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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Short Title: Subcutaneous ustekinumab in Crohn's disease.

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Abbreviations: CD: Crohn's disease, CRP: C-reactive protein, IBD: inflammatory bowel disease, IMIDs: immune-mediated-inflammatory diseases, TNF: tumor necrosis factor.

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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 (inter-quartile 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.

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 we await results from ongoing trials, ustekinumab can be considered for use in these patients.

KEY WORDS: IL12, IL23, inflammatory bowel disease, immunosuppressant

INTRODUCTION

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 CD patients, a persistent response is not obtained in certain patients. Controlled trials have shown that a primary response is not achieved in approximately 20 to 40% of patients with infliximab and adalimumab, and that up to 40% of patients who initially respond to the anti-TNF induction regimen will subsequently lose response over time. [7,8,9] 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 CD patients 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 one subcutaneous injection of ustekinumab from March 2011 to December 2014 and with a follow-up of at least three 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, biological, 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, the 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 (non-primary 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 above 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 three 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 three 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 three 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 (SD) 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 three months, expressed as odds ratios (OR) with 95% confidence intervals (CI). Three subgroups of patients according to the cumulative ustekinumab dose administered during the first two months (less than 90mg, between 135 and 180mg and more than 225mg) were created and incorporated in the logistic regression. Variables with a p value below 0.10 were used for multivariate analysis. A p value of 0.05 was considered to be significant.

RESULTS

Patient characteristics

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

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 methotrexate and at least one 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 three anti-TNF agents (42 exposed to infliximab, adalimumab and certolizumab, and three to infliximab, adalimumab and golimumab) and two (2%) who had received four anti-TNF agents.

Ustekinumab was given to 110 (90%) patients for luminal CD and to 12 (10%) for perianal disease. At inclusion 72/104 (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 non-passable stricture in one 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 two months: 39 (32%) patients received a dose lower than 90mg, 74 (61%) patients received a dose comprised between 135 and 180mg, and 9 (7%) patients received a dose higher than 225mg. At 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 two 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 56/115 (49%) of the patients.

Efficacy of ustekinumab

Clinical benefit at three months

After three months ustekinumab resulted in a clinical benefit in 79/122 (65%) patients (Figure 1B). A clinical benefit was obtained in 71/110 (65%) patients treated for luminal CD and in 8/12 (67%) patients treated for perianal disease. Among the 19 patients who received concomitant steroids when starting ustekinumab, a clinical benefit at three months was obtained in 11/19 (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

Fifty eight patients with a clinical benefit from ustekinumab at the three month follow-up had elevated CRP at inclusion and a second CRP levels measurement at three month follow-up; CRP levels decreased in 55/58 (95%) of these patients, including 24/58 (41%) with CRP normalization (below 5 mg/L) (Figure 2A). 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 three month follow-up. An endoscopic response was observed in 17/22 (77%) patients, and a

mucosal healing in 2/22 (9%) (Figure 2B). Clinical characteristics of the 22 patients with repeat endoscopic evaluation are summarized in the Supplementary Table 2.

Predictive factors of clinical benefit at three months

The independent predictive factors of benefit from ustekinumab at the three 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 three months (OR 5.43, 95% CI: 1.14- 25.77; p = 0.03). No difference was observed in patients receiving thiopurines or methotrexate.

Clinical benefit at 6 months and 12 months in initial responders to ustekinumab

The median follow-up in the 79 patients with clinical benefit at three 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 three month response experienced secondary ustekinumab failure during the maintenance phase leading to surgical resection (9 patients), immunosuppressant and/or re-administration of steroids (9 patients).

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

Evolution of patients without a clinical benefit with ustekinumab at three months

Median follow-up in the 43 non-responders was 4 months (IQR: 2.8-6.2 months). During the first three months of ustekinumab therapy 12/43 (28%) patients underwent

surgery, 8/43 (19%) had immunosuppressant or steroid introduction, and 16/43 (37%) permanently stopped ustekinumab treatment. Only 7 (16%) non-responders maintained ustekinumab (without surgery, steroids or IS introduction) for more than three months with a clinical benefit in 4 of them at 6 months: two achieved clinical benefit after 6 months without dose adjustment, receiving 90mg at weeks 0 and 4 and 90mg every 12 weeks in the maintenance phase and the two other patients have been optimized by shortening injection interval (from every 8 weeks to every 4 weeks).

Evolution of anti-TNF-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 two (14%) patients had psoriasis prior to anti-TNF treatment. An ustekinumab induced clinical improvement in CD was observed at three months in 11 (79%) patients and in skin lesions in 13 (93%).

Safety of ustekinumab

An adverse event developed in twenty 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 4/122 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 CD patients with prior and multiple anti-TNF failures, a clinical benefit was observed in nearly two thirds of the patients at three months. It was associated with a biological 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 two randomized placebo-controlled trials and in one 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% *vs*. 26% than in placebo (p=0.02).[15] A double blind placebo-controlled phase IIb trial, called CERTIFI, was performed in anti-TNF refractory CD patients who were randomly assigned to receive intravenous ustekinumab (1, 3, or 6mg/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 6mg/kg group than with placebo (39.7% *vs*. 23.5%; p=0.005), but clinical remission was not significantly different between the groups. It should be noted that treatment with two or three 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 CD patients also showed a 74% clinical response to subcutaneous ustekinumab at three months.[16]

The present study showed that concomitant immunosuppressant therapy may play an important role in the efficacy of ustekinumab possibly due to a synergistic immunosuppressant effect. As 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 psoriasis patients 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 psoriasis patients receiving ustekinumab as maintenance therapy.[18] Moreover, Kopylov et al have reported that increasing the dose of ustekinumab was successful in two thirds of CD patients who lost the treatment response to this drug.[16] 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, biological 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 CD patients treated with ustekinumab with a composite assessment of response (clinical, biological and endoscopic) and showed that the clinical benefit of ustekinumab was associated with a biological and endoscopic response in most patients. These data emphasize the objective improvement in CD patients treated with ustekinumab, and show that ustekinumab is a viable and efficient therapeutic option in anti-

TNF refractory CD patients. 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. recently reported the results in 7 IBD patients who switched from anti-TNF treatment to ustekinumab, due to severe psoriasiform skin lesions that did not respond to topical treatment requiring discontinuation of anti-TNF. Skin lesions improved in all patients.[21] In the present study, ustekinumab resulted in improvement in nearly all of the 14 CD patients with anti-TNF induced psoriasiform skin lesions. However, flare of psoriasis lesions with ustekinumab treatment have been described in the literature, suggesting that the use of ustekinumab should be carefully managed in CD patients 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 (IMIDs) 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 were comparable and one 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 one serious adverse event

(pneumonia) and 4 cases (3%) of ustekinumab withdrawal due to severe infection or intolerance reactions. No injection site reactions or malignancies were reported.

The present study has limitations due to its retrospective design. First, although validated clinical scores of disease activity were not used as a primary endpoint, clinical benefit was determined by physicians from tertiary centers. Moreover objective outcomes including biological 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.

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TABLES

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%)
MycophenolateMofetil	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 <5mg/L	32 (31%)
CRP >5mg/L	72 (69%)

Abbreviations: CD, Crohn's disease; TNF, Tumor Necrosis Factor; CRP, C-reactive protein; y, years; n, number of patients

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)	0.26	-	
Age	0.74 (0.35 - 1.59)	0.44	-	
CD duration	0.81 (0.38 - 1.70)	0.57	-	
Perianal CD	0.91 (0.43 - 1.95)	0.81	-	
Smoker status	0.92 (0.41 - 2.09)	0.84	-	
Previous resection	0.79 (0.36 - 1.71)	0.54	-	
Reasons for ustekinumab introduction (luminal/anal)	1.10 (0.31 - 3.90)	0.88	-	
Concomitant steroids at time of ustekinumab introduction	0.49 (0.17 - 1.44)	0.19	-	
Concomitant immunosuppressant at time of ustekinumab introduction	5.21 (1.09 - 24.85)	0.02	**5.43 (1.14 - 25.77)**	**0.03**
C-reactive protein > 5mg/L	0.44 (0.16 - 1.17)	0.09	0.37 (0.14 - 1.00)	0.06
Mean cumulative first month's dose	0.89 (0.42 - 1.90)	0.78		
Ustekinumab dose received during the first two months				
≤90mg	1		-	
135-180mg	1.82 (0.68 - 4.83)	0.22	-	
≥225mg	2.27 (0.51 – 10.08)	0.27	-	

Abbreviations: CI, confidence interval; CD, Crohn's disease.

Bold value indicates statistically significant odds ratios in the multivariate analysis.

Table 3: Adverse events related to ustekinumab

	No. 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		
Rhino pharyngitis	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		

Abbreviation: SAE, severe adverse event.

FIGURE LEGENDS

Figure 1: Flowchart of the 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.

Figure 2: (A) Proportions of patients with a C-reactive protein (CRP) decrease or CRP normalization among the 58 patients with clinical benefit to ustekinumab and having two 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 two endoscopic evaluations at time of ustekinumab introduction and at 3 months. Numbers of patients are indicated below the histograms.

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).

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

SUPPLEMENTARY MATERIAL

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 3/22 (14%)	Endoscopic response 17/22 (77%)	Mucosal healing 2/22 (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
≥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

Abbreviations: CD, Crohn's disease; TNF, Tumor Necrosis Factor; n, number of patients.

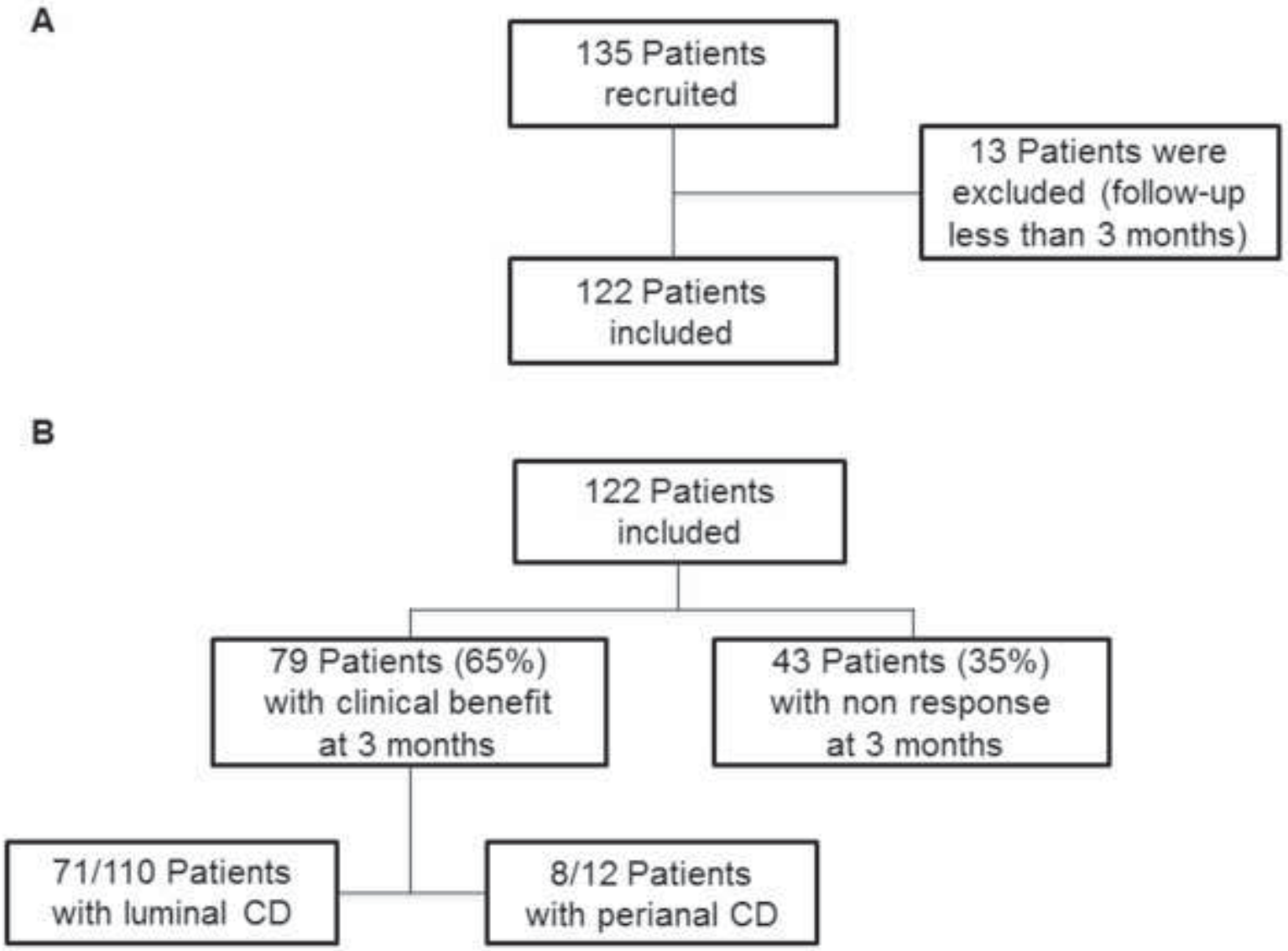

A
135 Patients recruited
13 Patients were excluded (follow-up less than 3 months)
122 Patients included
B
122 Patients included
79 Patients (65%) with clinical benefit at 3 months
43 Patients (35%) with non response at 3 months
71/110 Patients with luminal CD
8/12 Patients with perianal CD

Figure 1

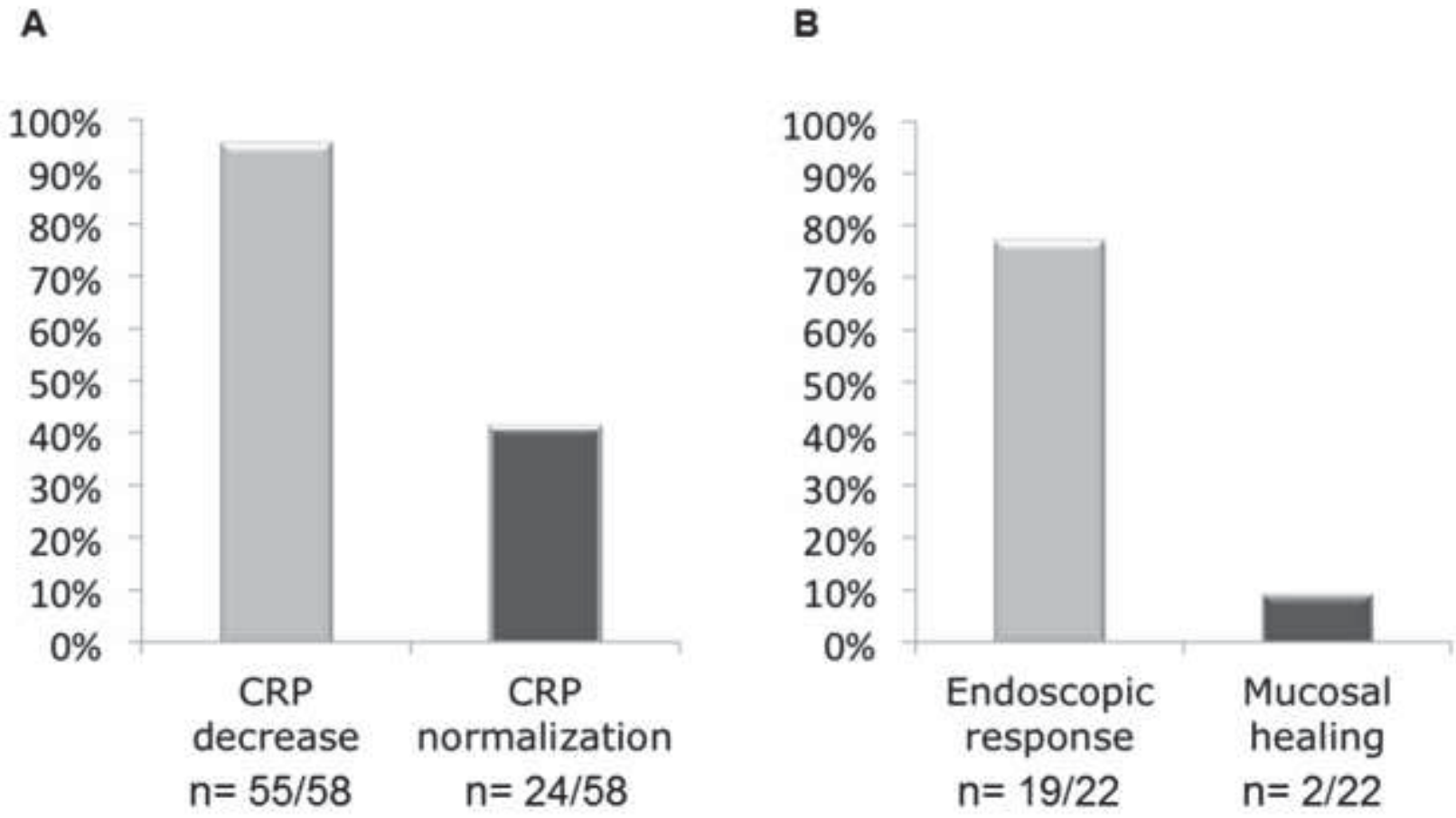
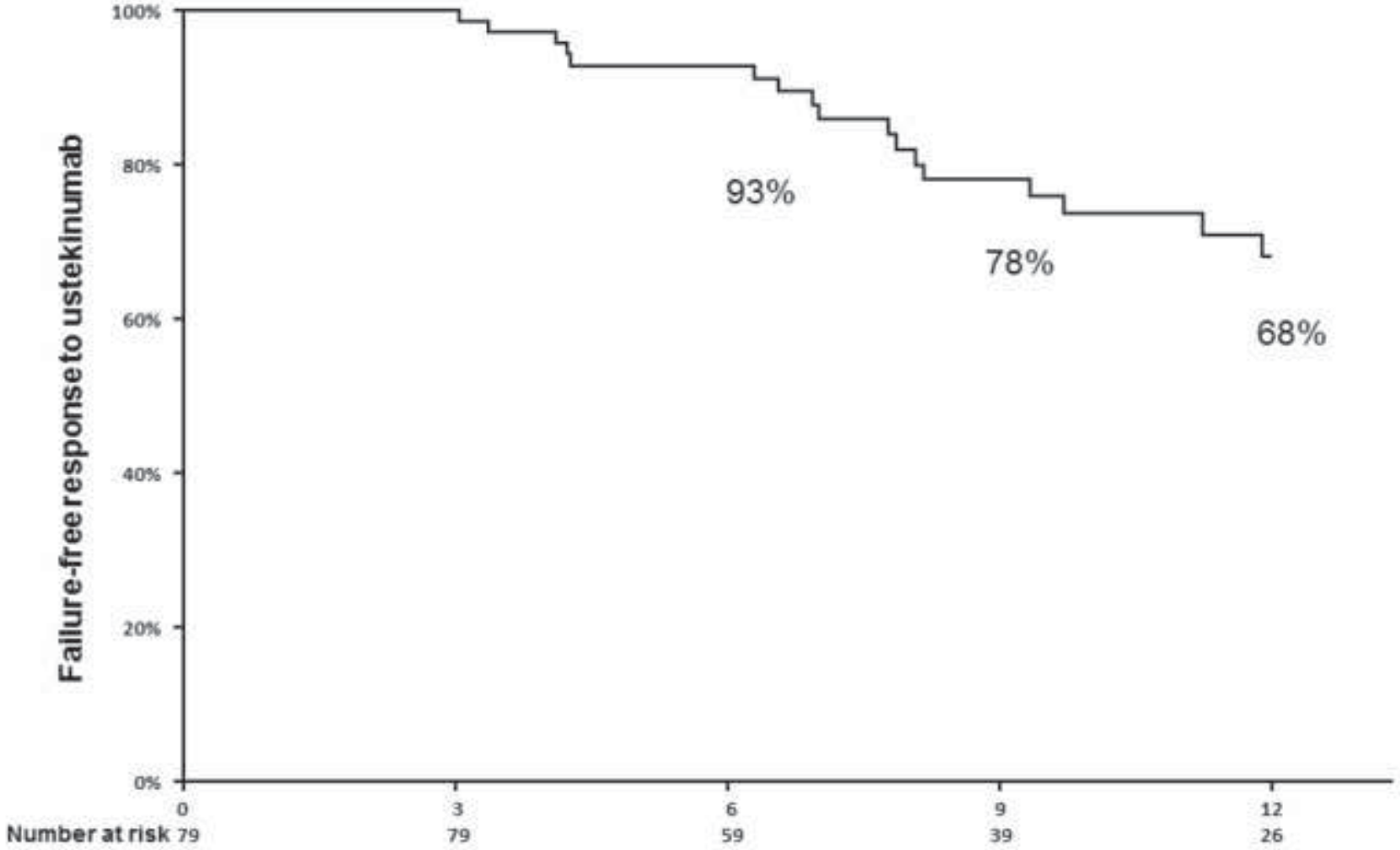
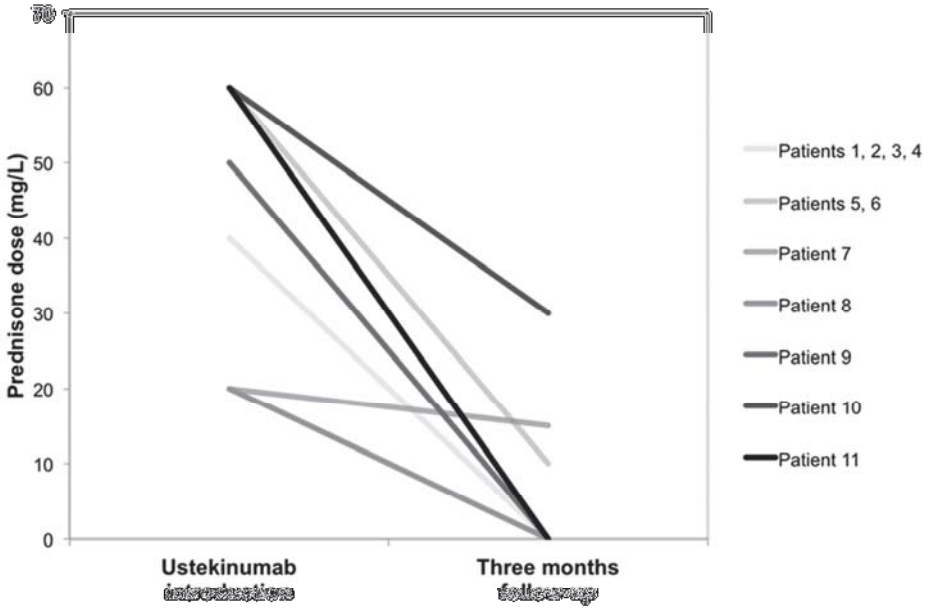

A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
CRP decrease n= 55/58
CRP normalization n= 24/58
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Endoscopic response n= 19/22
Mucosal healing n= 2/22

Figure 2



Kaplan-Meier analysis of failure-free response to ustekinumab

Figure 3



Supplementary Figure 1