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Original Article

Effectiveness and Tolerability of Anti-Tumor Necrosis Factor Alpha Therapy in Refractory Intestinal Behçet's Disease: A Large Single-Center Study

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Background/Aims: Intestinal Behçet's disease (BD) is a rare, chronic intestinal vascular disorder often refractory to conventional therapy. We aimed to assess the effectiveness and tolerability of anti-tumor necrosis factor alpha (anti-TNF-α) therapy in patients with moderate to severe refractory intestinal BD.

Methods: Clinical remission, clinical response, and biological response rates at 4, 12, and 24 months, as well as the adverse effects of anti-TNF-α therapy were investigated at the Inflammatory Bowel Disease Center of Severance Hospital, Seoul, Korea. We also examined the relapse rates and predictive factors for disease relapse.

Results: Of the 119 patients, 15 (12.6%) were bio-exposed, 68 (57.1%) received concomitant immunomodulators, and 56 (47.1%) received concomitant corticosteroids at anti-TNF-α treatment induction. At 4, 12, and 24 months, clinical remission rates were 23.5%, 40.3%, and 42.0%; clinical response rates were 84.0%, 62.2%, and 62.2%; and biological response rates were 61.3%, 68.9%, and 58.8%, respectively. Sixty-three patients (52.9%) relapsed, with a mean relapse time of 2.8 years. Higher initial C-reactive protein levels (hazards ratio [HR], 1.013; 95% confidence interval [CI], 1.008 to 1.018; p<0.001), history of previous intestinal surgery (HR, 4.282; 95% CI, 2.379 to 7.709; p<0.001), concomitant immunomodulator use (HR, 0.455; 95% CI, 0.267 to 0.775; p=0.004), and clinical response at 4 months (HR, 0.353; 95% CI, 0.181 to 0.687; p=0.002) were independent factors associated with the disease relapse. No mortality was observed during the study period; 26 (21.8%) and three patients (2.5%) experienced mild infection and infusion reactions, respectively.

Conclusions: Anti-TNF-α therapy could be an effective and tolerable option for refractory intestinal BD. **(Gut Liver, 2026;20:305-314)**

Key Words: Behcet disease; Tumor necrosis factor inhibitors; Recurrence

INTRODUCTION

Anti-tumor necrosis factor alpha (anti-TNF-α) agents have significantly improved the treatment options of inflammatory bowel disease (IBD) since their approval by the Food and Drug Administration for Crohn's disease in 1998 and for ulcerative colitis in 2005.[1] TNF-α is a key proinflammatory cytokine in IBD that activates acute phase protein expression and cellular pathways involved in migration and proliferation.[2] Anti-TNF-α therapy, such as infliximab and adalimumab, promotes T-cell apoptosis and induces regulatory macrophages, aiding mucosal healing.[3,4] These therapies have shown clinical effectiveness and are recommended for moderate to severe IBD.[5]

Behçet's disease (BD) is a chronic, recurrent inflammatory disorder that affects multiple organs and is defined

as intestinal BD when it involves the gastrointestinal tract, characterized by subjective symptoms and typical ileocecal ulcer lesions.[6-8] Intestinal BD could be a life-threatening disorder accompanied by gastrointestinal bleeding or perforation.[9] Accurate diagnosis and optimal treatment strategies are important because patients with intestinal BD frequently visit the emergency room and require early readmission or reoperation.[10-12] A randomized clinical trial for the treatment of intestinal BD is difficult to perform due to its rarity and the lack of evidence-based treatments.

Intestinal BD and Crohn's disease share many clinical manifestations, endoscopic findings, genetic backgrounds, and immune responses.[13,14] Therapeutic strategies for intestinal BD are similar to those for Crohn's disease based on the opinions of expert physicians.[15,16] In 2007, the Japanese consensus statements for the diagnosis and management of intestinal BD recommended standard therapeutic strategies including 5-aminosalicylic acid, corticosteroids, immunosuppressive agents, enteral nutrition, total parenteral nutrition, and surgical therapy.[17] In 2014, the 2nd edition of consensus statements was renewed regarding indications for anti-TNF-α as a standard therapy.[18]

Although several studies on anti-TNF-α therapy are available, only a very small number of patients with intestinal BD have been studied because of the rarity of the disease. Most of these are multicenter studies, and the lack of standardized treatment protocols among participating clinicians pose challenges for data analysis. Moreover, the independent risk factors related to sustained response and relapse have not been sufficiently reported. Therefore, this study aimed to assess the effectiveness and safety of anti-TNF-α therapy and to identify factors associated with clinical outcomes in a single large-volume Korean center.

MATERIALS AND METHODS

1. Study population

We analyzed 119 patients with intestinal BD treated with anti-TNF-α for more than 4 months, who were registered at the Inflammatory Bowel Disease Center of Severance Hospital, Seoul, Korea. The inclusion criteria were as follows: (1) age of 18 years or older; (2) diagnosis according to clinical, histological, and radiological criteria;[7] (3) moderate to severe disease activity status, as measured by the Disease Activity Index of Intestinal BD (DAIBD) score, despite intensive therapies with conventional agents;[19] and (4) administration of infliximab or adalimumab for more than 4 months. Patients were identified using the Severance Hospital IBD Clinic Registry, an internal web-based electronic medical record system that includes all patients with intestinal BD at Severance Hospital, Yonsei University College of Medicine.[20,21] This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Severance Hospital (number: 4-2020-068).

2. Treatment protocol and outcome measures

Patients received anti-TNF-α therapy according to a standardized institutional protocol. Before initiation, clinical disease activity was evaluated using the DAIBD. Anti-TNF-α agents were administered following approved dosing regimens, with dose adjustments based on clinical response and adverse events. Infliximab was administered at 5 mg/kg of body weight given intravenously at weeks 0, 2, and 6, and then every 8 weeks. Thirty minutes before each infusion, a 100 mg dose of hydrocortisone was administered intravenously to minimize the risk of infusion reactions. If no adverse reactions were observed for more than 6 months, hydrocortisone was discontinued. Adalimumab was administered at a dose of 160 mg at week 0, 80 mg at week 2, and 40 mg every other week. Cases of infliximab to adalimumab or adalimumab to infliximab switching due to loss of response were included in this study. For biologic-exposed patients, only data from second-line therapy were collected and analyzed. Follow-up visits were scheduled regularly, typically every 2 to 12 weeks, to receive anti-TNFα therapy and to reassess clinical symptoms and laboratory tests (complete blood count and serum aminotransferase levels) to monitor treatment efficacy and safety.

The primary outcomes of interest were clinical remission at 4, 12, and 24 months, defined as clinical remission with a DAIBD score <20,[19] and the identification of predictors of disease relapse. Relapse was defined as events requiring retreatment with corticosteroids, intestinal resection, or hospitalization after use of anti-TNF-α agents. Secondary endpoints were clinical response defined as Δ DAIBD score >20; biological response, defined as a decrease in serum C-reactive protein (CRP) levels from baseline of ≥50% and ≤3 mg/L,[22] predictors of endoscopic remission, defined as the absence of any signs of active disease, including inflammation, ulceration, or bleeding; persistence on treatment; adverse events; and predictors of short-term (4 months) and long-term (12 and 24 months) remission.

The DAIBD scores and CRP levels at baseline, 4, 12, and 24 months after anti-TNF-α therapy were evaluated to analyze the clinical remission rate, clinical response rate, and biological response rate. These outcomes were assessed according to both the intention-to-treat (ITT) and per-protocol (PP) principles. The ITT population included all patients who initiated anti-TNF-α therapy, regardless

of treatment adherence or discontinuation, and outcomes were analyzed based on the initial treatment assignment. The PP population consisted of patients with available outcome assessments at each time point who completed the prescribed anti-TNF-α therapy without major protocol deviations. Outcomes in the PP group reflected treatment effects among adherent patients.

For detailed evaluation of adverse events, patients reporting skin-related symptoms were referred to a dermatologist for clinical assessment. Dermatologists assessed the presence and relevance of skin lesions, and confirmed findings were documented in medical records. These data were then extracted and used for analysis. Persistence on treatment was defined as the ongoing use of anti-TNF-α at the time of data collection.

3. Data collection

We retrospectively collected the following data from the electronic medical records of patients: sex; age; weight; body mass index; disease duration; smoking history; history of intestinal resection; systemic symptoms and signs; ulcer characteristics (distribution, number, depth, shape, and type; localized, confined to a specific intestinal segment; diffuse, involving multiple, non-contiguous segments); previous medications; concomitant medications; DAIBD score; CRP, albumin and hemoglobin levels; indications for anti-TNF-α, duration of anti-TNF-α administration, reason for discontinuation of anti-TNF-α; and adverse events related to anti-TNF-α. Since our institution prospectively collected patient data using an electronic medical record system, relatively accurate data, such as the DAIBD score, could be obtained even though it was retrospectively reviewed.

4. Statistical analysis

Mean and standard deviation were calculated for all continuous variables, as appropriate. Cox proportional hazard analyses, including various confounders such as age, sex, disease duration at anti-TNF-α initiation, current smoking, body mass index, initial CRP level, systemic BD, previous history of surgery, concomitant medications, type of anti-TNF-α, presence of a typical ulcer, type of intestinal BD, and clinical remission, response, and biological response at 4 months, were performed to determine the independent factors associated with disease relapse, endoscopic remission, and persistence on treatment. Variables with $p \leq 0.06$ in the univariate analysis were entered into the multivariate Cox proportional hazards model.

Multivariate logistic regression analyses were performed to identify the independent predictors of short- and long-term clinical remission. The Kaplan-Meier analyses (log-rank tests) were carried out to determine the factors related to disease relapse after anti-TNF-α therapy. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 23.0; SPSS Inc., Armonk, NY, USA).

RESULTS

1. Patient baseline characteristics

A total of 119 patients were administered anti-TNF-α for the treatment of refractory intestinal BD. The mean age of patients was 52.5±15.6 years, 48 patients (40.3%) were male, and the mean disease duration was 10.5±6.6 years. Previous intestinal surgery before anti-TNF-α therapy was performed in 57 patients (47.9%). Before anti-TNF-α therapy, 118 patients (99.2%) had been treated with corticosteroids and 109 (91.6%) patients with immunomodulators. The baseline DAIBD score at anti-TNF-α therapy was 119.1±45.0. Most patients (84.0%) had typical intestinal ulcers with localized distribution patterns (Table 1).

2. Details of anti-TNF-α therapy

The mean age at initiation of anti-TNF-α was 47.4±13.8 years, and the mean disease duration at the time of anti-TNF-α initiation was 5.2±5.9 years. Among 104 patients for first-line therapy, 77 patients (64.7%) were treated with adalimumab and 27 patients (22.7%) with infliximab. The mean administration period of anti-TNF-α was 4.4±2.9 years, and the mean follow-up duration was 4.5±2.9 years. At the initiation of anti-TNF-α therapy, 56 (47.1%), 37 (31.1%), and 31 (26.1%) patients were concomitantly treated with corticosteroids, azathioprine, and methotrexate, respectively. There was no mortality with the use of anti-TNF-α agents, and only three patients (2.5%) experienced an infusion reaction. Infections were identified in 26 patients (21.8%) and occurred in the following order of frequency: herpes zoster skin infection (n=8), *Clostridioides difficile* colitis (n=6; diagnosed by stool polymerase chain reactiontest), urinary tract infection (n=4), pneumonia (n=3), abdominal abscess (n=2), otitis media (n=1), cytomegalovirus colitis (n=1), and COVID-19 (n=1) (Table 2). Among these patients, 10 required hospitalization for treatment.

3. Clinical outcomes of anti-TNF-α therapy

First, we assessed the DAIBD scores and CRP levels at baseline, 4, 12, and 24 months after anti-TNF-α therapy to analyze the clinical remission rate, clinical response rate, and biological response rate according to the ITT and PP principle (Fig. 1). In ITT analysis, the clinical remission

Table 1. Baseline Characteristics for Intestinal Behçet's Disease

Variable	Value (n=119)
Age, yr	52.5±15.6
Age at diagnosis, yr	42.2±14.3
Male sex	48 (40.3)
Weight, kg	56.1±10.4
Body mass index, kg/m^2	20.8±3.1
Disease duration, yr	10.5±6.6
Smoking history	18 (15.1)
Systemic symptoms and signs	
Oral ulcer	82 (68.9)
Genital ulcer	40 (33.6)
Ocular lesion	16 (13.4)
Skin lesion	34 (28.6)
Arthritis	35 (29.4)
Neurologic lesion	1 (0.8)
Vascular lesion	3 (2.5)
Clinical type of intestinal Behçet's disease	
Definite	104 (87.4)
Probable	11 (9.2)
Possible	4 (3.4)
Previous intestinal resection	57 (47.9)
Medication before anti-TNF-α therapy	
Mesalamine or sulfasalazine	119 (100.0)
Corticosteroids	118 (99.2)
Immunomodulator	109 (91.6)
DAIBD score at anti-TNF-α therapy	119.1±45.0
Laboratory findings at anti-TNF-α therapy	
C-reactive protein, mg/L	38.3±47.6
Albumin, g/dL	3.9±0.6
Hemoglobin, g/dL	11.2±2.0
Distribution of ulcers	
Localized	104 (87.4)
Diffuse	15 (12.6)
Number of ulcers	
Solitary	65 (54.6)
Multiple	54 (45.4)
Depth of ulcers	
Shallow	58 (48.7)
Deep	61 (51.3)
Shape of ulcers	
Oval	68 (57.1)
Aphthous	17 (14.3)
Volcano	34 (28.6)
Type of ulcers	
Typical	100 (84.0)
Atypical	19 (16.0)

Data are presented as mean±SD or number (%).
TNF, tumor necrosis factor; DAIBD, Disease Activity Index for Intestinal Behçet's Disease.

rates were 23.5%, 40.3%, 42%, and biological response rates were 61.3%, 68.9%, and 58.8% at 4, 12, and 24 months after anti-TNF-α therapy, respectively. Based on the PP analysis, the clinical remission rates were 23.9%, 43.6%, and 52.6%, and the biological response rates were 89%, 85.4%, and 87.5% at 4, 12, and 24 months after anti-TNF-α therapy, respectively.

Table 2. Details of Anti-TNF-α Drug Use for Intestinal Behçet's Disease

Variable	Value (n=119)
Age at initiation of anti-TNF-α, yr	47.4±13.8
Disease duration at initiation of anti-TNF-α, yr	5.2±5.9
Indication of anti-TNF-α	
1st line therapy	
Infliximab	27 (22.7)
Adalimumab	77 (64.7)
2nd line therapy	
Infliximab→Adalimumab	8 (6.7)
Adalimumab→Infliximab	7 (5.9)
Administration duration, yr	4.4±2.9
Follow-up duration, yr	4.5±2.9
Concomitant medication	
Mesalamine or sulfasalazine	119 (100)
Corticosteroids	56 (47.1)
Immunomodulator	68 (57.1)
Azathioprine	37 (31.1)
Methotrexate	31 (26.1)
Reason of discontinuation of anti-TNF-α therapy	
De-escalation	4 (3.4)
Side effect	5 (4.2)
Lack of efficacy	16 (13.4)
Self-discontinuation	2 (1.7)
Adverse event	
Infection	26 (21.8)
Infusion reaction	3 (2.5)
Others*	6 (5.0)

Data are presented as mean±SD or number (%).
TNF, tumor necrosis factor.
*Others include urinary stone, cholecystitis, avascular necrosis of hip joint, epididymitis.

Clinical remission rate at 4 months (Supplementary Table 1) was associated with DAIBD score at diagnosis (odds ratio [OR], 0.980; 95% confidence interval [CI], 0.967 to 0.993; p=0.003). Clinical remission rate at 12 months (Supplementary Table 2) was associated with history of previous surgery (adjusted OR [aOR], 0.297; 95% CI, 0.125 to 0.706; p=0.006), clinical remission at 4 months (aOR, 2.987; 95% CI, 1.069 to 8.345; p=0.037), and clinical response at 4 months (aOR, 10.201; 95% CI, 1.187 to 87.653; p=0.034). Clinical remission rate at 24 months (Supplementary Table 3) was associated with previous corticosteroid use at more than 20 mg per day (aOR, 0.166; 95% CI, 0.041 to 0.669; p=0.012) and clinical remission at 12 months (aOR, 30.093; 95% CI, 5.277 to 171.602; p<0.001).

4. Endoscopic outcomes of anti-TNF-α therapy

Of the 119 patients, a follow-up colonoscopy was performed in 100 patients, and endoscopic remission was confirmed in 40 patients (40%). The mean duration for follow-up endoscopy from anti-TNF-α therapy initiation was 1.7±1.2 years. In the univariate Cox analysis, only a

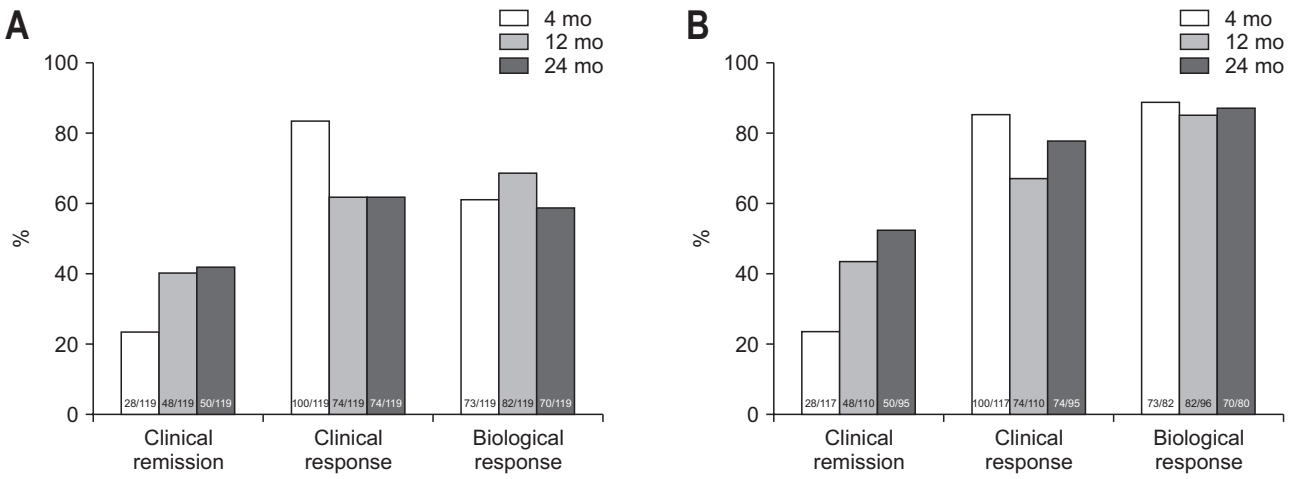

Fig. 1. Clinical remission rates, clinical response rates, and biological response rates of anti-tumor necrosis factor alpha therapy in patients with refractory intestinal Behçet's disease after 4, 12, and 24 months according to the intention-to-treat (A), and those according to the per-protocol principle (B). Anti-TNF-α, anti-tumor necrosis factor alpha.

Table 3. Predictors of BD-Related Relapse after Anti-TNF-α Therapy

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at diagnosis	0.999	0.981–1.017	0.911			
Age at anti-TNF-α initiation	1.002	0.983–1.021	0.844			
Female sex	1.206	0.720–2.021	0.505			
Disease duration at anti-TNF-α initiation	1.001	0.998–1.005	0.447			
Current smoking	0.995	0.429–2.311	0.991			
BMI (≥23 kg/m^2)	1.225	0.675–2.225	0.504			
Initial CRP	1.011	1.006–1.016	<0.01	1.013	1.008–1.018	<0.001
Systemic BD	1.567	0.875–2.804	0.131			
Previous surgery	3.277	1.918–5.600	<0.01	4.282	2.379–7.709	<0.001
Previous medication						
Corticosteroids (≥20 mg/day)	1.119	0.625–2.002	0.706			
Immunomodulator	0.667	0.286–1.555	0.348			
Concomitant medication						
Corticosteroids	1.513	0.916–2.501	0.106			
Immunomodulator	0.617	0.374–1.017	0.058	0.455	0.267–0.775	0.004
2nd line (vs 1st line)	1.984	1.055–3.731	0.034	1.222	0.620–2.410	0.562
Typical ulcer (vs atypical ulcer)	1.389	0.632–3.052	0.413			
Definite intestinal BD (vs probable or possible)	1.221	0.525–2.840	0.642			
Clinical remission at 4 mo	0.567	0.294–1.091	0.089			
Clinical response at 4 mo	0.434	0.229–0.825	0.011	0.353	0.181–0.687	0.002
Biologic response at 4 mo	0.907	0.323–2.550	0.854			

BD, Behçet's disease; TNF, tumor necrosis factor; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CRP, C-reactive protein.

history of previous surgery was a significant predictor of endoscopic remission after anti-TNF-α therapy (hazard ratio [HR], 0.488; 95% CI, 0.243 to 0.979; p=0.043) (Supplementary Table 4).

5. Relapse after anti-TNF-α therapy

During the follow-up period, 63 patients (52.9%) experienced disease relapse. The mean time before relapse was 2.8 years (median, 1.8 years). Among various confounders, initial CRP level (HR, 1.013; 95% CI, 1.008 to 1.018; p<0.001), history of previous surgery (HR, 4.282; 95% CI, 2.379 to 7.709; p<0.001), concomitant immunomodulator use (HR, 0.455; 95% CI, 0.267 to 0.775; p=0.004), and clinical response at 4 months (HR, 0.353; 95% CI, 0.181 to 0.687; p=0.002) were independent factors associated with the relapse of intestinal BD (Table 3). The cumulative risk of disease relapse based on Kaplan-Meier analysis revealed that previous surgery (p<0.001) increased the risk

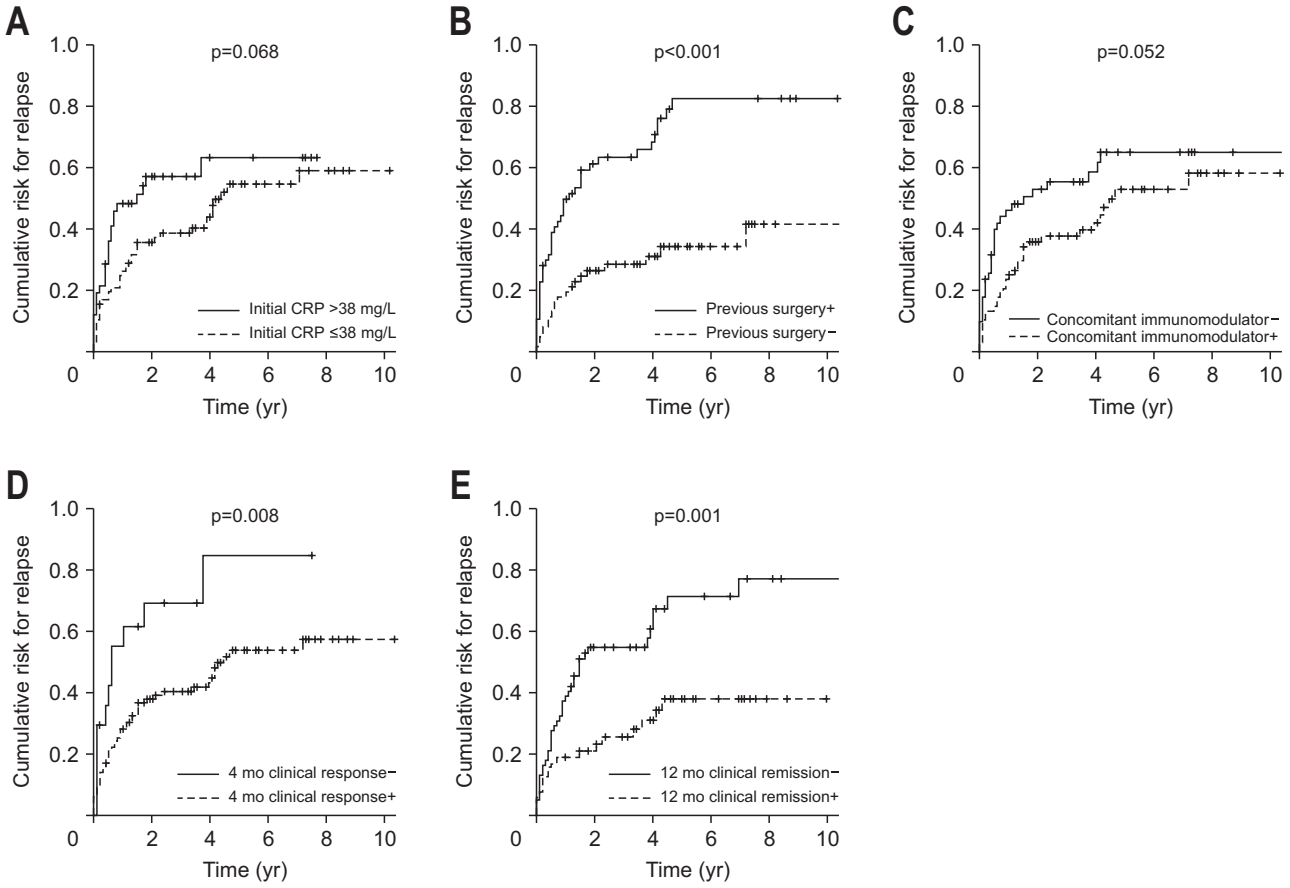

Fig. 2. Kaplan-Meier analysis (log-rank tests) comparing the cumulative rate of relapse during anti-tumor necrosis factor alpha therapy in patients with refractory intestinal Behçet's disease, according to (A) initial C-reactive protein (CRP)*, (B) previous abdominal surgery, (C) concomitant immunomodulator, (D) clinical response at 4 months, and (E) clinical remission at 12 months. *CRP levels were stratified based on the mean value of the cohort (38 mg/L), and patients were grouped into high- and low-CRP groups accordingly.

of relapse, whereas concomitant immunomodulator use (p=0.052), clinical response at 4 months (p=0.008), and clinical remission at 12 months (p=0.001) decreased it (Fig. 2).

6. Persistence on treatment after anti-TNF-α therapy

The cumulative number of patients that maintained anti-TNF-α therapy was 92 (77.3%). The reasons for discontinuing anti-TNF-α therapy were lack of effectiveness (13.4%), side effects (4.2%), symptom improvement (3.4%), and self-discontinuation (1.7%). Except for four patients who voluntarily discontinued the medication, the remaining patients discontinued the medication after consultation with their physicians. History of previous surgery (HR, 0.544; 95% CI, 0.354 to 0.836; p=0.005) (Table 4) was negatively associated with persistence in treatment.

DISCUSSION

We analyzed 119 patients with refractory intestinal BD treated with anti-TNF-α, and the mean follow-up duration was 4.5 years. To the best of our knowledge, this is the largest study to date to investigate the effectiveness of anti-TNF-α in intestinal BD. Both short-term and long-term clinical response rates were greater than 60%. Approximately half of the patients experienced a disease relapse after an average of 2.8 years following anti-TNF-α initiation. High inflammatory burden at the time of anti-TNF-α initiation and history of previous surgery increased the risk of disease relapse, and concomitant immunomodulator use and clinical response at 4 months were negatively associated with disease relapse. During the follow-up period, 92 patients (77.3%) sustained the use of anti-TNF-α.

Intestinal BD is difficult to study because of its heterogeneous clinical course and rarity. In a previous Korean multicenter study of 28 patients with moderate to severe intestinal BD treated with infliximab, the clinical remission

Table 4. Predictors of Persistence on Anti-TNF-α Therapy

Variable	Univariate analysis		
	HR	95% CI	p-value
Age at diagnosis	1.003	0.989–1.017	0.656
Age at anti-TNF-α initiation	1.000	0.985–1.016	0.985
Female sex	1.190	0.784–1.086	0.415
Disease duration at anti-TNF-α initiation	0.999	0.996–1.001	0.336
Current smoking	0.851	0.432–1.678	0.642
BMI (≥23 kg/m^2)	0.774	0.484–1.236	0.284
Initial CRP	1.000	0.995–1.004	0.937
Systemic BD	0.917	0.583–1.445	0.710
Previous surgery	0.544	0.354–0.836	0.005
Previous medication			
Corticosteroids (≥20 mg/day)	0.858	0.535–1.373	0.523
Immunomodulator	0.504	0.201–1.262	0.143
Concomitant medication			
Corticosteroids	0.798	0.529–1.204	0.282
Immunomodulator	1.089	0.717–1.652	0.690
2nd line (vs 1st line)	0.655	0.328–1.305	0.229
Typical ulcer (vs atypical ulcer)	0.927	0.514–1.671	0.801
Definite intestinal BD (vs probable or possible)	1.079	0.541–2.154	0.829
Clinical remission at 4 mo	1.440	0.906–2.287	0.123
Clinical response at 4 mo	0.939	0.430–2.049	0.874
Biologic response at 4 mo	0.734	0.330–1.631	0.448

TNF, tumor necrosis factor; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CRP, C-reactive protein; BD, Behçet's disease.

rates (DAIBD score <20 points) were 28.6%, 46.2%, and 39.1% and clinical response rates were 64.3%, 50.0%, and 39.1% (ΔDAIBD score >20 points) at 4, 30, and 54 weeks, respectively.[22] In a Japanese prospective, multicenter study of 11 patients with refractory intestinal BD treated with infliximab, the complete response rates, which were defined as both disappearance of clinical symptoms and healed or scarred ulcers, were 55%, 55%, and 60% at 14, 30, and 54 weeks, respectively.[23] In a Chinese single-center study of 27 patients with moderate to severe intestinal BD treated with infliximab, the clinical remission rates (DAIBD score <20 points) were 69.2%, 40.0%, and 55.0% and clinical response rates were 84.6%, 70.0%, and 70.0% (ΔDAIBD score >20 points) at 14, 30, and 52 weeks, respectively.[24] In a Japanese prospective, multicenter study of 20 patients with refractory intestinal BD treated with adalimumab, the complete remission rates, defined as both a marked improvement of global symptoms and endoscopic improvement, were 20% and 15% at 52 and 100 weeks, respectively. Furthermore, the clinical response rates, defined as marked improvement in global symptoms or endoscopic improvement, were 60% and 40% at 52 and 100 weeks, respectively.[25]

Unlike previous multicenter studies, our study was a single-center investigation that included a large number of patients treated with anti-TNF-α agents using standardized protocols and consistent clinical practice, which is a major strength. In addition, although the data were collected retrospectively, the quality of data management was comparable to that of prospective studies. We observed a gradual increase in clinical remission rates, reaching 42% and 52.6% at 24 months in the ITT analysis and PP analyses, respectively. This finding suggests a cumulative benefit of prolonged anti-TNF-α therapy and is consistent with previous studies that reported remission rates ranging from 30% to 60% depending on the study design, definitions of disease activity, clinical remission or response, treatment regimen, and follow-up duration.[26] Similarly, the biological response, measured by CRP normalization, peaked at 12 months and remained relatively high thereafter, indicating effective control of systemic inflammation. The reason for the relatively low remission rates might be that the patients included in our study had higher DAIBD scores and approximately half of them had previously undergone intestinal surgery. In addition, relatively delayed initiation of anti-TNF-α because of strict insurance coverage criteria could be part of the reason.

Clinical remission at 12 and 24 months was independently associated with clinical effectiveness at earlier time points (4 or 12 months). Achievement of remission at 4 weeks was demonstrated as a predictor of sustained response after infliximab treatment in Korean patients with intestinal BD (HR, 8.93; 95% CI, 1.457 to 55.536; p=0.018).[22] In addition, clinical effectiveness (response or remission) at 14 weeks was associated with clinical response and remission at 52 weeks in Chinese patients with intestinal BD (p<0.001).[24] These findings emphasize the importance of achieving early control of inflammation and the utility of early assessment as a decision-making tool to optimize long-term outcomes.

Another important observation was the strong association between previous intestinal surgery and poor outcomes across several domains. Patients with a history of intestinal surgery had significantly lower rates of clinical and endoscopic remission, higher relapse rates, and a reduced likelihood of sustained benefits. This may reflect a more refractory disease phenotype characterized by transmural inflammation, fibrotic strictures, or surgical complications. Surgical intervention for intestinal BD is generally reserved for severe or life-threatening complications such as perforation, massive bleeding, or obstruction, and such patients may inherently have a more aggressive disease course.[27,28]

The relapse rate in our study was 52.9% with a mean time to relapse of 2.8 years. Elevated baseline CRP levels, indicative of a higher inflammatory burden, were independently associated with an increased risk of relapse, con-

sistent with previous studies linking CRP levels to disease activity and prognosis in both IBD and intestinal BD.[29,30] In contrast, the concomitant use of immunomodulators and early clinical response significantly reduced the risk of relapse. These data support a combined immunosuppressive approach in patients receiving anti-TNF-α therapy, which may enhance treatment durability and prevent anti-drug antibody formation.[31-33]

Endoscopic remission was confirmed in 40% of patients undergoing follow-up colonoscopy, with a mean time to assessment of 1.7 years. Although a recent meta-analysis reported an endoscopic healing rate of 65% (95% CI, 52% to 78%),[26] there are no sufficient data regarding this topic, and endoscopic improvement does not always correspond to clinical improvement. Thus, combined clinical and endoscopic assessments are needed to evaluate treatment effectiveness.[34] Interestingly, prior intestinal surgery was the only factor associated with reduced endoscopic remission, further reinforcing its role as a marker of poor prognosis.

From a safety perspective, anti-TNF-α therapy was well tolerated. Infection was the most frequently reported adverse event (21.8%), which is consistent with known risks associated with biological therapy. However, no mortality and only a small number of infusion reactions (2.5%) were observed, indicating an acceptable safety profile over long-term treatment. These results align with previous reports on the relative safety of anti-TNF-α agents in BD, particularly in experienced centers with proper monitoring.[26]

Our study has the limitation of being a retrospective, cross-sectional, case-control study performed at a single tertiary university hospital. However, this problem seems to have been resolved considerably, as we prospectively input data using our electronic medical record system every time at patient visits. Second, the study population was limited to confirm the effectiveness and side effects of anti-TNF-α agents. Nevertheless, we included the largest number of patients with intestinal BD treated with anti-TNF-α therapy to date because our hospital is the largest single institution specialized in managing this disease. Third, although endoscopic disease activity was assessed in a substantial number of patients, the retrospective nature of the study precluded the collection of endoscopic remission data at standardized time points such as 4, 12, or 24 months. Therefore, endoscopic remission could not be included in the main Kaplan-Meier analyses, and this limitation restricted the ability to assess the prognostic impact of endoscopic healing in our cohort. Similarly, regular collection of fecal calprotectin, a more specific biomarker of intestinal inflammation than CRP, was not performed. Fourth, the definition of disease relapse was heterogeneous, defined as any use of corticosteroids, surgery, or hospitalization. Finally, the population might have been heterogeneous because we included both infliximab and adalimumab with or without concomitant agents.

In conclusion, anti-TNF-α therapy provided significant long-term clinical and endoscopic benefits for patients with refractory intestinal BD. Early clinical response, the absence of prior intestinal surgery, and concomitant immunomodulator use were associated with improved outcomes and reduced relapse risk. These findings highlight the importance of early treatment optimization and combination therapy for the management of intestinal BD. Large prospective studies are needed to validate these findings, explore biomarkers of treatment response, and further refine therapeutic algorithms for this complex disease.

CONFLICTS OF INTEREST

J.H.C. is an editorial board member of the journal but was 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

Study concept and design: J.P., J.H.C. Data acquisition: J.K., S.J.P., J.J.P., T.I.K., J.P., J.H.C. Data analysis and interpretation: J.Y.C., S.J.P., J.J.P., T.I.K. Drafting of the manuscript: J.Y.C. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: J.Y.C. Study supervision: J.P., J.H.C. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250346.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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