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Complete Endoscopic Healing Is Associated With Lower Relapse Risk After Anti-TNF Withdrawal in Inflammatory Bowel Disease

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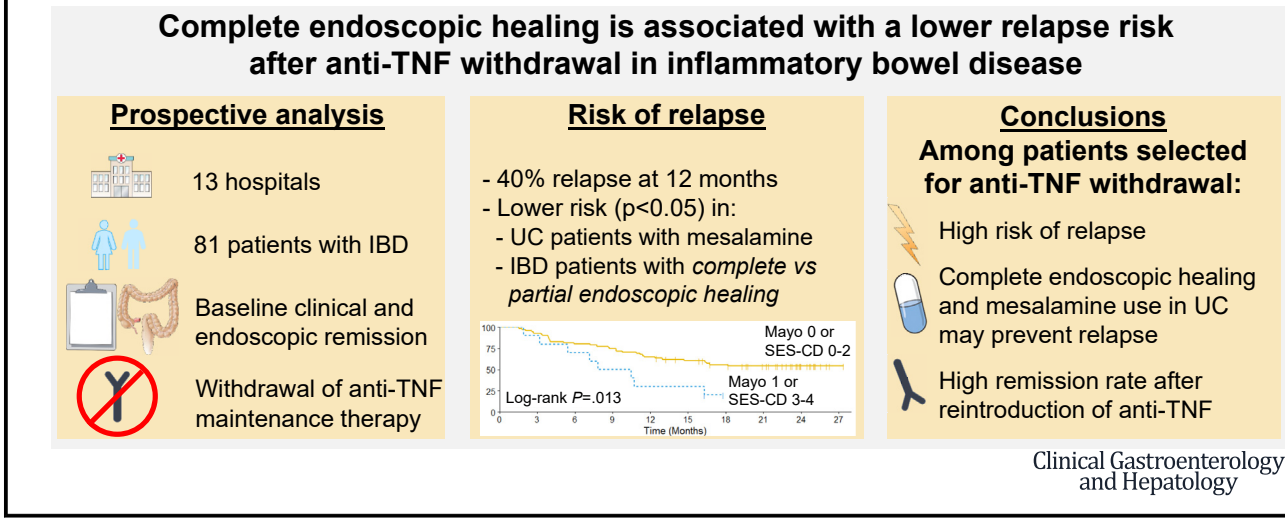

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Abbreviations used in this paper: aHR, adjusted hazard ratio; anti-TNF, anti-tumor necrosis factor-α; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease-unclassified; IQR, interquartile range; PGA, physician global assessment; RCT, randomized controlled trial; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIBDQ, Short Inflammatory Bowel Disease Quality of Life Questionnaire; UC, ulcerative colitis.

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BACKGROUND & AIMS: **Discontinuation of anti–tumor necrosis factor-α treatment (anti-TNF) (infliximab and adalimumab) in patients with inflammatory bowel disease (IBD) is associated with a high relapse risk that may be influenced by endoscopic activity at the time of stopping. We assessed the relapse rate after anti-TNF withdrawal in patients with endoscopic healing and studied predictors of relapse including the depth of endoscopic healing.**

METHODS: **This was a multicenter, prospective study in adult patients with Crohn's disease (CD), ulcerative colitis (UC), or IBD-unclassified (IBDU), with ≥6 months of corticosteroid-free clinical remission (confirmed at baseline) and endoscopic healing (Mayo <2/SES-CD <5 without large ulcers), who discontinued anti-TNF between 2018 and 2020 in the Netherlands. We performed Kaplan-Meier and Cox regression analyses to assess the relapse rate and evaluate potential predictors: partial (Mayo 1/SES-CD 3–4) versus complete (Mayo 0/SES-CD 0–2) endoscopic healing, anti-TNF trough levels, and immunomodulator and/or mesalamine use.**

RESULTS: **Among 81 patients (CD: n = 41, 51%) with a median follow-up of 2.0 years (interquartile range, 1.6–2.1), 40 patients (49%) relapsed. Relapse rates in CD and UC/IBDU patients were comparable. At 12 months, 70% versus 35% of patients with partial versus complete endoscopic healing relapsed, respectively (adjusted hazard rate [aHR], 3.28; 95% confidence interval [CI], 1.43–7.50). Mesalamine use was associated with fewer relapses in UC/IBDU patients (aHR, 0.08; 95% CI, 0.01–0.67). Thirty patients restarted anti-TNF, and clinical remission was regained in 73% at 3 months.**

CONCLUSIONS: **The relapse risk was high after anti-TNF withdrawal in IBD patients with endoscopic healing, but remission was regained in most cases after anti-TNF reintroduction. Complete endoscopic healing and mesalamine treatment in UC/IBDU patients decreased the risk of relapse.**

Keywords: De-escalation; Endoscopic Remission; Biologicals; Deep Remission.

De-escalation of anti–tumor necrosis factor-α (anti-TNF) treatment in patients with inflammatory bowel disease (IBD) in remission can potentially reduce side effects, including risks of serious infections and malignancies, decrease health care expenditures, and meet patients' preferences.[1–3] Data from randomized controlled trials (RCTs) have proven that anti-TNF withdrawal considerably increases the risk of relapse in both ulcerative colitis (UC) and Crohn's disease (CD).[4,5] Prospective studies and a meta-analysis have estimated that approximately 30%–45% of patients relapse at 12 months, whereas reintroduction of anti-TNF therapy restores remission in more than 80% of patients.[4–7] Currently, no consensus exists on patient selection for treatment de-escalation.[8,9]

Emerging evidence suggests that persistent inflammation compromises treatment outcomes in asymptomatic patients with IBD, when assessed endoscopically, histologically, or with fecal calprotectin.[10–14] A prior study suggests that the depth of endoscopic healing influences the rate of biological failure as well as long-term outcomes (hospitalizations and surgeries) in patients with CD.[13] In the context of de-escalation from anti-TNF therapy, the risk of relapse was lower in IBD patients with endoscopic healing in addition to clinical remission,[6,15,16] but it remains unclear which degree of endoscopic healing is needed to lower the risk of relapse.

We conducted a multicenter, prospective study in IBD patients in clinical remission and with endoscopic healing in whom anti-TNF treatment was discontinued. We aimed to assess the relapse rate, evaluate predictors of relapse including the degree of endoscopic healing, and study outcomes after reintroduction of anti-TNF therapy.

Methods

Study Design and Population

This was a prospective observational study in 2 tertiary referral centers and 11 general hospitals in the Netherlands. Patients were recruited between 2018 and 2020. Inclusion criteria were a diagnosis of CD, UC, or IBD-unclassified (IBDU), age ≥18 years, ≥6 months of corticosteroid-free clinical remission with infliximab or adalimumab, confirmed baseline clinical remission and endoscopic healing (as defined below), elective discontinuation of anti-TNF therapy (without starting another biological or tofacitinib), no current hospitalization, and no (intended) pregnancy. Withdrawal of anti-TNF treatment was discussed in a shared decision-making process between the patient and treating physician as part of usual care in which the risks versus benefits of discontinuing treatment while in confirmed remission were discussed, in accordance with the Dutch IBD treatment guideline.[17] Patients who opted to discontinue anti-TNF were offered to voluntarily participate in this observational study.

Study Procedures

Baseline measurements included fecal calprotectin, C-reactive protein (CRP), anti-TNF trough levels, and endoscopic evaluation of disease activity. Patients could continue or start mesalamine or immunomodulator (thiopurine or methotrexate) treatment at the discretion of the treating physician.

The follow-up started at the last administration of anti-TNF treatment. Recommended monitoring included measurements of CRP and fecal calprotectin at 3, 6, 12, and 24 months and an endoscopy at 12 months. In case of a (suspected) relapse, endoscopy and measurements of CRP and fecal calprotectin were recommended. The preferred treatment at relapse was reintroduction of the anti-TNF agent. After a relapse, monitoring included CRP, fecal calprotectin, and an anti-TNF trough level at 3 months.

Participants received questionnaires by email at 0, 3, 6, 12, and 24 months of follow-up, at the time of a relapse, and 3 months thereafter. Questionnaires included the patient Harvey-Bradshaw Index (HBI) for CD patients or patient Simple Clinical Colitis Activity Index (SCCAI) for UC and IBDU patients and the short IBD Quality of Life questionnaire (SIBDQ; used under license from McMaster University, Hamilton, Canada).[18–20] General well-being was scored on a scale ranging 1–10. In addition, patients received a non-validated patient perspective questionnaire at 0, 12, and 24 months, in which all items were scored on a visual analogue scale ranging 1–10 (Supplementary Table 1).

Data Collection and Definitions

Clinical data were collected from the electronic health records at each visit, including the physician global assessment (PGA) (remission versus active IBD), IBD-related medication, laboratory parameters, radiologic examinations, endoscopic and surgical procedures, and hospitalizations. No central reading or assessments were performed.

Clinical remission was defined as SCCAI/HBI <5, biochemical remission was defined as CRP <10 mg/L and fecal calprotectin <250 μg/g, and endoscopic healing was defined as endoscopic Mayo score <2 or Simple Endoscopic Score for CD (SES-CD) <5 without large ulcers. Endoscopic healing was subclassified as complete endoscopic healing (Mayo 0/SES-CD 0–2) versus partial endoscopic healing (Mayo 1/SES-CD 3–4).[10]

Clinical relapse was defined as SCCAI/HBI ≥ 5 with ≥ 3 points increase from baseline. Biochemical and endoscopic relapse were defined as absence of previously defined biochemical remission and endoscopic healing, respectively.

Trough levels <3 mg/L for infliximab and <5 mg/L for adalimumab were considered subtherapeutic. At most participating sites, anti-drug antibodies were only measured in case of trough levels <1.0 mg/L.

What You Need to Know

Background

The risk of relapse after withdrawal of anti-TNF treatment is high (33%–45% at 12 months) among patients with inflammatory bowel disease (IBD) in clinical remission but might be lower in patients with endoscopic healing. The degree of endoscopic healing that should be achieved before treatment de-escalation is unknown.

Findings

The risk of relapse after withdrawal of anti-TNF treatment among patients with endoscopic healing (Mayo <2 or SES-CD <5 without large ulcers) remained high (40% at 12 months). Complete endoscopic healing (Mayo 0 or SES-CD 0–2) was associated with a considerably lower risk of relapse than partial endoscopic healing (Mayo 1 or SES-CD 3–4). Mesalamine use was associated with a lower relapse risk in ulcerative colitis. Reintroduction of anti-TNF treatment restored clinical remission in 73% of patients at 3 months.

Implications for patient care

Strict patient selection based on complete endoscopic healing and mesalamine maintenance treatment in ulcerative colitis may lower the risk of relapse after anti-TNF withdrawal in patients with IBD.

Outcomes

The primary composite outcome was relapse, defined as any of the following: endoscopic relapse, clinical and biochemical relapse, step-up of medical therapy (any treatment for active IBD, including steroids and topical therapy, excluding antibiotics), IBD-related hospitalization or surgery, or newly diagnosed intestinal stenotic disease, (perianal) abscess or fistula.

Secondary outcomes included (the degree of) endoscopic relapse, IBD-related hospitalizations and surgeries, potential predictors of relapse, and effectiveness of reintroduction of anti-TNF treatment after 3 months.

Statistical Analysis

All data were censored on October 1, 2021, at which point all patients had ≥ 1 years of follow-up.

Baseline characteristics were described as frequencies (with % of patients without missing data) or median (interquartile range [IQR]) and compared with χ^2 tests or Mann-Whitney U test, respectively. Time to relapse was analyzed using Kaplan-Meier curves with log-rank tests for significance.

Subtherapeutic trough levels, complete versus partial endoscopic healing, and immunomodulator and/or mesalamine use were assessed as potential predictors of

relapse, using Cox regression analysis. The proportional hazards assumption was confirmed using Schoenfeld residuals, missing trough levels were replaced using multiple imputation, and study site was entered as a random effect on the baseline hazard. All covariates were selected a priori and directly entered in the multivariable model. Stratified analyses were conducted for patients with CD versus UC/IBDU. A sensitivity analysis was performed excluding patients with partial endoscopic healing. An exploratory post hoc univariable analysis was conducted for other clinically relevant potential predictors of relapse.

Pairwise comparisons (including pre- versus post-withdrawal trough levels) between time points in one individual were assessed with Wilcoxon signed-rank test. If trough levels were measured repeatedly after reintroduction of anti-TNF, the lowest serum concentration was analyzed. SIBDQ and well-being scores were analyzed using an unadjusted linear mixed model.

Other repeated measurements (PGA, fecal calprotectin, CRP, and HBI/SCCAI) were analyzed descriptively. Measurements were performed as part of routine care and not always at the exact predefined time points. We therefore clustered measurements in 3-monthly intervals (1 month before, 2 months after the predefined time point). If multiple measurements were performed in one interval, the value most indicative of active disease was analyzed.

Study Oversight

All patients provided written informed consent. This study received exempt status from the Institutional Review Board of the University Medical Center Utrecht because of its observational design.

Results

Population

We enrolled 81 patients (CD: n = 41, 51%; Supplementary Figure 1). At baseline, the median duration of remission was 3.5 years (IQR, 2.0–4.9) (Table 1). The median disease duration was 9.1 years (IQR, 4.5–14.3). All patients had endoscopic healing (Mayo <2/SES-CD <5 without large ulcers), and 71 patients (88%) met the strict criteria for complete endoscopic healing (Mayo 0/SES-CD 0–2). Anti-TNF trough levels were subtherapeutic in 24 patients (34%) (Table 2). Four patients (4.9%) had previously experienced primary non-response or loss of response to anti-TNF or vedolizumab (Table 1). After anti-TNF withdrawal, 21 patients (25.9%) continued immunomodulators, which was similar between patients discontinuing adalimumab versus infliximab (n = 6, 27% versus n = 15, 25%, respectively; $P = .87$). The median follow-up time was 2.0 years (IQR, 1.6–2.1).

Risk of Relapse

During follow-up, 40 of patients (49%) relapsed. Relapse rates were 7%, 21%, 28%, and 40% at 3, 6, 9, and 12 months, respectively (Figure 1*A*). The relapse was confirmed with endoscopy, fecal calprotectin, or CRP in 33 cases (83%), whereas 7 (17%) were declared on the basis of treatment escalation for a clinical flare. The relapse rate at 12 months was comparable between patients with UC/IBDU (n = 17, 43%) and CD (n = 15, 37%; Figure 1*B*; $P = .76$) and between patients discontinuing adalimumab (n = 8, 36%) and infliximab (n = 24, 41%; data not shown, $P = .96$).

Partial endoscopic healing (Mayo 1/SES-CD 3–4) was independently associated with a higher relapse risk (adjusted hazard ratio [aHR], 3.28; 95% confidence interval [CI], 1.43–7.50) compared with complete endoscopic healing (Mayo 0/SES-CD 0–2), and this remained significant in the stratified analyses for patients with UC/IBDU and CD (Table 3). At 12 months, 7 patients (70%) with partial endoscopic healing had relapsed, compared with 25 patients (35%) with complete endoscopic healing (Figure 1*C*). Of note, the time between the baseline endoscopy and withdrawal of anti-TNF (<6 months in 77 of patients [95%]) did not significantly affect the hazard ratio for partial versus complete endoscopic healing (Supplementary Table 2).

Mesalamine treatment was independently associated with a decreased risk of relapse in patients with UC/IBDU (aHR, 0.08; 95% CI, 0.01–0.67; Figure 1*D* and Table 3) or patients with UC only (aHR, 0.08; 95% CI, 0.01–0.71). Subtherapeutic anti-TNF trough levels and immunomodulator use were not associated with the risk of relapse (Figure 1*E* and *F*). No relevant changes to the hazard ratios for immunomodulators, mesalamine, and trough levels were observed in the sensitivity analysis excluding patients with partial endoscopic healing (Supplementary Table 3). No other potential predictors for relapse were identified in the exploratory post hoc analysis (Supplementary Table 4).

Secondary Outcomes

A follow-up endoscopy was available in 29 patients (73%) with UC/IBDU and 32 patients (78%) with CD after a median of 1.1 years (IQR, 0.9–1.2). The number of patients with complete endoscopic healing decreased considerably both in UC (from 28 [97%] to 14 [48%]) and CD (from 26 [81%] to 14 [44%]; Figure 2).

Other secondary outcomes are presented in Supplementary Table 5. Notably, 3 patients (4%) were hospitalized for active IBD, and 1 patient with CD (2%) underwent an ileocecal resection for a symptomatic stenosis.

Anti-Tumor Necrosis Factor Reintroduction

After relapse, 30 patients (75%) restarted anti-TNF treatment (of whom 1 withdrew consent for further

Table 1. Baseline Characteristics

	All patients (n = 81)	UC/IBDU (n = 40)	CD (n = 41)
Age, *y*	40.2 (29.7–53.1)	45.1 (32.2–52.7)	34.3 (28.7–54.4)
Female sex	42 (51.9)	18 (45.0)	24 (58.5)
Body mass index, kg/m^2	24.1 (22.5–26.8)	23.8 (22.4–25.5)	25.2 (22.5–27.7)
Smoking	7 (8.6)	3 (7.5)	4 (9.8)
Age at diagnosis, *y*	28.5 (22.1–37.5)	30.5 (23.1–40.1)	25.9 (21.2–36.8)
<18	6 (7.4)	2 (5.0)	4 (9.8)
18–40	57 (70.4)	28 (70.0)	29 (70.7)
>40	18 (19.5)	10 (25.0)	18 (22.2)
Disease duration, *y*	9.1 (4.5–14.3)	10.0 (7.7–12.9)	5.5 (4.0–14.9)
Duration of remission, *y*	3.5 (2.0–4.9)	3.6 (2.4–5.2)	3.3 (1.9–4.8)
Duration of anti-TNF treatment, *y*	4.2 (2.6–8.0)	4.3 (2.8–6.9)	4.2 (2.6–8.0)
Infliximab (versus adalimumab)	59 (72.8)	32 (80.0)	27 (65.9)
IBD-U	1 (1.2)	1 (2.5)	—
UC/IBDU extent			
E1 proctitis	—	3 (7.5)	—
E2 left-sided	—	14 (35.0)	—
E3 extensive	—	23 (57.5)	—
Disease location			
L1 ileum	—	—	5 (12.2)
L2 colon	—	—	14 (34.1)
L3 ileocolonic	—	—	22 (53.7)
L1/2/3 + L4 upper GI	—	—	2 (4.9)
Disease behavior			
B1 inflammatory	—	—	30 (73.2)
B2 stricture	—	—	7 (17.1)
B3 penetrating	—	—	4 (9.8)
Perianal disease	—	—	8 (19.5)
Anti-TNF (also) for perianal fistula	—	—	3 (7.5)
Prior anti-TNF exposure	12 (14.8)	9 (22.5)	3 (7.3)
Stopped for primary non-response	2 (2.5)	2 (5.0)	—
Stopped for loss of response	1 (1.2)	1 (2.5)	—
Stopped as de-escalation	3 (3.7)	3 (7.5)	—
Stopped for side effects	6 (7.4)	3 (7.5)	3 (7.3)
Prior medication exposure			
Systemic steroids	71 (87.7)	40 (100)	31 (75.6)
Thiopurines	74 (91.4)	37 (92.5)	37 (90.2)
Methotrexate	10 (12.3)	1 (2.5)	9 (22.0)
Immunomodulator failure before anti-TNF	45 (56.3)	21 (52.5)	24 (60)
Vedolizumab	1 (1.2)	1 (2.5)	—
Concomitant immunomodulator at the start of anti-TNF therapy	58 (72.5)	31 (77.5)	27 (67.5)
Treatment after anti-TNF withdrawal			
Mesalamine[a]	16 (19.8)	14 (35.0)	2 (4.9)
Immunomodulator[b]	21 (25.9)	10 (25.0)	11 (26.8)
Rectal therapy	3 (3.7)	2 (5.0)	1 (2.4)
None	44 (54.3)	17 (42.5)	27 (65.9)

NOTE. Presented as number (%) or median (interquartile range). Missing data: body mass index (n = 1), immunomodulator failure/concomitant immunomodulator at the start of anti-TNF (n = 1).

IBDU, Inflammatory Bowel Disease-unclassified; TNF, tumor necrosis factor GI, gastrointestinal; UC, ulcerative colitis.

[a]Started at baseline (n = 7).

[b]Started at baseline (n = 5).

Table 2. Baseline Diagnostic Assessment

	All patients (n = 81)	UC/IBDU (n = 40)	CD (n = 41)
SCCAI or HBI score	—	0 (0–1)	2 (1–3)
SIBDQ score	61 (54–64)	61 (56–66)	58 (51–63)
C-reactive protein (*mg/L*)	0 (0–2.1)	0 (0–1.1)	0.8 (0–3.1)
<10 mg/L, n (%)	78 (97.5)	38 (95.0)	40 (100)
Fecal calprotectin (*μg/g*)	11 (0–47)	9 (0–31.5)	14.5 (6–56.8)
<250 μg/g, n (%)	74 (96.1)	39 (100)	35 (92.1)
Endoscopic healing			
Complete (SES-CD 0–2/Mayo 0)	71 (87.7)	37 (92.5)	34 (82.9)
Partial (SES-CD 3–4/Mayo 1)	10 (12.3)	3 (7.5)	7 (17.1)
Anti-TNF trough levels			
Adalimumab (*mg/L*)	8 (4.6–11.8)	10.3 (3.0–15.8)	7.4 (4.7–10.7)
Infliximab (*mg/L*)	4 (2.0–6.0)	5.6 (3.1–7.7)	3.3 (0.2–5.0)
Subtherapeutic (n, %)	24 (33.8)	9 (26.5)	15 (40.5)
Undetectable (n, %)	9 (12.3)	1 (2.9)	8 (20.5)
Anti-drug antibodies detected	8 (19.5)	1 (2.5)	7 (17.1)
Not present	14 (17.3)	10 (25.0)	4 (9.8)
Not measured	59 (72.8)	29 (72.5)	30 (73.2)
Antibody titer (*AU/mL*)	145 (82–408)	110 (-)	180 (65–565)
Thiopurine metabolites[a]			
6-thioguanine nucleotides (6-TGN, pmol/8*10^8 red blood cells)	516 (368–582)	382 (255–520)	557 (453–654)
6-methylmercaptopurine (6-MMP, pmol/8*10^8 red blood cells)	326 (238–448)	203 (173–300)	369 (320–1288)

NOTE. Presented as number (%) or median (interquartile range). Missing data: CRP (n = 1), fecal calprotectin (n = 4), infliximab trough level (n = 7), adalimumab trough level (n = 3), 6-TGN (n = 4), 6-MMP (n = 5).
HBI, Harvey-Bradshaw Index; IBDU, Inflammatory Bowel Disease-unclassified; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIBDQ, Short Inflammatory Bowel Disease Quality of Life Questionnaire; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]For 16 patients using baseline thiopurine, excluding those who started at baseline (n=5).

follow-up), 3 (8%) started vedolizumab, and 7 (18%) did not (re)start a biological or tofacitinib during the study period.

Most patients (n = 26, 87%) restarted the same anti-TNF agent. Adalimumab (n = 10, 33%) or infliximab (n = 20, 66%) was (re)started after a median of 0.9 years (IQR, 0.4–1.2) since withdrawal of treatment and 24 days (IQR, 10–50) since the onset of the relapse. A concomitant immunomodulator was started or continued in 12 patients (40%).

After reintroduction of anti-TNF treatment, 73% and 90% of patients were in remission at 3 and 12 months, respectively, on the basis of the PGA. The remission rate at 3 months did not differ between patients restarting anti-TNF monotherapy or combination therapy (77% versus 67%, respectively; $P = .60$). Remission rates based on CRP, fecal calprotectin, or HBI/SCCAI were similar (Figure 3*A*). During a median follow-up of 1.0 year (IQR, 0.7–1.6) after reintroduction of anti-TNF treatment, 4 patients (14%) discontinued therapy (Figure 3*B*) because of primary non-response (n = 2) or incomplete response (n = 2).

Trough levels and/or anti-drug antibodies were measured at least once in 27 patients (93%) after restarting treatment. Pre-withdrawal trough levels were similar to those after reintroduction of infliximab (median of 5.4 versus 4.6 mg/L, $P = .53$, n = 14) or adalimumab (8.3 versus 8.1 mg/L, $P = 1.00$, n = 6) among patients who restarted the same compound. Anti-drug antibodies were detected in 3 patients (10%), of whom 1 used concomitant thiopurine.

Patient Perspective

Baseline perceptions and future expectations regarding IBD symptoms and anti-TNF treatment were similar between patients who relapsed during follow-up, compared with patients with sustained remission (Supplementary Table 1). Stopping anti-TNF treatment was generally considered a good decision (median score of 9/10 at 12 months and 8/10 at 24 months), although patients who had relapsed were less satisfied with the decision (median score of 5/10 at both 12 and 24 months) and reported more symptoms (Supplementary Table 1).

General well-being and SIBDQ scores remained stable over the entire follow-up and did not differ between patients with relapse versus without relapse on a population level (Supplementary Figure 2). However, among individual patients who relapsed, SIBDQ scores and general well-being (available in 85%) were significantly higher at baseline compared with the time point of relapse (SIBDQ: 62 [IQR, 56–66] at baseline versus 49 [IQR, 41–57] at relapse, $P < .001$; well-being: 9 [IQR, 8–10] versus 6 [IQR, 5–7], $P < .001$). Reintroduction of

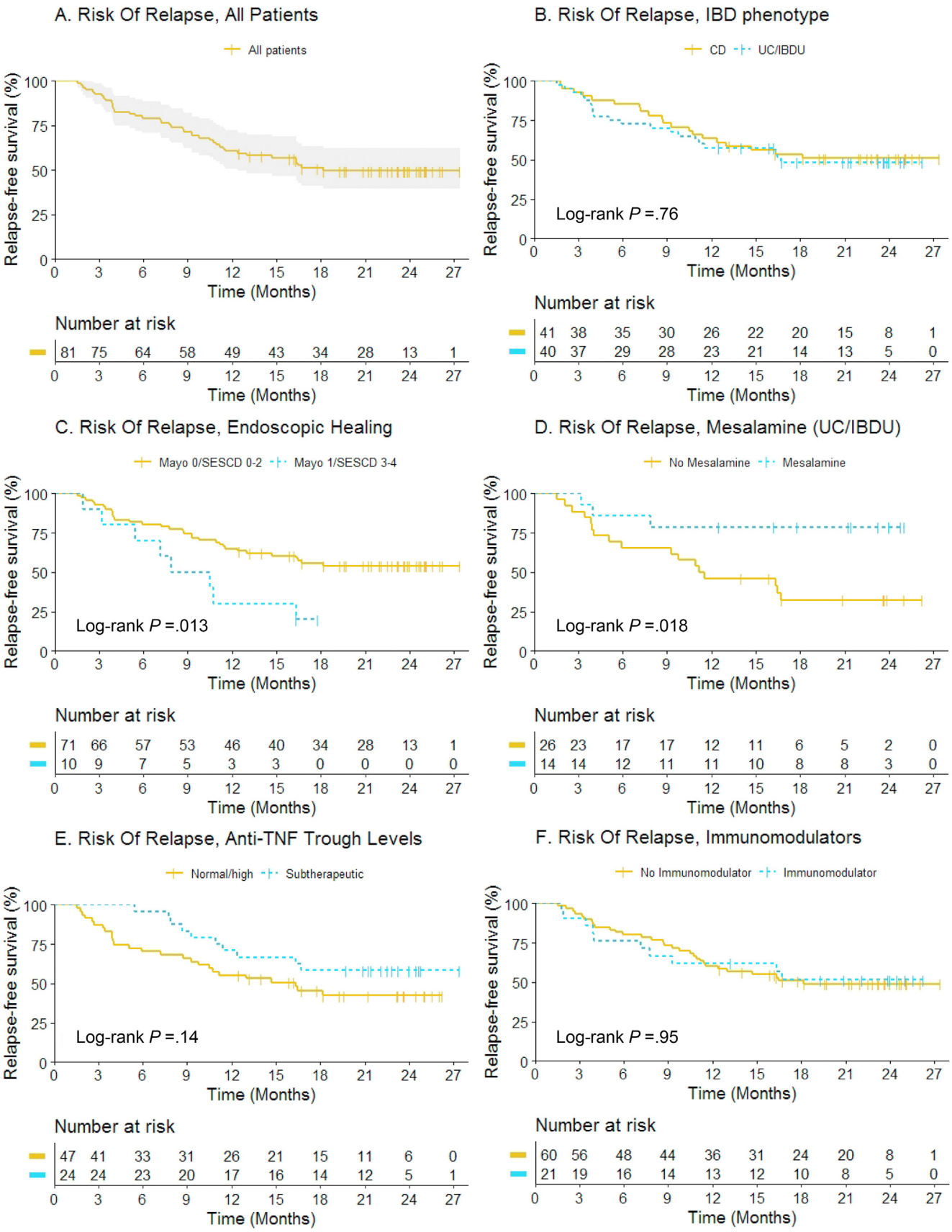


Figure 1. Relapse after anti-TNF withdrawal, Kaplan-Meier estimates (*A*). All patients (*B*), CD versus UC/IBDU. (*C*) Endoscopic healing. (*D*) Mesalamine use in UC/IBDU patients. (*E*) Anti-TNF trough levels. (*F*) Immunomodulator use. CD, Crohn's disease; IBDU, inflammatory bowel disease-unclassified; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 3. Predictors of Relapse, Multivariable Cox Regression Analysis

	All patients, aHR (95% CI)	*P* value	CD patients, aHR (95% CI)	*P* value	UC/IBDU patients, aHR (95% CI)	*P* value
Subtherapeutic anti-TNF trough level	0.61 (0.30–1.23)	.16	0.61 (0.24–1.54)	.30	1.26 (0.36–4.37)	.71
Partial (versus complete) endoscopic healing	3.28 (1.43–7.50)	.005[a]	4.16 (1.47–11.8)	.007 [a]	11.7 (1.02–133.4)	.05 [a]
Immunomodulator use	1.05 (0.50–2.18)	.90	2.06 (0.76–5.57)	.15	0.46 (0.14–1.52)	.20
Mesalamine use	0.27 (0.08–0.88)	.03 [a]	—	—	0.08 (0.01–0.67)	.02 [a]

aHR, adjusted hazard ratio; CD, Crohn's disease CI, confidence interval; IBDU, inflammatory bowel disease-unclassified; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]Significant at $P < .05$.

anti-TNF treatment restored quality of life and well-being (available in 66%) within 3 months (SIBDQ from 50 [IQR, 41–54] at anti-TNF reintroduction to 56 ([IQR, 52–65] three months after reintroduction, $P = .003$; well-being from 6 [IQR, 4–7] to 8 [IQR, 7–8], $P = .001$).

Discussion

In this prospective, multicenter study looking at withdrawal of anti-TNF therapy, the risk of relapse was high (40% at 12 months), despite a careful selection of patients with IBD in clinical remission and with endoscopic healing. Complete endoscopic healing (Mayo 0/SES-CD 0–2) was associated with a significantly lower risk of relapse. Mesalamine treatment was associated with a lower relapse risk in patients with UC or IBDU, but no protective effect of continuing treatment with immunomodulators could be detected. Reintroduction of anti-TNF therapy re-established remission in 73% of patients at 3 months.

Recent RCTs confirmed that withdrawal of anti-TNF considerably increases the risk of relapse in both UC and CD.[4,5] The observed relapse rate of 40% at 1 year in this study is in line with prior prospective studies, even though endoscopic healing was a prerequisite for anti-TNF withdrawal.[4–6] Of note, this is much higher than the risk of loss of response (4.8% per patient-year) among patients who continued anti-TNF therapy after a similar duration of treatment in a retrospective study performed at our centers.[21]

The main result of this study was that the risk of relapse was lower among patients with complete endoscopic healing, compared with partial endoscopic healing (70% versus 35% at 12 months). This large difference underscores the clinical importance of this finding. In the STORI trial, CD patients with complete endoscopic healing (Crohn's Disease Endoscopic Index of Severity 0) were also at lower risk of relapse after withdrawal of infliximab, but this was compared with all other participants, including those without endoscopic healing.[6] Among UC patients who discontinued infliximab in a recent RCT, complete endoscopic healing (Mayo 0 versus 1) was not associated with a decreased risk of relapse. However, a trend was observed for a lower risk in patients with histologic healing, supporting the concept of applying stringent remission criteria before withdrawal of anti-TNF therapy.[5] In retrospective studies, endoscopic healing was not associated with a lower risk of relapse in studies including both patients with CD and UC.[22,23] This may be attributed to the non-standardized criteria used in these studies and lack of patients without endoscopic healing for comparison.

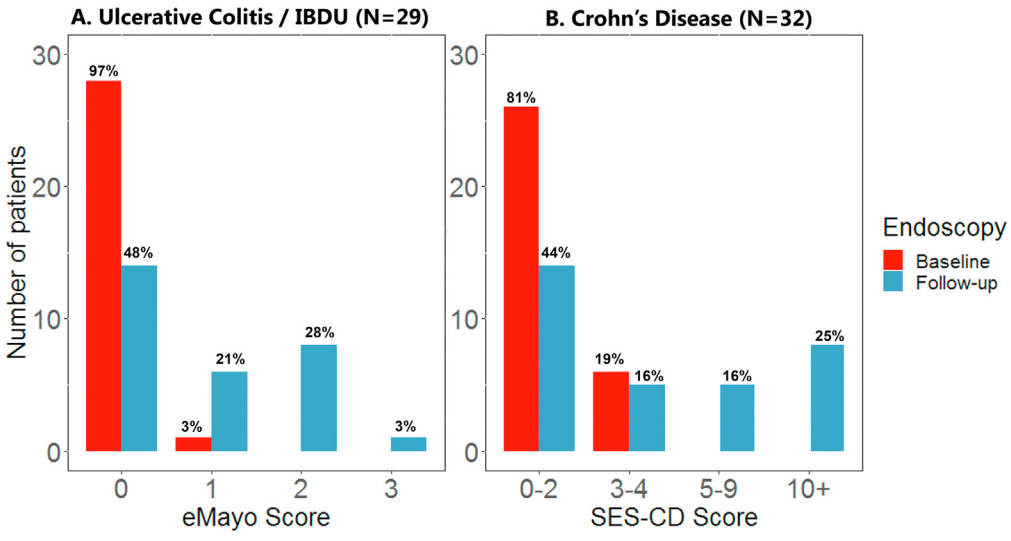
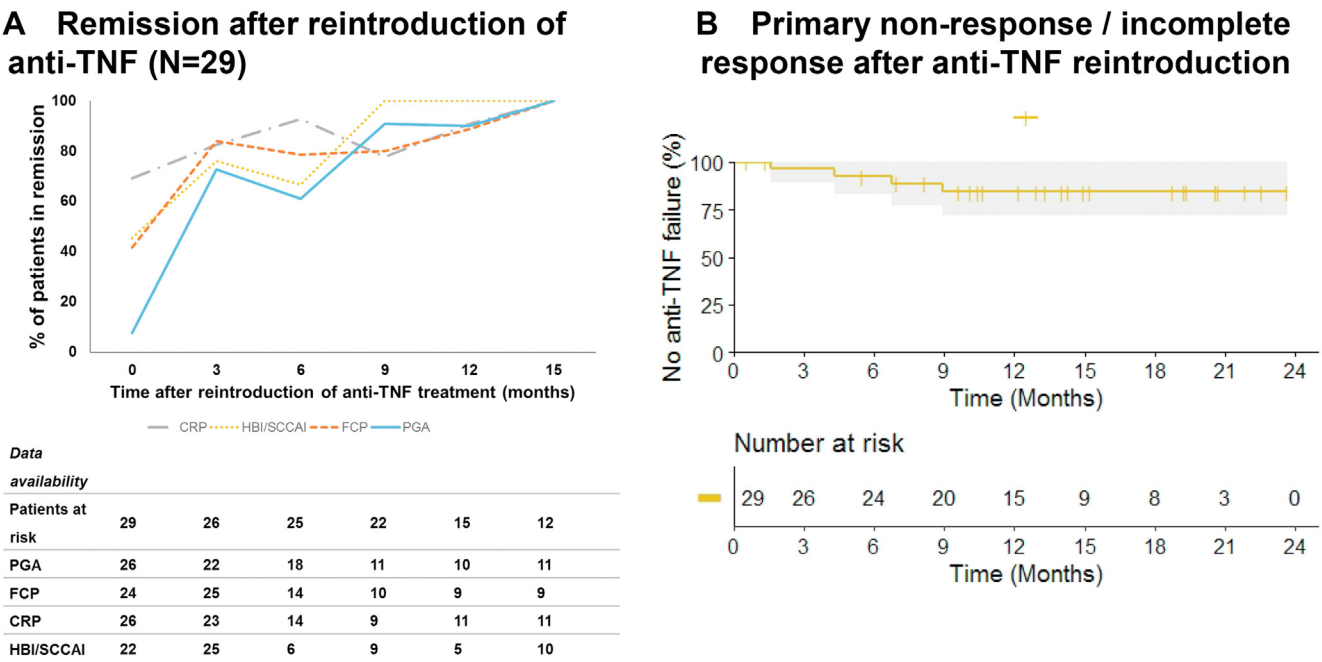


Figure 2. Endoscopic outcomes of patients with an available follow-up endoscopy (n = 61, performed after a median of 1.1 years). IBDU, inflammatory bowel disease-unclassified; SES-CD, Simple Endoscopic Score for Crohn's Disease.



Data availability						
Patients at risk	29	26	25	22	15	12
PGA	26	22	18	11	10	11
FCP	24	25	14	10	9	9
CRP	26	23	14	9	11	11
HBI/SCCAI	22	25	6	9	5	10

Figure 3. Outcomes after anti-TNF reintroduction. (*A*) Remission after starting anti-TNF, based on CRP >10 mg/L, HBI/SCCAI <5, fecal calprotectin (FCP) <250 μg/g, and physician global assessment (PGA). (*B*) Discontinuation of anti-TNF after reintroduction due to primary non-response/incomplete response. CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumor necrosis factor.

Continuing mesalamine treatment after de-escalation of anti-TNF therapy reduced the risk of relapse in patients with UC/IBDU, but continuation of immunomodulators and subtherapeutic trough levels did not affect the relapse risk in this study. Our finding regarding mesalamine is promising but should be interpreted with caution because of contradictory findings in a retrospective study in which UC patients continuing mesalamine after anti-TNF withdrawal had a higher relapse rate than those continuing immunomodulators.[24] A protective effect of continuing immunomodulators after anti-TNF withdrawal was established in a prior individual patient data meta-analysis with 1317 patients with CD.[25] Only one small retrospective study (n = 18) found a protective effect of immunomodulators in UC after anti-TNF withdrawal,[26] whereas other (larger) studies did not.[5,23,27] It is unknown why immunomodulators were not associated with a lower relapse risk in the present study. Unlike in prior studies, few patients (25.9%) continued immunomodulators after anti-TNF withdrawal, perhaps because most patients had failed immunomodulators before starting anti-TNF therapy. Moreover, for both mesalamine and immunomodulator use, selection bias may also have occurred because the decision to continue or start these agents was left to the treating physician. Interestingly, prior studies reported a protective effect of subtherapeutic pre-withdrawal anti-TNF trough levels.[6,28] In our study, this was not statistically significant, which can be the result of missing trough levels (12%) and limited sample size.

Reintroduction of anti-TNF agents after a relapse restored remission in 73% of patients within 3 months, in line with previous studies.[7] Furthermore, patient-reported quality of life (SIBDQ) and general well-being declined at the time of relapse but were restored with reintroduction of treatment. As a result, quality of life and general well-being were similar between patients who relapsed versus those who maintained remission, when considering the entire follow-up on a population level. Similarly, in the randomized controlled SPARE trial, CD patients discontinuing infliximab with reintroduction upon relapse spent only 6 or 14 days less in remission over the course of 2 years, compared with patients continuing combination therapy or stopping the immunomodulator, respectively.[4] This underscores the feasibility of a strategy combining withdrawal of anti-TNF treatment with reintroduction upon relapse.

Our findings are based on a selected cohort of patients with IBD in confirmed clinical remission and with endoscopic healing, with detailed clinical, pharmacokinetic, and endoscopic data as well as patient-reported outcomes. Nevertheless, we acknowledge some limitations. Although our sample size was relatively large for a prospective study with endoscopic data, few patients in our study had partial endoscopic healing (n = 10, 12%), resulting in wide CIs for this parameter. Ideally, larger prospective studies should confirm the importance of complete endoscopic healing and should also assess histologic remission, especially in UC.[5] A longer follow-up may be needed to detect major complications after withdrawal of anti-TNF treatment (eg, need for surgery).[29] De-escalation of anti-TNF therapy is performed exclusively in a highly selected patient group with stable remission (6.9% of patients using anti-TNF maintenance

therapy in a prior retrospective study).[21] Consequently, few patients with an unfavorable IBD phenotype, such as stricturing or penetrating CD, anti-TNF for perianal fistulizing CD, young age at diagnosis, or prior biological failure, were included in this study. Therefore, our findings may not be generalizable to patients with a more severe IBD phenotype.

In conclusion, among selected patients with IBD in clinical remission and with endoscopic healing, the risk of relapse after withdrawal of anti-TNF therapy remained high, but reintroduction of anti-TNF treatment was successful in most cases. Applying strict criteria for endoscopic healing and mesalamine treatment for patients with UC or IBDU may lower the risk of relapse after withdrawal of anti-TNF treatment.

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 http://doi.org/10.1016/j.cgh.2022.08.024.

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Conflicts of interest

FDMS has served on advisory boards or as speaker for Takeda, Dr. Falk, and Galapagos. HHF has served on advisory boards or as speaker or consultant for Janssen-Cilag, AbbVie, Takeda, Galapagos, and Ferring and has received research grants from Takeda. JMJ has served on advisory boards or as speaker or consultant for Janssen-Cilag, Takeda, Celltrion, Galapagos, and BMS. TEHR has served on advisory boards or as speaker or consultant for Takeda, Janssen-Cilag, Ferring, and Galapagos. J-FC reports receiving research grants from AbbVie, Janssen Pharmaceuticals, and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Inc Ferring Pharmaceuticals, Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Glaxo Smith Kline, Geneva, Iterative Scopes, Janssen Pharmaceuticals, Kaleido Biosciences, Landos, Otsuka, Pfizer, Prometheus, Sanofi, Takeda, and TiGenix; and hold stock options in Intestinal Biotech Development. FH has served on advisory boards or as speaker or consultant for AbbVie, Celgene, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr. Falk and has received unrestricted grants from Dr. Falk, Janssen-Cilag, and AbbVie. BO received research grants from AbbVie, Celltrion, Ferring, Takeda, Galapagos, and Pfizer and has served on advisory boards for Cablon, Pfizer, BMS, Janssen, MSD, Takeda, and Galapagos. The remaining authors disclose no conflicts.

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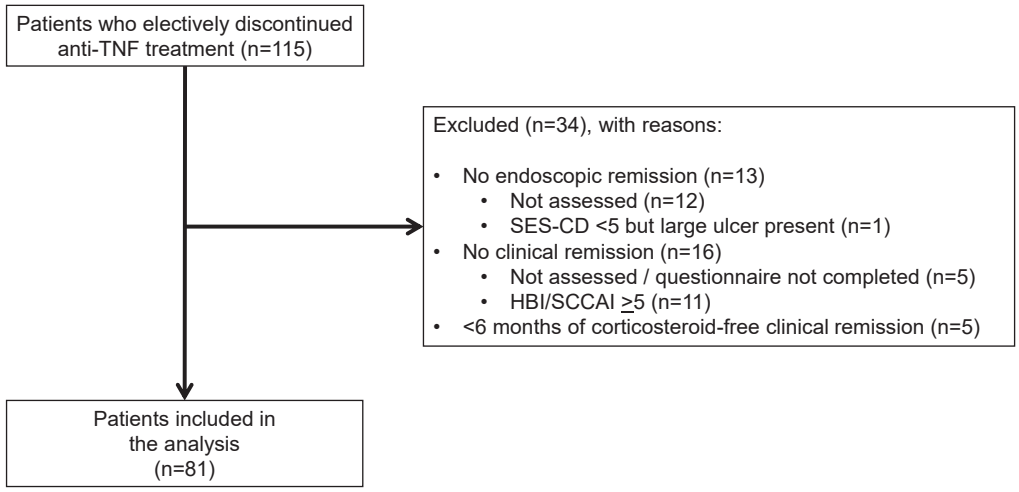
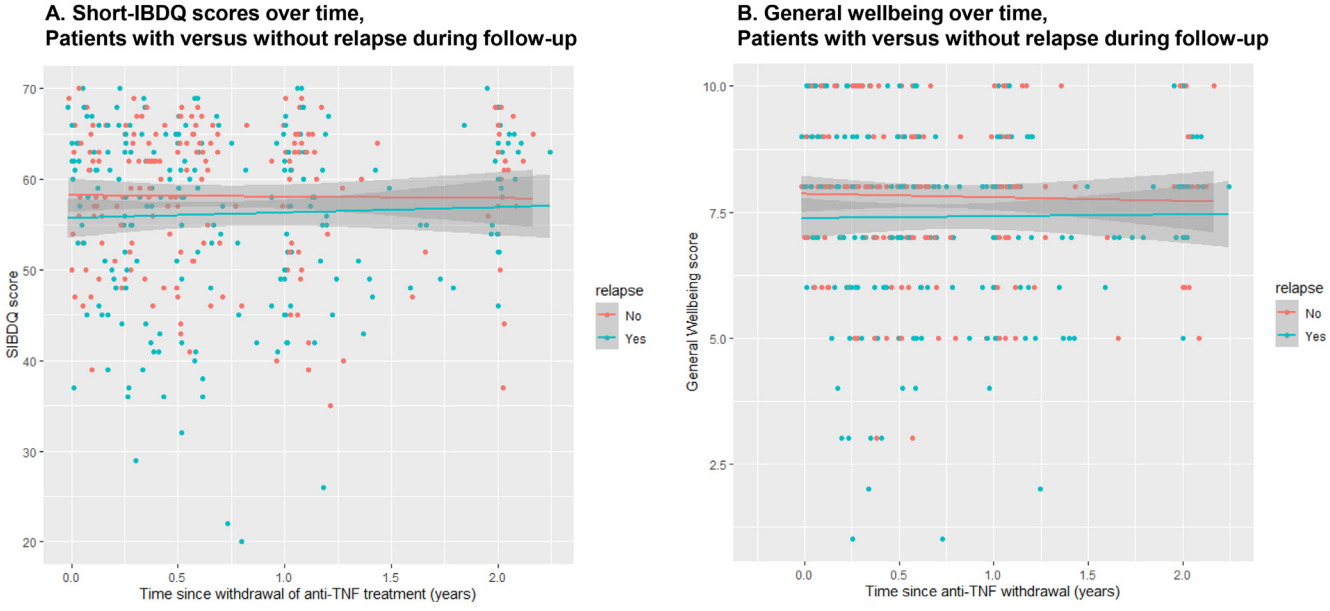


Supplementary Figure 1. Flowchart of patient identification. HBI, Harvey-Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.



Note: Higher SIBDQ-score indicates higher quality of life.
Effect of time: $-7.9*10^{-4}$, p=0.73; Effect of relapse: -2.8, p=0.13;
Effect of relapse-time interaction: $-1.9*10^{-3}$ p=0.53

Note: higher score indicates better wellbeing.
Effect of time: $-1.4*10^{-4}$, p=0.79; Effect of relapse: -0.47, p=0.13;
Effect of relapse-time interaction: $-1.2*10^{-4}$, p=0.87

Supplementary Figure 2. Short-IBDQ (*A*) and general well-being scores (*B*) over time, patients with versus without relapse during follow-up. SIBDQ, Short Inflammatory Bowel Disease Quality of Life Questionnaire.

Supplementary Table 1. Patient Perspective Questionnaire

	All patients (n = 81)	No relapse (n = 41)	Relapse (n = 40)	
Baseline[a]	N = 81	N = 41	N = 40	*P* value
Before I started anti-TNF treatment, my IBD symptoms were very severe.	9 (8–10)	9 (8–10)	9 (7–9)	.46
While being treated with anti-TNF in the past year, I did not experience any IBD-related symptoms.	9 (7–10)	9 (7–10)	9 (8–10)	.12
I worry that if I stop anti-TNF treatment, I will experience more IBD-related symptoms.	5 (4–7)	5 (4–7)	5 (4–6)	.53
I am experiencing many side effects from anti-TNF treatment.	3 (1–6)	3 (1–6)	2 (1–6)	.21
I worry about future side effects of anti-TNF treatment.	3 (1–6)	2 (1–5)	4 (1–6)	.65
Anti-TNF administration (going to the hospital for an infusion, self-administration in the skin) is burdensome or uncomfortable to me.	1 (1–2)	1 (1–2)	2 (1–3)	.52
Anti-TNF is a very effective treatment for my Crohn's disease/ulcerative colitis.	10 (9–10)	10 (8–10)	10 (9–10)	.51
I would like to stop anti-TNF treatment.	10 (7–10)	10 (8–10)	9 (6–10)	.10
12-Month follow-up[a]	N = 74	N = 44	N = 30	
In the past year, I did not experience any IBD-related symptoms.	7 (3–9)	9 (7–10)	3 (2–5)	<.00[b]
In the past year, I experienced fewer IBD-related symptoms than the year before.	5 (2–9)	7 (4–10)	3 (1–5)	.001 [b]
Stopping anti-TNF treatment was a good decision.	10 (5–10)	10 (10–10)	5 (2–7)	<.001 [b]
24-Month follow-up[a]	N = 40	N = 19	N = 21	
In the past year, I did not experience any IBD-related symptoms.	7 (4–9)	8 (6–9)	7 (3–8)	.10
In the past year, I experienced fewer IBD-related symptoms than the year before.	8 (5–10)	8 (5–10)	8 (3–10)	.79
Stopping anti-TNF treatment was a good decision.	9 (5–10)	10 (9–10)	5 (2–7)	<.001 [b]

IBD, inflammatory disease; TNF, tumor necrosis factor.
[a]At baseline, patients are classified as relapse versus no relapse based on the entire follow-up. During follow-up, patients are classified as relapse versus no relapse based on whether they had experienced a relapse before (or within 30 days of) answering the questionnaire.
[b]Significant at $P < .05$.

Supplementary Table 2. Time Between Baseline Endoscopic Assessment and Anti-TNF Discontinuation, With Corresponding Hazard Ratios for Partial Versus Complete Endoscopic Healing as Predictor for Risk of Relapse

	N	Partial endoscopic healing, aHR (95% CI)	*P* value
All patients	81	3.28 (1.43–7.50)	.005[a]
Colonoscopy <6 mo	77	3.44 (1.49–7.94)	.004[a]
Colonoscopy <3 mo	74	3.45 (1.49–8.01)	.004[a]
Colonoscopy <1.5 mo	67	3.45 (1.47–8.11)	.005[a]
Colonoscopy <3 wk	56	3.01 (1.10–8.25)	.03[a]

aHR, adjusted hazard ratio; CI, confidence interval.
[a]Significant at $P < .05$.

Supplementary Table 3. Predictors of Relapse Among Patients With Complete Endoscopic Healing (N = 71), Multivariable Cox Regression Analysis

	All patients, aHR (95% CI)	*P* value	CD patients, aHR (95% CI)	*P* value	UC/IBDU patients, aHR (95% CI)	*P* value
Subtherapeutic anti-TNF trough level	0.55 (0.23–1.28)	.16	0.63 (0.23–2.08)	.51	0.62 (0.12–3.25)	.57
Immunomodulator use	0.86 (0.38–1.93)	.72	1.40 (0.44–4.46)	.57	0.54 (0.16–1.76)	.30
Mesalamine use	0.13 (0.02–1.00)	.05[a]	—	—	0.12 (0.01–1.05)	.06

aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; IBDU, inflammatory bowel disease-unclassified; UC, ulcerative colitis.
[a]Significant at $P < .05$.

Supplementary Table 4. Post Hoc Analysis of Other Potential Predictors of Relapse, Univariable Cox Regression Analysis

	Univariable	
Variable	Hazard ratio	*P* value
Age at anti-TNF withdrawal (per 10 years)	0.92 (0.75–1.14)	.45
Male sex	0.62 (0.33–1.16)	.14
UC/IBDU (versus CD)	1.10 (0.59–2.05)	.76
Duration of remission (per year)	0.93 (0.82–1.06)	.28
Adalimumab (versus infliximab)	0.98 (0.49–1.97)	.96
C-reactive protein (*mg/L*, per 10-fold increase)	0.67 (0.27–1.67)	.39
Fecal calprotectin ($\mu g/g$, per 10-fold increase)	1.16 (0.71–1.90)	.55
White blood cell count (per $1*10^9$/L increase)	1.13 (0.97–1.31)	.11
Hemoglobin level (per 1 mmol/L increase)	0.92 (0.63–1.34)	.66
Prior primary non-response/loss of response to anti-TNF	0.81 (0.11–5.90)	.84

CD, Crohn's disease; IBDU, inflammatory bowel disease-unclassified; TFN, tumor necrosis factor.

Supplementary Table 5. Secondary Outcomes

	All patients (N = 81)	UC/IBDU (n = 40)	CD (n = 41)
Medication use			
Anti-TNF reintroduction	30 (37.0)	15 (37.5)	15 (36.6)
Other biological/tofacitinib started[a]	7 (8.6)	3 (7.5)	4 (9.8)
Corticosteroid use	19 (23.5)	10 (25.0)	9 (22.0)
Any medication step-up	38 (46.9)	20 (50.0)	18 (43.9)
Alternative definitions of relapse			
Endoscopic relapse	22 (27.2)	9 (22.5)	13 (31.7)
Patient-reported clinical relapse	23 (28.4)	12 (30.0)	11 (26.8)
Fecal calprotectin >250 μg/g	34 (42.0)	11 (27.5)	23 (56.1)
C-reactive protein >10 mg/L	21 (25.9)	6 (7.4)	15 (36.6)
Adverse events /complications			
IBD-related hospitalization	3 (3.7)	1 (2.5)	2 (4.9)
IBD-related surgery	1 (1.2)	0 (0)	1 (2.4)
Perianal abscess/fistula	1 (1.2)	0 (0)	1 (2.4)
Abdominal abscess/fistula	0 (0)	0 (0)	0 (0)
Intestinal stenosis	2 (2.5)	0 (0)	2 (4.9)

CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease-unclassified; TFN, tumor necrosis factor.
[a]Three patients started vedolizumab immediately after relapse. Four patients first reinitiated anti-TNF and then switched to vedolizumab (n = 1) or ustekinumab (n = 3).