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Differences in the need for adalimumab dose optimization between Crohn's disease and ulcerative colitis

David Olivares[1], Cristina Alba[1], Irene Pérez[2], Valentín Roales[3], Enrique Rey[3] and Carlos Taxonera[1]

[1]Inflammatory Bowel Disease Unit. Department of Gastroenterology. Hospital Clínico San Carlos. Instituto de Investigación del Hospital Clínico San Carlos (IdISSC). Madrid, Spain. [2]Department of Gastroenterology, Hospital Universitario La Paz. Madrid, Spain. [3] Department of Gastroenterology. Hospital Clínico San Carlos. Madrid, Spain

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Correspondence: Carlos Taxonera. Inflammatory Bowel Disease Unit. Department of Gastroenterology. Hospital Clínico San Carlos. C/Profesor Martín Lagos, s/n. 28040 Madrid, Spain

e-mail: carlos.taxonera@salud.madrid.org

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ABSTRACT

Aim: to compare the need for and time to adalimumab dose escalation and de-escalation between patients with Crohn's disease (CD) and ulcerative colitis (UC).

Methods: this observational cohort study included patients with luminal CD or patients with UC treated with adalimumab. Adalimumab dose optimization was decided based on the Harvey-Bradshaw index (CD) or the partial Mayo score (UC). The co-primary endpoints were the differences in the rate of dose escalation and the cumulative

probability of escalation-free survival between cohorts. We also evaluated the rates of de-escalation and predictors of adalimumab dose escalation and de-escalation.

Results: twenty-four of 43 CD patients (56%) and 28 of 43 UC patients (65%) required adalimumab dose escalation. UC patients had a higher adjusted rate of dose escalation (hazard ratio [HR] 2.33, 95% confidence interval [CI] 1.19-4.56; p = 0.013) than CD patients. The median time to dose escalation was significantly shorter for UC than CD patients (3.2 months, interquartile range [IQR]: 2.0-10.3 *vs* 12.2 months, IQR: 6.1-35.7; p = 0.001). Survival curves showed that UC patients had an increased probability of dose escalation (p < 0.001). Prior anti-TNF therapy was associated with dose escalation (HR 2.13, 95% CI 1.05-4.34; p = 0.037). Adalimumab dose de-escalation was attempted in 32% of UC patients and 50% of CD patients. Survival curves showed that CD patients had an increased probability of dose de-escalation (p = 0.030).

Conclusion: UC patients more frequently required adalimumab dose escalation than CD patients. UC patients required optimization earlier than CD patients. More CD patients than UC patients can be dose de-escalated later on during treatment.

Key words: Adalimumab. Crohn's disease. Ulcerative colitis. Dose optimization. Dose escalation. Dose de-escalation.

INTRODUCTION

Adalimumab is a fully humanized monoclonal antibody against the tumor necrosis factor (TNF)-α which is approved for induction and maintenance therapy in patients with Crohn's disease (CD) (1) and ulcerative colitis (UC) (2). Treatment with adalimumab is recommended for both anti-TNF-naïve or anti-TNF-experienced patients. Adalimumab was the second anti-TNF agent to be approved after infliximab, which is a chimeric monoclonal antibody also used in both CD and UC.

Although the efficacy of adalimumab is supported by randomized clinical trials, a significant subset of CD or UC patients have an inadequate response to induction or developed secondary loss of response during maintenance (1,2). Patients with an early nonresponse or a loss of response over time can benefit from adalimumab dose escalation before discontinuing the drug. A post hoc analysis of the CHARM trial

reported that escalation to weekly doses of adalimumab could induce a clinical response in a large proportion of CD patients (3). In a post hoc analysis of the ULTRA 2 trial, optimization to weekly adalimumab dosing demonstrated a clinical benefit for UC patients who lost response to the therapy and may be advantageous for patients that do not initially respond to induction doses (4). In summary, optimization to weekly adalimumab dosing demonstrated clinical benefits for CD and UC patients who lost response to therapy with no notable increase in side effects.

The need for and the outcomes of adalimumab dose escalation to overcome inadequate response or secondary loss of response in both CD and UC patients have also been reported in several "real life" studies. A meta-analysis showed that the annual rate of CD patients requiring adalimumab dose escalation was 24% per patient-year (5). In contrast, the "real life" outcomes of adalimumab dose optimization in UC are not so well known. A retrospective cohort study reported that 43.6% of UC patients were escalated to weekly adalimumab in English hospitals (6). Another retrospective study reported that 41.3% of patients required optimization to weekly adalimumab to overcome secondary loss of response during maintenance (7). Therefore, it seems that the need for adalimumab dose escalation could be higher in UC patients compared with CD patients.

No studies have directly compared the need for dose optimization in CD and UC, even though loss of response is a problem that is common to both diseases in the clinical practice. The primary objective of this study was to compare the need for and time to adalimumab dose escalation in patients with CD and patients with UC in the same clinical setting. As a secondary objective, the rate of patients in which the adalimumab dose was de-escalated to standard doses was also evaluated. The predictors of adalimumab dose escalation and de-escalation were also analyzed.

PATIENTS AND METHODS

Study design and patients

This was a single center, open-label, observational cohort study. Data were collected prospectively, as part of a well-established treatment protocol and were retrospectively analyzed by chart review. From January 2014 to November 2017, all

consecutive UC patients who received at least adalimumab induction doses in the Inflammatory Bowel Disease Unit of our center were enrolled into the study. Starting on January 2014, an equal number of consecutive CD patients treated with adalimumab were included as a comparator. CD patients with active perianal disease or prior surgery were excluded. Patients were classified according to the internationally accepted Montreal classification (8). Adalimumab was administered for CD or UC according to the indications accepted on the label. The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the design of the study and the preparation of the manuscript. The study was approved by the Ethics Committee of the center (C.I. 12/148-E de 18 de abril de 2012) and informed consent was obtained from each patient.

Criteria for adalimumab dose optimization

Patients were assessed for the need of adalimumab dose escalation by gastroenterologists of the Inflammatory Bowel Disease Unit. The prescription of adalimumab in our unit follows a standard protocol. Demographic data, prior anti-TNF use, concomitant steroid or immunosuppressant therapy and detailed information about adalimumab therapy (induction doses, dose escalation and de-escalation and any adverse reaction) were recorded in a prospectively maintained database. The initiation of treatment was taken as the baseline for the purposes of the analysis. The need for and time to dose optimization were recorded. The time on adalimumab was calculated as the interval between the first adalimumab induction dose and either the last follow-up visit or the time of adalimumab discontinuation for patients who did not require dose escalation.

Adalimumab dose optimization was decided at each visit by the attending gastroenterologists, which was based on the Harvey-Bradshaw index for patients with luminal CD and on the 9-point partial Mayo score for patients with UC. Adalimumab dose escalation was attributed to an inadequate response to induction in patients who did not achieve a response to adalimumab induction doses and required dose escalation before week 12. Secondary loss of response occurred in those patients who initially responded to adalimumab induction doses but subsequently relapsed. This

was defined as a Harvey-Bradshaw score ≥ 5 for luminal CD or partial Mayo score ≥ 4 for UC. Although these clinical scores were used as a guide, the final decision to optimize (escalation or de-escalation) the dose was made by the investigators. The biological and endoscopic data were taken into account when available. In patients with a suspected infection, other causes of persistent symptoms including coexistent cytomegalovirus or *Clostridium difficile* infection were ruled out before dose optimization.

Outcomes

The co-primary endpoints were the differences in the proportion of patients that required escalation (adjusted for time) of the adalimumab dose and the cumulative probability of escalation-free survival between the UC and CD cohorts. The interval between the first adalimumab induction dose and the first adalimumab escalated dose was also evaluated. The proportion of patients who de-escalated to adalimumab 40 mg every other week (EOW) was also assessed during follow-up. The predictors of adalimumab dose escalation and adalimumab dose de-escalation were analyzed, including age, gender, type of disease (CD or UC), duration of disease, extent of disease, smoker status, prior anti-TNF use and concomitant steroids or immunosuppressant at baseline.

Statistical analysis

Study variables were summarized descriptively using numbers and percentages for discrete variables and the mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate for continuous variables. Demographics and disease and treatment characteristics were tested for differences using the χ^2 test for qualitative variables and the Student's t-test or the median test if applicable for quantitative variables. Optimization-free survival was estimated using the Kaplan-Meier method and differences between the curves were evaluated using the Breslow test. Cox proportional hazards survival regression analysis was used to estimate the adjusted hazard ratios and their 95% confidence intervals (CI). Variables with $p < 0.20$ in the univariate analysis were included in the model. The null hypothesis was rejected in

each statistical test when $p < 0.05$.

RESULTS

Patient characteristics

A total of 86 patients were evaluated; this included 43 CD patients and 43 UC patients. At baseline, more patients with CD were smokers, whereas more patients with UC had received prior anti-TNF therapy. All anti-TNF experienced patients had received infliximab as the first-line biological therapy, except one UC patient who was treated with golimumab (1.9%). Baseline characteristics of both cohorts are summarized in table 1.

The need for adalimumab dose escalation

Fifty-two patients required adalimumab dose escalation, 24 of 43 patients (56%) with CD and 28 of 43 patients (65%) with UC. At the time of escalation, patients with luminal CD had a Harvey-Bradshaw score of 8.7 ± 4.1 (range 4-13) and the patients with UC had a 9-point partial Mayo score of 6.2 ± 1.3 (range 4-8). Adalimumab dose optimization was performed by shortening the interval between doses to 40 mg weekly in 45 patients (86%) and to 40 mg every ten days in seven patients (14%). There were no significant differences according to the type of optimization between the CD and UC cohorts ($p = 0.531$). At the time of escalation, 33 of 52 patients (63%) were on immunosuppressants; the proportion was similar regardless of the type of disease.

A numerical difference was found in the duration of exposure to adalimumab between patients with UC (13.9 months, IQR: 5.1-31.5) and patients with CD (median 22.8 months, IQR: 8.1-49.7), although this was not significant ($p = 0.139$). Total exposure to adalimumab was 1,043 months for the 43 patients with UC compared to 1,415 months for the 43 patients with CD. Univariate analysis showed that UC patients had a higher adjusted rate of adalimumab dose escalation (hazard ratio [HR] 2.51, 95% CI: 1.37-4.61; $p = 0.003$) compared with CD patients. After six months follow-up, seven of 43 CD patients (15.2%) and 21 of 43 UC patients (48.8%) had undergone adalimumab dose escalation ($p = 0.001$).

The median time from baseline to optimization in patients who needed adalimumab

dose escalation was significantly shorter in the UC cohort (3.2 months, IQR: 2.0-10.3) compared to the CD cohort (12.2 months, IQR: 6.1-35.7; p = 0.001). Among the 52 patients who required adalimumab dose escalation, the reasons for dose optimization were an inadequate response to adalimumab induction doses in 21 (40.4%) and secondary loss of response in 31 patients (59.6%). The reason for adalimumab dose escalation was an inadequate response to induction doses in five of 24 CD patients (20.8%) *vs* 16 of 28 UC (57.1%) (p = 0.008). As a result, the survival curves for the cumulative probability of avoiding adalimumab dose escalation rapidly separated for the CD and UC cohorts. The UC patients had an increased probability of adalimumab dose optimization compared to CD patients (p < 0.001) (Fig. 1).

Predictors of the need for adalimumab dose escalation

In the univariate analysis, adalimumab dose escalation was more likely in UC than in CD patients and also in patients with prior anti-TNF therapy compared to anti-TNF naïve patients (Table 2). Multivariate analysis was performed that included these variables and those that showed a statistical trend in the univariate analysis. This model retained the type of inflammatory bowel disease and prior anti-TNF therapy as independent predictors of adalimumab dose escalation. There was a higher proportion of UC patients (HR 2.33, 95% CI: 1.19-4.56; p = 0.013) and anti-TNF-experienced patients (HR 2.13, 95% CI: 1.05-4.34; p = 0.037) that required dose optimization.

The rates of adalimumab dose de-escalation

Adalimumab dose de-escalation was attempted in nine of 28 UC patients (32%) *vs* 12 of 24 CD patients (50%). At the time of de-escalation, patients with CD and UC had a Harvey-Bradshaw score of 1.6 (SD ± 0.5, range 0-3) and a partial Mayo score of 0.7 (SD ± 0.2, range 0-2), respectively. CD patients had a higher rate of adalimumab de-escalation (HR 2.32, 95% CI: 1.10-5.59; p = 0.030). Survival curves showed that CD patients had an increased probability of adalimumab dose de-escalation compared to UC patients (Fig. 2). The median time to dose de-escalation was 3.8 months (IQR 3-13) *vs* 8.9 months (IQR 3-30) for CD and UC patients, respectively (p = 0.120). There were no other factors associated with adalimumab dose de-escalation. Among patients with

de-escalated doses of adalimumab, one of nine UC patients (11.1%) and two of 12 CD patients (16.6%) subsequently required escalation of adalimumab dosage during follow-up.

DISCUSSION

This study compared the need for adalimumab dose optimization (escalation and de-escalation) between two cohorts of CD and UC patients. The main finding of the study was that adalimumab dose escalation was required more frequently in UC than in CD, in a real-life setting and following homogeneous criteria.

The CHARM trial demonstrated the efficacy and safety of adalimumab in active CD (1). According to the ULTRA 1 and ULTRA 2 studies, adalimumab was shown to be effective for the induction and maintenance of response in patients with moderately to severely active UC (2,9). However, a significant proportion of CD and UC patients had either an inadequate response to adalimumab induction doses or developed secondary loss of response during maintenance (1,2,9). In clinical trials, these patients were considered as failures to the treatment, but in real life, a benefit can be regained by escalation of the adalimumab dosage before discontinuing the drug. The rationale for adalimumab dose optimization is based on data from the open-label phase of the trials and results from real-life studies. Up to 46% of CD patients in the CHARM trial that were randomized to adalimumab EOW with a lack of response to induction or with an initial response that was then lost were moved to open-label therapy and treated with an open dose of adalimumab at 40 mg EOW. Of these patients included in the open label study, almost 60% were moved to a 40 mg weekly dose and 58% regained a clinical response (3). In the open label phase of the ULTRA 2 trial, escalation to a weekly adalimumab dose demonstrated clinical benefits for UC patients who lost the response to therapy. Thus, it may be beneficial for patients that do not respond initially to induction therapy (4).

The need for adalimumab dose escalation has been evaluated in the clinical practice for both CD and UC. The data to assess the need for dose optimization were more consistent for CD. In fact, a systematic review reported that the mean proportion of CD patients who required adalimumab dose escalation was 24% per patient-year (5). In

the case of UC, the "real-life" need for adalimumab dose optimization is less well defined. According to an observational study of only early responders to adalimumab induction, 41.3% of UC patients required escalation to weekly adalimumab to overcome the secondary loss of response during maintenance (7). Another retrospective study reported that escalation to weekly adalimumab was needed in 35% of UC patients during the first year (10). In a multicenter study performed in English hospitals, 43.6% of UC patients escalated to weekly adalimumab (6). Therefore, indirect comparisons in the clinical practice indicate that the need for adalimumab dose escalation is likely to be higher in UC than in CD. Our study is the first to directly compare the need for adalimumab dose optimization in CD and UC in the same clinical setting. This also confirms the following assumption that UC patients show a significantly longer time adjusted rate of adalimumab dose escalation compared to CD patients. Although it could be argued that the size of the cohorts and follow-up are limited, we have compared more than 1,043 and 1,415 months of follow-up for patients with UC and CD, respectively. Thus, there are highly significant differences in the primary endpoints. In addition, the differences were established very early on and it does not seem reasonable that it would change with a longer follow-up time.

Another main and novel finding of this study was that patients with UC required adalimumab dose escalation earlier than CD patients. This finding had been previously reported with infliximab but not with adalimumab. A previous study from our group compared the need for infliximab dose escalation in CD and UC patients using the same methodology. In this study, UC patients required dose escalation earlier and escalation-free survival was also lower in these patients (11). A subsequent study found similar results, reporting that infliximab dose optimization was required more frequently in UC than in CD. Furthermore, there was a significantly shorter time to dose escalation for UC cases than CD cases (12). Therefore, the results of our study showed that an increased need to optimize the infliximab dose in UC patients is reproduced with adalimumab. This is expected as the mechanism of action of the two TNF antagonists is similar. More recently, several observational studies have reported high rates of golimumab dose optimization in UC patients (13-15).

Several reasons might explain the increased need for anti-TNF dose optimization in UC

patients. A loss of response to anti-TNF agents in CD is generally thought to arise due to the immunogenic nature of these drugs. However, the available data indicate that the development of anti-drug antibodies is not increased in UC patients (16). Therefore, the development of anti-adalimumab antibodies over time that induces a drop in adalimumab trough serum levels and causes a secondary loss of response does not explain the difference reported in the need for adalimumab dose escalation in both diseases. Furthermore, survival curves in our study showed that UC patients required adalimumab dose escalation very early on, with a median time from baseline to escalation of 3.2 months. This is explained as more than half of dose escalation in patients with UC are due to an inadequate response to adalimumab induction doses. Conversely, dose escalation was attributed to an inadequate response to induction in only 20% of CD patients. The available evidence indicates that some patients with active UC had a higher inflammatory burden and/or accelerated anti-TNF clearance and therefore required a higher drug exposure to finally achieve a response to induction with TNF antagonists (17,18). Furthermore, a lack of response to anti-TNF therapy in UC has been associated with fecal losses of anti-TNF (19).

In the clinical practice, de-escalation to standard dose of anti-TNF has been considered due to safety or economic reasons in patients who achieved a long-term remission on the escalated dosage. In our study, adalimumab dose de-escalation was attempted in a higher number of CD than UC patients. In a real-life nationwide Belgian study, adalimumab dose de-escalation was attempted in 54% of CD patients, which is roughly similar to our findings for CD patients (20). Attempts at dose de-escalation in UC have not been well studied. Adalimumab dose de-escalation was attempted in 71% of patients in a recent retrospective study of UC patients (21), which is considerably higher than the dose de-escalation rates reported in our study for UC patients.

The main limitation of our study is that examinations outside those contemplated in the routine clinical practice to guide adalimumab dose optimization were not possible due to the retrospective design. Thus, the decision for adalimumab dose escalation or dose de-escalation was based solely on patient symptoms, which were assessed using the Harvey-Bradshaw index or the partial Mayo score. This assessment is subject to potential bias. The “real-life” approach to dose escalation contrasts with that in clinical

trials. The retrospective design also meant that neither the adalimumab trough levels nor the antibodies to adalimumab were measured. Drug levels and antidrug antibodies are very relevant to understand the mechanisms of an inadequate response to induction and the secondary loss of response to anti-TNF agents. Furthermore, they can help to guide therapeutic decisions (22).

Our study compares the need to optimize the dose of adalimumab in the same clinical setting and shows that patients with UC more frequently require adalimumab dose escalation compared with CD patients. Patients with UC require adalimumab dose escalation earlier than CD patients. Furthermore, more CD patients could be dose de-escalated later on compared to UC patients.

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Table 1. Baseline characteristics of patients

	Crohn's disease (*n = 43*)	*Ulcerative colitis* (*n = 43*)	*p value*
Sex, male	20/43 (46%)	18/43 (42%)	0.869
Age (mean ± SD), years	43.5 (11.5)	49.8 (13.7)	0.024
Duration of disease, median [IQR], years	14.0 (10.0-19.0)	13.0 (9.0-17.0)	0.818
Smoker at baseline	22/42 (52.4%)	3/39 (7.7%)	< 0.001
Prior anti-TNF therapy	19/43 (44.2%)	34/43 (79.1%)	0.001
Steroids at baseline	18/38 (47.4%)	22/35 (62.9%)	0.184
Immunosuppressant at baseline	23/43 (53.5%)	22/43 (51.2%)	0.924

SD: standard deviation; IQR: interquartile range; TNF: tumor necrosis factor.

Table 2. Univariate analysis of factors associated with adalimumab dose escalation

		Escalated (%)	*Escalated (n)*	*Total (n)*	*HR*	*95% CI*		*p*
Sex (M/F)	Male	68.4	26		1			0.127
	Female	54.2	26		0.63	0.35	1.14	
Age, years	≤ 44.5	60.5	26		1			0.320
	> 44.5	60.5	26		1.35	0.75	2.45	
Inflammatory bowel disease	CD	55.8	24		1			*0.003*
	UC	65.1	28		2.51	1.37	4.61	
Duration of disease, years	≤ 13.5	72.1	31		1			0.273
	> 13.5	48.8	21		0.72	0.40	1.30	
Smoker	No	66.1	37		1			0.140
	Yes	52.0	13		0.60	0.31	1.18	
CD phenotype, extension	L1	52.9	9		1			0.628
	L2	42.9	3		0.70	0.19	2.58	
	L3	61.1	11		1.30	0.51	3.29	
CD phenotype, behavior	B1	54.5	18		1			0.579
	B2/B3	60.0	6		1.31	0.50	3.42	
UC extension	E1/E2	53.8	7		1			0.891
	E3	70.0	21		0.94	0.38	2.31	

Prior anti-TNF therapy	No	45.5	15	1			*0.004*
	Yes	69.8	37	2.61	1.36	5.04	
Steroids at baseline	No	54.5	18	1			0.476
	Yes	65.0	26	1.25	0.67	2.32	
Immunosuppressant at baseline	No	46.1	12	1			0.865
	Yes	42.0	21	0.944	0.487	1.829	

HR: hazard ratio; CI: confidence interval; CD: Crohn's disease; UC: ulcerative colitis; TNF: tumor necrosis factor; CD phenotype by Montreal classification: Localization (L), L1: terminal ileum, L2: colon, L3: ileocolon; Behavior (B), B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating; UC phenotype by Montreal classification: E1: proctitis, E2: left-sided, E3: extensive.

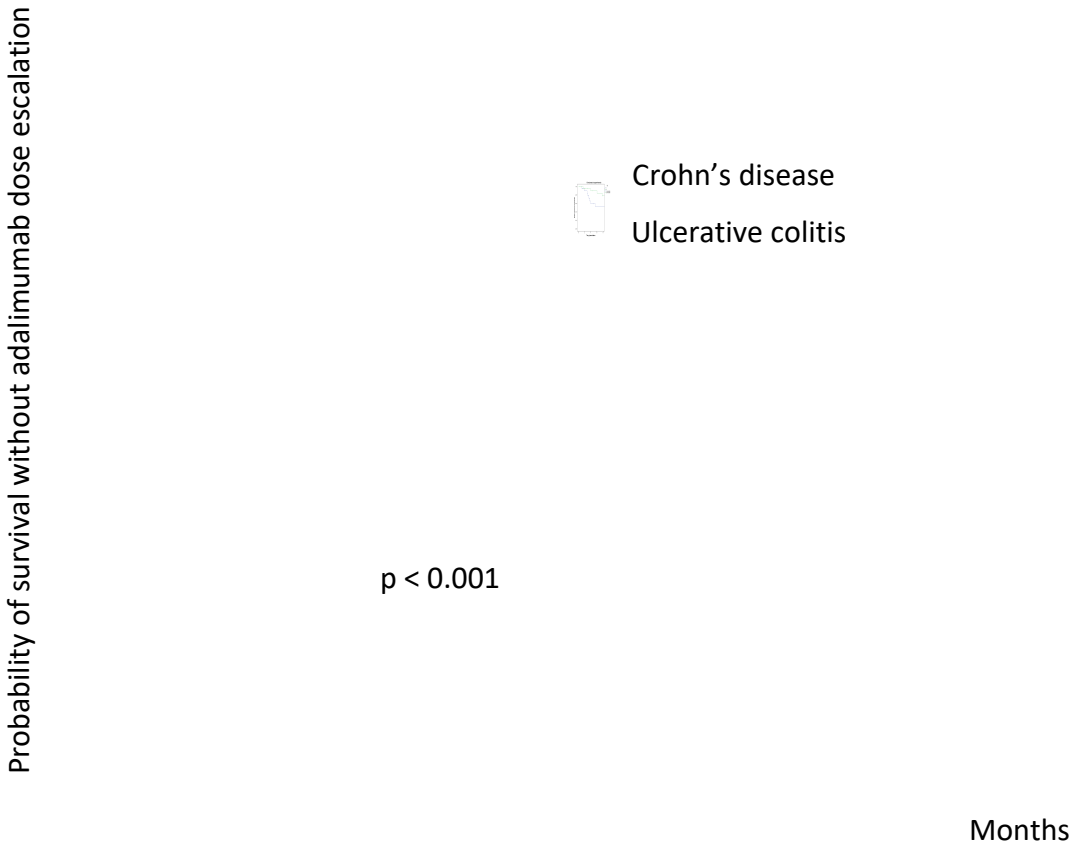

Fig. 1. Cumulative probability of avoiding adalimumab dose escalation: differences in the survival curves between patients with Crohn's disease and ulcerative colitis.

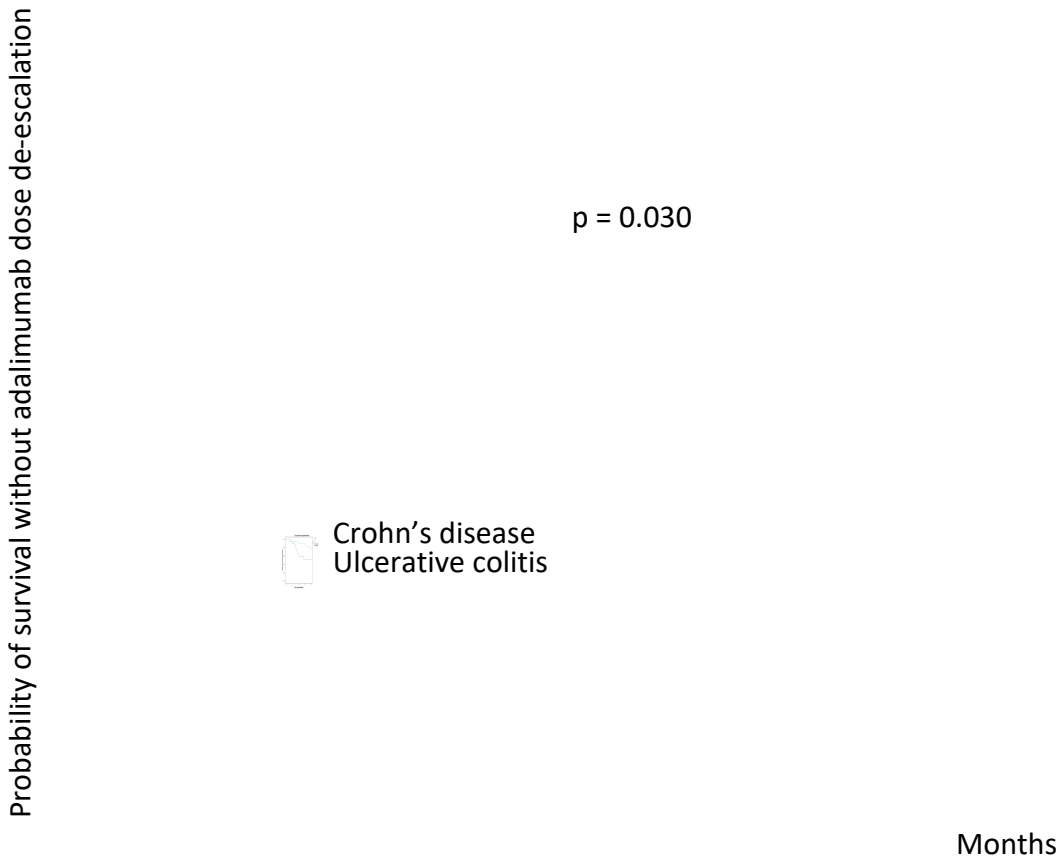

Fig. 2. Cumulative probability of adalimumab dose de-escalation: differences in the survival curves between patients with Cronh's disease and ulcerative colitis.