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ORIGINAL ARTICLE

Infliximab Dose Escalation as an Effective Strategy for Managing Secondary Loss of Response in Ulcerative Colitis

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Abstract

Background The outcomes of infliximab dose escalation in ulcerative colitis (UC) have not been well evaluated.

Aims To assess the short- and long-term outcomes of infliximab dose escalation in a cohort of patients with UC.

Methods This was a multicenter, retrospective, cohort study. All consecutive UC patients who had lost response to infliximab maintenance infusions and who underwent infliximab dose escalation were included. Post-escalation short-term clinical response and remission were evaluated. In the long term, the cumulative probabilities of infliximab failure-free survival and colectomy-free survival were calculated. Predictors of short-term response and event-free survival were estimated using logistic regression analysis and Cox proportional hazard regression analysis.

Results Seventy-nine patients were included. Fifty-four patients (68.4 %) achieved short-term clinical response and 41 patients (51.9 %) entered in clinical remission. After a median follow-up of 15 months [interquartile range (IQR) 8–26], 33 patients (41.8 %) had infliximab failure. Patients with short-term response had a significantly lower adjusted rate of infliximab failure [hazard ratio (HR) 0.24, 95 % confidence interval (CI) 0.12–0.49; $p < 0.001$]. During a median follow-up of 24 months (IQR 13–34), 9 patients (11.4 %) needed colectomy. Short-term response was identified as a predictor of colectomy avoidance (HR 0.14; 95 % CI 0.03–0.69; $p < 0.007$).

Conclusions In UC patients who lost response to infliximab during maintenance, infliximab dose escalation enabled recovery of short-term response in nearly 70 % of

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patients. In the long term, 58 % of patients maintained sustained clinical benefit, and 9 of 10 avoided colectomy. Short-term response was associated with an 86 % reduction in the relative risk of colectomy.

Keywords Ulcerative colitis · Infliximab · Dose escalation · Dose optimization · Colectomy · Cohort study

Introduction

Infliximab, an antibody that targets tumor necrosis factor α, is a safe and effective treatment for patients with moderate-to-severe ulcerative colitis (UC), both for inducing clinical response and as maintenance therapy [1]. However, during follow-up a substantial proportion of UC patients who respond to infliximab induction doses will lose response to infliximab standard maintenance doses [2]. In those patients, the secondary loss of response could be managed by escalation of infliximab therapy (higher doses and/or shortening the interval between doses) to regain therapeutic benefit. However, the response to infliximab dose escalation and the long-term outcomes after escalation have not been well evaluated. As an example, the pivotal active ulcerative colitis (ACT) trials did not allow infliximab dose escalation on loss of response during maintenance [1]. Despite the lack of good quality evidence for infliximab dose intensification in UC, a number of studies have reported high rates of therapy escalation in UC [2–10]. This uncontrolled retrospective studies provided limited data of the results of such strategy. Specifically, the short-term effectiveness of infliximab dose intensification for managing secondary loss of response has not been studied in depth. Regarding long-term outcomes, a retrospective study reported that patients with UC who required infliximab escalation have numerically lower remission rates at 12 months and higher colectomy rates over time [3]. Other clinically important outcomes such as tertiary loss of response after recapturing efficacy from dose escalation, need for further escalations to maintain response, rate of patients who were able to return to the standard infliximab regimen, and frequency of infliximab discontinuation due to intolerance or complete loss of response have not been previously well characterized.

There are currently two other TNF-α antibodies and an anti-integrin molecule approved for the treatment of UC, and switching to any is an alternative to escalating infliximab dosing in patients with UC who have lost response. Therefore, there is a need for the identification of predictors of long-term outcomes after infliximab dose escalation to help provide tailored therapy.

The aim of this study was to assess the short-term response to infliximab dose escalation in a cohort of UC patients who had lost response to the drug. We also examined long-term infliximab failure-free survival and colectomy-free survival rates. A secondary objective was to analyze factors predicting the short- and long-term outcomes of infliximab dose escalation.

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Methods

Study Design and Patients

The study consisted of a multicenter, open-label, uncontrolled, retrospective cohort study of UC patients treated with infliximab. Eligible patients included men or women at least 18 years of age with an established diagnosis of UC. The study population comprised all consecutive UC patients who had lost response to infliximab maintenance infusions from October 2008 to January 2012 and who underwent dose escalation during follow-up. The decision to escalate the infliximab dose and the therapeutic regimen (increasing the dose and/or shortening the infusion interval) was left to the investigators judgment. The demographic and clinical characteristics as well as the concomitant medications were recorded in prospectively maintained databases before the first infliximab dose escalation. The extension of disease was categorized using the Montreal classification [11]. The study was approved by the ethics committees of the participating centers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the design of the study and the preparation of the manuscript.

Outcomes Measures

Short-Term Clinical Response

The disease activity was evaluated by using the partial Mayo score (scores ranging from 0 to 9). Baseline was defined as the time of first infliximab dose escalation. Short-term response was assessed ideally at week 12 (patients received at least two infusions after infliximab dose escalation). The short-term primary endpoint was a clinical response, defined as a three-point decrease in the partial Mayo score or a decrease of $\geq$50 % in the partial Mayo score and a final partial Mayo score of $\leq$2, with a drop in the rectal bleeding subscore of at least one point or an absolute rectal bleeding score of 0 or 1. We assessed the following secondary endpoints: clinical remission, defined as a partial Mayo score of 0 or 1; decrease in the partial Mayo score; decrease in the proportion of patients with C-reactive protein $\geq$5 mg/L; and proportion of patients who were on corticosteroids at baseline and who discontinued these drugs in the short term. Patients were not included in the efficacy analysis if available data were insufficient to calculate the partial Mayo score.

Long-Term Outcomes

Long-term outcomes were evaluated at last follow-up visit. The long-term co-primary endpoints were the proportion of patients without infliximab failure at each study visit including the last follow-up visit and the need for colectomy. Infliximab failure was defined as discontinuation of the drug due to intolerance or complete loss of response, as judged by the treating physician. Infliximab withdrawals due to long-lasting remission or to other causes (like desire to get pregnant) were not considered as infliximab failures. We assess need for further infliximab dose escalations to maintain response. Patients who recaptured response after a second escalation of infliximab dosing were not considered as infliximab failures. We defined sustained clinical benefit as the absence of infliximab failure. The probability of avoiding infliximab failure was analyzed at weeks 20, 40, 52, and 60. The need for colectomy was also recorded during the entire duration of follow-up. For patients who discontinued infliximab, the period between infliximab withdrawal and the last follow-up visit was also considered in terms of the need for colectomy. The probability of avoiding colectomy was analyzed at weeks 20, 40, 52, 60, and 80. The secondary endpoints included the proportion of patients whose corticosteroid treatment was discontinued before the last follow-up visit and the rate of adverse events leading to infliximab withdrawal.

Predictors of Response

We analyzed predictors of short-term response including age, gender, disease duration, extent of disease, corticosteroid, or immunosuppressant use at escalation, having the first dose escalation as inpatient and type of infliximab dose escalation (increasing the dose or shortening the infusion interval). In the long term, we analyzed the predictive factors of infliximab failure and colectomy. The following variables were included: age, gender, disease duration, extent of disease, immunosuppressant use at escalation, having the first dose escalation as inpatient, type of infliximab dose escalation, and short-term response.

Statistical Analysis

Statistical analysis of short-term response and remission rates was limited to descriptive statistics. Proportions were expressed as percentages and 95 % confidence intervals (95 % CI). Paired parametric or nonparametric tests were used to compare continuous variables, expressed as the mean $\pm$ standard deviation (SD) or median and interquartile range (IQR) (P25–P75), while categorical

variables were compared using the Chi-squared or Fisher tests. Logistic regression was performed for predictors of short-term clinical response. Variables with p values below 0.20 in the univariate analysis and those that could plausibly exert clinical influence were included in a multivariate logistic regression analysis. Adjusted odds ratios (OR) and their 95 % CI were calculated. In the long term, two events—infliximab failure-free survival and colectomy-free survival rates—were estimated using survival analysis. The cumulative probabilities of the event-free survival were calculated by the Kaplan–Meier method. The time-to-event variables were analyzed from the date of the first infliximab dose escalation until the date of occurrence of the event or last follow-up. The Breslow exact test was used to evaluate differences in the survival curves. Time-to-event variables (infliximab failure and colectomy) were stratified by response at short term and compared using the Breslow exact test. A last observation carried forward approach was used to estimate the probability of avoiding infliximab failure or colectomy at weeks 20, 40, 52, 60, and 80. Adjusted rates ratios (hazard ratios, HR) were calculated using Cox proportional hazard survival regression analysis. Significance threshold was 0.05 for all analyses. Statistical analyses were performed using the SPSS software version 15.0.

Results

Patient Characteristics

Seventy-nine patients with active UC treated in 14 IBD referral centers were included in the study. The characteristics of the patients at baseline (time of first infliximab dose escalation) are summarized in Table 1. Thirty-three patients (43 %) were receiving corticosteroids at baseline; six of them were treated with beclomethasone dipropionate. Sixty-one patients (77 %) were receiving an immunosuppressant (56 patients received azathioprine or mercaptopurine, 4 patients received methotrexate, and 1 patient received tacrolimus). In 30 patients (38 %), infliximab escalation was performed by increasing the dose to 10 mg/kg every 8 weeks. In 49 patients (62 %), the interval between infliximab doses was shortened: 28 patients (35 %) received 5 mg/kg every 6 weeks and 21 patients (27 %) received 5 mg/kg every 4 weeks. In 13 patients (16 %), the first dose escalation was administered in an inpatient setting. Four additional patients were not included in the efficacy analysis because available data were insufficient to calculate the partial Mayo score; these patients were, however, included in the safety analysis.

The flowchart of infliximab dose escalation outcomes in the whole cohort is shown in Fig. 1.

Table 1 Baseline characteristics of the patients

Patients (n)	79
Male, n (%)	41 (52)
Mean age, years (SD)	46 (14)
Extension, n (%)	
Proctitis	3 (4)
Left sided	31 (39)
Pancolitis	45 (57)
Smoker status, n (%)	
No	67 (85)
Yes	12 (15)
Median disease duration, years (IQR)	7 (5–11)
Median time to escalation, weeks (IQR)	40 (19–115)
Partial Mayo score, mean (SD)	5.6 (1.2)
C-reactive protein ≥5 mg/L, n (%)	65 (82)
Drugs used at baseline	
Steroids, n (%)	34 (43)
mg/day (SD)	34.2 (17.4)
Immunosuppressant, n (%)	61 (77)

IQR interquartile range, *SD* standard deviation

Clinical Response to Infliximab Dose Escalation

Short-Term Clinical Response

Fifty-four of 79 patients (68.4 %; 95 % CI 58.1–78.6) achieved short-term clinical response. Forty-one patients (51.9 %; 95 % CI 40.9–62.9) entered in clinical remission. The mean partial Mayo score was 5.6 (range 4–8; SD ± 1.2) at baseline versus 2.3 (range 0–8; SD ± 2.4) at week 12 ($p < 0.0001$). At baseline, 65 patients (82 %) had C-reactive protein ≥5 mg/L. Twenty patients (25 %) presented C-reactive protein ≥5 mg/L at week 12 ($p = 0.001$). Of the 34 patients who were on corticosteroids at baseline, 25 (73.5 %) discontinued these drugs in the short term. None of the patients needed a colectomy before week 12.

Long-Term Outcomes

Sustained Clinical Benefit After a median follow-up after the first infliximab dose escalation of 15 months (IQR 8–26), 46 of 79 patients (58.2 %; 95 % CI 47.4–69.1) maintained sustained clinical benefit. Thirty-three patients (41.8 %; 95 % CI 30.9–52.6) had infliximab failure (Fig. 2). The reason for infliximab failure was complete loss of response in 26 patients and adverse events in 7 patients. Infliximab was discontinued in a further 6 patients: in 5 patients due to long-lasting remission and in 1 patient due to desire to get pregnant. The median time to infliximab discontinuation was 6 months (IQR 3–11). The

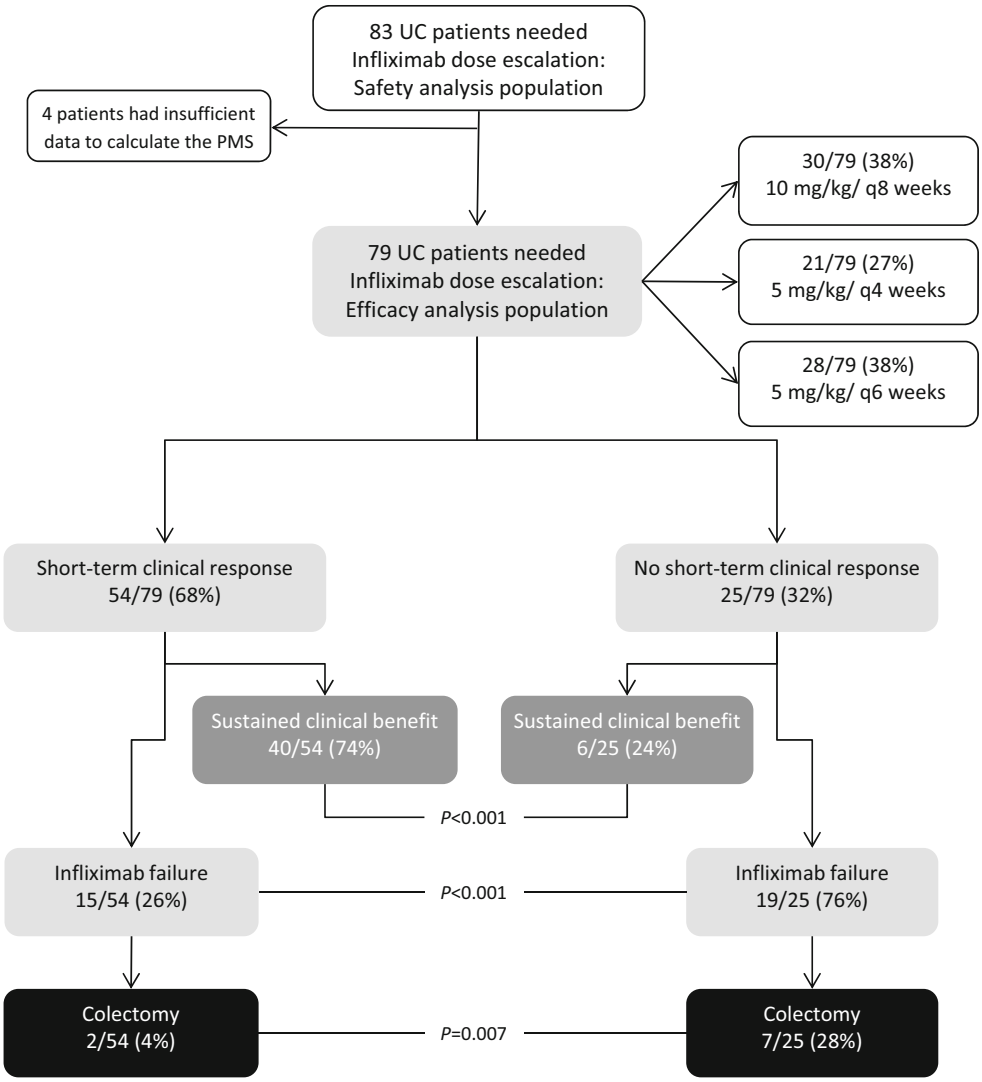

Fig. 1 Flowchart of infliximab dose escalation outcomes in the whole cohort. *UC* ulcerative colitis, *PMS* partial Mayo score

probability of maintaining sustained clinical benefit was 82, 67, 60, and 58 % at 20, 40, 52, and 60 weeks, respectively. Only 14 of 54 patients (26 %) who achieved short-term clinical response had infliximab failure at the last follow-up visit. Among the 28 patients who received 5 mg/kg every 6 weeks, 18 (64 %) required a second dose escalation (mainly to 5 mg/kg/every 4 weeks or to 10 mg/kg every 8 weeks). Median time to the second escalation was 5 months (IQR 2–14). After a median time from dose escalation of 6 months (IQR 4–11), 12 of 79 patients (24 %) were able to return to the standard infliximab regimen (5 mg/kg every 8 weeks). Among the 21 patients who were taking steroids at the time of infliximab dose escalation and continued on infliximab in the long term, 19 (90 %) were able to completely stop steroids during follow-up.

Colectomy During a median follow-up of 24 months (IQR 13–34), 9 of 79 patients (11.4 %; 95 % CI 4.4–18.4) needed colectomy (Fig. 3). The median time to colectomy was 9 months (IQR 7–12). The probability of avoiding colectomy was 99, 94, 91, 90, and 90 % at 20, 40, 52, 60, and 80 weeks, respectively. Colectomies were performed at weeks 19, 28, 34, 36, 37, 42, 43, 57, and 130. Seven of the colectomies occurred among the 25 short-term nonresponders (28 %). Only 2 of 54 patients (4 %) who achieved short-term clinical response required colectomy during the follow-up ($p = 0.005$) (Fig. 1). Of the 13 patients who received infliximab as in-patients, 3 (23 %) underwent colectomy at weeks 36, 42, and 130, respectively.

Predictive Factors

We explored the factors associated with short-term response, and we did not find any significant predictor in the univariate analysis. Our data showed a 63 % reduction in the short-term response rate in patients who received infliximab 5 mg/kg every 6 weeks compared to patients in

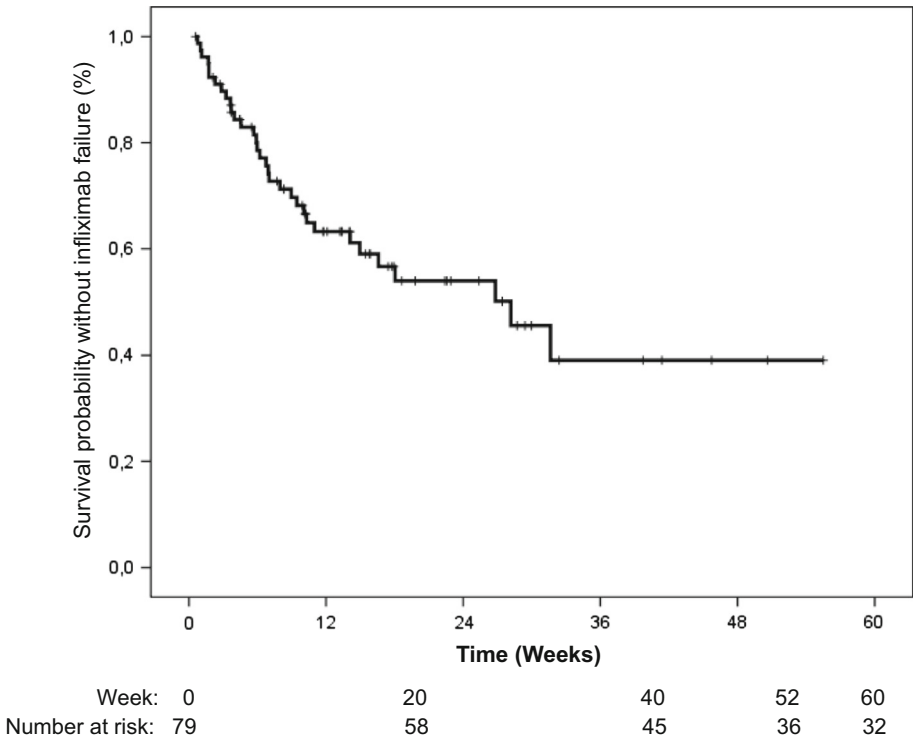

Fig. 2 Cumulative probability of avoiding infliximab failure during follow-up after dose escalation

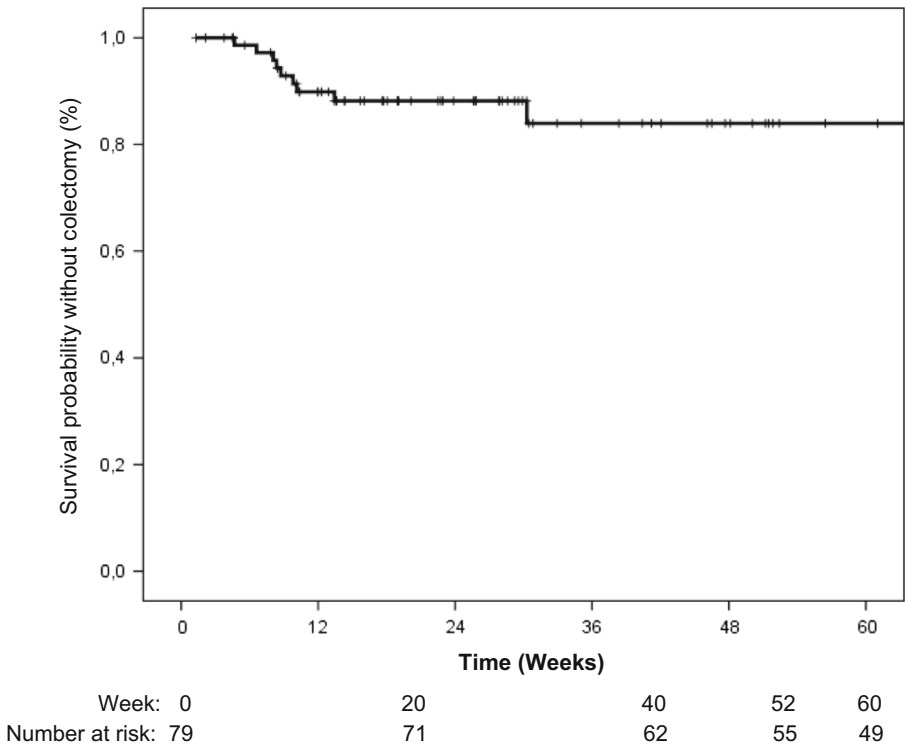

Fig. 3 Cumulative probability of avoiding colectomy during follow-up after dose escalation

whom infliximab was escalated by doubling the dose (OR 0.37; 95 % CI 0.11–1.17, $p = 0.09$).

Regarding long-term outcomes, survival curves showed that patients with short-term clinical response had an increased probability of remaining infliximab failure-free (Breslow $p < 0.001$) (Fig. 4a). The Cox proportional hazard survival regression analysis indicated that patients with short-term response had a significantly lower adjusted rate of infliximab failure (HR 0.24; 95 % CI 0.12–0.49; $p < 0.001$). Evaluation of the survival curves showed that

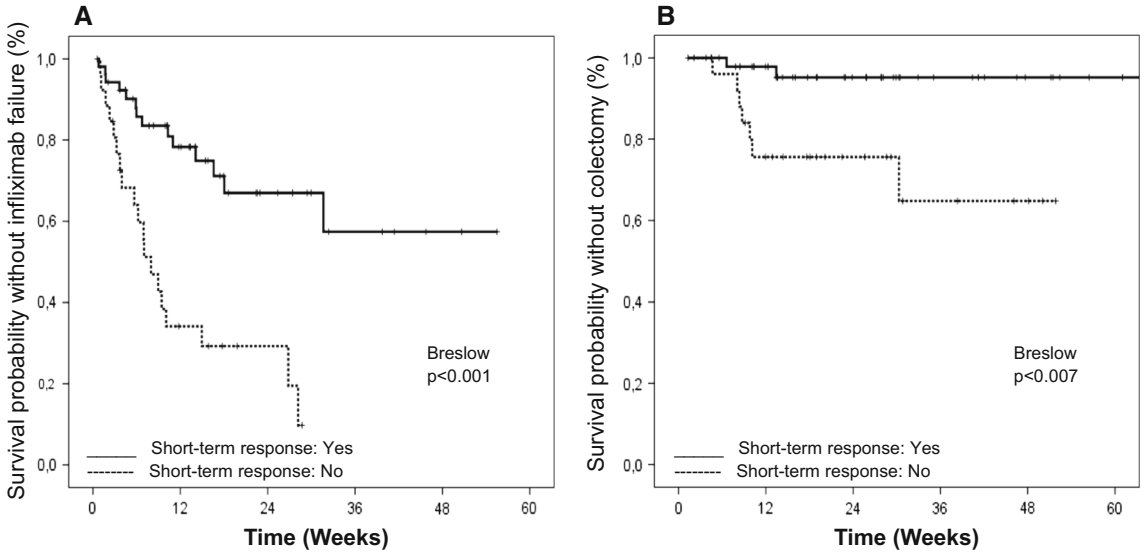

Fig. 4 **a** Cumulative probability of avoiding infliximab failure during follow-up: differences in the survival curves between patients with and without short-term clinical response after dose escalation (Kaplan–Meier method). **b** Cumulative probability of avoiding colectomy during follow-up: differences in the survival curves between patients with and without short-term clinical response after dose escalation (Kaplan–Meier method)

Table 2 Predictors of colectomy: univariate Cox regression analysis

Variable	HR	95 % CI	*p* value
Short-term response (yes)	0.14	0.03–0.69	0.007
Gender (male)	1.14	0.31–4.26	0.84
Extension (pancolitis)	1.51	0.69–3.32	0.27
IMM at intensification (yes)	0.59	0.15–2.37	0.47
IFX administration (inpatient)	2.24	0.56–9.01	0.28
Age	1.03	0.98–1.07	0.28
Duration of disease	1.03	0.93–1.13	0.59
Intensification			
5 mg/kg/6 weeks	1.31	0.29–1.07	0.69
5 mg/kg/4 weeks	1.00	0.17–6.01	0.86
10 mg/kg/8 weeks			

HR hazard ratio, *CI* confidence interval, *IMM* immunosuppressant, *IFX* infliximab

achieving short-term clinical response was associated with long-term colectomy-free survival (Breslow $p < 0.007$) (Fig. 4b). Short-term response was identified as an independent and highly significant predictor of colectomy avoidance (HR 0.14; 95 % CI 0.03–0.69; $p < 0.007$) (Table 2).

Safety

Eighty-three patients, exposed to high doses of infliximab for a total of 1175 months, were included in the safety analysis. Fifteen patients (18 %) experienced 18 adverse events, corresponding to an overall rate of 18 adverse events per 100 patients/years of therapy. Six adverse events were considered as serious, corresponding to an overall rate of 6 serious adverse events per 100 patients/years of therapy. The serious adverse events were as follows: 1 deep venous thrombosis, 1 cerebral thrombosis, 1 pneumonitis, 1 lymphocytic meningitis, 1 psoriasis de novo, and 1 prostate cancer. Seven adverse events led to the discontinuation of infliximab, including those in all the patients with serious adverse events (except the case of the deep venous thrombosis) and those in two other patients who had an acute infusion reaction.

Discussion

The present study reports the outcomes of infliximab dose escalation in a cohort of UC patients. Of note, the study assessed the effectiveness of increasing infliximab dosing to overcome the loss of response to the drug. The main finding of the study was that nearly 70 % of UC patients recaptured response after dose escalation and that response was a potent predictor of colectomy avoidance in the long term.

In Crohn's disease (CD), infliximab dose escalation has been established as an effective approach for managing secondary loss of response [12]. In the ACCENT I trial, approximately 90 % of patients receiving infliximab 5 mg/kg every 8 weeks who had lost response recaptured response on switching to 10 mg/kg [13]. The case for dose escalation in patients with UC who lose response to

infliximab is less clear. In the active UC (ACT) trials, patients were randomized to scheduled therapy with infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo. The results did not show differences in efficacy between the infliximab groups. The ACT trials did not allow infliximab dose escalation on loss of response during maintenance [1]. In the open-label extension of the ACT studies, 16 of 117 patients needed dose escalation, but the outcomes of such a procedure were not analyzed [4]. Evidence from uncontrolled retrospective studies regarding the results of infliximab dose escalation in UC is also scarce [3, 9, 14]. Surprisingly, despite the lack of good quality evidence, in clinical practice the rate of patients who have had infliximab dose escalation seems to be higher in UC [2–10] compared to CD [12].

The present study represents the largest cohort on the outcomes of infliximab dose escalation in UC patients reported to date. In our study, dose escalation recaptured response in nearly 70 % of patients. Regarding predictive factors, there was a trend toward a reduced response rate in the short term in patients who received infliximab 5 mg/kg every 6 weeks compared to patients in whom infliximab was escalated by doubling the dose. This seems to be logical because the latter patients received a greater dose prior to evaluation. In our cohort of UC patients, there were no differences between doubling the dose and halving the interval as escalation strategies. This equivalence of the two escalation strategies has already been reported for CD patients [15]. In the short term, more than 50 % of patients presented a partial Mayo score of 1 or 0 and were considered to be in clinical remission. Our results are in line with Cesarini et al., who reported that rapid clinical remission after infliximab optimization was achieved in 46 % of UC patients [14]. In the long term, 60 % of patients maintained sustained clinical benefit at 1 year after the first infliximab dose escalation. Among the patients who had sustained clinical benefit, 97 % were able to completely stop steroids during follow-up. In a "real-life" study that evaluated a large cohort of UC patients treated with infliximab, 66 % of initial responders maintained sustained clinical benefit after the first infliximab induction dose [2]. This study comprised both patients needing infliximab dose optimization and those who remained on infliximab standard dosing, while our study only included patients who needed dose escalation to overcome the loss of response.

The most objective and relevant outcome of the study is the observed colectomy rate. Patients with UC who lost response to infliximab maintenance doses are generally candidates for colectomy, given that all other previous medications will have likely failed. During the entire duration of follow-up, the colectomy rate in the whole study population was 11 %. In a systematic review of clinical trials, referral center studies and population-based cohorts between 10 and 36 % of adult patients treated with infliximab for UC underwent colectomy [16]. Data from the ACT trials showed infliximab to have a colectomy-sparing effect in UC out-patients. In the post hoc analysis of the ACT-1 and ACT-2 trials, the cumulative incidence of colectomy at 54 weeks was 12 and 8 % for the infliximab 5-mg/kg arm and the 10-mg/kg arm, respectively [17]. In our study, just 7 patients (9 %) needed colectomy 1 year after the first infliximab dose escalation. Again it should be emphasized that our study only included patients who needed dose optimization and not those who were doing well on infliximab standard dosing. Our result is consistent with a observational study that had reported a colectomy rate at 52 weeks of 11 % in a cohort of UC patients requiring dose optimization with infliximab [14].

We found no differences in the short-term response, infliximab failure, and colectomy rates according to the concomitant use of immunosuppressant drugs at escalation. In a recent study, UC patients treated with infliximab and azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving infliximab monotherapy [18]. Consistent with our study results, in the post hoc analysis of the ACT trials and in two large studies that evaluated the outcomes of infliximab in UC patients, concomitant use of immunosuppressants was not predictive of colectomy [2, 17, 19]. Having short-term clinical response after infliximab dose escalation was the only significant predictor of better outcomes in the long term. Among the cohort of patients achieving short-term response, 3 of 4 maintained sustained clinical benefits and only 4 % needed colectomy. Conversely in the cohort of short-term nonresponders, only 1 of 4 patients had sustained clinical benefits and 28 % needed colectomy. For patients who had short-term response, there was an 86 % reduction in the relative risk of colectomy. These marked differences help decide the best strategy in UC patients soon after optimizing the infliximab dosing.

There are currently two other TNF-α antibodies (adalimumab and golimumab) and a anti-integrin molecule (vedolizumab) approved for the treatment of UC [20–22], and switching to any of them is an alternative to escalating infliximab dosing in patients who have lost response to the drug. In CD patients, treatment optimization is considered the best alternative to counteract loss of response to an anti-TNF agent [23]. Thus, for CD patients, exhausting treatment options with infliximab by interval and/or dose optimization should always be considered before switching to another drug [24]. To the best of our knowledge, the findings of our study provide the best available evidence to recommend the same strategy in UC patients who have lost response to infliximab. On the other hand, clinical trial data in UC patients indicate that prior exposure to infliximab attenuates the response to a second anti-TNF agent [20]. However, in clinical practice adalimumab seems to be

useful as an alternative treatment in UC after discontinuation of infliximab due to an adverse effect or after loss of response [25].

The limitations of this study include the retrospective nature of the study and the lack of control group. With the retrospective design, it was not possible to preestablish examinations outside those contemplated in routine clinical practice. Thus, the definition of remission used in our study is weak, since no endoscopic evaluation was carried out. Another limitation of the study was the discretional criteria used to decide infliximab dose escalation, based only on patient symptoms assessed using the partial Mayo score and on C-reactive protein levels. The retrospective design also meant that neither the infliximab trough levels nor the antibodies to infliximab were available. Drug levels and anti-drug antibodies are very relevant to understanding the mechanisms of the secondary loss of response to anti-TNF agents and can help guide therapeutic decisions [26]. A recent study reports that therapeutic drug monitoring of infliximab in UC patients developing secondary failure strongly predicts the likelihood of achieving mucosal healing following infliximab dose escalation [27]. Genetic test was not available in our study. Genetic polymorphisms may contribute to predict efficacy of infliximab [28, 29].

In our study, high infliximab doses were generally well tolerated, with a safety profile consistent with that of large, controlled, or observational series [1, 2, 4, 19]. It should be noted that the patients in our cohort were exposed to high infliximab doses during a total of 1175 months and had an overall rate of 6 serious adverse events per 100 patients/years of therapy.

In conclusion, our cohort study reports the largest experience on outcomes of infliximab dose escalation in UC patients. In the real-life clinical setting, increasing infliximab dosing for managing secondary loss of response is beneficial and safe, with approximately 70 % of patients recovering the response after escalation. Our results suggest that for UC patients who have lost response to infliximab during maintenance infliximab dose escalation should be considered before switching to another drug. Patients who achieved short-term response have a very low colectomy rate in the long term, which may guide therapeutics decisions soon after optimizing the infliximab dosing.

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Conflict of interest C.T., M.B., M.C., C.S., G.B., M.D.M., J.P.G., V.G., I.M., F.B., M.Ch., M.P.M., J.L.M., and I.F. have served as a speaker and consultant for MSD and AbbVie. M.Ch. has received research funding from MSD and AbbVie. The remaining authors declare that they have nothing to disclose. Writing support was provided by G. Morley and funded by MSD of Spain.

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