Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti–Tumor Necrosis Factor Agents

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BACKGROUND & AIMS: **Ustekinumab, a human monoclonal antibody against the p40 subunit of interleukins-12 and -23, is effective in inducing and maintaining remission in patients with luminal Crohn's disease (CD). We assessed the efficacy and safety of subcutaneous ustekinumab in patients with anti–tumor necrosis factor (anti-TNF) refractory CD.**

METHODS: **We performed a retrospective observational study, collecting data from the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif on 122 consecutive patients with active CD refractory to anti-TNF therapy who received at least 1 subcutaneous injection of ustekinumab from March 2011 to December 2014, in 20 tertiary centers in Europe. Subjects were followed for at least 3 months. The primary outcome was clinical benefit, defined as reductions in symptoms and biochemical markers of CD and complete weaning from steroids, without surgery or immunosuppressant therapies.**

RESULTS: **Seventy-nine patients (65%) had a clinical benefit within 3 months of receiving ustekinumab. Concomitant immunosuppressant therapy at study inclusion increased the odds for a clinical benefit from ustekinumab (odds ratio, 5.43; 95% confidence interval, 1.14–25.77; $P = .03$). Over a median follow-up period of 9.8 months (interquartile range, 5.3–14.5 months), the cumulative probabilities that patients maintained the clinical benefit for 6 and 12 months after introduction of ustekinumab were 93% and 68%, respectively.**

Abbreviations used in this paper: CD, Crohn's disease; CRP, C-reactive protein; IQR, interquartile range; TNF, tumor necrosis factor

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CONCLUSIONS: **Almost two-thirds of patients with CD refractory to at least 1 anti-TNF agent receive clinical benefit from ustekinumab therapy, not requiring steroids for up to 12 months afterward. While awaiting results from ongoing trials, ustekinumab can be considered for use in these patients.**

Keywords: IL12; IL23; Inflammatory Bowel Disease; Immunosuppressant.

Crohn's disease (CD) is a chronic inflammatory bowel disorder that alternates between periods of disease activity and clinical remission. Conventional immunosuppressants (thiopurines[1] and methotrexate[2]) and tumor necrosis factor (TNF) antagonists (infliximab and adalimumab[3,4]) are the main therapeutic agents to obtain long-term clinical remission and prevent irreversible intestinal damage and disability.[5,6] Although anti-TNF therapies have been shown to be effective in the medical management of patients with CD, a persistent response is not obtained in certain patients. Controlled trials have shown that a primary response is not achieved in approximately 20%–40% of patients with infliximab and adalimumab, and that up to 40% of patients who initially respond to the anti-TNF induction regimen subsequently lose response over time.[7–9] Moreover, several anti-TNF side effects, such as drug reactions, infections, or paradoxical manifestations, can also lead to treatment discontinuation.[10,11] Therefore, the number of patients with CD who are refractory to anti-TNF therapies and conventional immunosuppressants is increasing.

New drug options with alternative modes of action are now expected in this population. Recently, the anti-integrin agent vedolizumab was shown to be effective for CD following anti-TNF failure.[12] Ustekinumab, a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23 that targets both the T-helper 1 and T-helper 17 pathways involved in the pathogenesis of CD, has also been explored. In a phase II study including 526 patients with CD refractory to anti-TNF, ustekinumab has shown to be more effective than placebo for inducing and maintaining a clinical response.[13] It is important to note that in this trial patients were randomly assigned to receive intravenous ustekinumab induction followed by subcutaneous maintenance. In France, subcutaneous ustekinumab has only been licensed to treat refractory psoriasis. Since 2011, subcutaneous ustekinumab is also occasionally used for patients with CD who are refractory to conventional immunosuppressants and anti-TNF. The aim of the present study was to assess the benefit and safety of subcutaneous ustekinumab in a multicenter cohort of patients with refractory anti-TNF CD.

Methods

Selection of Patients

A retrospective observational study was performed in tertiary French and Swiss centers affiliated with the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). All consecutive patients with active CD who received at least 1 subcutaneous injection of ustekinumab from March 2011 to December 2014, and with a follow-up of at least 3 months, were included in the study. Patients who received ustekinumab in a controlled trial were excluded from the analysis. The protocol was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS N°15.177). All authors had access to the study data and reviewed and approved the final manuscript.

Data Collection

The date of inclusion corresponded to the first administration of ustekinumab. Patient files were retrospectively reviewed and demographic, biologic, and endoscopic data were obtained from the medical records.

The following characteristics were anonymously recorded for each included patient: age at inclusion, gender, duration of disease, location and phenotype of CD according to the Montreal classification,[14] smoking status, number of previous intestinal resections, prior exposure to CD treatment including conventional immunosuppressants (thiopurines, methotrexate) and anti-TNF (infliximab, adalimumab, certolizumab pegol, or golimumab), type of response (nonprimary response, secondary loss of response, intolerance), occurrence of paradoxical skin lesions during anti-TNF, main indication for beginning ustekinumab (luminal or perianal CD), induction and maintenance doses, duration of ustekinumab treatment, association with immunosuppressants or steroids at inclusion, C-reactive protein (CRP) levels (elevated if >5 mg/L), and endoscopic findings at inclusion and during follow-up.

Outcomes

The primary objective was to assess percentage of patients with a clinical benefit from ustekinumab after 3 months. A clinical benefit was defined as a significant improvement in CD-related clinical symptoms and laboratory tests assessed by the patient's physician leading to continued ustekinumab treatment, associated with complete weaning from steroids if they were being taken at inclusion, without surgery, or immunosuppressant introduction.

Secondary outcomes were (1) biologic and endoscopic response (defined as a significant reduction in the

number of visible ulcerations) and mucosal healing (defined as a lack of any visible ulcerations or friable mucosa), (2) the identification of predictive factors of a ustekinumab-induced clinical benefit at 3 months, (3) rates of sustained clinical benefit (without surgery, steroids, or immunosuppressant introduction) at 6 and 12 months in ustekinumab initial responders, (4) evolution of patients without a clinical benefit from ustekinumab at 3 months, (5) evolution of anti-TNF-induced paradoxical skin lesions, and (6) the safety of ustekinumab. The rate of ustekinumab optimization was also recorded, but was not considered to be a loss of clinical benefit.

To determine safety, all adverse events, defined as any significant event that occurred from the date of inclusion to the last follow-up, were recorded. Severe adverse events were defined as any adverse event that resulted in hospitalization or extension of the hospital stay, was fatal or life threatening, or led to a significant disability.

Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics. Medians with interquartile ranges (IQR) or means with standard deviations were calculated for continuous data, and percentages were computed for discrete data. The Kaplan-Meier method was used to assess a sustained clinical benefit from ustekinumab over time. Univariate and multivariate logistic regression were performed to identify predictive factors of a clinical benefit to ustekinumab at 3 months, expressed as odds ratios with 95% confidence intervals. Three subgroups of patients according to the cumulative ustekinumab dose administered during the first 2 months (<90 mg, between 135 and 180 mg, and >225 mg) were created and incorporated in the logistic regression. Variables with $P < .10$ were used for multivariate analysis. $P = .05$ was considered to be significant.

Results

Patient Characteristics

From March 2011 to December 2014, a total of 135 patients with CD with active disease received at least 1 subcutaneous ustekinumab injection in 20 GETAID centers in France and Switzerland. Thirteen patients without a follow-up of at least 3 months were excluded and 122 patients were included (Figure 1*A*).

The baseline demographic and clinical characteristics are presented in Table 1. Eighty-seven (71%) patients were women, the median age at inclusion was 33.8 years old (IQR, 27.5–43.9), and the median duration from CD diagnosis to inclusion was 11.5 years (IQR, 6.9–17.1). Seventy-five (62%) patients had undergone prior intestinal resection. One hundred nineteen (98%) patients had experienced failure or intolerance to thiopurines or

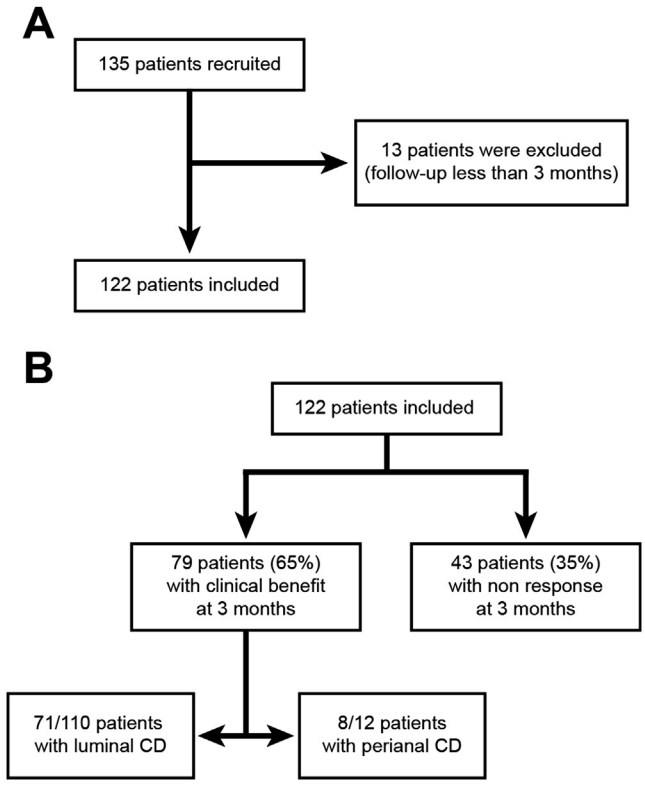

Figure 1. Flowchart of patients in the study. (*A*) Disposition of all included patients receiving subcutaneous ustekinumab. (*B*) Disposition of all included patients with a clinical response assessment to ustekinumab at 3 months.

methotrexate and at least 1 anti-TNF agent (infliximab or adalimumab) had failed in 122 (100%) patients, including 112 (92%) who had received both infliximab and adalimumab, 45 (37%) who had received 3 anti-TNF agents (42 exposed to infliximab, adalimumab, and certolizumab; and 3 to infliximab, adalimumab, and golimumab), and 2 (2%) who had received 4 anti-TNF agents.

Ustekinumab was given to 110 (90%) patients for luminal CD and to 12 (10%) for perianal disease. At inclusion 72 of 104 (69%) patients had elevated CRP levels and active endoscopic lesions were observed in all 78 patients who were assessed at inclusion, including 77 with ulcerations associated with an inflammatory passable stricture in 17 cases and a nonpassable stricture in 1 case.

Thirteen different ustekinumab induction regimens were used in the 122 patients evaluated in the study (summarized in Supplementary Table 1). The most common regimen was 90 mg at Weeks 0 and 4 (47% of patients). The mean cumulative dose of ustekinumab administered during the first month was 149 ± 64 mg. When analyzing the 122 patients into subgroups according to the cumulative ustekinumab dose received during the first 2 months, 39 (32%) patients received a dose lower than 90 mg, 74 (61%) patients received a dose comprised between 135 and 180 mg, and 9 (7%) patients received a dose higher than 225 mg. At

Table 1. Demographic and Clinical Characteristics

	N = 122
Female, n (%)	87 (71)
Median age (IQR) at time of ustekinumab introduction (*y*)	33.8 (27.5–43.9)
Median disease duration (IQR) at time of ustekinumab introduction (*y*)	11.5 (6.9–17.1)
CD location (Montreal classification), n (%)	
L1	15 (12)
L2	19 (16)
L3	87 (71)
L4	16 (13)
Perianal	71 (58)
CD phenotype (Montreal classification), n (%)	
Inflammatory	61 (50)
Stricturing	27 (22)
Penetrating	34 (28)
Smoker status, n (%)	
No smoker	65 (53)
Former smoker	16 (13)
Current Smoker	41 (34)
Previous intestinal resections, n (%)	75 (62)
Previous immunosuppressant, n (%)	119 (98)
Thiopurines	113 (93)
Methotrexate	78 (64)
Previous anti-TNF, n (%)	122 (100)
Infliximab	118 (97)
Adalimumab	111 (91)
Certolizumab pegol	44 (36)
Other previous medications, n (%)	
Ciclosporin	5 (4)
Thalidomide	6 (5)
Mycophenolate mofetil	2 (2)
Cyclophosphamide	3 (3)
Sirolimus	2 (2)
Tacrolimus	5 (4)
Golimumab	5 (4)
Reason of ustekinumab introduction, n (%)	
Luminal disease	110 (90)
Perianal disease	12 (10)
Concomitant immunosuppressant, n (%)	18 (15)
Thiopurines	11
Methotrexate	7
Concomitant steroids, n (%)	19 (16)
CRP level at the initiation, n = 104 (%)	
CRP <5 mg/L	32 (31)
CRP >5 mg/L	72 (69)

inclusion, 18 (15%) patients received concomitant immunosuppressant (11 thiopurines and 7 methotrexate) and 19 (16%) steroids. Among the 122 patients included, 115 received at least 2 injections of ustekinumab; 7 different regimens were administered during the maintenance phase (summarized in Supplementary Table 1). The most common protocol was 90 mg every 8 weeks in 56 of 115 (49%) of the patients.

Efficacy of Ustekinumab

Clinical benefit at 3 months. After 3 months ustekinumab resulted in a clinical benefit in 79 of 122 (65%) patients (Figure 1*B*). A clinical benefit was obtained in 71 of 110 (65%) patients treated for luminal CD and in 8 of 12 (67%) patients treated for perianal disease. Among the 19 patients who received concomitant steroids when starting ustekinumab, a clinical benefit at 3 months was obtained in 11 of 19 (58%) patients with a steroid discontinuation in 7 (37%) patients and a dose reduction in 4 (21%) patients (Supplementary Figure 1).

Biologic and endoscopic response to ustekinumab. A total of 58 patients with a clinical benefit from ustekinumab at 3-month follow-up had elevated CRP at inclusion and a second CRP levels measurement at 3-month follow-up; CRP levels decreased in 55 of 58 (95%) of these patients, including 24 of 58 (41%) with CRP normalization (<5 mg/L) (Figure 2*A*). The median decrease in CRP levels was 18 mg/L (IQR, 8–32 mg/L).

An endoscopic evaluation was available in 22 patients at inclusion and at the 3-month follow-up. An endoscopic response was observed in 17 of 22 (77%) patients, and a mucosal healing in 2 of 22 (9%) (Figure 2*B*). Clinical characteristics of the 22 patients with repeat endoscopic evaluation are summarized in the Supplementary Table 2.

Predictive factors of clinical benefit at 3 months. The independent predictive factors of benefit from ustekinumab at the 3-month follow-up on univariate and multivariate analysis are shown in Table 2. In multivariate analysis, concomitant immunosuppressant at inclusion was the only predictive factor of a clinical benefit to ustekinumab at 3 months (odds ratio, 5.43; 95% confidence interval, 1.14–25.77; $P = .03$). No difference was observed in patients receiving thiopurines or methotrexate.

Clinical benefit at 6 and 12 months in initial responders to ustekinumab. The median follow-up in the 79 patients with clinical benefit at 3 months was 9.8 months (IQR, 5.3–14.5 months). Among them, the cumulative probability of a persistent clinical benefit (without surgery, steroids, or immunosuppressant introduction) at 6 and 12 months by the Kaplan-Meier was 93% and 68%, respectively (Figure 3). Eighteen (23%) of the patients with a 3-month response experienced secondary ustekinumab failure during the maintenance phase leading to surgical resection (9 patients), immunosuppressant, and/or readministration of steroids (9 patients).

Six (8%) of the 79 patients with a clinical benefit at 3 months required optimization of ustekinumab. The optimization was performed by doubling the dose in 1 patient who was initially started on 45 mg every 12 weeks, and by shortening injection interval in 5 other patients: 45 mg every 12 weeks to every 6 weeks for 3 patients, 90 mg every 12 weeks to every 6 weeks in 1 patient, and 90 mg every 8 weeks to every 4 weeks in 1 patient. Ustekinumab optimization was successful in 50% of patients.

Evolution of patients without a clinical benefit with ustekinumab at 3 months. Median follow-up in the 43

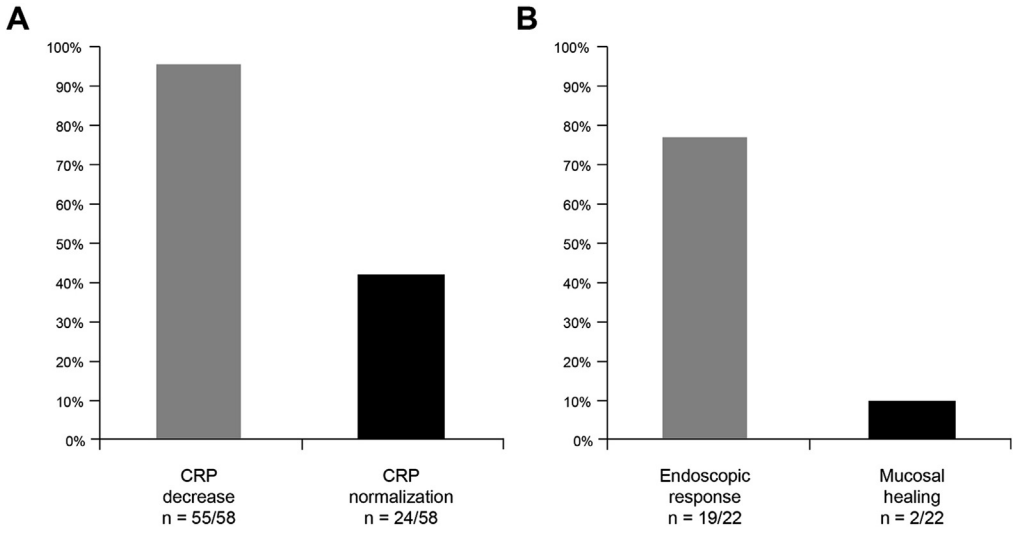

Figure 2. (*A*) Proportions of patients with a CRP decrease or CRP normalization among the 58 patients with clinical benefit to ustekinumab and having 2 CRP evaluations at time of ustekinumab introduction and at 3 months. (*B*) Proportions of patients with an endoscopic response or a mucosal healing at 3 months among the 22 patients with clinical benefit to ustekinumab and having 2 endoscopic evaluations at time of ustekinumab introduction and at 3 months. Numbers of patients are indicated below the histograms.

nonresponders was 4 months (IQR, 2.8–6.2 months). During the first 3 months of ustekinumab therapy 12 of 43 (28%) patients underwent surgery, 8 of 43 (19%) had immunosuppressant or steroid introduction, and 16 of 43 (37%) permanently stopped ustekinumab treatment. Only 7 (16%) nonresponders maintained ustekinumab (without surgery, steroids, or immunosuppressant introduction) for more than 3 months with a clinical benefit in 4 of them at 6 months: 2 achieved clinical benefit after 6 months without dose adjustment, receiving 90 mg at Weeks 0 and 4 and 90 mg every 12 weeks in the maintenance phase and the 2 other patients have been optimized by shortening injection interval (from every 8 weeks to every 4 weeks).

Evolution of anti–tumor-necrosis-factor-induced paradoxical skin lesions. No patient received ustekinumab treatment for skin adverse event only; however, 14 (11%) patients received ustekinumab for active CD and also had paradoxical anti-TNF-induced psoriasiform skin lesions. Among them, only 2 (14%) patients had psoriasis before anti-TNF treatment. A ustekinumab-induced clinical improvement in CD was observed at 3 months in 11 (79%) patients and in skin lesions in 13 (93%).

Table 2. Univariate and Multivariate Logistic Regression Analysis of Factors Predicting Clinical Benefit to Ustekinumab at 3 Months

Factors predicting ustekinumab response	Univariate odds ratio (95% CI)	*P* value	Multivariate odds ratio (95% CI)	*P* value
Female gender	1.58 (0.70–3.57)	.26	—	
Age	0.74 (0.35–1.59)	.44	—	
CD duration	0.81 (0.38–1.70)	.57	—	
Perianal CD	0.91 (0.43–1.95)	.81	—	
Smoker status	0.92 (0.41–2.09)	.84	—	
Previous resection	0.79 (0.36–1.71)	.54	—	
Reasons for ustekinumab introduction (luminal/anal)	1.10 (0.31–3.90)	.88	—	
Concomitant steroids at time of ustekinumab introduction	0.49 (0.17–1.44)	.19	—	
Concomitant immunosuppressant at time of ustekinumab introduction	5.21 (1.09–24.85)	.02	**5.43 (1.14–25.77)**	**.03**
C-reactive protein >5 mg/L	0.44 (0.16–1.17)	.09	0.37 (0.14–1.00)	.06
Mean cumulative first month's dose	0.89 (0.42–1.90)	.78		
Ustekinumab dose received during the first 2 months				
≤90 mg	1		—	
135–180 mg	1.82 (0.68–4.83)	.22	—	
≥225 mg	2.27 (0.51–10.08)	.27	—	

CI, confidence interval.
Bold value indicates statistically significant odds ratios in the multivariate analysis.

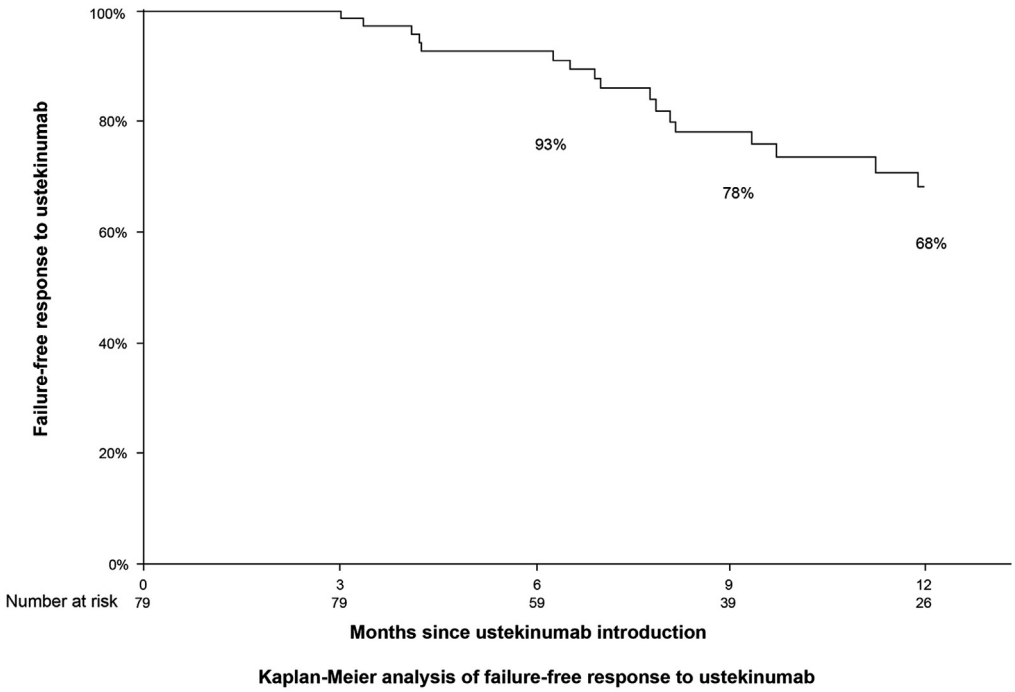

Figure 3. Kaplan-Meier survival curve of failure-free response to ustekinumab among the 79 initial responders at 3 months. The median follow-up duration was 9.8 months (interquartile range, 5.3–14.5 months).

Safety of Ustekinumab

An adverse event developed in 20 patients (16%) (Table 3). Myalgia and infections were the most frequent events, observed in 3% and 7% of patients, respectively.

One severe adverse event led to ustekinumab withdrawal in a 72-year-old woman with CD for 33 years who developed severe pneumococcal pneumonia. One patient presented with an allergic reaction (rash, edema, dyspnea) immediately after the second ustekinumab injection. Two other patients developed disabling myalgia requiring the discontinuation of ustekinumab. Thus, ustekinumab was discontinued in 4 of 122 patients (3%) because of severe infection, myalgia, or intolerance. No malignancies or deaths were reported during follow-up. No injection site reactions were observed.

Discussion

In the present study evaluating the response to subcutaneous ustekinumab induction and maintenance in patients with CD with prior and multiple anti-TNF failures, a clinical benefit was observed in nearly two-thirds of the patients at 3 months. It was associated with a biologic and endoscopic response as well as a good safety profile. Interestingly, concomitant immunosuppressant therapy was associated with greater efficacy and the clinical benefit of ustekinumab was maintained in the first year in most primary responders.

Ustekinumab has been evaluated in patients with moderate-to-severe CD in 2 randomized placebo-controlled trials and in 1 cohort study. In a double-blind phase IIa placebo-controlled trial, the clinical response at Week 8 was not better than with placebo. However, when patients were stratified for previous infliximab exposure, the response to ustekinumab was significantly better in previously treated patients: 59% versus 26% than in placebo ($P = .02$).[15] A double-blind placebo-controlled phase IIb trial, called CERTIFI, was

Table 3. Adverse Events Related to Ustekinumab

	Number of patients	SAE	Discontinuation of ustekinumab
Patients with any adverse events, n (%)	20 (16)	1 (1)	4 (3)
Serious infections			
Severe pneumococcal pneumonia	1	1	1
Infections			
Folliculitis	1		
Staphylococci	1		
Bronchitis	1		
Sinusitis	1		
Pneumonia	1		
External otitis	1		
Rhinopharyngitis	1		
Urinary tract infection	1		
Cutaneous adverse event			
Eczema	2		
Psoriasis	1		
Other adverse events			
Arthralgia	3		
Myalgia	3		2
Depression	1		
Allergic reaction	1		1
Injection site reaction	0		
Malignant disease	0		
Death	0		

SAE, severe adverse event.

performed in anti-TNF-refractory patients with CD who were randomly assigned to receive intravenous ustekinumab (1, 3, or 6 mg/kg) or placebo in the 8-week induction phase, then initial responders received subcutaneous ustekinumab or a placebo in the 28-week maintenance phase.[13] At Week 6, the clinical response was significantly better in the 6 mg/kg group than with placebo (39.7% vs 23.5%; $P = .005$), but clinical remission was not significantly different between the groups. It should be noted that treatment with 2 or 3 anti-TNF agents had failed in nearly half the patients in the CERTIFI trial. This is different from our cohort, which included more severe patients because 91% of them experienced both infliximab and adalimumab failure at inclusion. However, the higher proportion of patients with clinical benefit from induction with ustekinumab in our series may be related to a less strictly defined clinical outcome, a different route of administration, and a longer follow-up for the assessment of clinical response. Results from a retrospective Canadian cohort of 38 anti-TNF-refractory patients with CD also showed a 74% clinical response to subcutaneous ustekinumab at 3 months.[16]

The present study showed that concomitant immunosuppressant therapy may play an important role in the efficacy of ustekinumab possibly because of a synergistic immunosuppressant effect. Because only few patients (15%) received concomitant immunosuppressant, this synergistic effect on ustekinumab efficacy should be confirmed providing further data from randomized controlled trials. Although adjustment of the dose of ustekinumab for body weight, as recommended in patients with psoriasis, might also improve the clinical efficacy of this drug,[17] a dose effect was not identified as a predictor of response in the present study. It has been shown that optimizing treatment can improve the response in patients with psoriasis receiving ustekinumab as maintenance therapy.[18] Moreover, Kopylov et al[16] have reported that increasing the dose of ustekinumab was successful in two-thirds of patients with CD who lost the treatment response to this drug. In the present study, optimization was effective in 50% of the patients. Of note, we reported that ustekinumab maintenance and optimization could be effective in patients without initial clinical benefit. These results underline that long time exposition to ustekinumab may be necessary.

Deep remission, defined as clinical remission, biologic remission, and mucosal healing, has been established as a new therapeutic goal and is associated with more clinical remission rates, fewer flares, hospitalizations, and surgeries.[19] Moreover, it has recently been shown that deep remission could be obtained by optimizing medical treatment.[20] The present study is the largest cohort of patients with CD treated with ustekinumab with a composite assessment of response (clinical, biologic, and endoscopic) and showed that the clinical benefit of ustekinumab was associated with a biologic and endoscopic response in most patients. These data emphasize the objective improvement in patients with CD treated with ustekinumab, and show that ustekinumab is a viable and efficient therapeutic option in anti-TNF-refractory patients with CD. We acknowledge that a limited number of patients from the present cohort had an endoscopic assessment, showing an improvement in most of them and a mucosal healing in 9% of the patients. Nevertheless, in patients refractory to multiple anti-TNF therapies, an endoscopic improvement could be considered as a relevant objective.

Tillack et al[21] recently reported the results in 7 patients with inflammatory bowel disease who switched from anti-TNF treatment to ustekinumab, because of severe psoriasiform skin lesions that did not respond to topical treatment requiring discontinuation of anti-TNF. Skin lesions improved in all patients. In the present study, ustekinumab resulted in improvement in nearly all of the 14 patients with CD with anti-TNF-induced psoriasiform skin lesions. However, flare of psoriasis lesions with ustekinumab treatment has been described in the literature, suggesting that the use of ustekinumab should be carefully managed in patients with CD with psoriasiform skin lesions induced by anti-TNF therapies.[22–24]

The safety of ustekinumab has been evaluated in more than 3000 patients with chronic immune-mediated inflammatory diseases included in controlled trials.[25] In the phase III placebo-controlled trial performed in patients with moderate-to-severe psoriasis,[18,26] adverse events were comparable in the placebo and ustekinumab groups after a 5-year follow-up duration. Infections including respiratory tract infections and nasopharyngitis were the most common adverse event reported; they were mild and did not require ustekinumab withdrawal. Injection site reactions were rare and occurred in an estimated 1%–2% of patients. The rates of severe infections and malignancies were low and similar in the placebo and ustekinumab groups. There were no reported cases of tuberculosis. In the CERTIFI trial, the occurrence of adverse events in the placebo and ustekinumab groups was comparable and 1 basal-cell carcinoma was reported in the ustekinumab group.[13] In the present study, ustekinumab was found to be safe and well tolerated with only 1 serious adverse event (pneumonia) and 4 cases (3%) of ustekinumab withdrawal because of severe infection or intolerance reactions. No injection site reactions or malignancies were reported.

The present study has limitations because of its retrospective design. First, although validated clinical scores of disease activity were not used as a primary end point, clinical benefit was determined by physicians from tertiary centers. Moreover objective outcomes including biologic and endoscopic findings were also analyzed. Despite several different ustekinumab induction and maintenance regimens, most patients received high doses of treatment showing the probable benefit of a subcutaneous ustekinumab induction regimen in CD.

In conclusion, subcutaneous ustekinumab was effective and well tolerated in a selected cohort of patients with active CD and previous and multiple anti-TNF failures. Pending results from ongoing clinical trials and other series, ustekinumab should be considered in patients with CD that is refractory to currently licensed drugs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.09.018.

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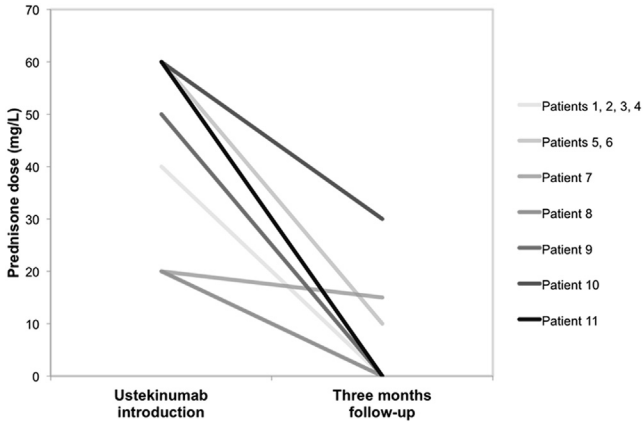

Supplementary Figure 1. Steroid discontinuation and reduction in patients with CD with ustekinumab clinical benefit at 3 months.

Supplementary Table 1. Induction and Maintenance Regimens of Ustekinumab

Induction regimens, n	122
90 mg Week 0/4	58
90 mg Week 0	24
45 mg Week 0/4	9
90 mg Week 0/6	8
45 mg Week 0	6
135 mg Week 0	4
270 mg Week 0 / 90 mg Week 4	3
45 mg Week 0 / 90 mg Week 4	3
135 mg Week 0 / 90 mg Week 4	2
90 mg Week 0/1/2	2
396 mg Week 0	1
90 mg Week 0/2/4	1
45 mg Week 0/2/4	1
Maintenance regimens, n	115
90 mg q 8 weeks	56
45 mg q 12 weeks	18
90 mg q 4 weeks	14
90 mg q 12 weeks	12
90 mg q 6 weeks	9
45 mg q 8 weeks	5
45 mg q 4 weeks	1

Supplementary Table 2. Clinical Characteristics of the 22 Patients With Repeat Endoscopic Evaluation of Response to Ustekinumab

Endoscopic evaluation at 3 months, n (%)	No endoscopic response 3 of 22 (14)	Endoscopic response 17 of 22 (77)	Mucosal healing 2 of 22 (9)
CD location (Montreal classification), n (%)			
L1	1 (33)	3 (18)	0
L2	0	4 (23)	0
L3	2 (67)	10 (59)	2 (100)
L4	0	0	0
Perianal	2 (67)	11 (65)	0
CD phenotype (Montreal classification), n (%)			
Inflammatory	1 (33)	8 (47)	2 (100)
Stricturing	2 (67)	4 (24)	0
Penetrating	0	5 (29)	0
Previous anti-TNF treatment	3 (100)	17 (100)	2 (100)
Number of previous anti-TNF			
1	1 (33)	1 (6)	2 (100)
2	0	12 (71)	0
$\geq$3	2 (67)	4 (23)	0
Reason of anti-TNF discontinuation			
Intolerance		1 (6)	2 (100)
Loss of efficacy	1 (33)	7 (41)	
Primary failure		1 (6)	
Both	2 (67)	8 (47)	
Concomitant immunosuppressant			
Thiopurines	1 (33)	2 (12)	0
Methotrexate	0	1 (6)	0