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Loss of response to anti-TNFα agents depends on treatment duration in patients with inflammatory bowel disease

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Summary

Background: Inflammatory bowel disease (IBD) is often managed with anti-tumour necrosis factor-α therapy (anti-TNFα), but treatment efficacy is compromised by high annual rates of loss of response (13%-21% per patient-year).

Aims: To assess whether the incidence of loss of response decreases with longer treatment duration

Methods: This was a multicentre, retrospective cohort study of patients with ulcerative colitis (UC) or Crohn's disease (CD) who received anti-TNFα for at least 4 months between 2011 and 2019. We studied the incidence of loss of response as a function of treatment duration, employing parametric survival modelling. Predictors of loss of response were identified by Cox regression analysis. Secondary outcomes included overall anti-TNFα discontinuation and dose escalation.

Results: We included 844 anti-TNFα treatment episodes in 708 individuals. Loss of response occurred in 211 (25.0%) episodes, with anti-drug antibodies detected in 66 (31.3%). During the first year, the incidence of loss of response was three-fold higher than after four years of treatment (17.2% vs 4.8% per patient-year, $P < 0.001$). The incidence of anti-TNFα discontinuation (28.6% vs 14.0% per patient-year, $P < 0.001$) and dose escalations (38.0% vs 6.8% per patient-year, $P < 0.001$) also decreased significantly from the first year to after four years, respectively. Predictors of loss of response included UC (vs CD, adjusted hazard ratio [aHR] 1.53, 95% CI 1.10-2.15) and, among patients with CD, stricturing or penetrating disease (aHR 1.68, 95% CI 1.15-2.46) and male sex (aHR 0.55, 95% CI 0.38-0.78). Immunomodulators were protective against loss of response with anti-drug antibodies (aHR 0.42, 95% CI 0.24-0.74).

Conclusions: Patients with sustained benefit to anti-TNFα after 2 years are at low risk of subsequent loss of response.

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1 | INTRODUCTION

Anti-tumour necrosis factor α (anti-TNFα) agents are widely used as maintenance treatment for patients with inflammatory bowel disease (IBD). After successful induction of remission, the risk of a subsequent loss of response to anti-TNFα has been estimated to be as high as 13%-21% per patient-year, mostly based on studies with less than two years of follow-up.[1-4] In clinical practice, however, anti-TNFα treatment is frequently continued much longer with, anecdotally, favourable long-term outcomes. Quantitative characterisation of long-term efficacy might help to balance the benefits of prolonged treatment against the risks of infections and malignancies, as well as treatment costs.[5-7] We hypothesised that although the yearly risk of treatment failure is relatively high immediately after anti-TNFα initiation, it is likely to decrease with a longer treatment duration.

We conducted a large, multicentre, retrospective cohort study evaluating nine years of anti-TNFα treatment in patients with IBD. Our primary aim was to assess whether the incidence of loss of response—defined as drug discontinuation because of disease activity—declines with a longer treatment duration. Secondary aims were to identify predictors of loss of response (with and without anti-drug antibodies), and to define the time-dependent risk of overall drug discontinuation and anti-TNFα dose intensifications.

2 | METHODS

2.1 | Design

This was a multicentre, retrospective cohort study of patients with IBD receiving anti-TNFα maintenance treatment in a general hospital (St. Antonius Hospital Nieuwegein) and a referral centre (University Medical Centre Utrecht) in the Netherlands. A data query in databases of the gastroenterology departments and hospital pharmacies (with complete data available from 2011 onwards) was performed. We identified all adult IBD patients with at least one prescription for infliximab or adalimumab between 01.01.2011 and 01.01.2019, using ICD-10 codes for the IBD diagnosis and ATC codes for medication.

Individual charts were reviewed for the following inclusion criteria: an established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC), at least one year of follow-up for treatment of IBD at the participating site, and at least one anti-TNFα treatment episode that could be included in the analysis. Treatment episodes were included if the first dose of anti-TNFα was administered after 01.01.2011 and before 01.01.2019, and the duration of treatment was at least four months. We excluded patients with IBD-unclassified and patients treated only with golimumab or certolizumab-pegol during the study period, due to small sample sizes. Treatment episodes initiated more than four months before the patient reached the age of 18 were excluded. This was necessary to reduce selection bias, as patients who started anti-TNFα during childhood were only identified by our search strategy if the anti-TNFα was continued after the transition to the adult gastroenterology department (ie, patients with a longer treatment duration).

In case individual patients were treated repeatedly with anti-TNFα compounds during the study period, all treatment episodes that met the eligibility criteria were analysed. Switching to other anti-TNFα agents or restarting anti-TNFα after a drug holiday of more than 90 days was categorised as a new treatment episode.

2.2 | Data collection and definitions

We collected data on demographics, disease characteristics, prior medical treatment, IBD-related surgical interventions and comorbidity (including primary sclerosing cholangitis [PSC] and rheumatologic comorbidities). For included patients, data from all anti-TNFα treatment episodes were recorded, including episodes that were not eligible for the primary analysis (in order to account for any prior anti-TNFα exposure). We noted the date of first anti-TNFα administration, indication for anti-TNFα (luminal vs perianal disease), and whether and when the anti-TNFα agent was withdrawn. Reasons for anti-TNFα discontinuation were classified as primary non-response, loss of response, side effects, de-escalation, patient's decision or "other." De-escalation was defined as elective anti-TNFα withdrawal in patients having achieved durable remission.[8] Primary non-response was defined as discontinuation of anti-TNFα because of disease activity within four months of anti-TNFα initiation. Loss of response was defined as anti-TNFα discontinuation because of disease activity after four months of treatment. Disease activity was based on the physician's interpretation (usually based on symptoms with at least one adjunctive endoscopic, radiographic or biochemical finding). Prior anti-TNFα failure was defined as primary non-response or loss of response in any previous treatment episode.

Dose escalations, defined as any increase in the dose or decrease of the dosing interval from standard regimens (5mg/kg every eight weeks for infliximab, 40mg every two weeks for adalimumab), and corresponding dates were recorded. Prior immunomodulator failure (azathioprine, 6-mercaptopurine, thioguanine and methotrexate) was defined as persisting disease activity despite immunomodulator use for at least three months before the first anti-TNFα administration. Concomitant immunomodulator use during treatment episodes was recorded, with dates of discontinuation and/or (re)initiation if applicable. Any (interruption in) use of immunomodulators of less than 30 days was ignored. Baseline immunomodulator use was defined as either initiation of an immunomodulator within 30 days, or continuation of the immunomodulator for at least 30 days, following anti-TNFα initiation.

Anti-TNFα trough levels and anti-drug antibodies were recorded, if available. Anti-drug antibodies were typically only measured in patients with anti-TNFα trough levels <1.0mg/L. Therefore, antibodies were considered absent if the trough level was ≥1.0mg/L. Of note, the standard of care at both participating sites is best characterised by reactive therapeutic drug monitoring (TDM). CRP and faecal calprotectin levels were recorded at the start of anti-TNFα (available in

71% and 31% respectively), and at the time of anti-TNFα discontinuation (maximum of six weeks prior to start/stop).

Data from endoscopic procedures performed between six months before the start until six months after the end of a treatment episode were extracted from endoscopy reports. The most proximal bowel segment examined and degree of disease activity (none, mild, moderate and severe) in the most severely affected bowel segment were noted. Mucosal healing was defined as the absence of endoscopically visible inflammation. Procedures performed at least 90 days after anti-TNFα initiation were analysed as potential predictors of loss of response. Endoscopies performed less than 90 days before anti-TNFα discontinuation were considered to indicate a concurrent outcome of interest (eg, loss of response), and were excluded from the analyses aimed to identify predictors of future loss of response.

2.3 | Statistical analysis

Descriptive characteristics were reported according to the distribution of the data, with continuous parameters noted as medians with interquartile ranges (IQR) unless stated otherwise. Kaplan-Meier curves are presented with log-rank test for significance. We corrected for multiple comparisons with the Benjamini-Hochberg procedure to decrease the false discovery rate (FDR). Time-at-risk started at anti-TNFα maintenance therapy (4 months after anti-TNFα initiation). If the outcome of interest did not occur, patients were censored at anti-TNFα discontinuation, last follow-up at the study site or end of the study period (01.12.2019).

The incidence rate per patient-year of all outcomes was calculated for different time spans. To formally test whether the incidence of outcomes declined or increased with treatment duration, we performed parametric survival modelling with the Wald test for significance (Supplementary methods). Subgroup analyses were performed in patients with UC or CD. Sensitivity analyses were performed for patients without prior anti-TNFα exposure (resulting in only one episode per individual patient), and for patients with at least one year of treatment, as high rates of anti-TNFα discontinuation in the first year might be attributed in part to unintentional inclusion of primary non-responders (only excluded from this study if the anti-TNFα was withdrawn within four months).

To identify predictors of loss of response, a Cox regression model was constructed, accounting for multiple treatment episodes per patient (details in Supplementary methods). Due to the amount of missing data, pharmacokinetic and biochemical parameters were not incorporated in the regression models. Mucosal healing was analysed as a time-varying covariate. Immunomodulators were primarily analysed by baseline use, and additional analysis was performed with immunomodulator use as a time-changing covariate, with a 90-day delay after starting/stopping an immunomodulator. Separate analyses were performed for the outcomes of loss of response with and without anti-drug antibodies, and for the subgroups of patients with UC or CD and anti-TNFα naïve patients.

All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered significant.

2.4 | Study oversight

This study was carried out in accordance with the ethical guidelines of the Institutional Review Board of the University Medical Centre Utrecht. The study received exempt status from the Institutional Review Board due to the observational design.

3 | RESULTS

3.1 | Cohort characteristics

The eligibility criteria were fulfilled in 708 individual patients, yielding a total of 844 treatment episodes and 2270 patient-years of follow-up (Table 1, Supplementary Figure S1). The median treatment duration was 2.4 years (IQR 1.2-4.4) per episode, and treatment duration was longer than four years in 247 (29.3%) episodes (Table 2). Anti-TNFα trough levels and/or anti-drug antibodies were measured at least once in 681 (80.7%) treatment episodes.

Several characteristics differed significantly between patients with UC and CD, including a lower frequency of smoking, older age at diagnosis (Table 1), older age at anti-TNFα initiation, a shorter treatment duration and a lower frequency of prior anti-TNFα failure (Table 2) in those with UC. Notably, patients with UC more frequently used infliximab (and less often adalimumab) and were more often prescribed combination therapy.

Irrespective of the IBD phenotype, infliximab was more often combined with immunomodulators at anti-TNFα initiation, as compared to adalimumab (79.0% vs 58.6%, $P < 0.001$). During follow-up, 285 (47.9%) patients discontinued the immunomodulator, after a median of 0.9 years (IQR 0.6-2.1).

3.2 | Incidence of loss of response

Anti-TNFα discontinuation because of loss of response occurred in 211 (25.0%) episodes (Figure 1). Patients who experienced loss of response, did so after a median of 11.2 (IQR 3.8-27.2) months since the start of the maintenance phase (ie, four months after anti-TNFα initiation). The overall incidence of loss of response was 9.3% (95% CI 8.1%-10.6%) per patient-year.

The incidence rates of anti-TNFα discontinuation with corresponding reasons are presented in Table 3. The incidence of loss of response was as high as 17.2% per patient-year (95% CI 13.7-21.2) during the first year of treatment, but declined more than threefold to 4.8% per patient-year (95% CI 3.1-7.2) after 4 years. Indeed, the hazard of loss of response dropped significantly with a longer treatment duration in all patients (Figure 1B, $P < 0.001$), in patients with

TABLE 1 Baseline characteristics

	Total cohort (N = 708)	CD (N = 532)	UC (N = 176)	*P*-value
Female Sex	378 (53.4)	292 (54.9)	86 (48.9)	0.16
BMI	25.1 (22.3-28.7)	25.1 (22.3-28.7)	25.3 (22.2-28.9)	0.61
Smoking	179 (26.2)	162 (23.8)	17 (10.0)	<0.001*
Concomitant PSC	24 (3.4)	16 (3.0)	8 (4.5)	0.33
Rheumatologic comorbidity	102 (14.4)	83 (15.6)	19 (10.8)	0.12
Age at IBD diagnosis	26.1 (20.6-38.8)	24.9 (20.0-37.3)	29.8 (22.9-43.8)	<0.001*
Medication exposure prior to first anti-TNF				
Systemic steroids	543 (82.4)	286 (79.3)	157 (91.3)	<0.001*
Thiopurines	596 (85.0)	452 (86.1)	144 (81.8)	0.17
Methotrexate	95 (13.6)	84 (16.0)	11 (6.2)	0.001*
Disease behavior	-		-	-
Inflammatory (B1)		235 (44.2)		
Stricturing (B2)		201 (37.8)		
Penetrating (B3)		95 (17.9)		
Disease location	-		-	-
Ileal (L1)		152 (28.6)		
Colonic (L2)		99 (18.6)		
Ileocolonic (L3)		276 (51.9)		
Isolated upper GI (L4)		5 (0.9)		
L1/L2/L3 + upper GI (L4)		62 (11.8)		
Perianal disease	-	177 (33.3)		-
Disease extent	-	-		-
Proctitis (E1)			13 (7.4)	
Left-sided (E2)			61 (34.7)	
Extensive (E3)			102 (58.0)	

Note: Missing data: BMI (n = 36), Smoking (n = 26), Disease behavior (n = 1), upper GI involvement (n = 2). Prior exposure to steroids (n = 49), thiopurines (n = 7), methotrexate (n = 8).

*Significant at $P < 0.05$.

UC, patients with CD (both $P < 0.001$) and in the sensitivity analyses of patients with at least one year of treatment ($P = 0.002$) and anti-TNFα naïve patients ($P < 0.001$). The incidences of loss of response during the first year, second year, and after four years were 29.5%, 8.9%, 7.4% per patient-year for UC, 13.4%, 10.5% and 4.2% for CD and 18.4%, 9.4% and 3.7% for anti-TNFα naïve patients respectively. Of note, the incidence of loss of response in patients with UC continued to decrease beyond six months of treatment ($P < 0.001$), but this was no longer significant beyond 1 year ($P = 0.34$).

Anti-drug antibodies were detected at any point during the treatment in 66 (31.3%) episodes with loss of response. The last available trough level was ≤1.0 mg/L in 53 (80%) episodes and the median antibody titre was 255AU/mL (IQR 82-755, Supplementary Table S1). The remaining 145 (68.7%) cases were classified as loss of response *without* anti-drug antibodies. In these patients, the most recent median trough level (available in 114, 78.6%) was within the therapeutic window (infliximab: 6.0 mg/L, IQR 3.9-8.5; adalimumab: 7.7 mg/L, IQR 5.0-12.2, Supplementary Table S1). Of note, faecal calprotectin, but not CRP, was significantly higher among patients with loss of response *without* anti-drug antibodies (Supplementary Table S1, $P = 0.03$).

Again, the incidences of loss of response both with and without anti-drug antibodies declined with a longer treatment duration ($P = 0.003$ and $P < 0.001$ respectively, Supplementary Table S2). Results were similar in the subgroup and sensitivity analyses, although in patients with UC and patients with more than one year of follow-up, the decreasing trends in loss of response *with* anti-drug antibodies were not significant ($P = 0.07$ and $P = 0.14$ respectively).

3.3 | Predictors of loss of response

Univariable analyses revealed a significantly higher incidence of loss of response in UC patients vs CD patients (Figure 2A, $P = 0.02$).

TABLE 2 Treatment characteristics

	Treatment episodes (n = 844)	CD (n = 636)	UC (n = 208)	*P*-value
Treatment episode				0.05[1]
First anti-TNF	555 (65.8)	402 (63.2)	153 (73.6)	
Second anti-TNF	225 (26.7)	180 (28.3)	45 (21.6)	
Third anti-TNF	57 (6.8)	48 (7.5)	9 (4.3)	
Fourth anti-TNF	7 (0.8)	6 (0.9)	1 (0.5)	
Prior anti-TNF failure	152 (18.0)	130 (20.4)	22 (10.6)	0.001[1]
Primary non-response	21 (2.5)	18 (2.8)	3 (1.4)	0.26
Loss of response	137 (16.2)	116 (18.2)	21 (10.1)	0.006[1]
Treatment duration	2.4 (1.2-4.4)	2.6 (1.3-4.5)	2.1 (0.9-3.7)	0.001[1]
Disease duration at start	4.6 (1.4-12.6)	4.9 (1.3-14.1)	4.1 (1.6-9.6)	0.10
Age at start	36.2 (26.5-51.7)	35.5 (25.9-50.5)	38.0 (28.8-53.2)	0.006[1]
Anti-TNF agent				0.002[1]
Infliximab	518 (61.4)	371 (58.3)	147 (70.7)	
Adalimumab	326 (38.6)	265 (41.7)	61 (29.3)	
Prior immunomodulator failure[1]	311 (56.4)	222 (55.8)	89 (58.2)	0.61
Any concomitant immunomodulator use	638 (75.9)	465 (73.5)	173 (83.2)	0.005[1]
At start anti-TNF	598 (71.1)	432 (68.2)	166 (79.8)	0.001[1]
Withdrawn during the episode[2]	285 (47.9)	208 (48.4)	77 (46.7)	0.71
Added during the episode[3]	42 (17.9)	33 (16.8)	9 (23.1)	0.35
Prior IBD-related surgery[4]	180 (21.3)	179 (28.1)	1 (0.5)	<0.001[1]

[1]Subgroup of anti-TNF naïve patients (n = 555).

[2]Subgroup of patients with immunomodulator at start (n = 598) with anti-TNF continued at least 30 days after immunomodulator withdrawal.

[3]Subgroup of patients without immunomodulator at start anti-TNF (n = 243).

[4]Bowel resections, stricturoplasty or faecal diversion. Missing data: Concomitant immunomodulator use (n = 3), Prior immunomodulator failure (n = 4).

*Significant at $P < 0.05$.

Baseline immunomodulator use (Figure 2B, $P = 0.16$), use of adalimumab compared with infliximab (Figure 2C, $P = 0.30$), or year of inclusion did not significantly predict loss of response (Figure 2D, $P = 0.06$). Baseline CRP and faecal calprotectin did not differ significantly between those who did and did not experience loss of response during follow-up (median CRP 11.5 vs 7.9mg/L, $P = 0.06$, median faecal calprotectin 1377 vs 942 μg/g, $P = 0.20$).

On multivariable analysis, patients with UC were at higher risk of loss of response compared with patients with CD (Table 4, adjusted hazard ratio [aHR] 1.53, 95% CI 1.10-2.15). In the sensitivity analysis of patients without prior anti-TNFα exposure, this remained significant. Among anti-TNFα naïve patients, higher age at diagnosis (aHR 1.01 per year, 95% CI 1.00-1.03, $P = 0.03$) or higher age at starting anti-TNFα (aHR 1.01 per year, 95% CI 1.00-1.02, $P = 0.08$, trend) were also associated with loss of response but could not be assessed simultaneously due to collinearity (Pearson R^2: 0.66, $P < 0.001$).

In the subgroup of patients with CD, stricturing or penetrating disease was associated with a higher risk of loss of response (aHR 1.68, 95% CI 1.15-2.46) (Supplementary Table S3), while male sex was protective (aHR 0.55, 95% CI 0.38-0.78). No predictors were identified in patients with UC (Supplementary Table S4).

PSC was a significant independent predictor of loss of response *with* anti-drug antibodies (Supplementary Table S5, aHR 3.06, 95% CI 1.05-8.91), while male sex (aHR 0.53, 95% CI 0.31-0.93) and baseline immunomodulator use were protective (aHR 0.42, 95CI: 0.24-0.74). The risk of loss ofresponse *without* antibodies was significantly higher among patients with UC, compared with CD (aHR 1.57, 95% CI 1.07-2.30, Supplementary Table S6).

Immunomodulators were still not significantly protective of loss of response after adjusting for immunomodulator withdrawal or (re) initiation during follow-up in all patients (aHR 1.02, 95CI 0.77-1.35), nor in the subgroups of patients without prior anti-TNFα exposure, patients with CD or UC (data not shown). Furthermore, in this time-varying analysis, immunomodulators were no longer protective of loss of response *with* anti-drug antibodies (aHR 0.67, 95% CI 0.40-1.15), and were associated with a higher risk of loss of response *without* anti-drug antibodies (aHR 1.47, 95% CI 1.02-2.12).

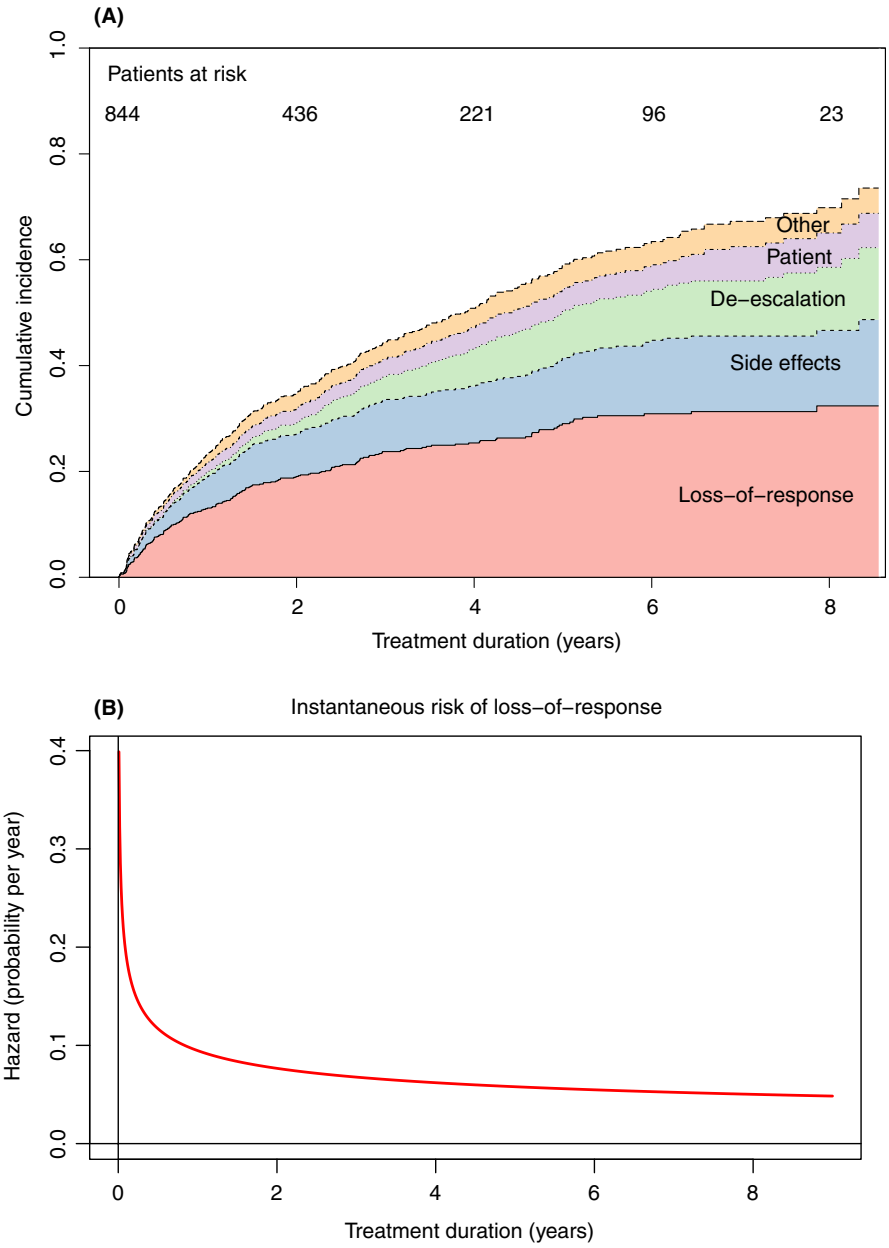


FIGURE 1 (A) Cumulative incidence of anti-TNFα discontinuation with corresponding reasons, Aalen Johansen curve accounting for competing events. (B) Hazard function of loss of response (parametric model) showing significant decrease in hazard over time ($P < 0.001$)

3.4 | Anti-TNFα discontinuation

Overall, anti-TNFα discontinuation occurred in 428 (50.7%) treatment episodes, with a median drug survival of 3.9 years (95% CI 3.3-4.4) since the start of the maintenance phase. Longer treatment duration was associated with decreased incidence rates of anti-TNFα discontinuation (28.6% in the first year to 14.0% per patient-year beyond four years, $P < 0.001$, Table 3). Regarding discontinuation reasons other than loss of response, longer treatment duration was associated with lower rates of anti-TNFα withdrawal for side effects ($P = 0.001$) and higher rates of elective anti-TNFα withdrawal as a de-escalation strategy ($P < 0.001$, Table 3). These findings were similar in patients with UC and CD, as well as in patients with at least one year of anti-TNFα treatment and anti-TNFα naïve patients. However, in patients with UC, the decrease in anti-TNFα discontinuation for side effects and the increase of anti-TNFα discontinuation for remission did not reach statistical significance ($P = 0.09$ and $P = 0.07$ respectively). Among patients who stopped anti-TNFα, CRP, faecal calprotectin and anti-drug antibody titres were significantly higher among those who stopped anti-TNFα due to loss of response, compared with anti-TNFα discontinuation for any other reason (all $P < 0.001$, Supplementary Table S7), while infliximab ($P = 0.02$) and adalimumab ($P = 0.01$) trough levels were significantly lower.

3.5 | Dose escalations

Dose escalation occurred in 386 (45.9%) treatment episodes, of which 76 (19.7%) occurred within four months following anti-TNFα initiation (Figure 3). Thereafter, the incidence rate of dose escalation was 38.0% (95% CI 32.3% - 44.4%) per patient-year between four months and one year, and decreased significantly to 6.8% (95% CI

TABLE 3 Summary of incidence rates of loss of response and anti-TNFα discontinuation by treatment duration

Discontinuation of anti-TNFα	Cumulative incidence, n (%)	Incidence rate, % per patient-year (95% confidence interval)					
Patients at risk	N = 844	4months-1year N = 844	1-2 years N = 684	2-3 years N = 477	3-4 years N = 343	>4 years N = 247	Trend (*P*-value)[1]
All reasons	428 (50.7)	28.6 (24.1-33.7)	20.8 (17.3-24.9)	13.0 (9.7-17.0)	14.4 (10.3-19.5)	14.0 (10.9-17.7)	Decrease[2] ($P < 0.001$)
Loss of response	211 (25.0)	17.2 (13.7-21.2)	10.2 (7.7-13.1)	5.6 (3.6-8.4)	6.7 (4.0-10.4)	4.8 (3.1-7.2)	Decrease[2] ($P < 0.001$)
Side effects	93 (11.0)	6.9 (4.8-9.6)	5.1 (3.4-7.3)	2.2 (1.0-4.2)	2.1 (0.7-4.6)	2.8 (1.5-4.7)	Decrease[2] ($P = 0.001$)
De-escalation	58 (6.9)	0.8 (0.2-2.0)	1.8(0.8-3.2)	3.7 (2.1-6.1)	3.2 (1.4-6.0)	4.0 (2.5-6.2)	Increase[2] ($P < 0.001$)
Patient's initiative	35 (4.1)	2.4 (1.2-4.1)	1.4 (0.6-2.8)	0.7 (0.2-2.1)	1.7 (0.6-4.1)	1.4 (0.6-2.9)	Decrease ($P = 0.14$)
Other	31 (3.7)	1.4 (0.6-2.9)	2.5 (1.3-4.1)	0.7 (0.2-2.1)	0.7 (0.1-2.5)	1.0 (0.3-2.3)	Decrease ($P = 0.21$)

Note: Red (>20%), orange (10%-20%), yellow (5%-10%), green (0%-5%). Note that the intervals of treatment duration have different lengths, but incidence rates are reported as % per patient-year and can be compared directly.

[1]Based on parametric survival modelling with Wald test for significance of decreasing/increasing versus constant hazard.

[2]Significant at $P < 0.05$.

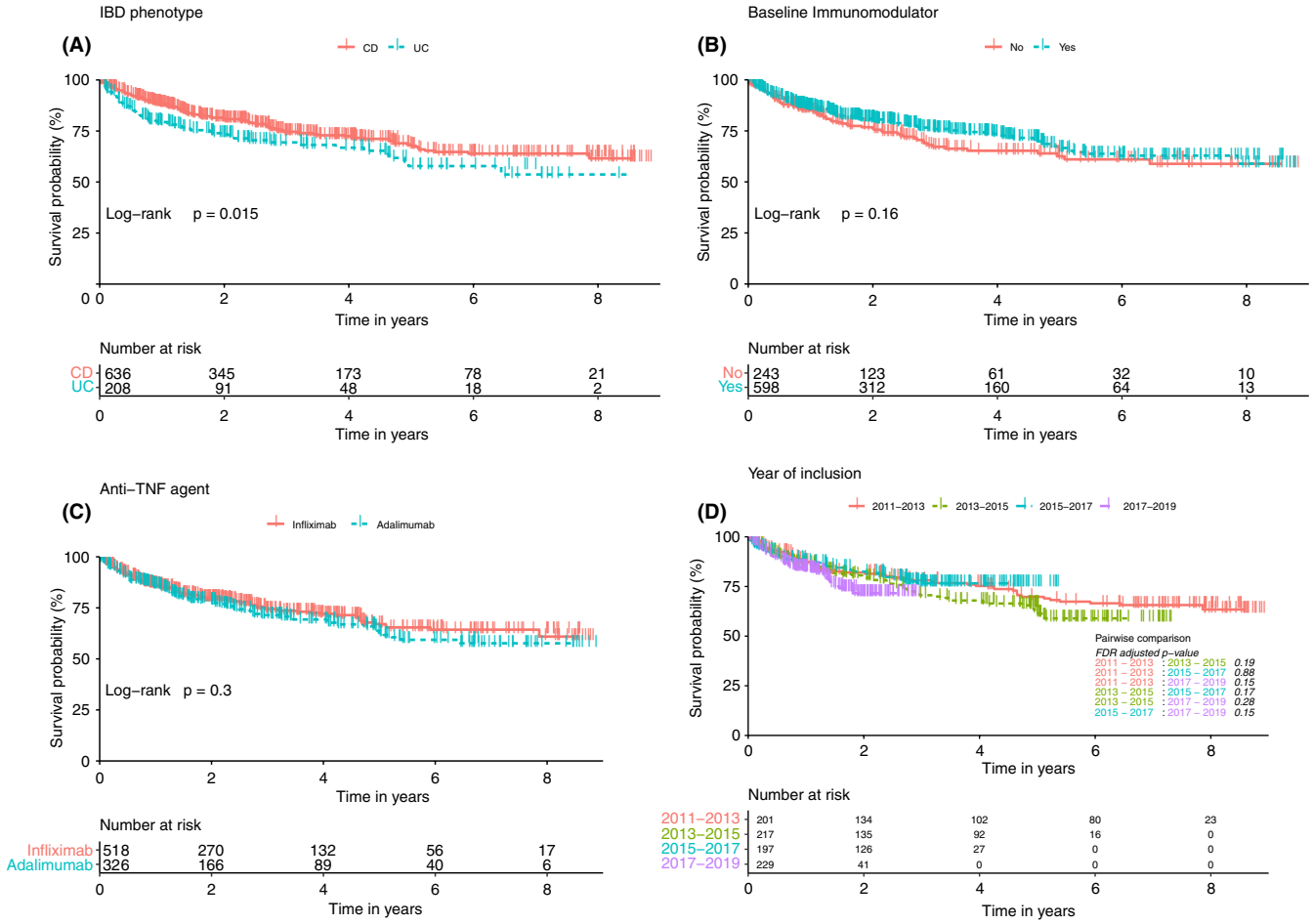


FIGURE 2 Incidence of loss of response (Kaplan-Meier curves), subgroups analyses per (A) IBD phenotype, (B) baseline immunomodulator use, (C) anti-TNFα agent and D) Year of inclusion

TABLE 4 Cox regression analysis for loss of response (all patients)

	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male sex	0.82 (0.61-1.08)	0.16	0.76 (0.57-1.02)	0.07
UC (versus CD)	**1.50 (1.09-2.05)**	**0.01**[3]	**1.53 (1.10-2.15)**	**0.01**[3]
Smoking	0.84 (0.60-1.18)	0.31	0.96 (0.68-1.37)	0.82
BMI	0.99 (0.96-1.02)	0.49	0.99 (0.96-1.02)	0.47
PSC	1.60 (0.84-3.07)	0.15	1.73 (0.89-3.36)	0.1
Age at diagnosis	1.01 (1.00-1.02)	0.07	1.01 (1.00-1.02)	0.07
Age at start anti-TNFα[2]	1.01 (1.00-1.02)	0.19	NA	
Adalimumab (versus Infliximab)	1.15 (0.87-1.52)	0.34	1.15 (0.85-1.55)	0.38
Mucosal healing[1]	0.88 (0.48-1.61)	0.67	0.79 (0.42-1.46)	0.45
Prior anti-TNFα failure	1.13 (0.81-1.58)	0.47	1.20 (0.83-1.73)	0.34
Baseline immunomodulator use	0.80 (0.60-1.09)	0.16	0.80 (0.58-1.09)	0.16

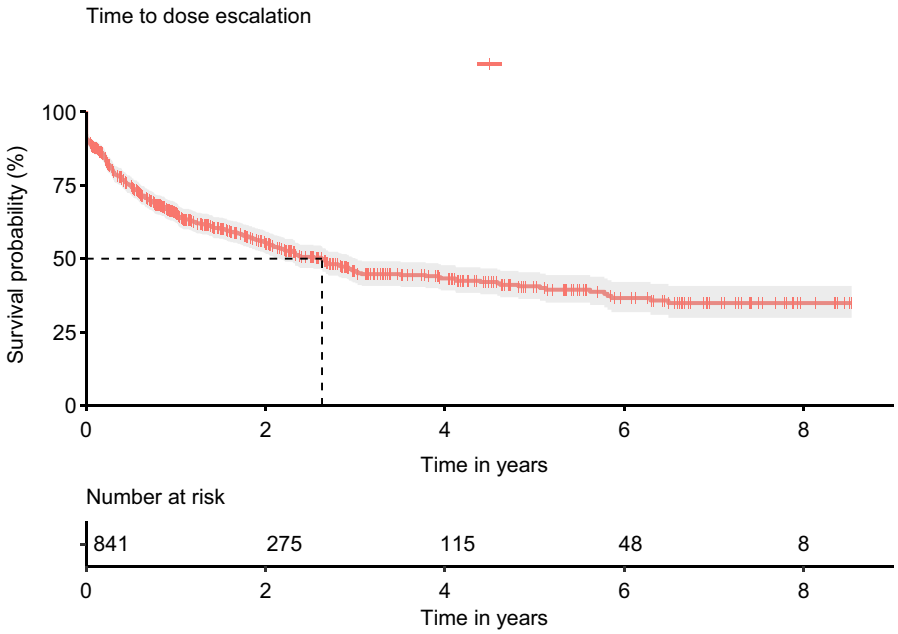
Note: Multivariable model corrected for disease duration.

[1]Entered as a time changing covariate.

[2]Not entered in the multivariable model due to collinearity with age at diagnosis.

*Significant at $P < 0.05$.

FIGURE 3 Kaplan-Meier curve displaying the incidence of anti-TNFα dose escalation



3.9%-10.8%) beyond four years of treatment duration (Supplementary Table S8, $P < 0.001$). In 222 (71.6%) out of 310 dose escalations during follow-up, TDM was performed within the four months prior to the dose escalation (median trough level of 1.6mg/L and 3.8mg/L for infliximab and adalimumab respectively Supplementary Table S9). Dose escalation was followed by loss of response in 130 (33.7%) episodes (aHR 4.97, 95% CI 3.64-6.78), while in 58 (15.0%) episodes, patients were able to return to the standard dosing regimen during follow-up. In the subgroup and sensitivity analyses of patients with UC, patients with CD, patients with more than one-year follow-up and anti-TNFα naïve patients, the incidence of dose escalations also decreased significantly over time (data not shown, all $P < 0.001$).

4 | DISCUSSION

Based on a large retrospective cohort of 844 episodes of anti-TNFα treatment, we observed that after four years of anti-TNFα treatment, the incidence of loss of response was more than threefold lower than during the first year. Additionally, a significant decrease over time was noted for the incidences of anti-TNFα discontinuation, anti-TNFα discontinuation because of side effects, and dose escalations. Not surprisingly, the incidence of elective anti-TNFα withdrawal as a de-escalation strategy increased with a longer treatment duration. Taken together, our findings indicate that patients with IBD with sustained benefit to anti-TNFα for more than approximately two

years, represent a selected population with a favourable efficacy-tolerability balance to anti-TNFα.

A meta-analysis in patients with CD with a mean follow-up of 1.8 years reported an incidence of loss of response to anti-TNFα of up to 20.9% per patient-year.[1] Of note, prior studies employed heterogeneous definitions for loss of response, ranging from symptom scoring to need for surgical intervention.[1,2] The substantially lower overall incidence of loss of response in our study (9.6% per patient-year) can be partially explained by our longer follow-up. Furthermore, our definition of loss of response required anti-TNFα discontinuation, thereby excluding transient or mild disease activity during anti-TNFα therapy. Notably, dose escalations are often an effective first-line strategy in case of flares in real-world clinical practice,[9-11] and the incidence of dose escalations also decreased with a longer treatment duration in our cohort.

It may seem intuitive that the incidence of loss of response declines with a longer treatment duration.[3] However, this has not been assessed quantitatively as in our study, and this has several implications. From a biological perspective, our results imply that loss of response to anti-TNFα does not occur randomly. Instead, over time patients with a better response and tolerability are selected—either due to specific benefit from anti-TNFα treatment, or a milder IBD phenotype in general. From a clinical point of view, we provide detailed long-term outcomes of anti-TNFα treatment—which may aid clinicians to adequately inform patients on the benefits and risks of continued treatment beyond 1-2 years, for example when considering anti-TNFα withdrawal as a therapeutic de-escalation strategy.[8,12] Notably, longer duration of anti-TNFα use does not seem to protect from relapse after elective withdrawal of anti-TNFα.[13]

Several predictors of loss of response were identified in our cohort. In line with a recent retrospective study, UC patients were at higher risk of loss of response than patients with CD, with a high incidence of loss of response among UC patients within the first year.[14] Female patients were at an increased risk of loss of response *with* anti-drug antibodies, and at an increased risk for any loss of response among patients with CD. Female sex has previously been associated with shorter anti-TNFα treatment persistence and higher risk of side effects in patients with IBD or rheumatologic conditions.[14-17] Our findings suggest that this might be related to immunogenicity. Notably, PSC was also associated with a higher risk of antibody-mediated loss of response, although this finding should be interpreted with caution given the small number of patients with PSC in our study. In contrast to prior studies—including long-term follow-up of the CALM study,[18] achieving mucosal healing did not prevent subsequent loss of response to anti-TNFα. However, our findings should primarily be regarded as exploratory analyses, as only 40.9% of patients underwent endoscopy during follow-up and our definition (absence of visible inflammation) was stricter than most prior studies.[19,20]

Immunomodulators protected from loss of response with anti-drug antibodies, in line with prior studies reporting decreased risks of loss of response and immunogenicity to anti-TNFα,[21,22] as well as higher infliximab trough levels among patients receiving combination therapy.[23,24] Our findings additionally suggest against a relevant independent effect of the thiopurine on the intestinal mucosa—as immunomodulators did not protect from loss of response without anti-drug antibodies. In line with a recent long-term observational study,[14] loss of response (regardless of anti-drug antibodies) was not significantly lower among patients receiving combination therapy. However, relatively few patients received monotherapy (likely highly selected on clinical grounds), and withdrawal and initiation of immunomodulators during maintenance treatment occurred frequently. Counterintuitively, accounting for changing immunomodulator use further diminished any protective effect of immunomodulators on loss of response. It is likely that patients perceived to be at low risk of loss of response would preferentially stop the immunomodulator during maintenance treatment, while only high-risk patients would continue or (re)initiate the immunomodulator.

This study has several strengths. In general, our results, coming from a large cohort with meticulous data collection, substantially add to the existing literature on long-term maintenance treatment with anti-TNFα. The substantial sample size allowed us to precisely estimate incidence rates even beyond four years of treatment. In identifying predictors of loss of response, we accounted for potential confounders and assessed changes over time in immunomodulator use or achieving mucosal healing. Most importantly though, we focused on the dynamic aspects of long-term anti-TNFα treatment and detected a substantial change in incidences and reasons for anti-TNFα discontinuation with a longer treatment duration.

As with all retrospective studies, several limitations of the current study need to be acknowledged. Faecal calprotectin, CRP levels and pharmacokinetic measurements were not available in all patients and were therefore only analysed descriptively. Limited misclassification of patients as having loss of response with vs without anti-drug antibodies may have occurred among the minority in whom trough levels or anti-drug antibodies were not measured shortly before loss of response. Loss of response was pragmatically distinguished from primary non-response by treatment duration (after vs before four months), but our sensitivity analysis confirmed that the risk of loss of response decreased beyond 1 year. Although our cohort is a mixed population of secondary and tertiary care patients, the generalisability is partially limited by the exclusion of patients who started an anti-TNFα agent before adulthood. Finally, we reported several relevant predictors of loss of response, but none were identified within the smaller subgroup of patients with UC.

The therapeutic armamentarium for IBD is rapidly expanding with alternatives for anti-TNFα, including non-anti-TNFα biologicals and small molecules.[25,26] Current literature provides little guidance to clinicians for selecting the optimal therapy for individual patients, as only one head-to-head trial has been published and no drug-specific biomarkers are available.[27,28] For a chronic, life-long disease such as IBD, it is essential to not only characterise the initial treatment response but also to examine long-term outcomes. Our results coming from a nine-year retrospective analysis indicate that patients on long-term anti-TNFα treatment represent a distinct population with high clinical benefit and tolerability of maintenance treatment.

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AUTHORSHIP

Guarantor of the article: Bas Oldenburg.

Author contributions: RM and JS contributed to study design, collected data, conducted the analyses and drafted the manuscript. JL, MK and BH collected data and critically reviewed the manuscript. PB, NM and BJ provided important intellectual contributions and critically reviewed the manuscript. HF and BO contributed to study design, provided important intellectual contributions, critically reviewed the manuscript and supervised the study.

DATA AVAILABILITY STATEMENT

The data underlying this study are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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