March 2010 and December 2014 in 42 Spanish centers (see Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B284). The eligibility criteria included an established CD diagnosis, refractory, or intolerant to one or more anti-TNF drug and a follow-up with ustekinumab of at least 2 months from the start of treatment. A retrospective observational open-label study was conducted. The study protocol was approved by the Balearic ethics committee in March 2011 (IB 1554/11PI).

Demographic and clinical characteristics, including age, sex, weight, smoking habits, disease duration, age at onset, involvement, phenotype, perianal disease, previous and current medication, and intestinal resection history were collected. Investigators were also asked about the reason for ustekinumab administration, dosage, schedule of administration, intensification, and any adverse events during ustekinumab therapy.

Outcomes

The primary end point was the percentage of patients with a clinical benefit at the last visit. Secondary end points included: clinical benefit after loading dose (initial response, between 8–12 weeks), at 6 and 12 months, biological response defined by C-reactive protein (CRP) decrease, identification of factors that predict early and long-term clinical response with ustekinumab, percentage of patients with clinical improvement of perianal CD with ustekinumab, evaluation of psoriatic skin lesions and finally, the tolerance and safety of ustekinumab.

The clinical outcome was evaluated based on the Harvey-Bradshaw index score and defined as remission (Harvey-Bradshaw index score score ≤ 4), response (reduction of 3 points or more from the baseline), and failure (decrease <3 or increase >1 from 4 points regarding baseline). A clinical benefit was defined as a clinical improvement, including both remission and response. Clinical relapse after the initial response, surgery, and ustekinumab withdrawal due to adverse events were considered as failure. Drug intensification was defined as increasing dose or shortening of interval. Therapy intensification was not considered as a definitive failure if patients recovered their clinical benefit before worsening. Perianal CD was evaluated based on the physician judgment and defined as improvement or not. An adverse event was defined as any significant event attributable to ustekinumab during the therapy. A severe adverse event was defined as any adverse event resulting in hospitalization, disability, or death.

Statistical Analysis

Percentages with 95% CI were used to describe categorical variables. Continuous variables were estimated by means with SDs or medians with interquartile range (IQR) depending on distribution. We used Chi Square test to compare proportions and T-test for mean, whereas the Wilcoxon test was used for nonparametric continuous variables. Kaplan–Meier curve was plotted for cumulative failure-free survival. In addition, a multiple logistic regression analysis by Cox's regression model was performed. The response to ustekinumab therapy was the dependent variable, whereas the independent variables were sex, smoking, disease duration, history of bowel resection, previous medication, concomitant therapy, CRP level at baseline, and initial response. We used a backward modeling strategy, and the statistic for model comparison was the log-likelihood ratio. We considered variables with a P value of <0.1 for the multivariate testing. A P value of <0.05 was considered significant.

RESULTS

We included one hundred sixteen patients with CD treated with ustekinumab in the study. Patients were followed up for a median of 10 (IQR: 5–21) months. The clinical and demographic characteristics are summarized in Table 1. Most patients had ileocolonic involvement (51%), nonstenosing nonpenetrating behavior (56%), and long standing disease (mean 10 years, IQR 6–17). Fifty-six (48%) patients had, at least, one previous

TABLE 1. Clinical and Demographic Characteristics of the Patients Treated with Ustekinumab

Sex, female, n (%)	73 (62.9)
Age, yrs, median (IQR)	37 (28–48)
Smokers, n (%)	33 (28.4)
Weight, kg, median (IQR)	65 (53–74)
Duration, yrs, median (IQR)	10 (6–17)
Age at onset, n (%)	
A1 (<17)	24 (20.7)
A2 (17–40)	80 (69)
A3 (>40)	12 (10.3)
Location, n (%)	
L1 (ileal)	22 (19)
L2 (colon)	21 (18.1)
L3 (ileocolonic)	59 (50.9)
L1-3 + L4 (upper GI)	14 (12)
Phenotype, n (%)	
B1 (inflammatory)	65 (56)
B2 (stricturing)	27 (23.3)
B3 (penetrating)	24 (20.7)
Perianal disease, n (%)	58 (50)
History of resective surgery, n (%)	56 (48.3)
Previous IMS treatment, n (%)	
Thiopurines	111 (95.7)
Methotrexate	69 (59.5)
Tacrolimus	10 (8.6)
Mycophenolate mofetil	5 (4.3)
2 or more IMS	73 (62.9)
Previous anti-TNF treatment, n (%)	
Infliximab	105 (90.5)
Adalimumab	108 (93.1)
Certolizumab	28 (24.1)
1 anti-TNF	116 (100)
2 or more anti-TNF	101 (87.1)
Reason for anti-TNF discontinuation, n (%)	
Primary nonresponse	48 (41.4)
Lose of response	116 (100)
Unacceptable side effects	74 (63.8)
Concomitant medications, n (%)	
Systemic steroids	37 (31.9)
IMS	42 (36.2)
Baseline HBI, median (IQR)	9 (6–12)
Baseline CRP >5 mg/L, n (%)	74/88 (85)

HBI, Harvey-Bradshaw index score; IMS, immunosuppressive drugs; n, number of patients.

intestinal resection. All the patients had failed with at least 1 immunomodulator and 1 anti-TNF. One hundred one (87%) patients had failed with at least 2 anti-TNF drugs. Baseline CRP was available in 88 patients of which 74 (84%) had elevated levels. Figure 1 shows the distribution of patients included in the study.

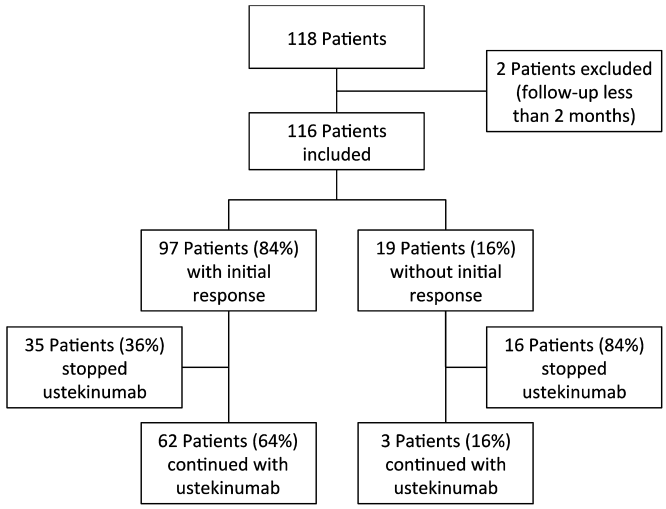

FIGURE 1. Flowchart of the patients included in the study.

Dosage and Therapeutic Schedules

Different induction regimens and maintenance schedule of treatment with ustekinumab was used in Spanish centers (see Table 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B284). The most frequent induction regimen was 90 mg of ustekinumab at weeks 0, 1, 2, and 3 (47%). We categorized patients into 3 subgroups according to the cumulative ustekinumab dose administrated during the induction phase: 30 (26%) patients received 90 mg or lower, 30 (26%) patients were treated with doses between 135 and 270 mg, and finally 56 (48%) patients received 360 mg or higher. One hundred (86%) patients received ustekinumab for maintenance during the follow-up. The most prevalent maintenance regimen was 90 mg every 8 weeks (75%).

Clinical Response

Ninety-seven of 116 (83.6%; 95% CI: 76.0–90.3) patients presented a clinical benefit after ustekinumab loading dose (Fig. 2A). Clinical remission was achieved in 33 patients (28.4%, 95% IC: 20.2–36.6) at this timepoint. After 6 and 12 months, ustekinumab had a clinical benefit in 81 of 106 (76.4%, 95% CI: 68.3–84.5) and 56 of 88 (63.6%, 95% CI: 53.5–73.7) patients. Overall, 67 of 116 patients (57.8%, 95% CI: 48.8–66.8) maintained a clinical benefit at the end of follow-up (Fig. 2B). More than half of them (43 patients) were in clinical remission at the last follow-up visit. Steroids were discontinued in 13 of 37 (35.1%) patients receiving them at the time of ustekinumab introduction.

The failure-free survival curve for treatment in patients with initial response with ustekinumab is shown in Figure 3. The cumulative probability for maintained clinical benefit at 6 and 12 months was 86% (95% CI: 83.1–88.9) and 74% (95% CI: 70.3–77.7), respectively. Ustekinumab was stopped in 35/97 (36%) primary-responder patients during the follow-up. The main reason for treatment withdrawal was the loss of clinical response, which occurred in 29 of 97 (29.9%) patients. In addition, 2 patients decided to discontinue therapy (one patient due to

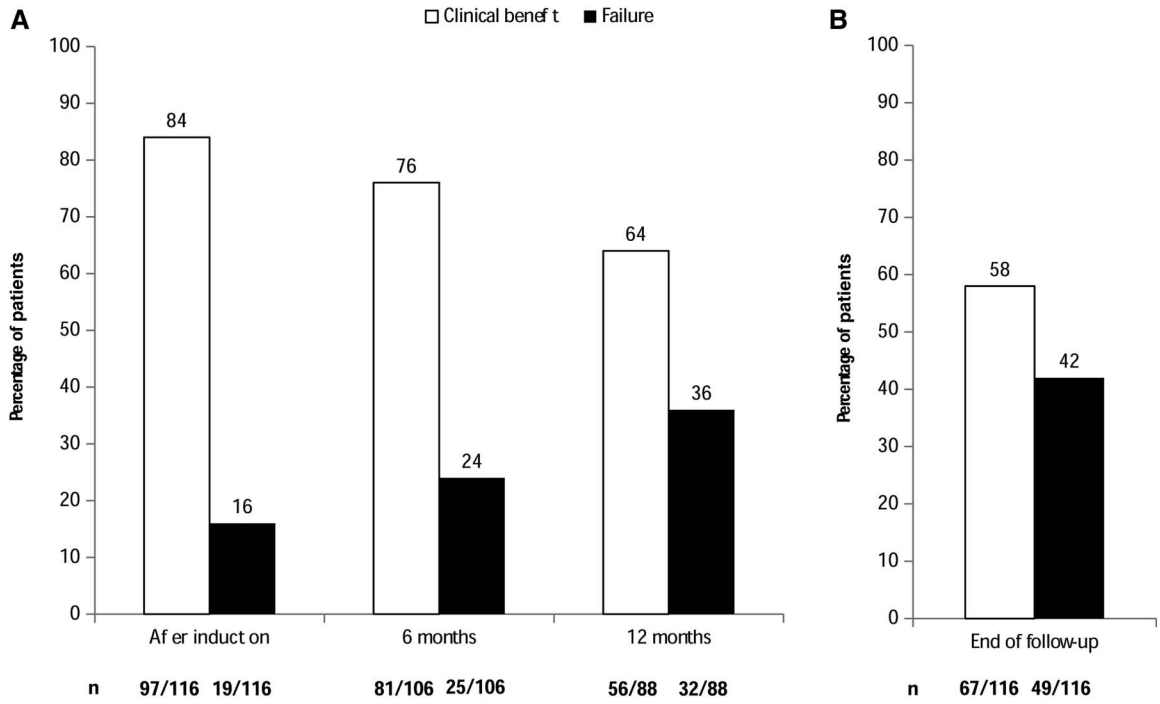

FIGURE 2. Response rates of patients treated with ustekinumab at evaluating time-points. A, Proportion of clinical benefit (white box) and failure (black box) after loading dose, at 6 and 12 months. B, Proportion of clinical benefit and failure at the end of the follow-up. Absolute number of patients is indicated at the bottom.

maintained clinical remission and another to pregnancy), and 2 more cases after new onset perianal disease.

Therapy intensification was required in 11 primary responders and resulted in clinical improvement in 8 (73%) of them. Interval reduction was the chosen strategy in all cases: 90 mg every 8 weeks to every 4 weeks for 8 patients, 90 mg every 8 weeks to every 6 weeks in 1 patient, 45 mg every 8 weeks to every 6 weeks in 1 patient, and 45 mg every 12 weeks to every 8 weeks for 1 patient. After ustekinumab withdrawal, 12 (41.4%) patients underwent surgery, 1 patient was changed to vedolizumab and 2 patients were proposed for hematopoietic stem cell transplantation.

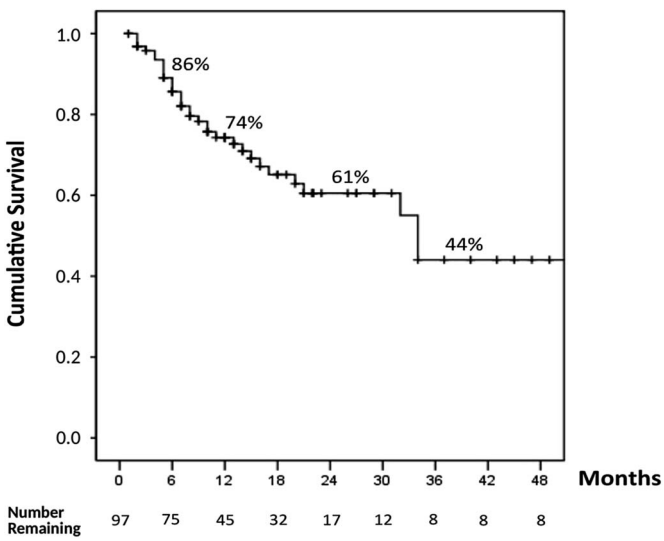

FIGURE 3. Kaplan–Meier curve showing the failure-free survival of ustekinumab therapy during the follow-up in primary responders to ustekinumab. The percentages correspond to 6, 12, 24, and 36 months of follow-up.

Among the 19 patients with no clinical benefit after ustekinumab loading, 16 (84%) discontinued therapy: 8 required surgery, 1 began vedolizumab, 1 was evaluated for hematopoietic stem cell transplantation, and the rest received steroids or immunosuppressant drugs. One of 3 noninitial responders, who continued with ustekinumab 90 mg every 8 weeks, achieved clinical response at 5 months and avoided surgery.

Elevated CRP levels (>5 mg/L) at baseline were observed in 74/88 (85%) patients. CRP levels decreased from baseline (median 23 mg/L; IQR 33) to last follow-up visit (median 6 mg/L; IQR 23) in primary responders ($P = 0.001$) (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/IBD/B285). Endoscopic data during the follow-up was only available in 13 patients. We observed an endoscopic response in 9 patients, 4 of whom presented mucosal healing besides achieving clinical remission (deep remission).

Perianal Disease

Fifty-eight (50%) patients with CD had a history of perianal disease. Eighteen of them suffered from active perianal disease when ustekinumab therapy was started. Eleven (61%) patients

presented clinical improvement of perianal fistulae. New perianal abscesses were reported in 2 cases during the treatment with ustekimunab.

Psoriasis

Twelve patients had concomitant active psoriasis. Five patients presented severe paradoxical psoriasis induced by anti-TNF beside the CD symptoms. All of them showed a marked improvement of skin lesions with ustekinumab.

Predictors of clinical Benefit

No factors, including sex, weight, disease duration, Montreal classification, perianal disease, bowel resection, previous immunosuppressive drugs or anti-TNF, concomitant medication, baseline CRP level, and cumulative loading dose predicted the initial clinical response with ustekinumab (Table 2). The percentages of initial clinical benefit in high (equal or more than 360 mg of ustekinumab) and low (less than 360 mg) loading dose groups were 86% (48 of 56 patients) and 82% (49 of 60 patients), respectively ($P = 0.56$).

The independent predictive factors of long-term clinical benefit with ustekinumab are shown in Table 3. The initial response to ustekinumab and history of 2 or more different immunosuppressive drugs were associated with clinical benefit at the end of follow-up. By contrast, history of previous intestinal resection was associated with long-term failure to ustekinumab. More details are shown in Tables 3 and 4 (Supplemental Digital Content 1, http://links.lww.com/IBD/B284).

TABLE 2. Univariate Analysis of Predictive Factors Associated with Initial Clinical Benefit with Ustekinumab

Predictor Factor	Univariate Odds Ratio (95% CI)	*P*
Female sex	0.78 (0.28–2.11)	0.62
Age	1.01 (0.97–1.04)	0.77
Smokers	1.59 (0.57–4.48)	0.38
Disease duration	1.05 (0.99–1.12)	0.11
Perianal disease	1.98 (0.72–5.46)	0.18
Intestinal resection	2.06 (0.75–5.69)	0.16
Previous ≥2 IMS	1.01 (0.36–2.8)	0.98
Previous ≥2 anti-TNF	0.69 (0.17–2.75)	0.7
Concomitant steroids	1.3 (0.47–3.64)	0.61
Concomitant IMS	0.58 (0.19–1.74)	0.33
Baseline CRP >5 mg/L	2.7 (0.32–22.61)	0.69
Cumulative loading dose, mg		
≤90	1	—
135–270	0.31 (0.07–1.29)	0.11
≥360	0.46 (0.15–1.38)	0.16

No independent factors have been associated to the initial clinical benefit in multivariate analysis.
IMS, immunosuppressive drugs; n, number of patients.

Adverse Events

Fourteen adverse events were reported in 11 (9.5%; 95% CI: 4.2–14.8) patients treated with ustekinumab (Table 4). All were mild and none required ustekinumab withdrawal. Three (2.6%) infectious events were observed: 1 case of pharyngitis, 1 case of otitis, and 1 epididymal-orchitis. No tuberculosis infection, anaphylactic reactions, malignancy, or death was reported.

DISCUSSION

Despite the many advances in the understanding of the IBD pathogenesis, the therapeutic arsenal currently available for the treatment of CD is limited. A significant proportion of patients do not respond, or lose their initial response, or suffer serious adverse events with immunosuppressant and anti-TNF agents, resulting in the emerging multidrug refractory condition. Most of these patients are forced to repeat cycles of steroids or extensive bowel resection with devastating consequences. The promising results of trials with ustekinumab and its availability on the health market have made it possible to access under compassionate use in selected cases.

This extensive real-life study contributes to support the efficacy of ustekinumab in patients with CD who have failed with other medical therapies. Our study included long standing and highly refractory patients with CD. Almost 90% of them had failed or were intolerant to 2 or more anti-TNFs. In this unfortunate scenario, more than 80% of patients achieved initial clinical benefit with a maintained clinical response in about 60% of them. We also observed a significant improvement in inflammatory markers among responders to ustekinumab. In addition, approximately two-thirds of patients who achieved a clinical benefit were on clinical remission. Dose escalation was also an effective strategy when loss of response occurred.

Both subcutaneous and intravenous ustekinumab (90 mg every week during 4 weeks and a unique 4.5 mg/kg dose, respectively) were better than placebo for inducing clinical response at weeks 6 (53% versus 30%, $P = 0.019$) in a phase 2 double blind, placebo-controlled, parallel, crossover trial in patients with moderate-to-severe CD.[15] However, the primary study end point defined as a reduction of 25% or more than 70 points from baseline CDAI score at 8 weeks was not achieved (49% versus 40%, $P = 0.34$), probably due to the high placebo-response rate. Among the subgroup of patients previously treated with infliximab, the response rate to ustekinumab at 8 weeks was significantly greater than to placebo (59% versus 26%, $P = 0.02$). Treatment with ustekinumab also reduced CRP levels at week 8 as compared with baseline, especially in infliximab-experienced patients, in comparison with placebo.[17] In the CERTIFI study that includes patients with moderate-to-severe CD refractory to TNF antagonists, 6 mg/kg of ustekinumab intravenously induced clinical response at 6 weeks in 39.7% of patients in comparison to 23.5% for the placebo group ($P = 0.005$).[16] Responders were then randomized for maintenance phase with 90 mg or placebo at weeks 8 and 16. The response rate of sustained clinical response

TABLE 3. Univariate and Multivariate Analysis of Predictive Factors Associated with Long-term Clinical Benefit with Ustekinumab

Predictor Factor	Univariate Odds Ratio (95% CI)	*P*	Multivariate Hazard Ratio (95% CI)	*P*
Female sex	1.13 (0.52–2.43)	0.76	—	
Age	0.99 (0.97–1.02)	0.73	—	
Smokers	2.53 (1.11–5.76)	0.03	1.3 (0.7–2.4)	0.4
Disease duration	0.99 (0.94–1.04)	0.67	—	
Perianal disease	1.77 (0.84–3.74)	0.13	—	
Previous intestinal resection	3.14 (1.45–6.77)	0.003	2.09 (1.16–3.79)	0.02
Previous ≥2 IMS	0.39 (0.18–0.84)	0.015	0.5 (0.28–0.88)	0.02
Previous ≥2 anti-TNF	0.68 (0.22–2.1)	0.5	—	
Concomitant steroids	0.81 (0.36–1.79)	0.6	—	
Concomitant IMS	0.59 (0.27–1.29)	0.18	—	
Baseline CRP >5 mg/L	0.81 (0.24–2.74)	0.73	—	
Initial responders	0.36 (0.26–0.49)	0.001	0.16 (0.09–0.31)	0.001
Intensification	0.5 (0.13–1.99)	0.36	—	
Adverse events	1.26 (0.35–4.58)	1	—	

IMS, immunosuppressive drugs; n, number of patients.

to ustekinumab at week 22 was higher than in the placebo group (69.4% versus 42.5%, $P = 0.001$).

Recently, early data from phase 3 UNITI-1 trial in moderate-to-severely active CD who previously failed or were intolerant to at least 1 TNF antagonist have been presented.[18] Both intravenous ustekinumab doses (≈6 mg/kg and 130 mg) induced higher rates of clinical response at week 6 (33.7% and 34.3%, respectively) than placebo (21.5%) ($P = 0.003$ and $P = 0.002$, respectively). At week 8, 20.9% and 15.9% of patients in ≈6 mg/kg and 130 mg ustekinumab groups were in remission versus 7.3% of placebo ($P < 0.001$ and $P = 0.003$, respectively).

Subcutaneous ustekinumab has been evaluated in 2 retrospective cohort studies in anti-TNF resistant patients with CD.

TABLE 4. Adverse Events During Therapy with Ustekinumab

Total with any adverse event, n (%)	11 (9.5)
Headache	2 (1.7)
Nausea	2 (1.7)
Pruritus	1 (0.8)
Arthralgia	1 (0.8)
CD event	2 (1.7)
Infections	3 (2.6)
Pharyngitis	1 (0.8)
Otitis	1 (0.8)
Epididymo-orchitis	1 (0.8)

n, number of patients.

Kopylov et al[19] reported an initial clinical response in 74% of the patients, among whom 71% maintained response at the last follow-up. Recently, Wils et al[20] from GETAID published a large study with a similar design, in 122 patients followed-up during 10 months. Authors observed a clinical benefit within 3 months in 65% of the patients receiving ustekinumab.

Ustekinumab has not been previously evaluated in perianal CD. We observed a clinical improvement in most of the patients with active perianal fistulas. However, these promising findings should be considered with caution because of the small number of patients assessed.

It is well established that IL-12 and IL-23 axis play a key role in the pathogenesis of CD and psoriasis.[21] Anti-TNF antibodies may cause paradoxical psoriasiform skin lesions characterized by Th17 and Th1 cell infiltrates.[22–24] The efficacy of ustekinumab in the treatment of psoriasis has been strongly demonstrated. Tillack et al[23] reported that ustekinumab is highly effective in anti-TNF–induced psoriasis in patients with IBD. However, some paradoxical psoriasis cases associated with ustekinumab have been reported in the literature.[25] All patients with CD with paradoxical psoriasis included in this study improved their skin lesions.

No factors were identified for predicting the initial clinical benefit after ustekinumab loading dose in this study. Unfortunately, our study was not powered enough to explore the influence of loading dose, induction regimens, or administration schedule. However, we identified several clinical factors that predicted clinical long-term response to ustekinumab. As expected, the initial response to ustekinumab was associated with a long-term maintained clinical benefit. This finding is in accordance with data

from the CERTIFI study where nonresponders to ustekinumab as induction therapy had a similar rate of clinical response at week 22 to patients who received placebo beside the maintenance therapy with 90 mg of ustekinumab.[17] Previous exposure to 2 or more immunosuppressant drugs was also associated with better long-term results with ustekinumab. Unlike the French study, we observed no clear benefit for concomitant immunosuppressant therapy on the clinical outcome. Smoking has been associated with a worse clinical response to biological drugs and an increased risk of perianal disease and surgery.[26] We found a similar trend for current smoking in ustekinumab therapy, but the effect was diluted after adjustment for surgery history. It is well known that recurrence is more frequent in smokers, who present more risk for severe and refractory disease.[27] Finally, history of intestinal resection was associated with a higher risk for ustekinumab failure. Operated patients might suffer a more aggressive disease with an increased risk of being refractory to medical treatment.[28] However, this point should be carefully considered because surgically related symptoms might be confused with inflammation, overestimating the clinical failure in our cohort.

Subcutaneous ustekinumab has an excellent safety profile. Only a few adverse events (including 3 mild infections) were reported. No deaths, cancers, cardiovascular events, or serious opportunistic infections were observed. The retrospective design of this study may lead to an underestimation of the mild adverse effects. There were no differences between the ustekinumab and placebo groups in the incidence of infections or serious infections in the PHOENIX 1 and PHOENIX 2 trials.[11,12] In the recently published PSOLAR registry, the incidence of serious infections for infliximab (2.91/100 patient-year) were higher compared with ustekinumab (0.93/100 patient-year).[29] In the CD population, the incidence of serious adverse events was similar for the treatment and placebo groups in both phase II trials.[15,17] The authors suggested a need for larger and longer studies to assess the long-term safety. Therefore, ustekinumab may be especially attractive for patients with a high risk of complications associated with the use of immunosuppressants and anti-TNF drugs.

Our study has several limitations. The most important is the retrospective design. We used a validated clinical score for the primary endpoint, routinely used in clinical practice. Unfortunately, fecal calprotectin and endoscopic data were not available in most of the cases, and therefore not analyzed. Ustekinumab doses and regimens were extrapolated from phase 2 trials and experience in psoriasis, and varied widely between medical centers. However, the bioavailability of subcutaneous administration might be lower than intravenous. In attempt to reduce this heterogeneity, patients were stratified into high-loading (360 mg or higher) and low-loading dose with ustekinumab. High-loading dose approximated the most efficient dose administrated in CERTIFI and UNITI trials for induction of response. However, our study was not powerful enough to detect any differences between the groups. Data from UNITI-1, UNITI-2, and IM-UNITI trials are expected to provide the optimal dosing for induction and maintenance therapy in CD.

In conclusion, ustekinumab was effective and safe as a rescue therapy in a high proportion of multidrug refractory patients with CD.

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The USTEK Study Group (in order of cases collected): Mariana Fé García-Sepulcre, Hospital General Universitario de Elche, Elche; Lucía Márquez, Hospital del Mar, IMIM, Barcelona; Isabel Ferrer, Hospital de Manises, Valencia; José Luis Cabriada, Hospital de Galdakao, Galdakao; Joan Gelabert, Hospital Mateo Orfila, Menorca; David Busquets, Hospital Universitari Dr. Josep Trueta, Girona; Noemí Manceñido, Hospital Infanta Sofía, Madrid; Nieves Martínez, Hospital de Albacete, Albacete; Juan Ramón Pineda, Complejo Hospitalario Universitario de Vigo, Instituto de Investigación Biomédica Ourense-Pontevedra-Vigo, Vigo; Juan María Vázquez, Hospital Juan Ramón Jiménez, Huelva; Ángel Ponferrada, Hospital Universitario Infanta Leonor. Madrid; Montserrat Rivero, Hospital Universitario Marqués Valdecilla, Santander; Jesús Barrio, Hospital Universitario Río Hortega, Valladolid; Guillermo Alcaín, Hospital Virgen de Victoria, Málaga; Santiago García, Hospital Universitario Miguel Servet, Zaragoza; Joan Riera, Hospital Son Llàtzer, Palma de Mallorca; Francesc Casellas, Hospital Universitari Vall D'Hebrón, CIBERehd, Barcelona; Daniel Hervias, Hospital Virgen de Altagracia, Manzanares; Andreu Sansó, Hospital de Manacor,

Manacor, Esther García-Planella, Hospital Sant Pau, Barcelona; Raquel García-Castellanos, Fundación Jiménez Díaz, Madrid; Pilar Canelles, Hospital General de Valencia, Valencia; Olga Merino, Hospital Universitario Cruces, Bilbao; Manuel Van-Domselaar, Hospital de Torrejón, Torrejón; Marta Carrillo, Hospital Universitario de Canarias, Tenerife; Manuel Barreiro-de Acosta, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela; María Teresa Diz-Lois, Complejo Hospitalario Universitario A Coruña, Coruña; Ana Isabel Muñagorri, Hospital de Donostia, San Sebastián; Fernando Gomollón, Hospital Clínico Universitario Lozano Blesa, IIS Aragón, CIBERehd, Zaragoza; Jordi Guardiola, Hospital Universitari de Bellvitge, IDIBELL, Barcelona.

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