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Original Article

Long-term Outcomes after the Discontinuation of Anti-Tumor Necrosis Factor-α Therapy in Patients with Inflammatory Bowel Disease under Clinical Remission: A Korean Association for the Study of Intestinal Disease Multicenter Study

Joo Hye Song[1], Eun Ae Kang[2], Soo-Kyung Park[3], Sung Noh Hong[1], You Sun Kim[4], Ki Bae Bang[5], Kyeong Ok Kim[6], Hong Sub Lee[7], Sang-Bum Kang[8], Seung Yong Shin[9], Eun Mi Song[10], Jong Pil Im[11], and Chang Hwan Choi[9], IBD Research Group of the Korean Association for the Study of Intestinal Diseases

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, [2]Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, [3]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [4]Department of Internal Medicine, Seoul Paik Hospital, Inje University College of Medicine, Seoul, [5]Department of Internal Medicine, Dankook University College of Medicine, Cheonan, [6]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, [7]Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, [8]Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, [9]Department of Internal Medicine, Chung-Ang University College of Medicine, [10]Department of Internal Medicine, Ewha Womans University Seoul Hospital, Ewha Womans University School of Medicine, and [11]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

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Corresponding Author
Sung Noh Hong
ORCID https://orcid.org/0000-0002-4140-3717
E-mail gisnhong@gmail.com

Soo-Kyung Park
ORCID https://orcid.org/0000-0001-8822-9632
E-mail skparkmd@gmail.com

Joo Hye Song and Eun Ae Kang contributed equally to this work as first authors.

Background/Aims: Our study aimed to evaluate the long-term outcomes and risk factors for relapse after anti-tumor necrosis factor (TNF)-α cessation in inflammatory bowel disease (IBD) patients because they are not well established.

Methods: A retrospective multicenter cohort study was conducted involving patients with Crohn's disease (CD) or ulcerative colitis (UC) from 10 referral hospitals in Korea who discontinued first-line anti-TNF therapy after achieving clinical remission.

Results: A total of 109 IBD patients (71 CD and 38 UC) with a median follow-up duration of 56 months were analyzed. The cumulative relapse rates at 1, 3, and 5 years were 11.3%, 46.7%, and 62.5% for CD patients and 28.9%, 45.3%, and 60.9% for UC patients. Multivariable Cox analysis revealed that discontinuation owing to the clinician's decision was associated with lower risk of relapse (vs patient's preference: hazard ratio [HR], 0.13; 95% confidence interval [CI], 0.04 to 0.48; p=0.002) and adalimumab use was associated with higher risk of relapse (vs infliximab: HR, 4.42; 95% CI, 1.24 to 17.74; p=0.022) in CD patients. Mucosal healing was associated with lower risk of relapse (vs nonmucosal healing: HR, 0.12; 95% CI, 0.02 to 0.83; p=0.031) in UC patients. Anti-TNF re-induction was provided to 52 patients, and a response was obtained in 50 patients. However, 25 of them discontinued retreatment owing to a loss of response (n=15), the patient's preference (n=6), and other factors (n=4).

Conclusions: More than 60% of IBD patients in remission under anti-TNF therapy relapsed within 5 years of treatment cessation. Anti-TNF re-induction was effective. However, half of the patients discontinued anti-TNF therapy, and 50% of these patients discontinued treatment owing to loss of response. **(Gut Liver 2021;15:752-762)**

Key Words: Inflammatory bowel diseases; Tumor necrosis factor inhibitors; Withholding treatment; Recurrence

INTRODUCTION

Anti-tumor necrosis factor (TNF)-α, which has revolutionized treatment of inflammatory bowel disease (IBD), induces not only clinical remission but also mucosal healing and maintains improved quality of life and decreased risk of surgery and hospitalization in IBD patients.[1-3] However, in real-world practice, the discontinuation of anti-TNF has been attributed to various factors, including costs, or concerns regarding long-term safety.[4]

Opportunistic infections have become a major safety concern in patients undergoing anti-TNF.[5-7] The risk of lymphoma has not been decisively associated with anti-TNFs; however, malignancy may still be a concern with continued anti-TNF.[8] In addition, cutaneous reactions and paradoxical immune-mediated complications have been reported.[9] Furthermore, despite the introduction of biosimilars, high costs of biologics increase the likelihood of discontinuation. Healthcare costs associated with IBD have shifted from hospitalization/surgery towards medication, such as anti-TNF.[10]

A significant number of IBD patients may experience remission or minimal symptoms for >10 years after initial presentation, suggesting that the relapsing-remitting course of IBD may allow—at least in some patients—abstinence from medication.[11] Although several studies have been performed, the long-term outcomes of IBD patients after anti-TNF cessation are unclear.[12-18] The current data are insufficient to recommend discontinuation of anti-TNF.[19-21] This study aimed to evaluate the long-term outcomes and risk factors for relapse following discontinuation of anti-TNF in IBD patients with remission.

MATERIALS AND METHODS

1. Study population

We conducted a retrospective multicenter cohort study involving patients from 10 referral hospitals of the IBD research group of the Korean Association for the Study of Intestinal Diseases. The inclusion criteria were as follows: (1) Crohn's disease (CD) or ulcerative colitis (UC) treated with first-line anti-TNF maintenance and (2) discontinuation of anti-TNF after achieving clinical remission. The exclusion criteria were as follows: (1) irregular treatment; (2) follow-up duration <1 year after discontinuation of anti-TNF; and (3) unclear reasons for discontinuation of anti-TNF.

The study protocol was approved by the institutional review board of each participating hospital. On January 14, 2019, the institutional review board of Samsung Medical Center provided their approval to conduct this study (IRB number: 2019-01-003-001). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The requirement for informed consent from patients was waived because only de-identified data routinely collected during hospital visits were used.

2. Anti-TNF induction and maintenance therapy

The enrolled patients followed a prespecified schedule of anti-TNF induction and maintenance therapy. Infliximab (IFX; Remicade®, Janssen Pharmaceutical, Beerse, Belgium or Remsima®, Celltrion, Incheon, Korea) was administered intravenously, as induction, at 5 mg/kg at 0, 2, and 6 weeks; we then administered 5 mg/kg, as maintenance, every 8 weeks.[22,23] Adalimumab (ADA; Humira®, AbbVie Inc., Chicago, IL, USA) was administered as induction with 160 mg followed by 80 mg after 2 weeks via subcutaneous injection followed by maintenance of 40 mg every other week.[23,24] Patients with subsequent loss of response (LOR) during maintenance, were administered an escalated dose of IFX at 10 mg/kg every 8 weeks or a weekly ADA injection.[25,26]

3. Definition of clinical remission, response, and relapse

Clinical remission was defined as Crohn's Disease Activity Index <150 or the absence of fistula in CD or Mayo score of 0–2 or partial Mayo score of 0–1 for UC. Clinical response was defined as a decrease of 70 points in the Crohn's Disease Activity Index for luminal CD, a 50% decrease in the number of fistulas from baseline for fistulizing CD, or a decrease of 30% or 3 points in the Mayo score compared to the baseline for UC. Relapse was defined as Crohn's Disease Activity Index >220 or new-onset fistula in CD or Mayo score ≥6 and endoscopic subscore ≥2 in UC, requirement for hospitalization/surgery associated with IBD progression, or re-initiation of steroids or biologics.

4. Outcome measurements

The laboratory findings, including hemoglobin, albumin, and C-reactive protein levels were measured before discontinuation of anti-TNF. The clinical features, including age at the time of discontinuation, Montreal location (L1, ileum; L2, colon; or L3, ileocolon), behavior (B1, no strictures and no penetration; B2, strictures; or B3, penetration) and perianal modifier (with or without perianal disease) in CD and Montreal disease extent in UC (E1, ulcerative proctitis; E2, left-sided UC; or E3, extensive UC), were retrospectively reviewed. History of intestinal operation, indication for anti-TNF (luminal or fistulizing CD), type of anti-TNF agent (IFX or ADA), duration of anti-

TNF treatment, reasons for discontinuation of anti-TNF (clinician's decision, patient's preference, intolerance, and other factors), mucosal healing before discontinuation, and concomitant use of immunomodulators after discontinuation were also assessed retrospectively. Mucosal healing was defined as no definite ulceration on endoscopy in CD or Mayo endoscopic score <2 in UC. The final disease status and laboratory findings at the time of relapse or at the latest outpatient visit for patients without relapse, were recorded. In addition, the efficacy and safety of retreatment during the follow-up period were assessed in patients with anti-TNF retreatment after relapse.

The primary outcome was the rate of relapse at 1, 2, 3, and 5 years after discontinuation of anti-TNF. The secondary outcomes included risk factors associated with relapse, relapse-free survival after discontinuation of anti-TNF, and efficacy of anti-TNF retreatment.

5. Statistical analysis

Continuous variables are expressed as median with interquartile range, while categorical variables are presented as absolute values and percentages. Continuous variables were analyzed using the unpaired Student t-test and Mann-Whitney U test, while categorical variables were analyzed using the chi-square test and Fisher exact test. Using the Cox hazards model, the risk factors for relapse after anti-TNF cessation were investigated. The survival curve representing the cumulative rate of relapse after discontinuation of anti-TNF was analyzed using the Kaplan-Meier method. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 25.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline characteristics of the enrolled patients

A total of 125 IBD patients were eligible for this study. Sixteen patients were excluded as their follow-up period was <1 year. A total of 109 IBD patients (71 CD and 38 UC) were eventually analyzed (Fig. 1). The baseline characteristics of the patients are shown in Table 1. Most patients were aged ≤40 years at diagnosis. A greater number of CD patients discontinued anti-TNF ≤40 years compared to UC patients (p<0.001). Eighteen CD patients (25.4%) had a history of intestinal surgery and 28 CD patients (39.4%) were treated with anti-TNF for fistulizing. Ninety-three IBD patients (85.3%) were treated with IFX. The median duration of anti-TNF before discontinuation was 12.0 months (range, 9.0 to 26.5 months), and the duration between treatment with IFX and ADA were not significantly different (12.0 months [10.0 to 27.0] vs 12 months [5.0 to 21.5]). The most common factors underlying discontinuation of anti-TNF were clinician's decision (29.4%) and patient's preference (27.5%). Among UC patients, 28.9% of them discontinued anti-TNF owing to intolerance to adverse events (AEs), while 23.9% of the CD patients discontinued treatment owing to insurance/reimbursement

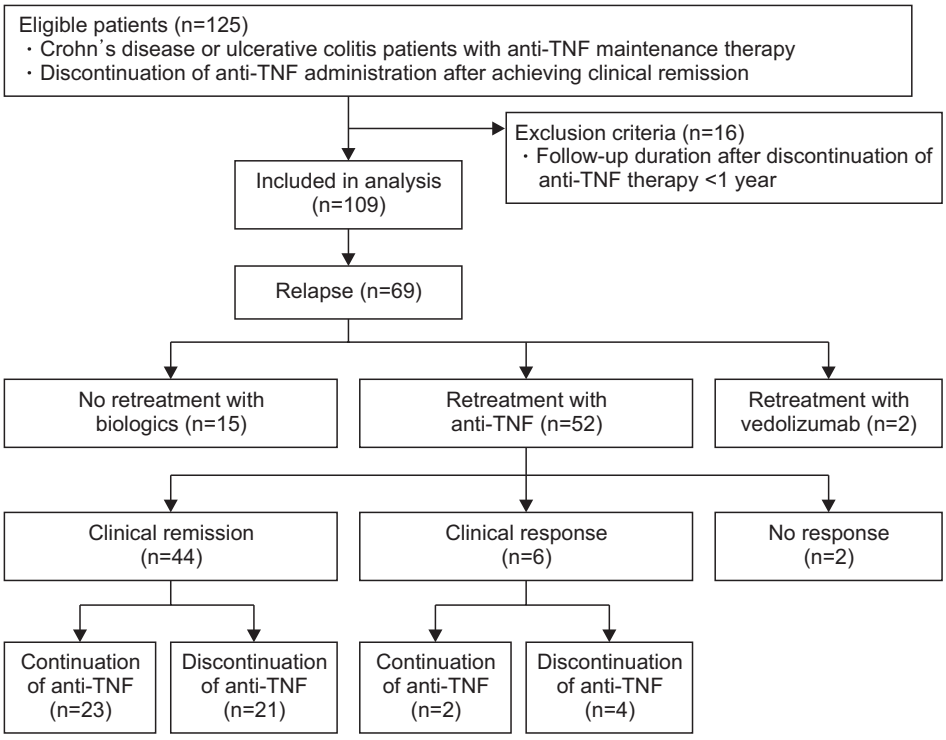

Fig. 1. Flowchart outlining the study protocol.
TNF, tumor necrosis factor.

Table 1. Baseline Characteristics of the Enrolled Patients

Characteristics		Total (n=109)	CD (n=71)	UC (n=38)	p-value*
Sex	Male	73 (67.0)	50 (70.4)	23 (60.5)	0.295
	Female	36 (33.0)	21 (29.6)	15 (39.5)	
Age at diagnosis, yr	Median (IQR)	26.0 (20.0–37.0)	23.0 (19.0–29.0)	38.0 (26.0–48.3)	<0.001
	≤40	88 (80.7)	67 (94.4)	21 (55.3)	<0.001
	>40	21 (19.3)	4 (5.6)	17 (44.7)	
Age at the time of discontinuation of anti-TNF therapy, yr	Median (IQR)	31.7 (24.9–43.0)	28.0 (22.0–34.1)	44.0 (33.0–58.0)	<0.001
	≤40	77 (74.0)	63 (88.7)	14 (36.8)	<0.001
	>40	32 (26.0)	8 (11.3)	24 (63.2)	
Smoking status after discontinuation of anti-TNF therapy	Non-/ex-smoker	104 (95.4)	66 (93.0)	38 (100.0)	0.161
	Current smoker	5 (4.6)	5 (7.0)	0	
Previous intestinal surgery	Yes	18 (16.5)	18 (25.4)	0	0.008
	No	91 (83.5)	53 (74.6)	38 (100.0)	
Indications for starting anti-TNF therapy	Active luminal	81 (74.1)	43 (60.6)	38 (100.0)	<0.001
	Fistulizing	28 (25.9)	28 (39.4)	0	
Type of anti-TNF	Infliximab	93 (85.3)	62 (87.3)	31 (81.6)	0.343
	Remicade	86	59	27	
	Remsima	7	3	4	
	Adalimumab	15 (13.8)	9 (12.7)	6 (15.8)	
	Golimumab	1 (0.9)	0	1 (2.6)	
Duration of anti-TNF treatment, mo	Median (IQR)	12.0 (9.0–26.5)	12.0 (10.0–24.5)	12.0 (8.0–32.0)	0.824
Montreal classification					
CD: Location	Ileum		10 (14.1)	-	
	Colonic		11 (15.5)	-	
	Ileocolonic		50 (70.4)	-	
CD: Behavior	Inflammatory		37 (52.1)	-	
	Stricturing		16 (22.5)	-	
	Penetrating		18 (25.4)	-	
CD: Perianal disease	No		29 (40.8)	-	
	Yes		42 (59.2)	-	
UC: Disease extent	Proctitis		-	9 (23.7)	
	Left-side		-	13 (34.3)	
	Extensive		-	16 (42.1)	
Reasons for discontinuation of anti-TNF therapy	Patient's preference	30 (27.5)	21 (29.6)	9 (23.7)	0.006
	Clinician's decision	32 (29.4)	18 (25.4)	14 (36.8)	
	Intolerance to adverse effects	18 (16.5)	7 (9.9)	11 (28.9)	
	Adverse effects	11	4	7	
	Opportunistic infection	7	3	4	
	Others	29 (26.6)	25 (35.2)	4 (10.5)	
	Pregnancy/nursing	7	6	1	
	Insurance/reimbursement	17	17	0	
	Other factors	5	2	3	
Hemoglobin level at the time of discontinuation of anti-TNF therapy, g/dL	Median (IQR)	13.9 (12.3–14.9)	14.1 (12.5–15.2)	13.4 (12.1–14.6)	0.242
Albumin level at the time of discontinuation of anti-TNF therapy, mg/dL	Median (IQR)	4.3 (3.8–4.5)	4.3 (3.9–4.7)	4.1 (3.7–4.5)	0.111
CRP at the time of discontinuation of anti-TNF therapy, mg/dL	Median (IQR)	0.29 (0.05–0.73)	0.29 (0.04–0.74)	0.31 (0.07–0.92)	0.666
Mucosal healing before discontinuation of anti-TNF therapy	No	19 (17.4)	13 (18.3)	6 (15.8)	0.025
	Yes	34 (31.2)	16 (22.5)	18 (47.4)	
	Unknown	56 (51.4)	42 (59.2)	14 (36.8)	
Immunomodulator use after discontinuation of anti-TNF treatment	No	44 (40.4)	22 (31.0)	22 (57.9)	0.006
	Yes	65 (59.6)	49 (69.0)	16 (42.1)	

Data are presented as number (%).

CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range; TNF, tumor necrosis factor; CRP, C-reactive protein.

*For the comparisons between CD and UC.

issues. The mucosal healing status was assessed in approximately half of the patients before discontinuation. Among them, two-thirds achieved mucosal healing. Immunomodulator therapy was prescribed for 65 IBD patients (59.6%) after discontinuation of ant-TNF.

2. Characteristics of the enrolled patients and relapse rates after discontinuation of anti-TNF

The median follow-up duration (months) after discontinuation of anti-TNF was 56.0 (34.5 to 90.0) for IBD patients, 73.0 (37.0 to 117.0) for CD and 42.5 (27.3 to 65.3) for UC patients. After anti-TNF cessation, relapse was noted in 69 IBD patients (63.3%), including 50 CD (70.4%) and 19 UC (50.0%). The cumulative relapse rates at 1, 2, 3, and 5 years for IBD patients were 17.4%, 32.9%, 46.7%, and 62.9%, respectively, 11.3%, 31.4%, 46.7%, and 62.5%, respectively for CD patients. The cumulative relapse rates for UC patients, were 28.9%, 34.8%, 45.3%, and 60.9%, respectively (Fig. 2).

3. Predictors of relapse after discontinuation of anti-TNF

In CD patients, the multivariable Cox analysis showed that ADA use was associated with higher risk of relapse (vs IFX: hazard ratio [HR], 4.42; 95% confidence interval, 1.24 to 17.74; p=0.022) and discontinuation of treatment owing to clinician's decision was associated with lower risk of relapse (vs patient's preference: HR, 0.13; 95% confidence interval, 0.04 to 0.48; p=0.002) (Table 2). The relapse-free survival curves based on the type of anti-TNF agent and reasons for discontinuation of anti-TNF in CD patients are shown in Fig. 3. However, for UC patients, the Cox analysis revealed that the risk of relapse was negatively associated with the mucosal healing before discontinuation of anti-TNF (vs non-mucosal healing: HR, 0.12; 95% confidence interval, 0.02 to 0.83; p=0.031) (Table 3). The relapse-free survival curves for mucosal healing in UC patients are shown in Fig. 4.

4. Efficacy and safety of retreatment with anti-TNF

After relapse, 52 IBD patients (75.4%; 40 CD and 12 UC), underwent anti-TNF re-induction. Two patients (3.8%) experienced anti-TNF-related infusion reactions. Forty-four patients achieved remission, and six patients showed response to retreatment. However, anti-TNF retreatment was discontinued in 25 IBD patients (50%; 17 CD and eight UC). The reasons for discontinuation were LOR for 15 patients (including three cases of intolerance); patient's preference, six patients; clinician's decision, two patients; and other factors, two patients. The median time to LOR was 60.0 months (range, 45.7 to 74.3 months). The cumulative rate of LOR during retreatment was 11.3% at 1 year, 20.6% at 2 years, 31.5% at 3 years, and 55.4% at 5 years.

The same anti-TNF agents were re-induced in 44 patients; however, the anti-TNF agents were switched (IFX to ADA [n=6], or vice versa [n=2]) in eight patients. Thirty-six of 44 patients (81.6%) in whom anti-TNF agents were same achieved clinical remission, whereas 23 of these (54.8%) discontinued retreatment. All eight patients for whom the anti-TNF agent was switched achieved clinical remission; however, treatment was discontinued owing to patient's preference (n=1) and intolerance to AE (n=1, skin eruption; same AE to first-line anti-TNF). Although there was no statistically difference (p=0.247), the rate of

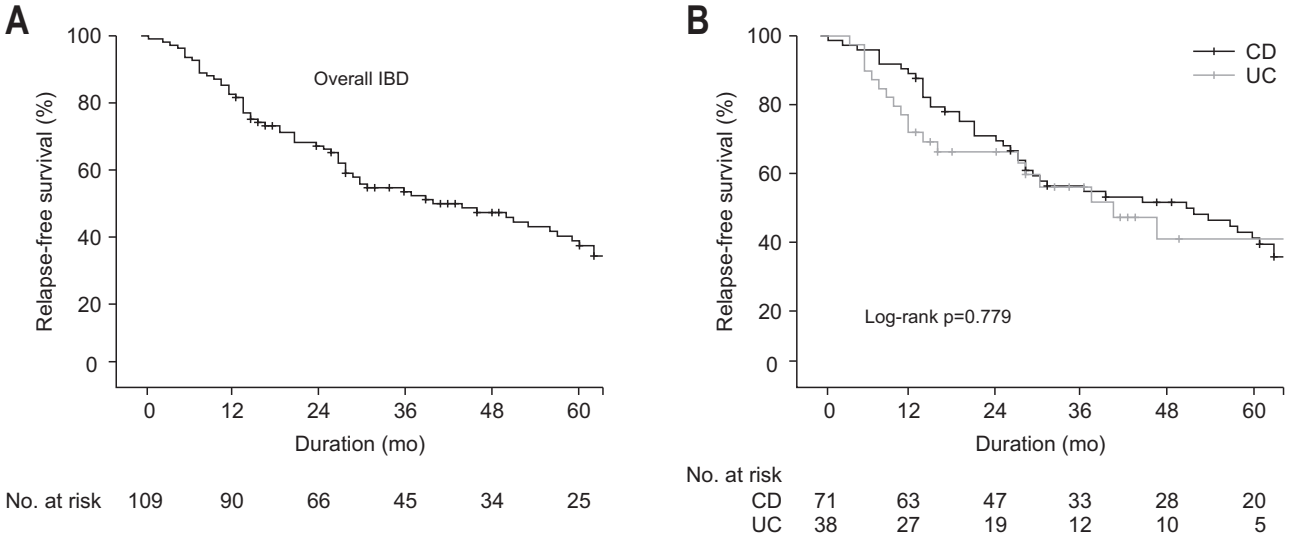

Fig. 2. Relapse-free survival rates after the discontinuation of anti-tumor necrosis factor therapy. (A) Overall inflammatory bowel diseases (IBD); (B) Crohn's disease (CD) and ulcerative colitis (UC).

Table 2. Predictors of Relapse after the Discontinuation of Anti-TNF Therapy in Patients with Crohn's Disease

Characteristics		HR (95% CI)*	p-value*
Sex	Female	1	
	Male	0.59 (0.19–1.85)	0.367
Age at diagnosis, yr	≤40	1	
	>40	0.30 (0.03–3.27)	0.324
Age at the time of discontinuation of anti-TNF therapy, yr	≤40	1	
	>40	2.04 (0.39–10.79)	0.402
Smoking status after discontinuation of anti-TNF therapy	Non-/ex-smoker	1	
	Current smoker	0.53 (0.06–4.72)	0.571
Previous intestinal surgery	No	1	
	Yes	2.16 (0.87–5.38)	0.097
Indications for initiation of anti-TNF therapy	Active luminal	1	
	Fistulizing	0.57 (0.25–1.29)	0.179
Type of anti-TNF	Infliximab	1	
	Adalimumab	4.42 (1.24–17.74)	0.022
Duration of anti-TNF treatment, mo		1.01 (0.98–1.03)	0.704
Montreal location	Ileum or ileocolonic	1	
	Colonic	0.97 (0.31–3.04)	0.961
Montreal behavior	Inflammatory	1	
	Stricturing or penetrating	1.10 (0.46–2.63)	0.835
Perianal disease	No	1	
	Yes	1.49 (0.62–3.55)	0.372
Reason for discontinuation of anti-TNF therapy	Patient's preference	1	0.023
	Clinician's decision	0.13 (0.04–0.48)	0.002
	Intolerance to adverse effects	0.43 (0.11–1.75)	0.240
	Others	0.62 (0.26–1.51)	0.296
Hemoglobin level at the time of discontinuation of anti-TNF therapy, g/dL		0.86 (0.61–1.20)	0.370
Albumin level at the time of discontinuation of anti-TNF therapy, mg/dL		0.58 (0.23–1.43)	0.234
CRP level at the time of discontinuation of anti-TNF therapy, mg/dL		1.01 (0.96–1.05)	0.795
Mucosal healing before discontinuation of anti-TNF therapy	No	1	0.865
	Yes	0.84 (0.21–3.37)	0.804
	Unknown	0.74 (0.22–2.49)	0.629
Immunomodulator use after discontinuation of anti-TNF therapy	No	1	
	Yes	0.70 (0.30–1.64)	0.411

TNF, tumor necrosis factor; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein.
*Multivariable analysis.

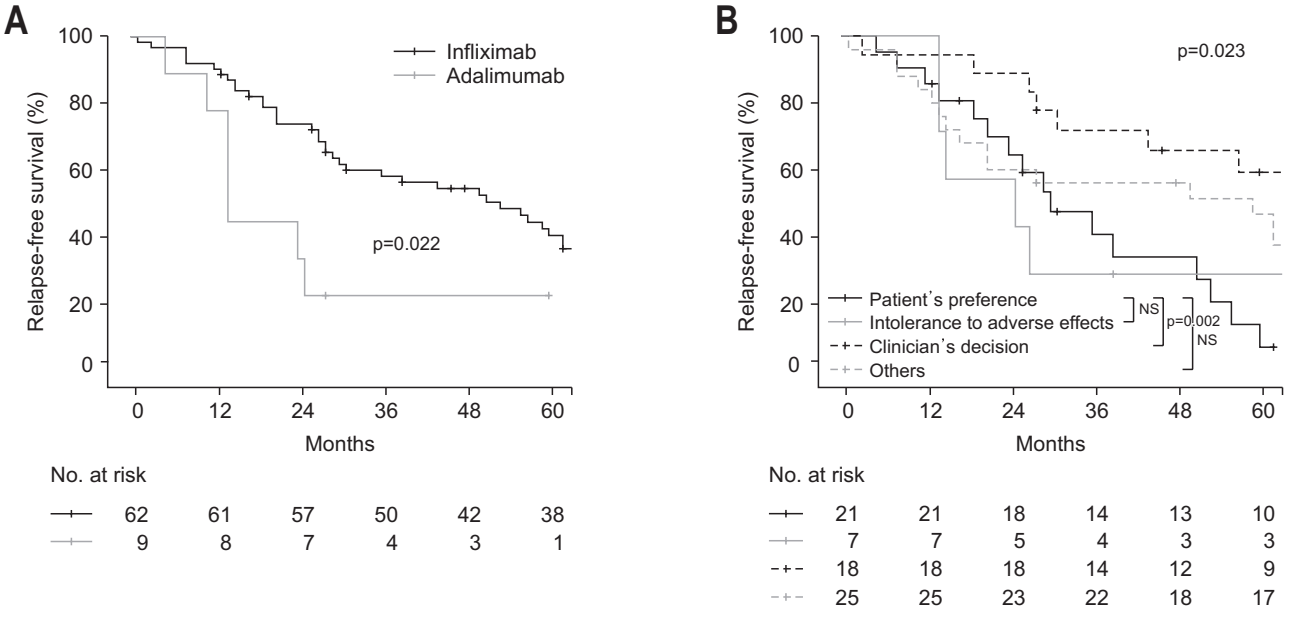

Fig. 3. Relapse-free survival rates in patients with Crohn's disease after the discontinuation of anti-tumor necrosis factor (TNF) according to type of anti-TNF agent (A) and reason for the discontinuation of anti-TNF (B).

Table 3. Predictors of Relapse after the Discontinuation of Anti-TNF Therapy in Patients with Ulcerative Colitis

Characteristics		HR (95% CI)*	p-value*
Sex	Female	1	
	Male	0.44 (0.05–4.10)	0.473
Age at diagnosis, yr	≤40	1	
	>40	0.51 (0.08–3.20)	0.468
Age at the time of discontinuation of anti-TNF therapy, yr	≤40	1	
	>40	2.46 (0.39–15.60)	0.339
Type of anti-TNF	Infliximab	1	
	Adalimumab or golimumab	0.56 (0.07–4.22)	0.571
Duration of anti-TNF treatment, mo		0.98 (0.94–1.02)	0.301
Disease extent	Proctitis or left side	1	
	Extensive	1.44 (0.33–6.37)	0.629
Reasons for discontinuation of anti-TNF therapy	Patient's preference	1	0.594
	Clinician's decision	1.65 (0.30–9.05)	0.566
	Intolerance to adverse effects	2.27 (0.24–21.86)	0.480
	Others	4.51 (0.48–42.29)	0.187
Hemoglobin level at the time of discontinuation of anti-TNF therapy, g/dL		1.52 (0.73–3.17)	0.266
Albumin level at the time of discontinuation of anti-TNF therapy, mg/dL		2.57 (0.30–21.80)	0.388
CRP level at the time of discontinuation of anti-TNF therapy, mg/dL		1.07 (0.58–1.98)	0.818
Mucosal healing before discontinuation of anti-TNF therapy	No	1	0.089
	Yes	0.12 (0.02–0.83)	0.031
	Unknown	0.22 (0.03–1.53)	0.126
Immunomodulator use after discontinuation of anti-TNF therapy	No	1	
	Yes	0.61 (0.18–2.04)	0.418

TNF, tumor necrosis factor; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein.
*Multivariable analysis.

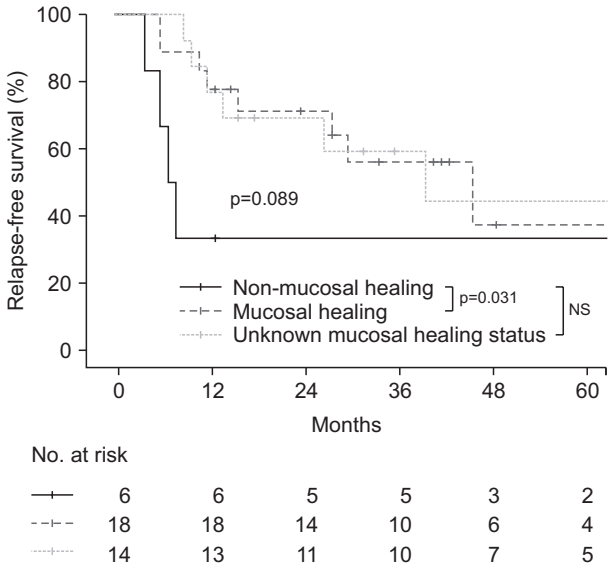

Fig. 4. Relapse-free survival rates in patients with ulcerative colitis after the discontinuation of anti-tumor necrosis factor according to the mucosal healing status.

retreatment cessation was lower in patients for whom the anti-TNF agent was switched than for those retreated with the same agent (25.0% vs 54.8%). LOR was noted in one patient for whom the anti-TNF agent was switched.

AEs following anti-TNF retreatment were noted in six IBD patients (11.5%; five CD and one UC). They were newly developed, except for one CD patient. AEs included pruritis and skin eruptions. Only one patient, among them, retreated with switched anti-TNF.

DISCUSSION

After discontinuation of anti-TNF for IBD patients under remission, relapse was noted in 70.4% of CD and 50.0% of UC patients during 73.0 and 42.5 months, respectively. The relapse rates at 1 and 5 years for CD patients were 11.3% and 62.5%, respectively, while those for UC patients were 28.9% and 60.9%, respectively. Type of anti-TNF agent and reasons for discontinuation of anti-TNF were associated with relapse in CD patients. The mucosal healing before discontinuation of anti-TNF was associated with a low risk of relapse in UC patients.

In most studies reporting on the outcomes of IBD patients after discontinuation of anti-TNF, follow-up duration was 1 to 2 years, and they reported similar relapse rates of approximately 50%.[4,12,13,27-30] Few studies have reported on the long-term outcomes. The follow-up duration in our study was 4.7 years (range, 2.9 to 7.5 years). In a follow-up study of the STORI trial (102 patients with follow-up of 7 years), the relapse rates for CD patients at

1 year (43.9%) and 2 years (52.2%) were higher than our observed rates.[13] In a meta-analysis, the risk of relapse in CD patients at 12 months (40%) and at ≥25 months (49%) was also higher than our observed rates at 1 and 3 years.[14] However, in a Spanish study (1,055 patients with follow-up of 2.4 years), the relapse rates for IBD patients at 1 year (24%) were similar with our observed rates.[12]

Several studies have identified the risk factors for relapse after discontinuation of anti-TNF. The STORI trial suggested that the risk factors for relapse included male, low hemoglobin, increased C-reactive protein and fecal calprotectin levels.[4] According to a Spanish study, the risk of relapse was increased by ADA use, elective discontinuation, intolerance to AEs, colonic involvement, and stricturing behavior.[12] Immunomodulator treatment following discontinuation and age decreased the risk in CD patients.[12,31] According to Papamichael *et al.*,[15] diagnosis of IBD at age ≥25 years was associated with sustained remission. A prospective study reported that a history of biologics and dose-intensification during the 1-year of biological therapy (p=0.011 and p=0.024, respectively) were associated with the need for and time to biologics re-initiation.[30] We found that ADA use was associated with the risk of relapse compared with IFX use in CD patients, consistent with the findings of the Spanish study; however, our reported HR was relatively higher.[12] Furthermore, both median time to relapse and follow-up duration after discontinuation were shorter for patients on ADA (14.0 and 36.0 months, respectively) than for those on IFX (39.0 and 78.5 months, respectively). The 1-year relapse rate was higher with ADA (22.2%) than with IFX (9.7%). The onset of action was faster for IFX than for ADA. Therefore, patients with ADA may report less deep remission compared with patients with IFX for similar treatment periods. However, this result should be interpreted carefully because as the proportion of patients treated with ADA was only 12.7%, the possibility of bias cannot be disregarded; moreover, undetectable variables, which may have been associated with relapse, were not evaluated.

In CD patients, discontinuation of anti-TNF based on the clinician's decision was associated with a lower risk of relapse compared with the patient's preference. Discontinuation based on the clinician's recommendation was an attempt at de-escalation. The clinician evaluated the patient's disease activity, confirmed clinical/endoscopic remission, and then decided to withdraw anti-TNF. CD patients who discontinued anti-TNF on the clinician's recommendation showed a higher degree of inflammatory behavior and presented with unknown mucosal healing status compared with those who discontinued treatment for other reasons; however, statistically significant differences were not observed. In our study, we found that the risk of relapse was negatively associated with mucosal healing before the discontinuation of anti-TNF in UC patient although this observation was not validated in other studies. Even though the rate of unknown cases of mucosal healing before discontinuation was too high, patient without mucosal healing before discontinuation showed definitely higher rate of relapse after discontinuation of anti-TNF therapy than patients with mucosal healing before discontinuation. The most common reason for discontinuation of anti-TNF was clinician decision (33.9%) in patients with unknown mucosal healing status. In clinical settings, patients were reluctant to perform endoscopy, when the reason for discontinuation of anti-TNF therapy was patient's preference or intolerance. We estimated that symptoms were completely relieved and general conditions improved in many cases of patient's preference, but we could not quantify it. We assumed that meaningful proportion of patients with unknown mucosal healing status, achieved mucosal healing, even though 51.4% of patients could not be confirmed mucosal healing. A systematic review reported that the relapse rate was lower when anti-TNF was withdrawn based on both clinical and endoscopic remission (mucosal healing) rather than clinical remission alone.[32] Therefore, mucosal healing should be evaluated when considering anti-TNF cessation.

Similar to other studies, retreatment of relapsed patients with anti-TNF was effective and safe.[12,14] However, LOR or intolerance was noted for a significant number of patients who responded to anti-TNF; these factors may lead to retreatment cessation. Fifty IBD patients (30%), including 11 CD and four UC, showed LOR and the cumulative rate of LOR during retreatment was 11.3% at 1 year, 20.6% at 2 years, 31.5% at 3 years, and 55.4% at 5 years. The median duration of retreatment was 47.0 months (range, 24.4 to 69.6 months) and cumulative rate of retreatment cessation was 69.8% during the entire follow-up period. According to study of Ben-Horin and Chowers,[33] the incidence of LOR showed in the steep slope in the first year and became more gradual in ensuing years. And Casanova *et al.*[34] revealed that the probability of achieving remission in the short term was associated with the reason for discontinuing the first anti-TNF. The rate of LOR during anti-TNF maintenance was 52.1% at 5 years in our previous study, including IBD patients with first anti-TNF treatment, in contrast to present study, composed of selected patients who achieved clinical remission and sustained good response during 12.0 months (range, 9.0 to 26.5 months) of first anti-TNF treatment.[35] Considering these points, we assumed that patients analyzed in our present study, showed less incidence of LOR than patients with first

anti-TNF treatments. To take into account the relatively high cumulative rate of LOR and discontinuation during retreatment, in the present study, despite the effectiveness and safety of retreatment, the decision for discontinuation of anti-TNF should be re-considered. It would be better that patient who achieved only clinical remission without deep remission did not cease anti-TNF.

Most patients were retreated with the same anti-TNF agent, and only eight patients were retreated with switched agent. The rate for clinical remission was higher, rate of retreatment cessation was lower, and rate of LOR during retreatment was lower for patients for whom the anti-TNF agent was switched compared to those for patients retreated with the same agent (p=0.330, p=0.247, and p=0.412, respectively); however, the difference was not statistically significant. Therefore, switching the type of anti-TNF agent may be considered when patients are retreated with anti-TNF; this finding is consistent with previous studies.[34,36]

There are several limitations. First, this study was a retrospective study. Selection bias could not be disregarded, despite adjustment for the relevant variables. Second, since our cohort only included Koreans, the generalization of our findings to IBD patients of other ethnicities is not clear. Third, therapeutic drug monitoring and anti-drug antibody were not evaluated before discontinuation, although conventional reactive therapeutic drug monitoring and anti-drug antibody were used to evaluate the efficacy of anti-TNF. Forth, the mucosal healing was assessed in approximately half of the patients before discontinuation, because of a real-world study.

In conclusion, despite the proven efficacy of anti-TNF treatment for IBD patients, some patients discontinued treatment in the real-world practice for various reasons. In this study, we identified that the 1-year relapse rate was approximately 20% lower than that expected, although about 60% of IBD patients with anti-TNF in remission, relapsed at 5 years after treatment cessation. Anti-TNF re-induction appeared to be effective and safe; however, half of the patients discontinued retreatment, and 50% of such patients discontinued retreatment owing to LOR. Therefore, before deciding on anti-TNF cessation, the type of anti-TNF agent, reason for discontinuation, and mucosal healing status should be carefully considered for IBD patients. In addition, switching the anti-TNF agent may be better for reducing the risk of LOR when patients were retreated with anti-TNF. Further prospective studies are needed to validate these findings.

CONFLICTS OF INTEREST

Y.S.K. and J.P.I. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conception and design of the study, analysis and interpretation of data, and preparation of the manuscript: J.H.S., E.A.K. Conception and design of the study, analysis and interpretation of data and critical revision of the manuscript for important intellectual content, and final approval of the manuscript: S.K.P., S.N.H. Critical revision of the manuscript for important intellectual content, and final approval of the manuscript: Y.S.K., K.B.B., K.O.K., H.S.L., S.B.K., S.Y.S., E.M.S., J.P.I., C.H.C.

ORCID

Joo Hye Song https://orcid.org/0000-0002-1166-0085
Eun Ae Kang https://orcid.org/0000-0003-0220-937X
Soo-Kyung Park https://orcid.org/0000-0001-8822-9632
Sung Noh Hong https://orcid.org/0000-0002-4140-3717
You Sun Kim https://orcid.org/0000-0002-5156-3458
Ki Bae Bang https://orcid.org/0000-0002-9961-9318
Kyeong Ok Kim https://orcid.org/0000-0001-5799-7436
Hong Sub Lee https://orcid.org/0000-0002-2962-0209
Sang-Bum Kang https://orcid.org/0000-0002-1946-7896
Seung Yong Shin https://orcid.org/0000-0001-8970-2444
Eun Mi Song https://orcid.org/0000-0002-2428-1551
Jong Pil Im https://orcid.org/0000-0003-1584-0160
Chang Hwan Choi https://orcid.org/0000-0001-7089-532X

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