Incidence and Predictors of Success of Adalimumab Dose Escalation and De-escalation in Ulcerative Colitis: a Real-World Belgian Cohort Study

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Background: Adalimumab (ADM) has been shown efficacious in ulcerative colitis (UC). In randomized controlled trials, dose escalation from 40 mg ADM every other week to 40 mg every week was required in 20%–25% of patients within 1 year. Real-life data suggest higher escalation rates. Attempts for dose de-escalation have not been studied yet. We assessed the need for, outcome of, and predictors of dose escalation and de-escalation in a large retrospective cohort of UC patients treated with ADM.

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Abbreviations: ADM, adalimumab; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; LOR, loss of response; NS, not significant; OR, odds ratio; PNR, primary non response; PRO, patient reported outcome; TNF, tumor necrosis factor; UC, ulcerative colitis; 95%CI, 95% confidence interval

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Methods: We included 231 consecutive patients from 10 Belgian centers initiating ADM treatment for active UC before September 1, 2015 (follow-up ≥1 year in each patient). We performed detailed chart review to identify variables associated with short-term clinical benefit (based on physician global assessment and absence of rectal bleeding at week 10), success of dose escalation, and dose de-escalation. Backward Cox regression and Wald Logistic regression were used to identify predictive variables.

Results: Short-term clinical benefit was achieved in 101 patients (44%) and was less frequent in infliximab failures [37% vs 50%, Odds ratio 0.57 (95% CI 0.34–0.97), $P = 0.038$]. After a median of 2.8 (1.7–5.1) months, 164 patients (71%) needed ADM discontinuation (n = 35, 15%) or dose escalation (n = 129, 56%). Dose escalation was successful in 77/129 (60%). Dose de-escalation was attempted in 71% (55/77) after a median of 4.3 (2.9–7.2) months and was successful in 80% (43/54).

Conclusions: In this cohort, 56% of patients with UC required ADM dose escalation with a 60% success rate. Of note, most patients could be successfully de-escalated later on.

Key Words: adalimumab, dose-optimization, dose escalation, dose de-escalation, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting inflammatory bowel disease (IBD) that is characterized by inflammation of the colorectal mucosa due to a dysregulation of the adaptive immune system towards commensal enteric bacteria in a genetic susceptible host.[1,2] The impact of IBD on patients' quality of life should not be underestimated and early introduction of medical treatment is recommended to ensure induction and maintenance of clinical remission. According to the algorithm for management of moderate to severe UC, conventional (first-line) therapy consists of mesalamine, corticosteroids, and thiopurines.[3–5] The introduction of infliximab (IFX) dramatically changed the treatment objectives, since IFX proved not only to be associated with clinical remission, but also with complete steroid tapering, mucosal healing, decreased surgery and hospitalization rates, and increased quality of life.[6] Some years later, adalimumab (ADM), a fully human monoclonal antibody directed against tumor necrosis factor (TNF), showed its efficacy in patients with moderate to severe UC. Indeed, in both ULTRA 1 and ULTRA 2 ADM was associated with improved clinical outcomes in patients with moderate to severe UC not responsive to conventional or IFX therapy.[7,8] The classic induction dose consists of 160 mg of ADM subcutaneously at week 0 and 80 mg at week 2, followed by a maintenance dose of 40 mg ADM every other week.

In randomized trials, dose escalation from 40 mg every other week to 40 mg every week was required in 20%–25% of patients within 1 year.[8] A recent systematic review, estimated the risk for dose intensification to ADM 40 mg every week in clinical practice to be around 24.8% per patient-year.[9] Whereas data are available for Crohn's disease (CD),[10] real-world data on ADM dose escalation and de-escalation are scarce for UC. Similarly, the knowledge of factors associated with the need for and success of dose escalation and de-escalation is very limited. Dose de-escalation may have an important impact on reducing health care costs. Therefore, this study aimed to assess the need for, the outcome of, and predictors of dose escalation and dose de-escalation in a large cohort of patients with UC treated with ADM.

MATERIALS AND METHODS

Study Population

This retrospective multicentric Belgian observational cohort study included 231 consecutive patients initiating ADM treatment for active UC before September 1, 2015 in 10 Belgian IBD centers. All consecutive UC patients that had started ADM could be identified as these centers maintained a prospective database. By excluding patients who had initiated ADM after September 1, 2015, the follow-up was at least 1 year in each patient.

All patients met the Belgian reimbursement criteria for ADM in UC: having failed mesalamine, steroids, or thiopurines for at least 3 months, or intolerance to any of these therapies. At start of ADM, patients had a total Mayo score of at least 6 with an endoscopic subscore of at least 2.[11] Exclusion criteria for this cohort included: subjects previously treated with ADM, subjects treated with ADM for other indications than moderate to severe UC, or subjects who underwent subtotal colectomy or proctocolectomy before ADM initiation. As a consequence, asymptomatic patients who switched from other biological therapy (including IFX) to ADM because of adverse events or immunogenicity were excluded.

A detailed retrospective chart review was performed, including patients' demographics, disease characteristics, previous and concomitant medication including prior IFX use, and the reason for IFX discontinuation. Data on concomitant medications, C-reactive protein (CRP), hemoglobin, serum albumin, patient reported outcomes (PRO2, based on stool frequency and rectal bleeding), and Mayo endoscopic subscore were collected for baseline (before initiation of ADM) and follow-up visits.

Objectives and Endpoints

The primary objective was to assess the need and the success rate of ADM dose escalation from 40 mg every other week to 40 mg every week in patients with moderate to severe UC. The secondary objective was to assess short-term clinical benefit to ADM in patients with moderate to severe UC and the

success rate of ADM dose de-escalation back to 40 mg every other week, and the need for ADM discontinuation.

The primary endpoint was the need for ADM discontinuation or dose escalation, which was defined as the increase of ADM 40 mg every other week to ADM 40 mg every week (with or without addition of an immunomodulator or any type of steroid) based on absence of short-term clinical benefit or loss of response.

Short-term clinical benefit was assessed at week 10 and was based on physician global assessment with absence of rectal bleeding. Due to the retrospective nature of this study, a Mayo-based clinical response and remission could not be evaluated. However, mucosal healing could be evaluated as part of the reimbursement criteria and was defined as a Mayo endoscopic subscore of 0 or 1 at lower endoscopy performed between weeks 8 and 14.

Dose escalation was defined as the increase of ADM 40 mg every other week to ADM 40 mg every week (with or without addition of an immunomodulator or any type of steroid) based on absence of short-term clinical benefit or loss of response. Loss of response was based on a physician global assessment. Success of dose escalation was defined based on a positive physician global assessment with absence of rectal bleeding following this intervention on 2 consecutive visits at least 3 months apart. Dose de-escalation was defined as the decrease from ADM 40 mg every week back to ADM 40 mg every other week after successful dose escalation. Success of dose de-escalation was defined as persistent ADM use at a dose of 40 mg every other week for at least 6 months after dose de-escalation. Of note, dose de-escalation due to adverse events alone was not accounted for in this study.

Statistical Analysis

Continuous data were presented as medians with interquartile ranges. LogRank, ChiSquare, Mann-Whitney *U* statistics and backward Cox regression and backward Wald Logistic regression were used to identify (independent) predictors of short-term clinical benefit, need, and success of ADM dose escalation and dose de-escalation. All statistical tests were performed using the IBM SPSS Statistics 23.0 software package (Armonk, NY). Independent variables included sex, age, disease duration, extent of disease, presence of extraintestinal manifestation, smoking behavior, prior anti-TNF exposure, concomitant therapy, baseline body weight, body mass index, total Mayo score, endoscopic Mayo subscore, hemoglobin, CRP, and serum albumin. Results were expressed as odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (95% CI), following by the corresponding P value. P values less than 0.05 were considered as statistically significant. Only factors that were significantly associated with a specific outcome in univariate analysis ($P < 0.05$) were included in the multivariate analysis.

RESULTS

Study Population

In total, 231 consecutive patients [67% male, median (interquartile, IQR) age at start of ADM 39.7 (30.5–53.7) years] were included. Patients' characteristics are listed in Table 1. Two thirds of the patients were included from 4 different university hospitals, whereas the other third were included from 6 nonuniversity IBD centers. Sixty-three percent (n = 146) of the patients were previously treated with IFX. The main reasons for discontinuation of IFX were loss of response (62%), adverse events (28%), and immunogenicity (22%). Two hundred and twenty-six patients (98%) received an induction dose of 160/80 mg of ADM, whereas 5 patients received 80/40 mg induction as part of the ULTRA-trials. Eighty-two percent of the patients were using immunosuppressive agents during induction therapy with ADM, which was considered as concomitant therapy. Patients who had received induction with placebo followed by maintenance therapy with ADM as part of the same ULTRA-trials were excluded. Median (IQR) time of follow-up was 40.7 (20.0–71.6) months.

Short-term Evaluation

Induction treatment with ADM resulted in a short-term clinical benefit in 101 (44%) patients. Factors associated with short-term clinical benefit in univariate analysis are summarized in Table 2. Previous primary or secondary IFX failure was the only independent factor associated with a worse short-term clinical benefit at multivariate analysis [37% vs 50%, OR 0.57 (95% CI 0.34–0.97), $P = 0.038$].

Results of short-term mucosal healing between week 8 and 14 were only available in 141 of the 231 patients. In the subgroup of patients who underwent an endoscopic evaluation, short-term mucosal healing was observed in 46% (n = 65/141). Factors associated with short-term mucosal healing in this subpopulation are depicted in Table 2. In multivariate analysis, previous primary or secondary failure of IFX [OR 0.27 (0.12–0.62), $P = 0.002$] and a baseline endoscopic Mayo subscore of 3 [0.31 (0.14–0.71), $P = 0.006$] were both associated with absence of short-term mucosal healing.

Need and Success of Dose Escalation (or Discontinuation)

ADM discontinuation (n = 35, 15%) or dose escalation (n = 129, 56%) was needed in 164 patients (71%) after a median of 2.8 (1.7–5.1) months (Figs. 1, 2). None of the patients underwent dose discontinuation or dose escalation during the 4 week induction period. Several factors predicted the need for ADM discontinuation or dose escalation in univariate analysis (Table 2). Disease duration of a least 5 years [HR 1.72 (95%CI 1.26–2.35), $P = 0.001$], absence of previous IFX failure [HR 1.40 (95%CI 1.02–1.92), $P = 0.036$], and short-term clinical

Table 1: Patients' Characteristics at Initiation of ADM (n = 231)

Male sex (%)	154/231 (67)
Median (IQR) age at diagnosis (y)	30.6 (22.9–44.8)
Median (IQR) age at start of ADM (y)	39.7 (30.5–53.7)
Median (IQR) disease duration at start of ADM (y)	5.5 (2.6–11.8)
University setting (%)	154/231 (67)
Extent of disease[a]	
Proctitis (%)	9/227 (4)
Left-sided colitis (%)	124/227 (55)
Extensive colitis (%)	94/227 (41)
Extraintestinal manifestations of interest	
Primary sclerosing cholangitis (%)	8/231 (3)
Spondylartropathy (%)	18/231 (8)
Smoking behavior	
Never smoking (%)	113/196 (58)
Discontinued smoking (%)	68/196 (35)
Active smoking (%)	15/196 (7)
Prior anti-tumor necrosis factor therapy	
IFX (%)	146/231 (63)
Golimumab (%)	0/231 (0)
Reason to discontinue IFX	
Primary nonresponse (%)	24/146 (16)
Loss of response (%)	90/146 (62)
Immunogenicity (%)	32/146 (22)
Adverse events (%)	41/146 (28)
Pregnancy (%)	1/146 (1)
Induction dose of ADM	
160–80 mg (%)	226/231 (98)
80–40 mg (%)	5/231 (2)
Concomitant therapy	
Any mesalamine (%)	150/231 (65)
Oral mesalamine (%)	141/231 (61)
Rectal mesalamine (%)	34/231 (15)
Any steroid (%)	113/231 (49)
Oral or intravenous steroid (%)	106/231 (46)
Rectal steroid (%)	11/231 (5)
Thiopurines (%)	73/231 (32)
Median (IQR) body length (cm)	172 (167–180)
Median (IQR) body weight (kg)	70 (60–83)
Median (IQR) body mass index (kg/m^2)	23.75 (20.41–26.87)
Median (IQR) total Mayo score	8.0 (7.0–9.5)
Median (IQR) Mayo endoscopic subscore	2.0 (2.0–3.0)
Mayo endoscopic subscore of 3 (%)	96/205 (47)
Median (IQR) hemoglobin (g/dL)	13.2 (12.1–14.3)
Median (IQR) CRP level (mg/L)	4.4 (1.5–14.0)
CRP > 5 mg/L (%)	79/168 (47)
Median (IQR) serum albumin (g/L)	42.0 (39.2–45.0)

[a]According to the Montreal classification[23]

benefit to ADM [HR 3.37 (95%CI 2.39–4.74), $P < 0.001$] were independently associated with ADM discontinuation or dose escalation free survival in Cox regression multivariate analysis.

After dose escalation, 77 out of 129 patients (60%) regained clinical benefit (Fig. 1). Factors associated with successful dose-escalation in univariate analysis are depicted in Supplementary Table 2. Only short-term clinical benefit to ADM independently predicted successful dose escalation [OR 3.08 (95%CI 1.46–6.49), $P = 0.003$].

Dose De-escalation

Dose de-escalation from ADM every week to ADM every other week was attempted in 71% (55/77) after a median of 4.3 (2.9–7.2) months (Fig. 1). Dose de-escalation was successful in 80% (43/54), but no predictive markers could be identified either in univariate or in multivariate analysis. In one patient, success of dose de-escalation could not be evaluated since follow-up was too short.

Long-term Outcome

Among the 113 patients who were taking concomitant steroids (intravenous, oral, or rectal) at initiation of ADM, 49% (n = 57) were able to discontinue all steroids throughout follow-up.

In total, 56 (24%) patients discontinued ADM after a median of 40.7 (20.0–71.6) months. In 35 patients (15%) this was without an attempt to increase the dose to 40 mg ADM every week. The main reasons for discontinuation of ADM were primary nonresponse (13%), ADM-related adverse events (7%), secondary loss of response (2%), and clinical remission (2%). Factors associated with ADM discontinuation in univariate analysis are listed in Table 2. Short-term clinical benefit [HR 2.12 (95%CI 1.51–2.99), $P < 0.001$] was independently associated ADM discontinuation free survival.

After a median of 40.7 (20.0–71.6) months, 35 (15%) patients needed colectomy (Fig. 3). Several factors predicted the need for colectomy in univariate analysis, summarized in Table 2. However, at multivariate level, the only independent predictors for colectomy free survival included absence of primary sclerosing cholangitis [HR 6.70 (95%CI 2.06–21.81, $P = 0.002$], Mayo < 3 at baseline endoscopic activity [HR 2.53 (95%CI 1.01–6.38), $P = 0.049$], and short-term clinical benefit [HR 2.66 (95%CI 1.12–6.29), $P = 0.026$].

DISCUSSION

In this large retrospective cohort study, short-term clinical benefit with absence of rectal bleeding was achieved in 44% of patients 10 weeks after initiation of ADM. In total, 71% of the patients required dose discontinuation or dose escalation. Dose escalation was more frequent in patients with a shorter disease duration, patients with previous primary or secondary loss of response to IFX, and patients without short-term

Table 2: Univariate Analysis for Various Clinical Endpoints

Endpoint	Risk Factor	Odds Ratio (95% CI)	*P* value
Short-term clinical benefit	Previous use of IFX	0.51 (0.30–0.88)	0.015
	IFX stopped due to PNR/LOR	0.57 (0.34–0.97)	0.037
Short-term mucosal healing	Female	2.39 (1.21–4.72)	0.012
	Previous use of IFX	0.48 (0.24–0.95)	0.033
	IFX stopped due to PNR/LOR	0.33 (0.17–0.66)	0.001
	Body weight ≤ 70 kg	2.08 (1.01–4.29)	0.045
	Baseline endoscopic Mayo 3	0.29 (0.14–0.59)	0.001
ADM dose escalation or discontinuation free survival*	Female sex		0.049
	Disease duration at least 5 years		0.013
	Initial short-term clinical benefit		<0.001
	No prior use of IFX		0.008
	No prior PNR/LOR to IFX		0.003
Success of ADM dose escalation	IFX stopped due to PNR/LOR	2.04 (1.00–4.18)	0.049
	Initial short-term clinical benefit	3.08 (1.46–6.48)	0.003
ADM discontinuation free survival*	Initial short-term clinical benefit		<0.001
Colectomy free survival[a]	Absence of PSC		0.018
	No prior use of IFX		0.046
	Endoscopic subscore <3		0.025
	CRP < 5 mg/L		0.024
	Hemoglobin ≥ 12 g/dL		0.037
	Serum albumin ≥ 35 g/L		0.050
	Initial short-term clinical benefit		<0.001

[a]LogRank P value after Kaplan-Meier analysis
PNR: primary nonresponse; LOR: loss of response

clinical benefit to ADM. Dose de-escalation back to every other week was attempted in 71% of patients and was successful in 80%. No predictors of successful dose de-escalation could be identified.

Out of the 164 patients who required dose adaptation, 129 patients (56%) underwent dose escalation, which was successful in 60%. The high proportion of early discontinuation and dose escalation of ADM in UC suggest the possibility that higher induction doses of ADM are needed to induce and maintain remission. Compared to a large retrospective cohort study in 720 patients with Crohn's disease (CD), dose escalation was needed in only 34% of patients after a median follow-up of 14 months.[10] In the ULTRA studies, a plateau in the dose-response curve was not achieved suggesting that higher doses could be more efficacious.[7, 8] Therefore, the SERENE UC study (NCT02065622), a double-blind, randomized, multicenter study, is currently evaluating the safety and efficacy of an intensified induction regimen with ADM 160 mg at weeks 0, 1, 2, and 3 in subjects with moderate to severe UC. Interestingly, we could not observe a relationship of concomitant therapy with immunomodulators such as azathioprine and the need for ADM dose escalation.

Dose de-escalation was attempted in 71% of patients after a median duration of 4.3 (2.9–7.2) months and was successful in 80%, but no predictive markers could be identified. Compared to the same retrospective cohort study in 720 patients with CD who were treated with ADM, dose de-escalation was attempted in 54% of patients after a median duration of 3 months and was successful in 63%.[10] Also in rheumatology, data are available on successful dose de-escalation and even on discontinuation of biological therapy, but these findings can certainly not be extrapolated to IBD.[12] A recently published single center experience showed that ADM could be de-escalated even to 40 mg every 3 weeks in patients with CD, providing they had high ADM serum levels and no objective signs of disease activity.[13] Also during the optimization phase of the TAXIT study, patients with UC or CD could be dose de-escalated based on IFX serum levels.[14]

Short-term clinical benefit was achieved in 44% and was less frequent in patients previously failing IFX, reflecting a more refractory disease and consistent with previous studies.[15–17]

We could not observe a relationship between concomitant therapy with immunomodulators and need for

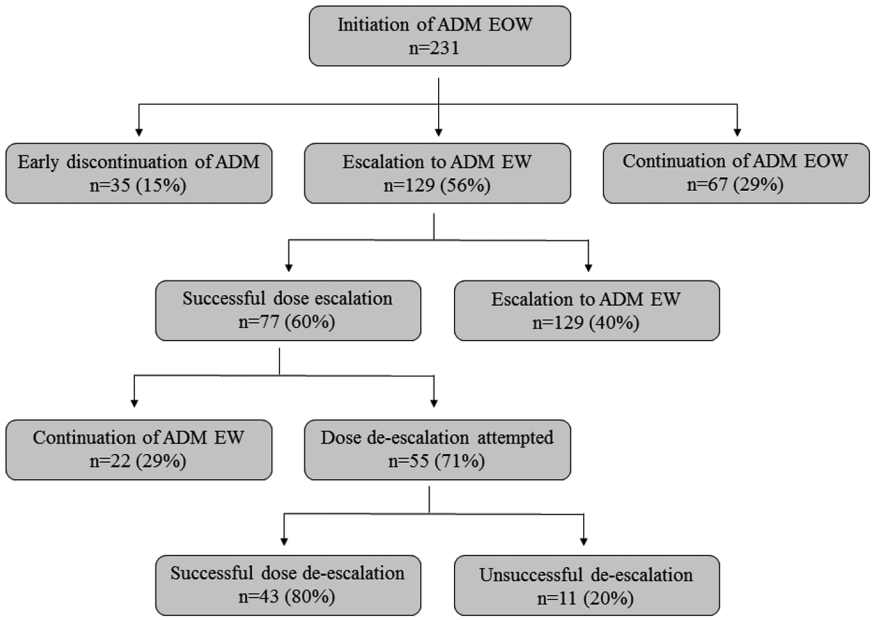

FIGURE 1. Overview on dose escalation and dose de-escalation of ADM. Median follow-up since start of ADM: 40.7 (20.0–71.6) months. Median follow-up under ADM: 8.5 (3.0–19.3) months.

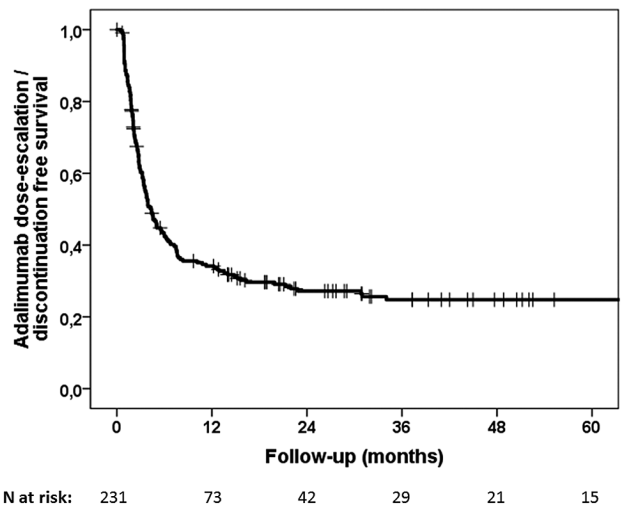

FIGURE 2. Dose escalation / discontinuation free survival. [total cohort (n = 231); dose escalation / discontinuation (n = 164)].

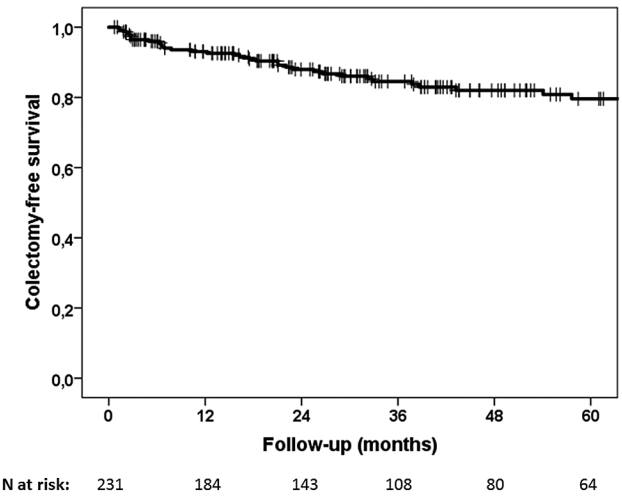

FIGURE 3. Colectomy free survival. [total cohort (n = 231); colectomy (n = 35)].

ADM dose escalation. Similarly, we didn't observe a benefit of concomitant therapy with immunomodulators in achieving short-term clinical benefit. Although combining immunomodulators with IFX lowers TNF-induced immunogenicity,[18, 19] the benefit of combination therapy of immunomodulators with ADM still remains controversial.[17, 20–22] This probably reflects the difference between chimeric and human monoclonal antibodies, the latter inducing less immunogenicity. As we did not measure antibodies and serum drug levels routinely as part of our study, these conclusions warrant further investigations. In the absence of a clear randomized controlled trial the need of combination therapy with ADM remains controversial.

Our study has several limitations. Due to the retrospective nature of the study, objective markers such as ADM serum levels, fecal calprotectin, and endoscopy and items to calculate the Mayo score were not available in all patients. Individualized dosing, based on ADM exposure, could have helped to optimize ADM treatment in a more rational and objective way. Instead, short-term clinical benefit was based on physician global

assessment and absence of rectal bleeding at week 10. Although all patients in this retrospective study were treated according to the Belgian reimbursement criteria, there was neither predefined algorithm for ADM dose escalation or de-escalation, nor for initiation of concomitant therapy. Therefore, clinical decisions might have been biased. On the other hand, this is a large cohort study collecting consecutive UC patients treated in real life and the first study looking at dose escalation and dose de-escalation of ADM in UC. We speculate that individualized dosing based on ADM exposure could help to optimize ADM treatment in a more rational and objective way.

CONCLUSIONS

In conclusion, in this real-world Belgian cohort of patients with UC treated with ADM, short-term clinical benefit was achieved in 44% of patients at week 10. A vast majority of patients needed ADM dose escalation to weekly dosing after a median of 2.8 (1.7–5.1) months. Dose escalation was successful in 77/129 (60%) and was predicted by short-term clinical benefit from the treatment. Dose de-escalation was attempted in 71% (55/77) after successful dose escalation and was successful in 80% (43/54).

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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