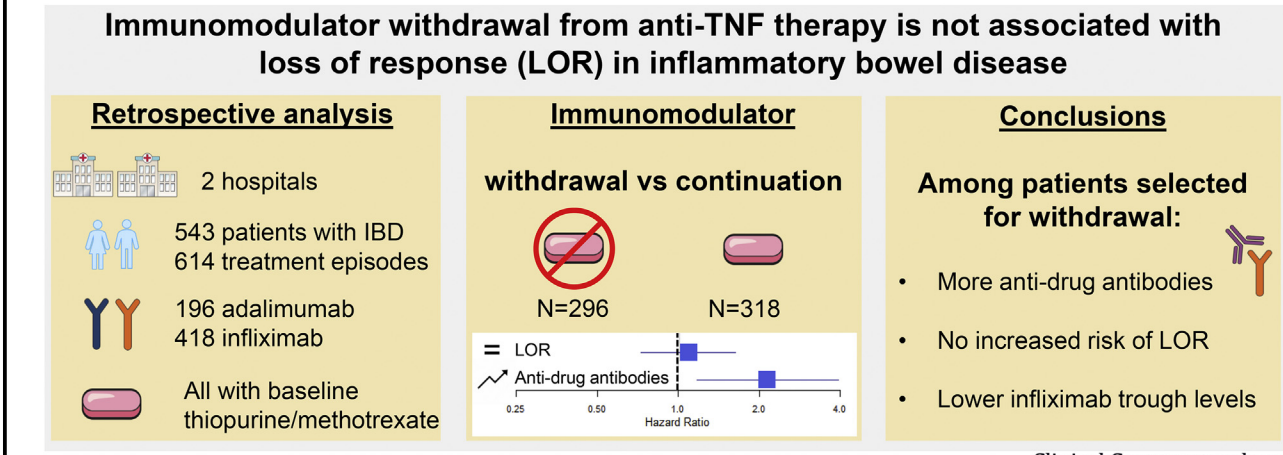
Clinical Gastroenterology and Hepatology 2022;20:2577–2587

INFLAMMATORY BOWEL DISEASE

Immunomodulator Withdrawal From Anti-TNF Therapy Is Not Associated With Loss of Response in Inflammatory Bowel Disease

Remi Mahmoud,[*,a] Hans-Paul Schultheiss,[*,a] Jonas Louwers,[*] Michiel van der Kaaij,[*] Boris van Hellemondt,[*] Nofel Mahmmod,[‡] Petra van Boeckel,[‡] Bindia Jharap,[§] Herma Fidder,[*,b] and Bas Oldenburg[*,b]

*Division of Internal Medicine and Dermatology, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, the Netherlands; ‡Division of Internal Medicine, Department of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, the Netherlands; and §Division of Internal Medicine, Department of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, the Netherlands



BACKGROUND AND AIMS: The benefit of concomitant immunomodulators (thiopurines or methotrexate) in patients with inflammatory bowel disease (IBD) on anti-tumor necrosis factor α (anti-TNF) (infliximab or adalimumab) maintenance therapy is debated. We compared outcomes after immunomodulator withdrawal vs continuation of combination therapy.

METHODS: This was a retrospective cohort study in a general hospital and a tertiary referral center. We included adult IBD patients, receiving anti-TNF therapy for ≥4 months, plus an immunomodulator at baseline, between January 1, 2011, and January 1, 2019. The primary endpoints were loss of response (LOR) (ie, anti-TNF discontinuation because of disease activity) and anti-drug antibodies. Adjusted hazard ratios (aHRs) were calculated by mixed-effects Cox regression analysis.

RESULTS: We included 614 treatment episodes of combination therapy in 543 individuals, yielding 1664 patient-years of follow-up. The immunomodulator was withdrawn in 296 (48.2%) episodes after 0.9 (interquartile range, 0.6–2.1) years, which was not associated with a higher risk of LOR

[a]Authors co-first authorship; [b]Authors share co-senior authorship.

Abbreviations used in this paper: aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; ICD, international classification of diseases; IQR, interquartile range; UC, ulcerative colitis.

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2022.01.019

(aHR, 1.08; 95% confidence interval [CI], 0.72–1.61), although anti-drug antibodies were detected more frequently (aHR, 2.14; 95% CI, 1.17–3.94), compared with continuation. Clinical remission at the time of withdrawal reduced the risk of LOR (aHR, 0.48; 95% CI, 0.25–0.93), while longer duration of combination therapy before withdrawal decreased the risk of anti-drug antibodies (HR per year, 0.56; 95% CI, 0.32–0.91). Higher prewithdrawal infliximab trough levels reduced the subsequent risks of anti-drug antibodies and LOR. Infliximab trough levels were lower after immunomodulator withdrawal ($P = .01$).

CONCLUSIONS: **Patients who withdrew the immunomodulator in this retrospective cohort were not at increased risk of LOR within the following 1–2 years, but an increase in anti-drug antibodies was observed. Our findings require prospective validation, preferably in adequately powered randomized controlled trials.**

Keywords: De-escalation; Biologicals; Remission; Azathioprine.

Combination of the anti-tumor necrosis factor α (anti-TNF) agent infliximab with immunomodulators (thiopurines or methotrexate) is superior to infliximab monotherapy and is universally recommended in patients with inflammatory bowel diseases (IBDs) who start anti-TNF therapy.[1–7] However, the benefit of combining adalimumab with immunomodulators remains controversial.[8,9] American guidelines recommend adalimumab combination therapy, while the European guideline recommends monotherapy for patients with Crohn's disease (CD).[1,2,5]

The increased effectiveness of combining anti-TNF therapy with thiopurines must be carefully balanced against potential side effects, as combination therapy can increase the risks of serious infections and malignancies, including lymphoma.[10,11] In clinical practice, immunomodulators are frequently discontinued during anti-TNF maintenance therapy because of these risks, but the evidence underlying this strategy is limited. Three small randomized controlled trials found no difference in clinical relapse after immunomodulator discontinuation vs continuation, but these studies were underpowered to detect noninferiority.[12–14]

We aimed to compare immunomodulator withdrawal vs continuation in a large retrospective cohort of patients with IBD receiving maintenance therapy with infliximab or adalimumab. Next, we aimed to determine whether a longer duration of combination therapy is associated with lower risks of loss of response and anti-drug antibodies after immunomodulator withdrawal.

Materials and Methods

Population

In this retrospective cohort study, we identified patients with IBD through the hospital pharmacy and adult gastroenterology department databases of a tertiary referral center (University Medical Center Utrecht) and a large general hospital (St. Antonius Hospital, Nieuwegein) in the Netherlands, using Anatomic Therapeutic and Clinical codes for medication and International Classification of Diseases–Tenth Revision codes for the diagnosis of IBD, as described previously.[15] Inclusion criteria were a confirmed diagnosis of IBD, at least 1 year of follow-up at a participating site, at least 4 months of infliximab or adalimumab treatment started between January 1, 2011, and January 1, 2019, and combination therapy with an immunomodulator at the start of anti-TNF. We excluded patients with ulcerative colitis (UC) after (sub)total colectomy and patients <18 years of age at the start of anti-TNF to avoid selection bias (because only adult patients were identified systematically).

If patients were treated repeatedly with anti-TNF during the study period, all episodes meeting the criteria were analyzed. A treatment episode is defined as a continuous timespan of scheduled anti-TNF treatment. The end of a treatment episode was defined as anti-TNF discontinuation, a switch to another anti-TNF agent, or a drug holiday of more than 90 days. Thus, for example, if a patient was treated with infliximab between 2011 and 2013 and then with adalimumab from 2015 to 2016, both episodes were analyzed separately.

Data Collection and Definitions

Data were collected from the patients' electronic health records, including demographics, disease characteristics, prior medical treatment, and relevant comorbidity.

Combination therapy was defined as continuing an immunomodulator (methotrexate, azathioprine, 6-mercaptopurine, or thioguanine) after starting anti-TNF treatment, or starting an immunomodulator within 30 days. European guidelines were followed for dosing of immunomodulators.[16] Any (interruption in) immunomodulator use of <30 days was ignored. Immunomodulator withdrawal was defined as discontinuation of the immunomodulator, while continuing the anti-TNF for at least 30 days. At the time of immunomodulator withdrawal, we noted whether patients were in corticosteroid-free clinical remission, based on the assessment of the treating physician.

Reasons for discontinuing anti-TNF therapy or immunomodulators were classified as loss of response (anti-TNF only), therapeutic de-escalation, side effects, patient's initiative or "other." Loss of response was defined as anti-TNF discontinuation because of disease activity (as documented by the treating physician, usually based on symptoms with at least 1 adjunctive endoscopic, radiographic, or biochemical finding). De-escalation was defined as elective drug discontinuation, in order to reduce the risk of future drug-related adverse events, to meet patient preference, or to provide cost savings.[17]

Anti-TNF dose (de-)escalations were recorded, defined as any change in dosage or dosing interval from standard regimens (5 mg/kg per 8 weeks for infliximab and 40 mg per 2 weeks for adalimumab). C-reactive protein (CRP) and fecal calprotectin were recorded at the start of anti-TNF therapy, at immunomodulator withdrawal (maximum of 4 months before or 2 months after), and at anti-TNF discontinuation. All measurements of anti-TNF trough levels and anti-drug antibodies were extracted. Reactive therapeutic drug monitoring was the standard of care during the study period.

Outcomes

The primary outcomes were loss of response and detection of anti-drug antibodies to anti-TNF therapy. Secondary outcomes were anti-TNF dose escalations, anti-TNF discontinuation, and anti-TNF trough levels.

Statistical Analysis

Continuous parameters were described as median (interquartile range [IQR]) with Mann-Whitney *U* test for significance. For categorical parameters, chi-square or Fisher's exact tests were performed.

Immunomodulator withdrawal vs continuation was analyzed with mixed-effects Cox regression analysis, regardless of subsequent immunomodulator reintroduction (ie, intention to treat). Time at risk started at the maintenance phase (4 months after anti-TNF initiation). Immunomodulator withdrawal was analyzed as a time-varying covariate to prevent immortal time bias, meaning that all patients initially contributed follow-up time to the "continuation" group, and then switched to the "withdrawal" group, if applicable, with a delay of 90 days.[18] Of note, this time-varying analysis precluded construction of Kaplan-Meier curves comparing immunomodulator withdrawal vs continuation. Patients were censored at anti-TNF discontinuation, January 12, 2019, or last available follow-up.

Multiple imputations were performed to replace missing values, and the regression model was adjusted for multiple treatment episodes in individual patients (Supplementary Materials) and potential confounders age, sex, IBD phenotype, smoking, body mass index, primary sclerosing cholangitis, rheumatologic comorbidity, infliximab vs adalimumab, prior anti-TNF exposure, and disease duration. We performed subgroup analyses for patients with UC, patients with CD, infliximab-treated and adalimumab-treated patients, and anti-TNF–naïve patients (ie, no prior exposure to anti-TNF therapy or other biological therapy). Per definition, in the subgroup analysis of anti-TNF–naïve patients, only 1 treatment episode was analyzed per patient. Sensitivity analyses (Supplementary Table 1) were performed for the primary outcomes in patients with prior biological exposure, for patients with at least 4 months of combination therapy, and for thiopurine withdrawal (excluding methotrexate), and significant differences from the primary analyses are reported in the main text.

Among those who stopped the immunomodulator, predictors of loss of response and immunogenicity were identified using Cox regression analysis. Time at risk started at the time of immunomodulator withdrawal. Parameters with $P < .20$ on univariable analysis were entered in the multivariable model. Anti-TNF trough levels, CRP, and fecal calprotectin were only evaluated on univariable analysis, owing to limited data availability. Kaplan Meier curves are presented with log-rank tests for significance.

Longitudinal analysis of infliximab and adalimumab trough levels was performed employing mixed-effects

What You Need to Know

Background

Immunomodulators are often discontinued during anti-tumor necrosis factor α (anti-TNF) maintenance therapy to mitigate the risks of infections and malignancies in patients with inflammatory bowel disease.

Findings

Immunomodulator withdrawal was not associated with a higher risk of loss of response to anti-TNF, but anti-drug antibodies were detected more frequently. Longer duration of combination therapy and higher infliximab trough levels reduced the risk of anti-drug antibodies after immunomodulator withdrawal. Clinical remission, lower C-reactive protein and fecal calprotectin, and higher infliximab trough levels at the time of withdrawal decreased the risk of loss of response.

Implications For Patient Care

If confirmed by future (randomized controlled) prospective studies, immunomodulator withdrawal from anti-TNF may be considered as a de-escalation strategy in patients with inflammatory bowel disease. Objectifying remission and therapeutic drug monitoring prior to immunomodulator withdrawal may decrease the risk of loss of response.

Table 1. Baseline Characteristics

	IMM Continuation (n = 318)	IMM Withdrawal (n = 296)	*P* Value
Female	173 (54.4)	168 (56.8)	.56
IBD type			.37
CD	224 (70.4)	208 (70.3)	
UC	88 (27.7)	77 (26.0)	
IBD-U	6 (1.9)	11 (3.7)	
BMI, kg/m^2	24.6 (21.5–27.5)	25.2 (22.4–29.2)	.02[a]
Active smoker	77 (25.1)	67 (23.8)	.71
Concomitant PSC	13 (4.1)	7 (2.4)	.23
Rheumatologic comorbidity	42 (13.2)	41 (13.9)	.82
Age at IBD diagnosis, y	24.5 (19.6–36.0)	25.6 (21.0–38.3)	.18
CD behavior			.47
Inflammatory (B1)	99 (44.2)	86 (41.3)	
Stricturing (B2)	79 (35.3)	85 (40.9)	
Penetrating (B3)	46 (20.5)	37 (17.8)	
CD location			.51
Ileal (L1)	61 (27.2)	63 (30.3)	
Colonic (L2)	47 (21.0)	32 (15.4)	
Ileocolonic (L3)	114 (50.9)	111 (53.4)	
Isolated upper GI (L4)	2 (0.9)	2 (0.1)	
L1/L2/L3 + upper GI (L4)	27 (12.2)	24 (11.7)	.99
Perianal CD	75 (33.5)	72 (34.6)	.80
UC/IBD-U disease extent			.19
Proctitis (E1)	3 (3.2)	6 (6.8)	
Left-sided (E2)	35 (37.2)	23 (26.1)	
Extensive (E3)	56 (59.6)	59 (67.0)	
Prior IBD-related surgery[b]	59 (18.6)	64 (21.6)	.34
Treatment characteristics			
Adalimumab (vs infliximab)	107 (33.6)	89 (30.1)	.34
Duration of follow-up, y	1.7 (0.9–3.1)	3.6 (2.0–5.4)	<.001[a]
Disease duration at start, y	4.1 (1.2–11.8)	4.1 (1.3–11.0)	.69
Age at start, y	32.7 (24.9–49.9)	34.7 (25.8–50.0)	.40
Prior biological exposure			
None (anti-TNF naïve)	208 (65.4)	223 (75.3)	.01[a]
Prior anti-TNF	110 (34.6)	73 (24.7)	.01[a]
Prior anti-TNF and vedolizumab/ ustekinumab	8 (3.7)	0	.004[a]
Prior medication exposure			
Systemic steroids	258 (86.6)	240 (85.4)	.69
Thiopurines	277 (87.9)	267 (90.2)	.37
Methotrexate	37 (11.7)	38 (12.9)	.67
Prior IMM failure[b]	137 (66.5)	150 (67.3)	.87
Current immunomodulator			.22
Thiopurine	290 (92.1)	264 (89.2)	
Methotrexate	25 (7.9)	32 (10.8)	
Duration of combination therapy prior to IMM withdrawal, y	—	0.9 (0.6–2.1)	—
CRP at IMM withdrawal, mg/L	—	2.0 (0.0–4.0)	—
FCP at IMM withdrawal, μg/g	—	62 (24.0–194.0)	—

Table 1. Continued

	IMM Continuation (n = 318)	IMM Withdrawal (n = 296)	*P* Value
Infliximab trough level at IMM withdrawal, mg/L	—	5.3 (4.0–9.0)	—
Adalimumab trough level at IMM withdrawal, mg/L	—	9.3 (6.7–11.3)	—

Values are n (%) or median (interquartile range). Missing: BMI (n = 26), smoking (n = 25), upper GI involvement (n = 4), prior medication (thiopurines [n = 3], steroids [n = 35], methotrexate [n = 4]), CRP (n = 49), FCP (n = 175), trough levels (infliximab [n = 99], adalimumab [n = 53]).
anti-TNF, anti-tumor necrosis factor; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; FCP, fecal calprotectin; GI, gastrointestinal; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease–unclassified; IFX, infliximab; IMM, immunomodulator; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.
[a]Significant at $P < .05$.
[b]Bowel resection, stricturoplasty of fecal diversion.

linear regression analysis, adjusted for dose (de-)escalations, anti-drug antibodies, and repeated measurements in individual patients, among others (Supplementary Materials).

All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value of <.05 was considered significant.

Study Oversight

This study received exempt status from the institutional review board of the University Medical Center Utrecht because of its observational design.

Results

Cohort Characteristics

Among 614 episodes of combination therapy in 543 individual patients (Supplementary Figure 1), the immunomodulator was discontinued in 296 (48.2%) episodes, after a median of 0.9 (IQR, 0.6–2.1) years. Patients who discontinued the immunomodulator had a higher body mass index, were more often anti-TNF naïve, and had longer follow-up (until anti-TNF discontinuation or censoring) than those who continued the immunomodulator (Table 1). At the time of immunomodulator withdrawal, 85% of patients were in clinical remission. The immunomodulator was most frequently discontinued as a de-escalation strategy (Figure 1). The median follow-up after immunomodulator withdrawal was 1.7 (IQR, 0.8–3.5) years.

Loss of Response and Immunogenicity

After immunomodulator discontinuation, loss of response to anti-TNF therapy occurred in 46 (15.5%) patients, at a rate of 6.6% per patient-year (95% confidence interval [CI], 4.8%–8.8%). The estimated duration at which 25% of the cohort experienced loss of response was 4.4 years (95% CI, 3.8–upper limit not reached) (Figure 2*A*). At the time of loss of response, the median fecal calprotectin and CRP levels were 1004 (IQR, 254–2034) μg/g and 6.8 (IQR, 2.0–18.0) mg/L, respectively.

Immunomodulator withdrawal did not increase the risk of loss of response in the total cohort (adjusted hazard ratio [aHR], 1.08; 95% CI, 0.72–1.61), or in the subgroup analyses (Figure 3*A*), compared with immunomodulator continuation. Relative to CD, more UC patients experienced loss of response during combination therapy (n = 37 [39.4%]), resulting in a lower risk estimate for immunomodulator withdrawal vs continuation (aHR, 0.68; 95% CI, 0.29–1.55), albeit with a wide CI due to the smaller sample size (Figure 3*A*).

Anti-drug antibodies were detected in 30 (10.3%) patients following immunomodulator withdrawal, at a rate of 4.5% per patient-year (95% CI, 3.1%–6.5%) (Figure 2*B*). The incidence of anti-drug antibody detection was higher within vs after 12 months following withdrawal (9.1% per patient-year [95% CI, 5.7%–13.7%] vs 1.9% [95% CI, 0.8%–3.8%]). Immunomodulator discontinuation was associated with an increased risk of anti-drug antibodies in the entire cohort (aHR, 2.14; 95% CI, 1.17–3.94), which did not reach statistical significance in the subgroups of patients with adalimumab, CD patients, UC patients (Figure 3*B*), and biological-exposed patients (Supplementary Table 1).

After detection of anti-drug antibodies, 37 (57.8%) patients developed loss of response, of whom 75% discontinued anti-TNF within 3 months. In patients with anti-drug antibodies, the risk of loss of response (data not shown, $P = .31$) and the antibody titers were similar between those who had continued or withdrawn the immunomodulator (median 48 [IQR, 16–270] AU/mL vs 79 [IQR, 29–125] AU/mL; $P = .70$).

Predictors of Successful Immunomodulator Withdrawal

Among patients who discontinued the immunomodulator, clinical remission at the time of immunomodulator

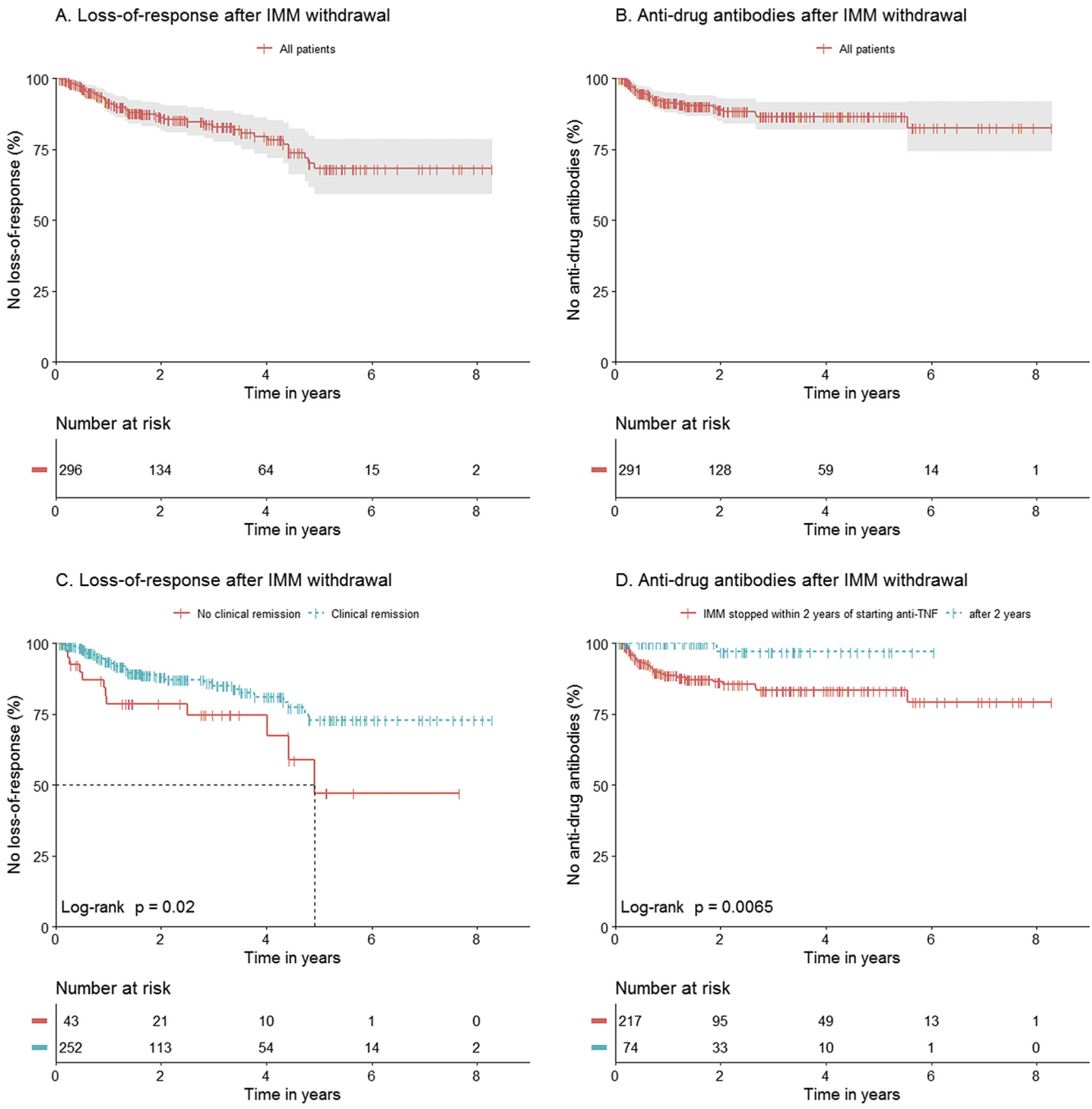


Figure 1. Kaplan Meier estimates. (*A*) Loss of response following IMM withdrawal, all patients. (*B*) Anti-drug antibodies following IMM withdrawal, all patients. (*C*) Loss of response following IMM withdrawal, stratified by clinical remission status at timing of IMM withdrawal. (*D*) Anti-drug antibodies following IMM withdrawal, stratified by duration of combination therapy prior to stopping the IMM.

withdrawal was independently associated with a lower rate of loss of response (aHR, 0.48; 95% CI, 0.25-0.93) (Table 2, Figure 1*C*). A higher CRP (HR, 1.31; 95% CI, 1.09–1.58, natural-log transformed) or fecal calprotectin (HR, 1.34; 95% CI, 1.06–1.70, natural-log transformed) at immunomodulator withdrawal was associated with loss of response (if available). Routinely used thresholds for disease activity, ie, CRP >10 mg/L (n = 25 [10.1%]) and fecal calprotectin >250 μg/g (n = 24 [19.8%]), resulted in numerically higher risk estimates for loss of response, but this did not reach statistical significance (HR for CRP, 2.00; 95% CI, 0.80–4.98; HR for fecal calprotectin, 2.36; 95% CI, 0.85–6.50).

Higher prewithdrawal infliximab trough levels (HR, 0.43; 95% CI, 0.24–0.77, natural-log transformed, available in 108 [52.2%]) were found to reduce the risk of loss of response (Table 2), and a similar trend was observed for adalimumab (HR, 0.12; 95% CI, 0.01–1.03). Details regarding the last trough level measurement prior to immunomodulator withdrawal are presented in Supplementary Table 2.

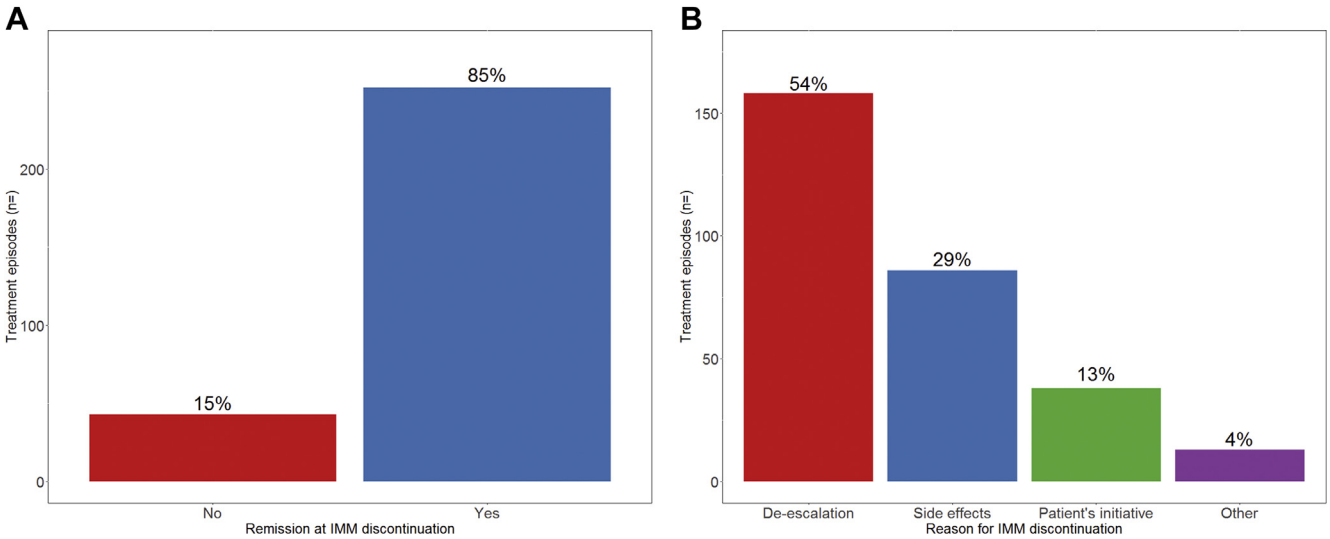


Figure 2. (*A*) Frequencies of clinical remission at the time of IMM withdrawal and (*B*) reasons for IMM withdrawal.

A longer duration of combination therapy prior to immunomodulator withdrawal was associated with a 46% reduced rate of anti-drug antibody detection after immunomodulator discontinuation (HR, 0.54; 95% CI, 0.32-0.91) (Table 2). Moreover, a 72% reduction in the detection rate of anti-drug antibodies (HR, 0.28; 95% CI, 0.13-0.60) was observed for higher infliximab trough levels prior to immunomodulator withdrawal, per point on the natural log scale (eg, between infliximab levels of 12.2 mg/L vs 4.5 mg/L, or 4.5 mg/L vs 1.6 mg/L). No multivariable analysis was conducted for anti-drug antibodies, as only 1 variable was identified with $P < .20$ on univariable analysis and limited trough level measurements.

Distinct intervals (<0.5, 0.5–1, 1–2, and >2 years) of combination therapy were analyzed, but no difference in the risk of loss of response was observed ($P = .39$) (Supplementary Figure 2*A*). In contrast, more than 2 years of combination therapy was associated with a lower risk of anti-drug antibodies ($P = .007$) (Figure 1*D*, Supplementary Figure 2*B*). Reasons for immunomodulator withdrawal were not associated with loss of response ($P = .41$) or anti-drug antibodies ($P = .11$) (Supplementary Figure 2*C* and *D*).

Dose Escalations and Anti-TNF Discontinuation

Dose escalations were required at a rate of 18.0% per patient-year (95% CI, 14.1%–22.6%) after immunomodulator withdrawal, which was higher compared with immunomodulator continuation (aHR, 1.36; 95% CI, 0.97–1.89). However, this did not reach statistical significance in the entire cohort, nor in the subgroup analyses (Supplementary Table 3). No differences were observed in the rate of anti-TNF discontinuation between those who stopped vs continued the immunomodulator (aHR, 0.95; 95% CI, 0.71–1.26) (Supplementary Table 4).

Evolution of Anti-TNF Trough Levels

Infliximab trough levels decreased significantly after immunomodulator withdrawal ($P = .01$) (Supplementary Figure 3*A*). Mean unadjusted trough levels of infliximab were 6.3 ± 5.6 mg/L (669 measurements) during combination therapy vs 5.7 ± 4.5 mg/L (533 measurements) after withdrawal of the immunomodulator. Adalimumab trough levels did not decrease after immunomodulator withdrawal ($P = .16$) (Supplementary Figure 3*B*).

Immunomodulator Reintroduction

The immunomodulator was reintroduced in 47 (16.2%) patients after a median of 0.6 (IQR, 0.4–1.6) years following withdrawal, which did not prevent subsequent loss of response in 15 (31.9%) patients. Seven (14.9%) patients reintroduced the immunomodulator after detection of anti-drug antibodies, which resulted in detectable anti-TNF trough levels in all 7 patients (range, 1.5–19.2), but anti-drug antibodies persisted or recurred in 2 (28.6%) patients.

Discussion

In this large retrospective cohort study, we comprehensively analyzed immunomodulator withdrawal vs continuation in patients with IBD treated with anti-TNF combination therapy. Although a quarter of patients experienced loss of response at 4.4 years after stopping the immunomodulator, this was not significantly different from patients in whom the immunomodulator was continued. Immunomodulator withdrawal was associated with increased detection of anti-drug antibodies, and with lower infliximab trough levels. A longer duration of combination therapy before immunomodulator withdrawal was associated

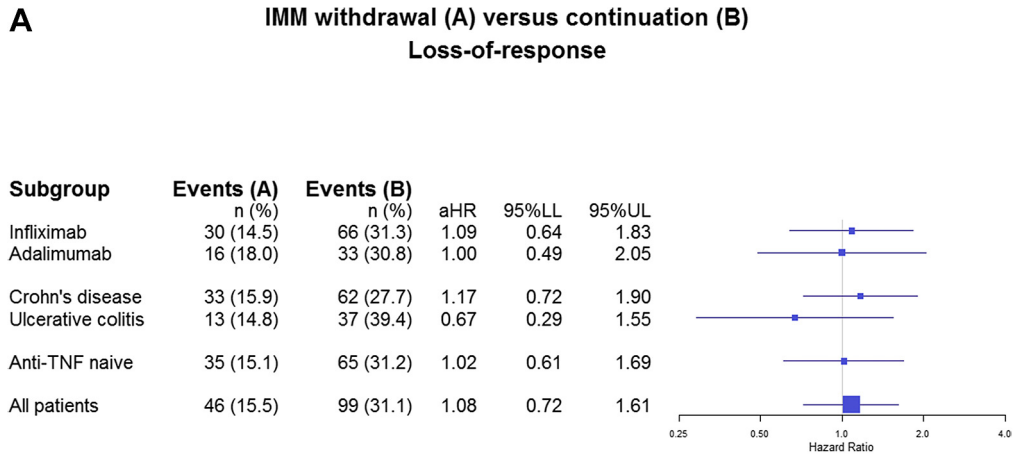


Figure 3. Multivariable HRs of IMM withdrawal vs continuation for (*A*) loss of response and (*B*) anti-drug antibodies. LL, lower limit; UL, upper limit.

with a subsequent lower rate of anti-drug antibody detection.

Given the safety profile of anti-TNF combination therapy with well-documented higher risks of malignant lymphoma and serious infections,[11,19] there is an urgent clinical need to define strategies for therapeutic de-escalation in patients with IBD in remission.[17] Withdrawal of immunomodulators in patients receiving combination therapy is currently recommended by the European guideline in patients with CD achieving long-term remission,[5] while other guidelines provide no recommendation.[1–4] Three small randomized controlled studies compared immunomodulator withdrawal vs continuation in patients with CD and detected no difference in clinical relapse or anti-TNF discontinuation, although in 1 study, CRP increased and infliximab trough levels decreased (as in our study).[12–14] Unfortunately, these studies were underpowered with limited follow-up. In line with previous studies, we report no increased risk of loss of response or anti-TNF discontinuation after immunomodulator withdrawal. However, we did find a significant increase in the detection rate of anti-drug antibodies after immunomodulator discontinuation, especially in patients treated with infliximab. The discrepancy between the increase in anti-drug antibodies and lower trough levels after stopping the immunomodulator, but no corresponding higher risk of loss of response after immunomodulator withdrawal, is striking. It has been reported that anti-drug antibodies can be overcome by dose escalation or immunomodulator (re)initiation.[20–22] This is line with the observed higher frequency of dose escalations after immunomodulator withdrawal, although this finding did not reach statistical significance.

Patients who received combination therapy for a longer time were at lower risk of anti-drug antibodies after immunomodulator withdrawal, but longer duration of combination therapy did not prevent loss of response. In contrast to our findings, several prior studies did report a significantly lower risk of loss of response with longer combination therapy (with optimal cutoffs at 6 months, 9 months, or 2.2 years)[23–25] but not all.[26,27] Notably, a protective effect of longer duration of combination therapy might also be attributed to selection of low-risk patients over time, rather than a direct protective effect of the continued immunomodulator. Thus, the optimal duration of combination therapy remains to be determined. Other risk factors for relapse after immunomodulator discontinuation were identified in prior retrospective studies, including low infliximab trough levels (<5 μg/mL), high CRP (>5 mg/L), high platelet count,[23] prior infliximab dose-escalation,[27]

Table 2. Predictors of Loss of Response and Anti-Drug Antibodies After Immunomodulator Withdrawal (n = 296)

	Loss of Response (46 Events)				Anti-Drug Antibodies (30 Events)	
	Univariable		Multivariable		Univariable	
	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Smoking	0.44 (0.19–1.05)	.06	0.47 (0.20–1.12)	.08	1.13 (0.48–2.66)	.78
UC (vs CD)	1.01 (0.53–1.93)	.96	—	—	1.29 (0.58–2.87)	.53
Male	0.96 (0.54–1.73)	.90	—	—	0.83 (0.39–1.79)	.64
BMI	1.01 (0.96–1.07)	.61	—	—	1.04 (0.97–1.11)	.24
ADA (vs IFX)	1.05 (0.57–1.94)	.87	—	—	1.11 (0.50–2.46)	.79
No prior anti-TNF exposure	1.06 (0.54–2.09)	.87	—	—	1.34 (0.53–3.39)	.53
Duration of combination therapy	0.85 (0.64–1.11)	.23	—	—	0.54 (0.32–0.91)	.02[a]
Clinical remission at IMM withdrawal	0.47 (0.24–0.90)	.02[a]	0.48 (0.25–0.93)	.03[a]	0.63 (0.24–1.62)	.34
CRP at IMM withdrawal[b]	1.31 (1.09–1.58)	.005[a]	—	—	1.14 (0.93–1.42)	.20
Fecal calprotectin at IMM withdrawal[b]	1.34 (1.06–1.70)	.01[a]	—	—	1.01 (0.82–1.25)	.90
ADA trough level[b]	0.12 (0.01–1.03)	.054	—	—	3.97 (0.06–250.5)	.51
IFX trough level[b]	0.43 (0.24 - 0.77)	.004[a]	—	—	0.28 (0.13–0.60)	.001[a]

ADA, adalimumab; aHR, adjusted hazard ratio; anti-TNF, anti-tumor necrosis factor α; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IFX, infliximab; IMM, immunomodulator; UC, ulcerative colitis.
[a]Significant at $P < .05$.
[b]CRP, fecal calprotectin, and ADA and IFX trough levels are natural log-transformed, and not entered in the multivariable model due to missing data.

discontinuation of methotrexate (instead of thiopurine),[25] and young age at diagnosis (<16 years).[25] In our study, we additionally found that absence of clinical remission and higher fecal calprotectin were risk factors for loss of response after immunomodulator discontinuation, and confirmed that higher anti-TNF trough levels are protective.

General strengths of our study include the systematic identification of patients, large sample size, relatively long duration of follow-up, and detailed data collection, allowing a comprehensive analysis of clinical, biochemical, and pharmacokinetic outcomes following immunomodulator withdrawal. We addressed knowledge gaps in prior literature by providing subgroup analyses for patients with UC[24] and adalimumab-treated patients.[13] In contrast to infliximab, the occurrence of anti-adalimumab antibodies was not increased after stopping the immunomodulator. Inclusion of patients using methotrexate (vs thiopurine) enhanced generalizability of our findings. While our primary findings remained unchanged in the sensitivity analysis excluding methotrexate, our study was not designed to detect differences between methotrexate vs thiopurine combination therapy.

The limitations inherent to the retrospective design of our study should also be acknowledged. Despite our careful employment of statistical techniques to balance patients' characteristics, there is a plausible, unmeasurable bias toward selection of low-risk patients for immunomodulator withdrawal from combination therapy that can only be overcome in randomized controlled studies. Furthermore, transient (symptomatic) flares that did not result in anti-TNF dose escalation or loss of response were not detected with our study design. Prospective studies may provide more details regarding clinical symptoms, endoscopic outcomes, dosing of immunomodulators, and scheduled measurements of CRP, fecal calprotectin, and trough levels and anti-drug antibodies. Nevertheless, these limitations must be contrasted with higher generalizability of our study providing real-world data, longer follow-up, and the large sample size that allowed assessment of predictors of successful immunomodulator withdrawal.

Expanding treatment options for IBD in case of failure of anti-TNF, including biologicals with other molecular targets and small molecules,[28] shed a new light on the risks vs benefits of prolonged combination therapy of anti-TNF with thiopurines. With new treatment options, the theoretically increased risk of anti-TNF failure after immunomodulator discontinuation may no longer outweigh the long-term side effects of thiopurines. In general, patients receiving combination therapy are willing to de-escalate medical therapy when remission is

achieved and prefer to stop the immunomodulator, rather than the anti-TNF agent.[29]

In conclusion, in this retrospective analysis, immunomodulator withdrawal did not result in an increased risk of loss of response to anti-TNF in the 1–2 years postcessation, although we observed an increase in anti-drug antibodies and lower infliximab trough levels. Therapeutic drug monitoring and objectifying (biochemical) remission prior to immunomodulator withdrawal may further reduce the risk of loss of response. As the majority of patients were selected by their treating physicians for treatment de-escalation, our findings require prospective validation, preferably in an adequately powered randomized controlled trial.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.01.019.

References

1. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology 2020;158:1450–1461.
2. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the Use of Thiopurines, Methotrexate, and Anti-TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn's Disease. Gastroenterology 2013;145:1459–1463.
3. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68(Suppl 3):S1.
4. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: current management. J Crohn's Colitis 2017;11:769–784.
5. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on therapeutics in Crohn's disease: medical treatment. J Crohn's Colitis 2020;14:4–22.
6. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
7. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–400.
8. Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. J Crohns Colitis 2016; 10:1259–1266.
9. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341–353.
10. Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. Gastroenterology 2018;155:337–346.
11. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA 2017;318:1679–1686.
12. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134:1861–1868.
13. Hisamatsu T, Kato S, Kunisaki R, et al. Withdrawal of thiopurines in Crohn's disease treated with scheduled adalimumab maintenance: a prospective randomised clinical trial (DIAMOND2). J Gastroenterol 2019;54:860–870.
14. Roblin X, Boschetti G, Williet N, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. Aliment Pharmacol Ther 2017;46:142–149.
15. Schultheiss JPD, Mahmoud R, Louwers JM, et al. Loss of response to anti-TNFα agents depends on treatment duration in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2021;54:1298–1308.
16. Gomollón F, Dignass A, Annese V, et al. European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: part 1:diagnosis and medical management. J Crohn's Colitis 2017;11:3–25.
17. Chapman TP, Gomes CF, Louis E, et al. De-escalation of immunomodulator and biological therapy in inflammatory bowel disease. Lancet Gastroenterol Hepatol 2020;5:63–79.
18. Levesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340:b5087.
19. Singh S, Facciorusso A, Dulai PS, et al. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020;18:69–81.
20. Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013; 11:444–447.
21. Papamichael K, Vajravelu RK, Osterman MT, Cheifetz AS. Long-term outcome of infliximab optimization for overcoming immunogenicity in patients with inflammatory bowel disease. Dig Dis Sci 2018;63:761–767.
22. Strik AS, van den Brink GR, Ponsioen C, et al. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2017; 45:1128–1134.
23. Oussalah A, Chevaux J-B, Fay R, et al. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. Am J Gastroenterol 2010; 105:1142–1149.
24. Filippi J, Laharie D, Michiels C, et al. Efficacy of sustained combination therapy for at least 6 months with thiopurines and infliximab in patients with ulcerative colitis in clinical remission: a retrospective multicenter French experience. J Crohns Colitis 2015;9:252–258.
25. Fischer M, Campbell SC, Calley CSJ, et al. Risk factors for rescue therapy in Crohn's patients maintained on infliximab after withdrawal of the immunomodulator: a long-term follow-up. Dig Dis Sci 2017;62:3131–3137.

26. Lambrescak E, Vaysse T, Allez M, et al. Duration of combination therapy and risk of treatment failure in patients with inflammatory bowel disease. Clin Res Hepatol Gastroenterol 2021;45:101503.
27. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. Clin Gastroenterol Hepatol 2015;13:514–521.
28. Katsanos KH, Papamichael K, Feuerstein JD, et al. Biological therapies in inflammatory bowel disease: beyond anti-TNF therapies. Clin Immunol 2019;206:9–14.
29. Siegel CA, Thompson KD, Walls D, et al. Perspectives from patients and gastroenterologists on de-escalating therapy for Crohn's disease. Clin Gastroenterol Hepatol 2021;19:403–405.

Reprint Requests
Address requests for reprints to Bas Oldenburg, MD, PhD, University Medical Centre Utrecht, Division of Internal Medicine and Dermatology, Department of Gastroenterology, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. e-mail: boldenbu@umcutrecht.nl; fax: +31 88 7555 081.

Conflicts of interest
These authors disclose the following: Remi Mahmoud has received a travel grant from Takeda. B. Oldenburg has received grants from MSD, AbbVie, Takeda, Cablon, Ferring, Falk, and Pfizer. H.H. Fidder has served as a consultant for AbbVie BV, Janssen BV, Ferring BV, and Takeda BV. The remaining authors disclose no conflicts.

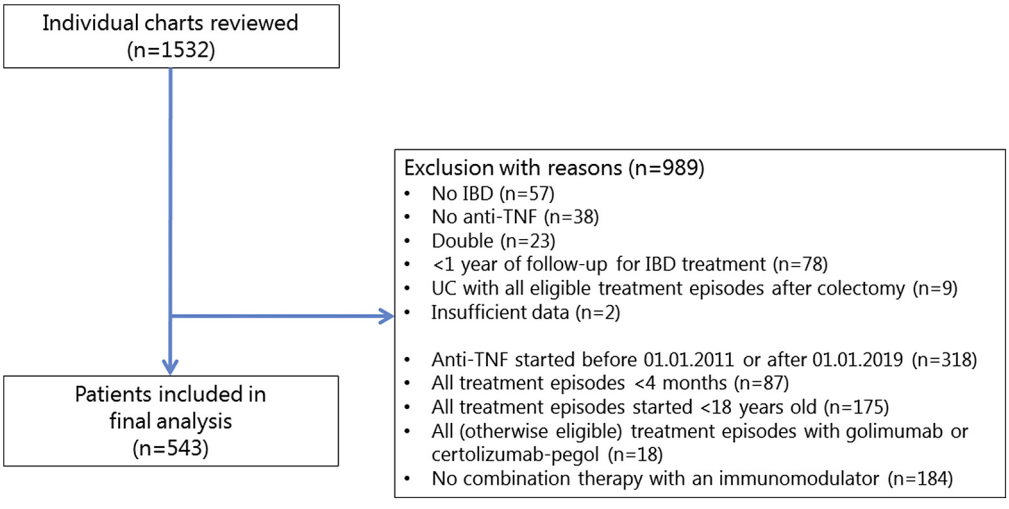
Supplementary Materials

Cox Regression Analysis

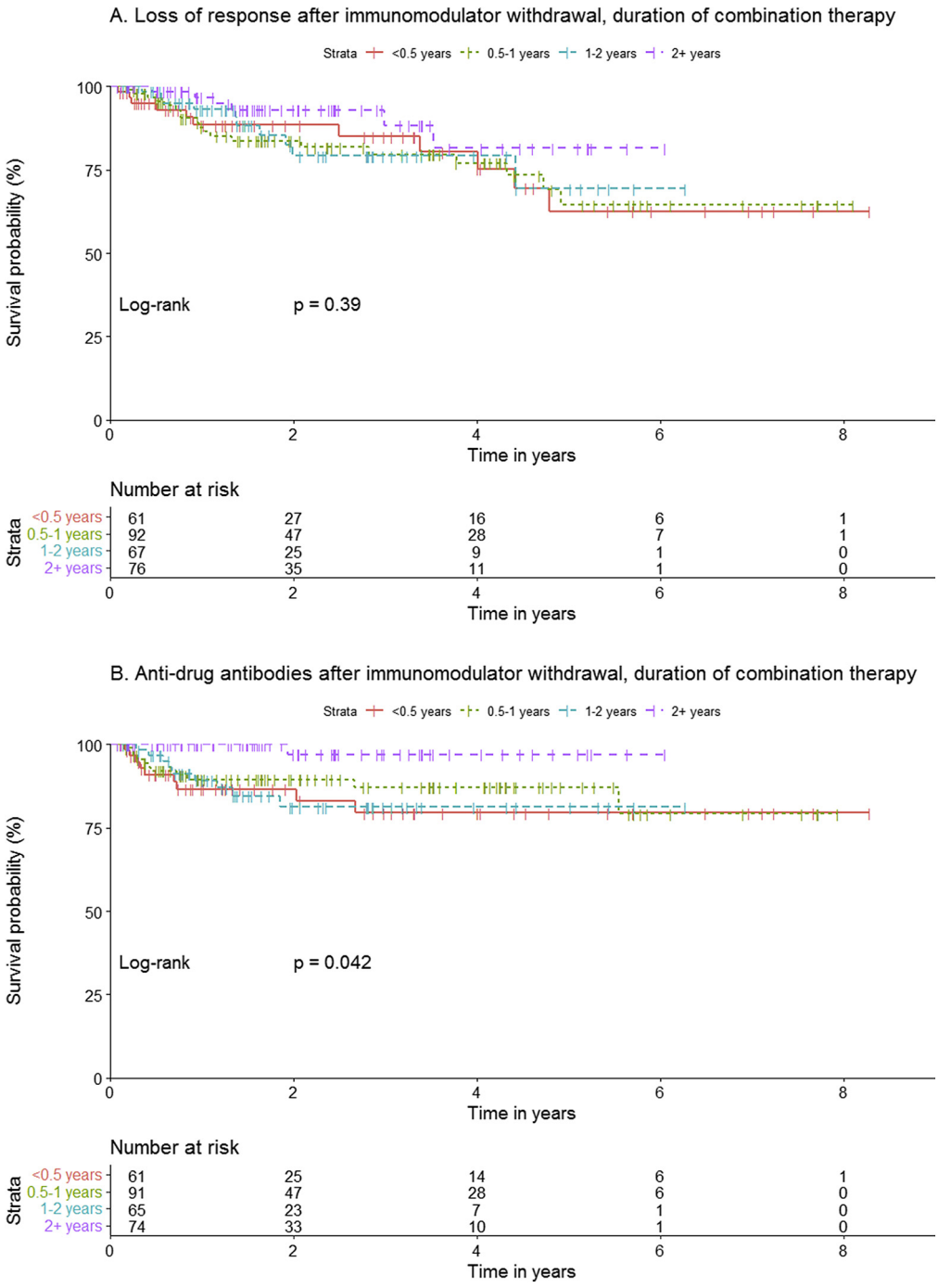
Adjusted hazard ratios were calculated utilizing mixed-effects Cox regression analysis, accounting for multiple treatment episodes in individual patients. The proportional hazards assumption was assessed using Schoenfeld residuals. Disease duration violated the assumption and was entered as a stratum instead of covariate in the model. Multiple imputations were performed to replace missing values for body mass index and smoking. C-reactive protein, fecal calprotectin, and infliximab trough levels were not imputed due to the larger amount of missing data. We assumed that the data were missing at random and performed multiple imputations based on iterative (20 iterations) chained equations with body mass index, smoking, length, weight, sex, age, inflammatory bowel disease phenotype, hazard of loss of response (Nelson-Aalen estimate), mucosal healing, dose escalations, adalimumab versus infliximab, number of prior anti-tumor necrosis factor α exposures, disease duration, Crohn's disease behavior, and upper gastrointestinal involvement. Thus, we created 10 imputed datasets using the MICE package in R version 13 (R Foundation for Statistical Computing, Vienna, Austria).

Longitudinal Analysis of Trough Levels

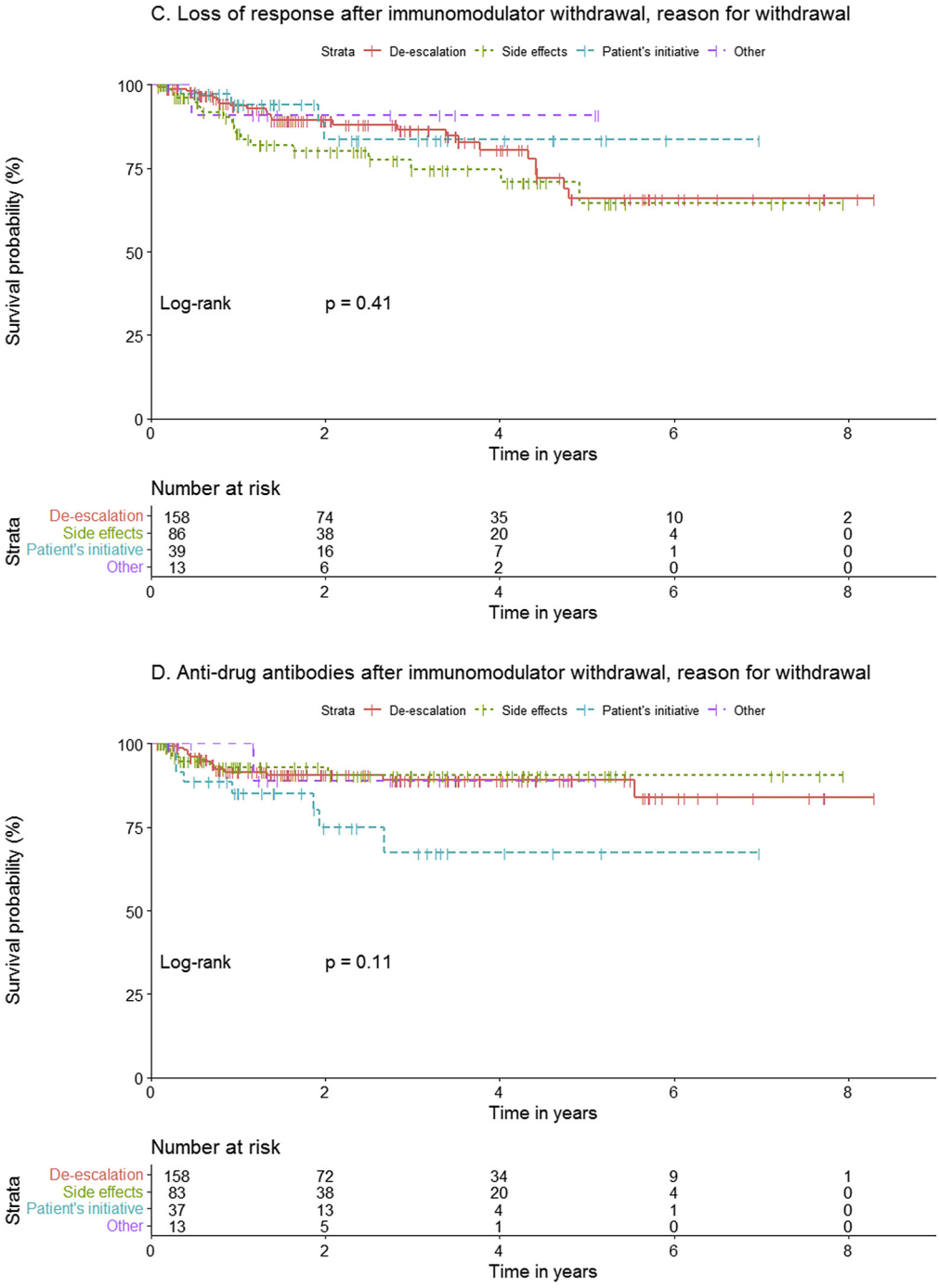
Trough levels were analyzed employing a mixed-effects linear regression model of log-transformed trough levels. We used a mixed-effects model, clustering measurements per individual patient. Stopping the immunomodulator was entered as a time-varying covariate. Relevant confounders and potential interactions between confounders were selected using forward and backward selection of models using the Akaike information criterion. The most optimal model for adalimumab was corrected for dose escalations, dose de-escalations, anti-drug antibodies, body mass index, and prior anti-tumor necrosis factor α exposure. The model for infliximab was adjusted for dose escalations, dose de-escalations, anti-drug antibodies, whether the measurement was performed during infliximab induction and a statistical interaction between dose de-escalations and presence of anti-drug antibodies. A thousand bootstraps of the model were performed to obtain both bias-reduced longitudinal profiles of trough levels and predictors.



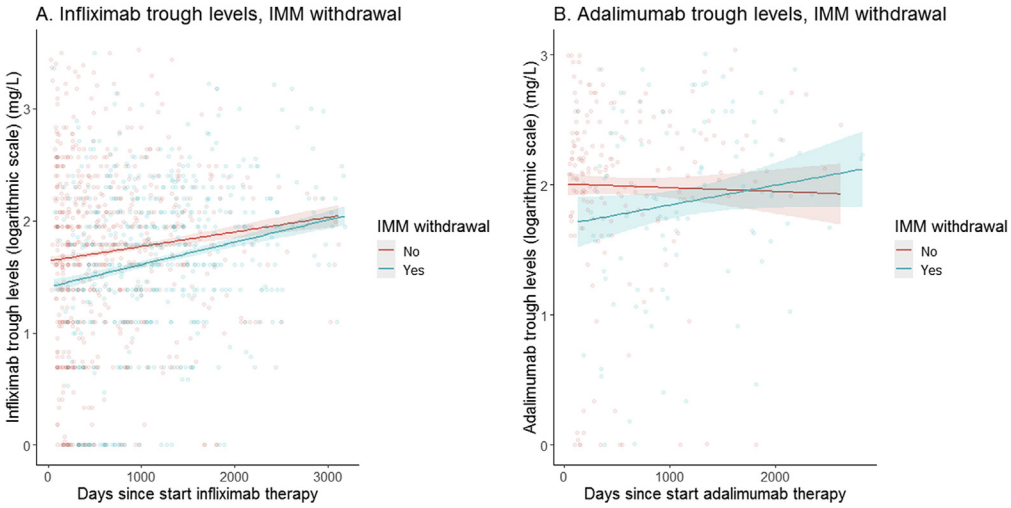
Supplementary Figure 1. Flow diagram of the selection process.



Supplementary Figure 2. Kaplan Meier curves. Incidence of loss of response (*A*) and anti-drug antibody detection (*B*) after immunomodulator withdrawal, stratified for duration of combination therapy. Incidence of loss of response (*C*) and anti-drug antibody detection (*D*) after immunomodulator withdrawal, stratified for reasons for withdrawal.



Supplementary Figure 2. (*continued*).



Supplementary Figure 3. Association of infliximab (*A*) and adalimumab (*B*) trough levels with anti-TNF treatment duration after IMM withdrawal.

Supplementary Table 1. Sensitivity Analyses With Multivariable HRs for Loss of Response and Anti-Drug Antibodies as Well as IMM Withdrawal vs Continuation

	IMM Withdrawal	IMM Continuation	aHR	95% CI
Loss of response				
Patients with >4 mo of combination therapy	41 (15.5)	99 (31.1)	1.07	0.71–1.61
Patients with prior biological exposure	11 (15.1)	34 (30.9)	1.09	0.51–2.35
Patients with a thiopurine (and not methotrexate) as IMM	41 (15.5)	91 (31.4)	1.02	0.66–1.58
Anti-drug antibodies				
Patients with >4 mo of combination therapy	25 (9.7)	34 (10.7)	2.18	1.18–4.05
Patients with prior biological exposure	6 (8.5)	14 (12.8)	0.83	0.25–2.81
Patients with a thiopurine (and not methotrexate) as IMM	28 (9.6)	26 (10.0)	1.96	1.02–3.77

Values are n (%), unless otherwise indicated.
aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IMM, immunomodulator.

Supplementary Table 2. Details of Last Anti-TNF Trough Level Measurement Prior to Immunomodulator Withdrawal, With Univariable HRs for Loss of Response and Anti-Drug Antibodies

	Available	Time From Last Measurement to IMM Stop (d)	Median Trough Level (mg/L)	Loss of Response	HR for Loss of Response (95% CI)	*P* Value	Antibodies	HR for Antibodies (95% CI)	*P* Value
Adalimumab	36 (40.4%)	100 (27–323)	9.3 (6.7–11.3)	8 (22.2)	0.74 (0.55-1.00)	.05	1 (2.9)	1.09 (0.74–1.59)	.66
Log transformed	—	—	—	—	0.12 (0.01–1.03)	.054	—	3.97 (0.06–250.5)	.51
Infliximab	108 (52.2%)	73 (25–196)	5.3 (4.0–9.0)	12 (11.1)	0.85 (0.69–1.05)	.13	6 (5.8)	0.74 (0.56–0.99)	.04[a]
Log transformed	—	—	—	—	0.43 (0.24–0.77)	.004[a]	—	0.28 (0.13–0.60)	.001[a]

Values are n (%) or median (interquartile range), unless otherwise indicated.
CI, confidence interval; HR, hazard ratio; IMM, immunomodulator.
[a]Significant at $P < .05$.

Supplementary Table 3. Multivariable HRs for Dose Escalation and IMM Withdrawal vs Continuation

(Sub)Group	IMM Withdrawal	IMM Continuation	aHR	95% CI
IFX	51 (32.1)	109 (49.1)	1.35	0.91–2.00
ADA	23 (29.5)	42 (42.4)	1.34	0.72–2.49
CD	54 (32.3)	107 (46.5)	1.34	0.92–1.96
UC	20 (28.6)	44 (48.4)	1.21	0.62–2.33
Anti-TNF naïve	58 (32.6)	101 (45.7)	1.43	1.00–2.07
All patients	74 (31.2)	151 (47.0)	1.36	0.97–1.89

Values are n (%), unless otherwise indicated.
ADA, adalimumab; aHR, adjusted hazard ratio; anti-TNF, anti-tumor necrosis factor α; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IFX, infliximab; IMM, immunomodulator; UC, ulcerative colitis.

Supplementary Table 4. Multivariable HRs for Anti-TNF Discontinuation and IMM Withdrawal vs Continuation

(Sub)Group	IMM Withdrawal	IMM Continuation	aHR	95% CI
IFX	72 (34.8)	130 (61.6)	0.95	0.66–1.36
ADA	38 (42.7)	64 (59.8)	1.02	0.62–1.68
CD	74 (35.6)	137 (61.2)	0.94	0.68–1.31
UC	36 (40.9)	57 (60.6)	0.94	0.55–1.60
Naïve	81 (36.3)	124 (59.6)	1.20	0.84–1.70
All patients	110 (37.2)	194 (61.0)	0.95	0.71–1.26

Values are n (%), unless otherwise indicated.
ADA, adalimumab; aHR, adjusted hazard ratio; anti-TNF, anti-tumor necrosis factor α; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IFX, infliximab; IMM, immunomodulator; UC, ulcerative colitis.