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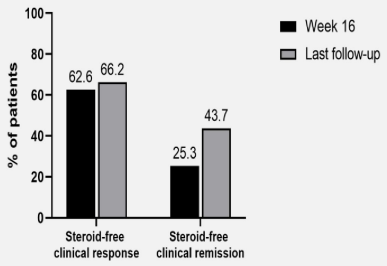

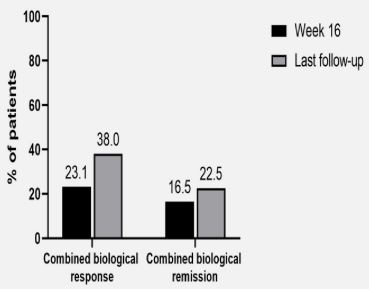

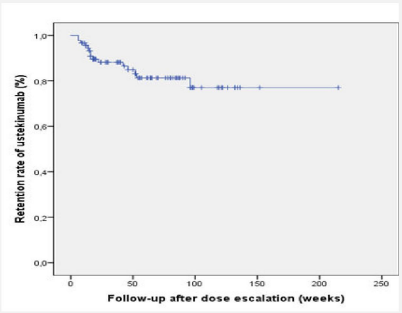

91 Crohn´s disease patients

Medium follow-up: 64 weeks

Median duration on conventional ustekinumab: 35 weeks

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Effectiveness and safety of ustekinumab dose escalation in Crohn's disease: a multicenter observational study

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Conflicts of interest: R. Olmedo has received payments as fees-for-service and advisory work from MSD, Abbvie, Takeda, Ferring, Faes Farma and Janssen. J. M. Vázquez has received payments as fees-for-service and advisory work from MSD, Abbvie, Takeda, Janssen, Pfizer, Kern, Ferring, Faes Farma and Shire Pharmaceuticals. M. Martín has received payments for advisory work, participation in scientific meetings and attendance from MSD, Takeda, Janssen, Abbvie, Tillots Pharma, Chiesi and Ferring. M. Lázaro has received payments as fees-for-service, participation in scientific meetings and funding for attendance from Janssen, Pfizer and Takeda. A. Hernández has received payments as fees-for-service, participation in scientific meetings and funding for attendance from Abbvie, Ferring, Janssen, MSD, Pfizer, Sandoz and Takeda. F. Argüelles has received payments for advisory work, consultancy and research fundings from Janssen, MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Sandoz, Takeda, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillots Pharma, Gebro Pharma, Amgen and Vifor Pharma.

ABSTRACT

Background: ustekinumab has proven effective in Crohn's disease (CD). However, some patients will partially respond or lose response over time. Data supporting the effectiveness of dose escalation in this scenario is scarce.

Aim: to evaluate the effectiveness of ustekinumab dose escalation in CD.

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Methods: patients with active CD (Harvey-Bradshaw ≥ 5) who had received intravenous (IV) induction and at least a subcutaneous (SC) dose were included in this retrospective observational study. Ustekinumab dose was escalated, either via shortening of the interval to six or four weeks or IV reinduction plus shortening to every four weeks.

Results: ninety-one patients were included, and ustekinumab dose was escalated after a median of 35 weeks of treatment. At week 16 after intensification, steroid-free clinical response and remission were observed in 62.6 % and 25.3 % of patients, respectively. Systemic corticosteroids were discontinued in 46.7 % of patients who were on corticosteroids at baseline. Follow-up data beyond week 16 were available for 78 % of patients; at the last visit, 66.2 % and 43.7 % were in steroid-free clinical response and remission, respectively. After a median follow-up of 64 weeks, 81 % of patients were still treated with ustekinumab. Adverse events were reported in 4.3 % of patients; these were all mild and did not lead to hospitalization or discontinuation of treatment. Five patients (5.5 %) underwent surgical resection, with no immediate postsurgical complications.

Conclusion: ustekinumab dose escalation was effective in recapturing response in over half of the patients. These findings suggest that dose escalation should be considered in patients who experience loss or partial response to the standard maintenance.

Keywords: Ustekinumab. Crohn's disease. Dose escalation. Reinduction.

INTRODUCTION

Ustekinumab is a human monoclonal IgG1 antibody that targets the p40 subunit of interleukins (IL) 12 and 23. It has been approved for the treatment of Crohn's disease (CD) and ulcerative colitis (1,2). The UNITI clinical trial program, for which five-year data are available, clearly showed the efficacy of ustekinumab in the induction and maintenance of response in moderate-to-severe CD (3). The approved dosing of ustekinumab for CD includes an intravenous (IV) induction dose of 6 mg/kg followed by subcutaneous (SC) administration of 90 mg at week 8, and a 90 mg maintenance dose every eight or 12 weeks (q8w or q12w) at the physician's discretion (1-3). As is the case

with anti-tumor necrosis factor agents (anti-TNF), around 25-30 % of patients lose response to ustekinumab in clinical trials (1,2). Real-world observational studies, where a large majority of patients are refractory to one or more biologics, report somewhat higher percentages for dose escalation (around 40 %) (4-6).

The demonstration of a dose-response relationship with anti-TNFs and the widespread therapeutic drug monitoring of anti-TNF levels and antidrug antibodies have led to the development of optimization strategies (dose increase, shortening of dosing intervals) (7,8). In the case of newer biologics, such as ustekinumab, the scenario is noticeably different, owing to the drug's low immunogenicity (development of antidrug antibodies in 5 % at five years in the UNITI program) and both lack routinely measured levels and consensus on therapeutic plasma concentrations (9).

Only a few studies have evaluated the safety and effectiveness of dose escalation with ustekinumab, with various strategies used, including SC administration q4w or q6w and IV reinduction alone or in combination with dose interval shortening (10-15).

Therefore, the objective of this study was to evaluate the effectiveness of dose escalation with ustekinumab in patients with CD who responded partially or lost response to the standard maintenance dose administered q8w.

METHODS

Study population

A multicenter, retrospective, observational study was performed. The study was carried out between June 15th 2022 and January 15th 2023. The protocol was reviewed and approved by the Málaga Research Ethics Committee. All patients gave their approval and signed the informed consent. Data from five Inflammatory Bowel Diseases (IBD) Andalusian referral centers in Spain were retrospectively collected. The study population comprised patients with active CD (Harvey-Bradshaw Index [HBI] ≥ 5) who had received at least two doses of ustekinumab (induction of 6 mg/kg IV followed by 90 mg SC at week 8) and then underwent dose escalation (90 mg SC q4w or q6w or IV reinduction of 6 mg/kg combined with shortening of the dosing interval to q4w). All included patients maintained the same dose-optimizing regimen until the last visit for which data were available. Patients who had started at 90 mg q12w could be included

if their dose had been optimized to 90 mg q8w before the new dose escalation. Patients with no clinically active disease and patients with a stoma were excluded.

Outcome measures

The primary objective of the study was to ascertain the steroid-free clinical response (decrease of HBI ≥ 3 points compared to baseline) at week 16 after ustekinumab dose escalation. The secondary objectives were steroid-free clinical remission (HBI ≤ 4), combined biologic response (reduction in fecal calprotectin [FC] and C-reactive protein [CRP] by 50 % from baseline) and combined biological remission (FC < 250 µg/g and CRP < 5 mg/dl) at week 16 after dose escalation. Steroid free response or remission was considered only in patients who were on corticosteroids at the start of the dose escalation strategy and who were able to discontinue it at 16 weeks or at the last recorded visit. In patients for whom data were available beyond week 16 after dose escalation, we also evaluated steroid-free clinical remission and response and biological remission and response at the last available follow-up visit. In addition, factors that predicted lack of response to ustekinumab dose escalation at week 16 were investigated. Lastly, safety and tolerability data were collected by recording patient-reported adverse events, severe adverse events leading to hospitalization or discontinuation of treatment, and the need for surgery associated with CD following dose escalation.

Statistical analysis

Descriptive statistics are presented as the mean and standard deviation for normally distributed continuous variables and as the median and interquartile range (IQR) for nonparametric variables. Categorical variables are presented as a percentage and were analyzed using the X^2 or Fisher's exact test; continuous variables were compared using the t test or Mann-Whitney test depending on the normality of the distribution. Factors predicting the response to dose escalation with ustekinumab at week 16 were analyzed using a univariate logistic regression model by calculating the odds ratio (OR)

and its confidence intervals (CI). Variables with a significance value of $p < 0.200$ were entered into a multivariate model and the OR and 95 % CI were calculated. The effect of the variables on ustekinumab treatment duration was investigated using Kaplan-Meier survival analysis. All analyses were performed using the Statistical Program for Social Sciences (SPSS Statistics Version 23, IBM Corp., Armonk, New York, United States). The statistical review of this study was performed by a biomedical statistician.

RESULTS

A total of 91 patients from five reference hospitals in Spain were included in the study. During the study period, 273 patients were in treatment with ustekinumab in the five participant centers which represents a mean percentage of ustekinumab dose escalation of 33 %. The clinical and demographic characteristics are shown in table 1.

Short term treatment outcomes

A total of 57/91 patients (62.6 %) achieved steroid-free clinical response at week 16 after intensification, including 23/91 (25.3 %) who were in steroid-free clinical remission (Fig. 1). The rates of combined biological response and remission were 21/91 (23.1 %) and 15/91 (16.5 %), respectively (Fig. 2). Twenty-one of the 45 patients (46.7 %) receiving systemic corticosteroids at the time of dose escalation were able to discontinue their use. Ustekinumab was suspended owing to lack of response in 10/91 patients (11 %) before week 16 of follow-up.

Factors predicting absence of steroid-free response at week 16 after dose escalation

The univariate analysis revealed that the factors associated with a lack of steroid-free response after dose escalation at week 16 were perianal involvement, a high HBI, concomitant steroid therapy at initiation of dose escalation, and previous use of three or more biologics. However, ileal location was associated with a higher probability of response. No significant differences were found between the different types of dose escalation. Steroid-free response at week 16 was significantly higher in patients for whom the indication was loss of response compared to insufficient primary response (72.3 % *vs* 38.5 %, $p = 0.003$). In the multivariate analysis, only perianal involvement

and steroid therapy at initiation of escalation remained statistically significant (Table 2).

Long term treatment outcomes

Data beyond week 16 after dose escalation were available for 71/91 (78 %) patients. The median duration of follow-up in patients who continued with ustekinumab was 64 weeks (IQR 39-92). Steroid-free clinical response at the last available follow-up visit was achieved by 47/71 (66.2 %) patients of whom 31/71 (43.7 %) were in steroid-free clinical remission (Fig. 1). The rates for combined biologic response and remission were 27/71 (38 %) and 16/71 (22.5 %), respectively (Fig. 2). A further five (7 %) patients discontinued ustekinumab owing to lack of response after week 16. Seventy-six patients (83.5 %) continued to receive ustekinumab at the last follow-up visit. Forty-five of 91 patients (49,4 %) were on steroids at the start of dose escalation. Systemic corticosteroids were discontinued in 20 (46.7 %) patients who were on corticosteroids at baseline. The retention rate for ustekinumab after dose escalation was 81 % at 64 weeks (median follow-up) (Fig. 3). Two out of 20 (10 %) patients who did not respond at 16 weeks after dose escalation and with available maintenance data, subsequently responded to treatment. The drug was switched to another biologic in eight cases (8.8 %).

Safety

Adverse effects were reported after dose escalation in 4/91 (4.3 %) patients. These were all mild and did not lead to hospitalization or discontinuation of treatment (two patients with mild herpes infection and two with joint pain). Five patients (5.5 %) underwent surgical resection during dose escalation, with no immediate postsurgical complications in any of them.

DISCUSSION

This multicenter, retrospective, observational study evaluated the safety and effectiveness of escalating ustekinumab dose in CD with partial or loss of response to standard dosing regimen. Most patients had previously received anti-TNF agents or

vedolizumab. In the short term, almost two-thirds of patients recaptured steroid-free clinical response, with 25 % of them achieving steroid-free clinical remission. Clinical effectiveness was maintained in the medium-to-long term, and even increased to 43 % for steroid-free remission. Furthermore, the results for combined normalization of CRP and FC were more modest, although appreciable, with almost one-quarter of patients achieving remission in the medium-to-long term. The percentage of secondary loss of response in patients treated with ustekinumab ranged from 20 % in the IM-UNITI trial (1,2) to 35-40 % in real-world studies (3-5). However, no prospective studies have yet evaluated the management of loss of response during treatment with ustekinumab. Randomized clinical trials evaluating the efficacy and safety of ustekinumab in CD did not specifically assess dose escalation. In IM-UNITI, patients whose dosing interval was reduced owing to loss of response (from 90 mg SC q12w to q8w) achieved remission and response rates of 41 % and 55 %, respectively (3).

Several retrospective observational studies have evaluated different strategies for optimizing ustekinumab dosing in patients with loss of response or partial response. In a European multicenter study by Kopylov et al. (10), various ustekinumab dose escalation strategies (90 mg q4w, 90 mg q6w, IV reinduction alone or in combination with shortening to 90 mg q4w) were analyzed in 142 patients. Clinical response at week 16 after dose escalation was achieved by 51 % of patients (38 % in remission). Moreover, clinical response and remission rates were maintained over time in patients with longer available follow-up data. The probability of ustekinumab persistence after dose escalation was higher than 70 % at 50 weeks of follow-up. These results are very similar to those observed in our study. However, it should be noted that the concept of persistence of treatment does not always imply the effectiveness of ustekinumab but rather the absence of other available therapeutic options. Three retrospective observational studies have specifically evaluated dose escalation by interval shortening to 90 mg q4w. Ollech et al. (11) reported 42 % clinical response rate (28 % clinical remission) in 110 patients with active CD, normalization of CRP values in 22 % and reduced FC levels in 50 % after a median follow-up of nine months. Fumery et al. (12) evaluated the effectiveness of interval shortening to 90 mg q4w in 100 patients from eleven French centers. After a median of 2.4 months, 61 % of patients achieved clinical

response, 31 % clinical remission and 27 % steroid-free clinical remission. At six months, 49 % were in steroid-free clinical remission. Sixty-one percent continued to receive ustekinumab after a median follow-up of eight months. For patients for whom endoscopic data were available, 36 % were in endoscopic remission (defined as absence of ulcers) six months after ustekinumab escalation. Lastly, using the Physician Global Assessment Score (PGA) as a criterion for evaluation, Haider et al. (13) reported improved PGA, decreased CRP and increased albumin in 15 patients whose dose was escalated to q4w compared with 15 patients who had not responded to the standard dose and remained on q8w dosing.

Two recent studies evaluated the effectiveness of ustekinumab IV reinduction. A Canadian study included 15 patients with an incomplete response or loss of response who were already receiving ustekinumab SC q4w and received ustekinumab IV reinduction. Clinical response was observed in 66 % of the patients and remission in 53.3 %. For the eight patients for whom endoscopy and imaging results were available, response and remission were noted in 87.5 % and 62.5 % (14). Similarly, a Spanish study by Bermejo et al. (15) evaluated short-term effectiveness of ustekinumab IV reinduction in 53 patients, of which half were already with interval shortening before IV reinduction. Sixteen weeks after ustekinumab IV reinduction, clinical response and remission rates were 53 % and 43 %, respectively.

Factors predicting ustekinumab dose escalation success or failure in CD patients are poorly understood. In our study, variables indicating more severe CD, such as perianal disease and concomitant use of steroids at initiation of dose escalation, were associated with a lower probability of steroid-free clinical response at week 16 after intensification. These findings are consistent with those reported by Dalal et al. (16) in a retrospective cohort study of 123 CD patients undergoing various dose escalation strategies. The authors found that perianal disease, elevated HBI, opioid use for abdominal pain, and current use of corticosteroids were associated with ustekinumab dose escalation failure.

In terms of pharmacokinetics, and given the notably lower immunogenicity of ustekinumab compared with anti-TNF agents, designing algorithms to guide dose escalation becomes more challenging. The UNITI studies revealed a positive correlation

between ustekinumab dosing, plasma concentrations and clinical efficacy (3). However, real-world studies are still scarce. A Belgian study reported a clear exposure-response relationship during induction and maintenance for different targets, the authors observe that higher thresholds may be required to obtain an endoscopic response (17). Similarly, Battat et al. (18) in a cohort of 62 patients, of whom 48 were dose-escalated to 90 mg q4w, found that a concentration of 4.5 µg/ml was necessary to achieve a biologic and endoscopic response. Finally, in a study by Hanzel et al. analyzing the exposure-response relationship in 44 patients whose ustekinumab dose was escalated to 90 mg q4w, the authors observed that endoscopic remission and biomarker normalization were associated with concentrations > 3.5 µg/ml after optimization (19).

In a recent systematic review and meta-analysis, 55 % of patients with inadequate response or loss of response who underwent ustekinumab dose escalation achieved clinical response. Approximately 61 % of patients were able to achieve endoscopic response, including 29 % who achieved endoscopic remission. Dose interval shortening alone recaptured response in 57 % patients. No consistent factors associated with response to dose escalation were identified (20).

Regarding safety, neither our study nor the abovementioned studies have reported new alerts or a greater frequency of adverse events with respect to those observed with standard maintenance doses.

Our study has a series of limitations, and our results must be interpreted with caution. First, the multicentric retrospective design, lack of predefined visits, missing biologic data for some patients and heterogeneous treatment strategies. Second, our results are limited by the absence of endoscopy and ustekinumab trough levels, which are not routinely available in our setting. Third, in some patients, dose optimization strategies were implemented relatively early; therefore, they may have subsequently achieved a clinical response with the standard maintenance dose. Among the strengths of our study, we included consecutive patients from several reference hospitals covering a broad area of Spain whose baseline clinical and biological characteristics were available before dose escalation. This reflects the current picture of dose escalation with ustekinumab in the real-world clinical practice in refractory CD.

In conclusion, and given the limitations set out above, our results support the effectiveness and safety of ustekinumab dose escalation in patients who loose response or show insufficient response to the standard maintenance dose administered q8w. Prospective randomized dose-response studies are necessary to consolidate our findings and to define the best optimization strategy for each individual patient and setting.

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Table 1. Clinical and demographic characteristics of the study patients

Age at initiation of treatment, years, median (IQR)	40 (33-50)
Duration of disease, years, median (IQR)	13 (8-18)
Sex, n (%)	
Male	41 (45.1 %)
Female	50 (54.9 %)
Behavior, n (%)	
B1 Inflammatory	40 (44 %)
B2 Stricturing	31 (34.1 %)
B3 Penetrating	20 (22 %)
Active smoker, n (%)	24 (26.4 %)
Location, n (%)	
L1 Ileum	33 (36.3 %)
L2 Colon	6 (6.6 %)
L3 Ileum and colon	36 (39.6 %)
L4 Upper digestive tract	2 (2.2 %)
L1 + L4	11 (10 %)
L2 + L4	1 (0.9 %)
History of perianal disease, n (%)	26 (28.6 %)
History of surgical resection, n (%)	42 (46.2 %)
Previous biologic treatments, n (%)	
Infliximab	69 (75.8 %)
Adalimumab	63 (69.2 %)
Vedolizumab	14 (15.3 %)
Number of previous biologic treatments, n (%)	
None	1 (1.1 %)
1	42 (46.1 %)
2	36 (39.6 %)
3	12 (13.2 %)
Elevated CRP before dose escalation, n (%)	54 (59.3 %)
FC before dose escalation, µg/g, median (IQR)	1,159 (488-1,767)

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HBI before dose escalation, median (IQR)	9 (8-11)
Systemic corticosteroids at dose escalation, n (%)	45 (49.4 %)
Concomitant immunosuppressants at dose escalation, n (%)	21 (23.1 %)
Indication of dose escalation, n (%)	
Insufficient primary response	26 (28.6 %)
Loss of response	65 (71.4 %)
Duration on conventional ustekinumab regimen, weeks, median (IQR)	35 (20-51)

CRP: C-reactive protein; FC: fecal calprotectin; IQR: interquartile range; HBI: Harvey-Bradshaw Index.

Table 2. **Predictors of steroid-free clinical response at week 16 after dose escalation**

	Steroid-free response at week 16				**Univariate**		**Multivariate**	
	No n = 34 (37.4 %)		**Yes n = 57 (62.6 %)**		**p**	**OR**	**p**	**OR**
	No.	**%**	**No.**	**%**				
Sex					0.465			
Male	17	50.0	24	42.1				
Female	17	50.0	33	57.9				
Concomitant immunosuppressant	9	26.5	12	21.1	0.554			
Concomitant steroids	28	82.4	18	31.6	< 0.001	0.099 (0.035-0.281)	< 0.001	0.054 (0.014-0.205)
Type of dose escalation								
90 mg q6w	8	23.5	17	29.8	0.691			
90 mg q4w	21	61.8	32	56.1	0.939			
IV reinduction + 90 mg q4w	5	14.7	8	14.0	Ref.			
Extraintestinal manifestations	12	35.3	17	29.8	0.588			
Perianal disease	14	41.2	12	21.1	0.043	0.381 (0.150-0.969)	0.006	0.148 (0.038-0.579)
Previous surgery	17	50.0	25	43.9	0.570			

Smoking	6	17.6	18	31.6	0.150			
Location								
L1 Ileum	7	20.6	26	45.6	0.045	2.971		
L2 Colon	3	8.8	3	5.3	0.800	(1.027-8.597)		
L3 Ileum and colon	16	47.1	20	35.1	Ref.			
L4 Upper digestive tract	2	5.9	2	3.5	0.832			
L1 + L4	5	14.7	6	10.5	0.953			
L2 + L4	1	2.9	0	0	> 0.999			
Behavior								
B1 Inflammatory	14	41.2	26	45.6	0.705			
B2 Stricturing	12	35.3	19	33.3	0.927			
B3 Penetrating	8	23.5	12	21.1	Ref.			
2 previous biologics	13	38.2	23	40.4	0.842			
3 or more previous biologics	8	23.5	4	7.0	0.033	0.245 (0.068-0.89)		
Time to dose escalation					0.34			
< 35 weeks	19	55.9	26	45.6				
< 35 weeks	15	44.1	31	54.4				
Dose escalation indication					0.003			

Non primary response Loss of response	16 18	47.1 52.9	22 35	38.5 72.3				
	n	Mean ± SD Median (IQR)	n	Mean ± SD Median (IQR)				
Age	34	42.2 ± 12.3 40 (33-52)	57	45.1 ± 13.0 44 (37.0-52.5)	0.289			
HBI before dose escalation	34	10.8 ± 3.1 10 (8.8-14.0)	57	9.3 ± 2.8 8 (8-10)	0.030	0.849 (0.732-0.984)		

FC before dose escalation	25	1,399.5 ± 1,000.0 1,232 (556-1,800)	54	1,191.1 ± 941.8 1,119 (338.8-1,693.5)	0.372			
Age at ustekinumab initiation	34	39.8 ± 12.4 38 (31-50)	57	42.9 ± 13.1 41 (35.0-50.5)	0.260			
Duration of CD, years	34	15.1 ± 6.5 14 (10.8-20.0)	57	12.5 ± 7.1 11 (7.5-17.0)	0.098			

CD: Crohn’s disease; FC: fecal calprotectin; HBI: Harvey-Bradshaw Index; IQR: interquartile range; IV: intravenous; q4w: every four weeks; q6w: every six weeks; SD: standard deviation.

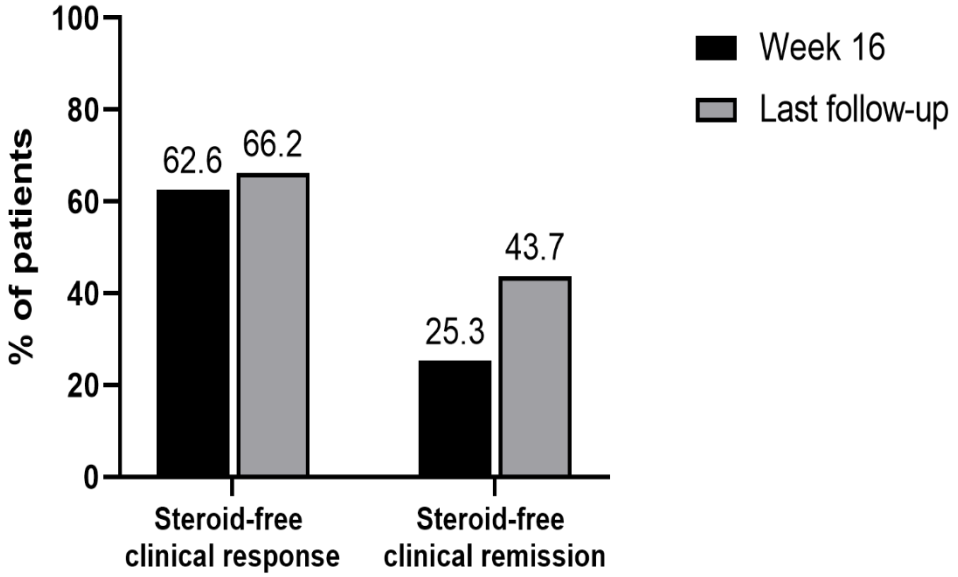

Fig. 1. Clinical effectiveness of ustekinumab dose escalation at week 16 after intensification and last follow-up visit. Steroid-free clinical response (decrease of Harvey-Bradshaw Index [HBI] ≥ 3 points compared to baseline). Steroid-free clinical remission (HBI ≤ 4).

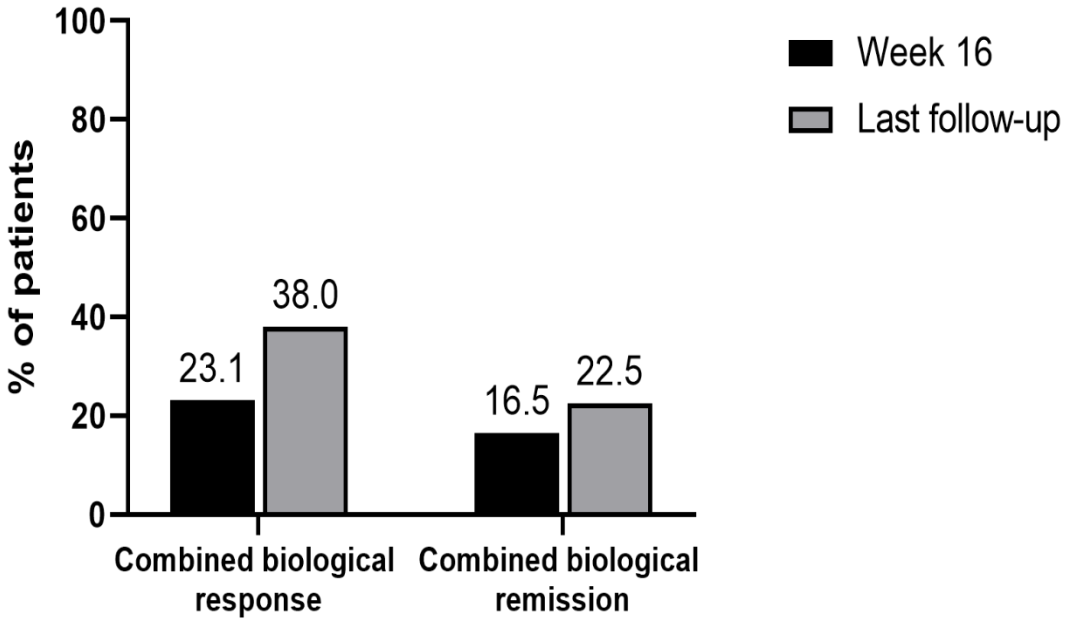

Fig. 2. Combined biological response and remission after dose escalation at week 16 after intensification and the last follow-up visit. Combined biologic response: reduction in fecal calprotectin (FC) and C-reactive protein (CRP) by 50 % from baseline. Combined biological remission (FC < 250 µg/g and CRP < 5 mg/dl).

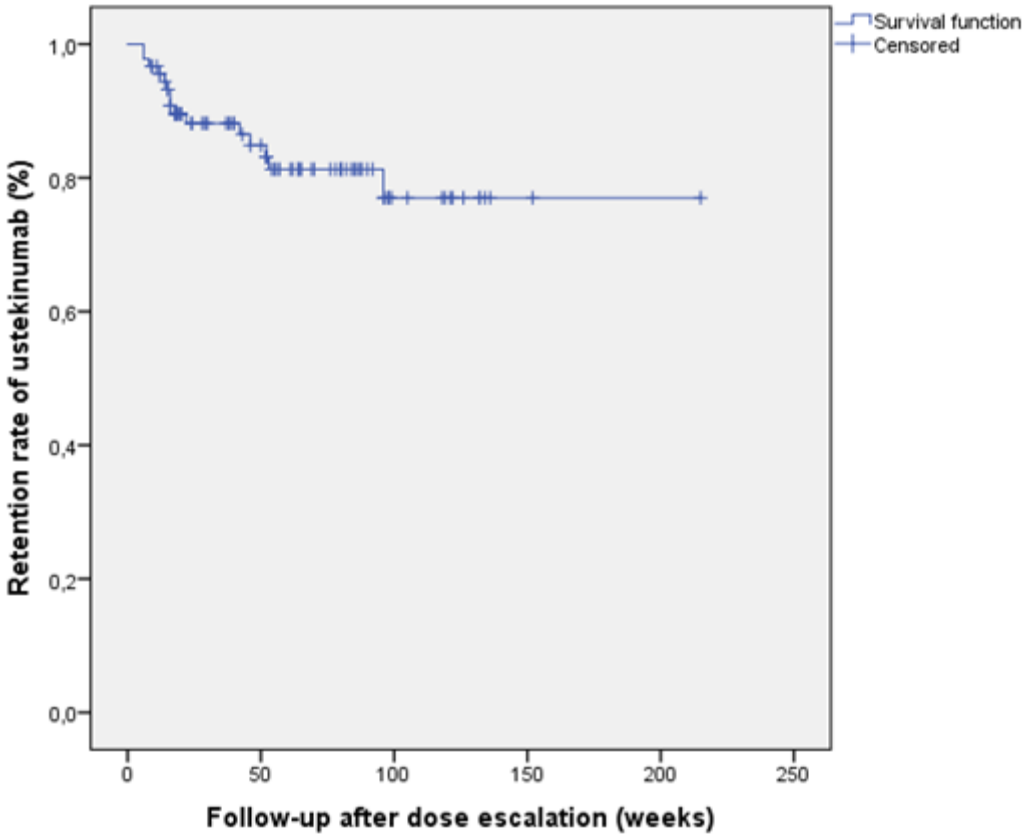

Fig. 3. Kaplan-Meier curve of ustekinumab treatment continuation after dose escalation.