



# Efficacy and Safety of Infliximab in Intestinal Behçet's Disease: A Multicenter, Phase 3 Study (BEGIN)

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**Background/Aims:** To date, there is no prospective study that specifically investigated the efficacy of infliximab in intestinal Behçet's disease (BD). This study evaluated the efficacy of infliximab in patients with moderate-to-severe active intestinal BD that are refractory to conventional therapies.

**Methods:** This phase 3, interventional, open-label, single-arm study evaluated clinical outcomes of infliximab treatment in patients with moderate-to-severe intestinal BD. The coprimary endpoints were clinical response, decrease in disease activity index for intestinal BD (DAIBD) score  $\geq 20$  from weeks 0 to 8 for the induction therapy and week 32 for the maintenance therapy.

**Results:** A total of 33 patients entered the induction therapy and were treated with infliximab 5 mg/kg intravenously at weeks 0, 2, and 6. The mean DAIBD score changed from  $90.8 \pm 40.1$  at week 0 to  $40.3 \pm 36.4$  at week 8, with a significant mean change of  $50.5 \pm 36.4$  (95% confidence interval, 37.5 to 63.4;  $p < 0.001$ ). Thirty-one (93.9%) continued to receive 5 mg/kg infliximab every 8 weeks during the maintenance therapy. The mean change in the DAIBD score after the maintenance therapy was statistically significant ( $61.5 \pm 38.5$ ; 95% confidence interval, 46.0 to 77.1;  $p < 0.001$ , from weeks 0 to 32). The proportion of patients who maintained a clinical response was 92.3% at week 32. No severe adverse reactions occurred during the induction and maintenance therapies.

**Conclusions:** This study provided evidence that infliximab 5 mg/kg induction and maintenance therapies are efficacious and well-tolerated in patients with moderate-to-severe active intestinal BD. (ClinicalTrials.gov identifier: NCT02505568) (*Gut Liver* 2023;17:777-785)

**Key Words:** Infliximab; Tumor necrosis factor-alpha; Behçet syndrome; Intestinal diseases; Clinical efficacy

## INTRODUCTION

Behçet's disease (BD) is a rare, chronically recurring multisystemic vasculitis disorder including recurrent oral or genital ulcers, ocular lesions, skin manifestations, vascular lesions, and intestinal ulcers. Intestinal BD is diagnosed

when a patient with BD has both dominant intestinal symptoms and typical intestinal ulcerative lesions on objective endoscopic examination.<sup>1</sup> Typical intestinal ulcer of intestinal BD is oval and deep with a discrete border primarily located in the ileocecal area. It causes abdominal pain, gastrointestinal hemorrhage, and bowel perforation,

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possibly leading to fatality. Moreover, intestinal BD is often refractory to conventional treatments, such as corticosteroids and immunomodulators.<sup>2</sup> Therefore, alternative therapies are urgently needed.

Reportedly, T-cell immune response is skewed toward T helper type 1 cell-dominance in intestinal BD and T helper type 1 cell-associated cytokines play a critical role in its pathogenesis.<sup>3</sup> Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) overproduction by specific T helper type 1 cell from the peripheral blood in patients with intestinal BD has been confirmed, which provides an immunological background for anti-TNF- $\alpha$  therapy as a potential strategy for intestinal BD.<sup>4,5</sup>

Several case studies have reported that TNF- $\alpha$  inhibition or blocking can induce and maintain remission in intestinal BD.<sup>6</sup> However, these studies had some limitations, such as a small sample size, retrospective design, or unspecified targets. Nonetheless, based on an open-label uncontrolled phase 3 clinical trial conducted in Japan with only 20 patients, adalimumab received regulatory approval for the treatment of intestinal BD in Japan, Korea, and Taiwan.<sup>7,8</sup> A recent large-scale prospective real-world study involving 473 patients in Japan demonstrated the long-term safety and effectiveness of adalimumab in patients with intestinal BD.<sup>9</sup> Infliximab received regulatory approval for treatment of intestinal BD in Japan based on the phase 3 study of Japanese patients with three types of BD, which had no hypothesis and included 11 patients with intestinal BD.<sup>10</sup> However, the efficacy and safety of infliximab in intestinal BD have not yet been demonstrated via a well-designed prospective study with larger sample size. Therefore, there is still the need for more evidence that infliximab is an effective and safe therapy for moderate-to-severe active intestinal BD, particularly refractory to con-

ventional therapies. Inhibiting TNF- $\alpha$  and related inflammatory pathways through infliximab constitutes a novel mechanism of action with substantial scientific rationale supported by recent clinical data, which could be a promising therapeutic approach for intestinal BD.

Here, we conducted a phase 3 study to evaluate the clinical outcomes of infliximab (Centocor BV, Leiden, Netherlands) therapy in patients with moderate-to-severe active intestinal BD refractory to conventional therapies.

## MATERIALS AND METHODS

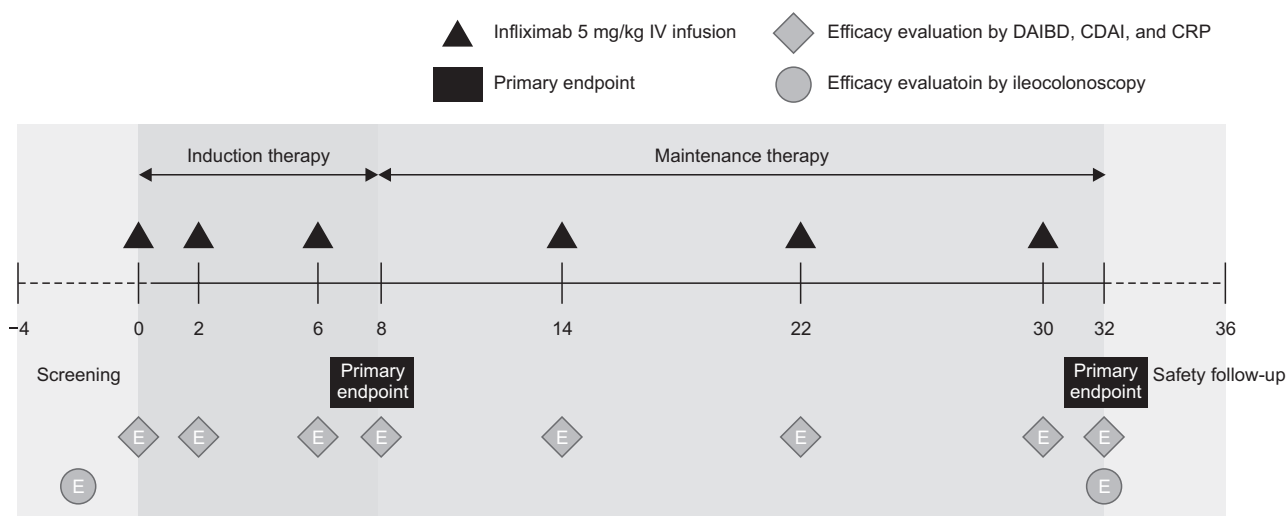
### 1. Ethical considerations

The study protocol was approved by institutional review boards of all participating institutions including Severance Hospital (approval number: 4-2015-0341) and was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov identifier: NCT02505568). Written patient consent form was obtained from all patients or their legal representatives. The study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration in 1975 (revised in 2000) and Good Clinical Practice.

### 2. Study design

This was an interventional, prospective, open-label, single-arm study conducted at nine medical centers in Korea from August 17, 2017, to July 13, 2018. All authors had access to the study data and reviewed and approved the final manuscript.

Patients were screened for eligibility 4 weeks prior to enrollment. Thirty-three eligible patients underwent 8



**Fig. 1.** Study diagram.

IV, intravenous; DAIBD, disease activity index for intestinal Behçet's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein.

weeks of induction therapy and 24 weeks of maintenance therapy, and safety evaluation 6 weeks after receiving the last dose of infliximab. For the induction therapy, patients were evaluated at weeks 0, 2, 6, and 8, and for maintenance therapy, at weeks 14, 22, 30, and 32. At each visit, disease activity index for intestinal BD (DAIBD), Crohn's Disease Activity Index (CDAI) scores, C-reactive protein (CRP) levels, adverse events (AEs), and other clinical laboratory assessments were obtained. Ileocolonoscopy images were obtained during the screening phase or within 3 months prior to week 0 and at week 32 (Fig. 1). Patients recorded a diary card for 7 days prior to their study visits for the evaluation of DAIBD and CDAI.

The coprimary efficacy objectives were the clinical response, defined as 20 or more decrease in mean DAIBD score from baseline to week 8 (induction therapy) and week 32 (maintenance therapy), respectively. The secondary objectives were set as follows: changes in disease activity; changes in CRP levels; mucosal healing based on ileocolonoscopy; safety. Additional *post hoc* analysis was performed to evaluate changes in extraintestinal manifestations (EIMs).

### 3. Patients

Inclusion criteria were as follows: (1) age between 19 and 75 years; (2) moderate-to-severe active intestinal BD with a DAIBD score of  $\geq 40$ , and endoscopic evidence of active intestinal BD within 3 months prior to week 0; (3) either definite (typical intestinal ulcer with systematic BD) or probable type of intestinal BD (typical intestinal ulcer with oral ulcer only); or (4) failure of conventional therapies using oral corticosteroids or immunomodulators.<sup>11</sup>

Patients were excluded if they (1) had an abscess, draining stoma, or ostomy, (2) had complications of intestinal BD anticipated to undergo surgery, or (3) received any type of bowel resections within 6 months or any other intra-abdominal surgeries within 3 months before week 0. Additional exclusion criteria included patients who were previously treated with TNF- $\alpha$  targeting or non-autologous stem cell therapies, or biologic agents depleting B or T cells. Further details of inclusion/exclusion and withdrawal criteria are described in the Supplementary Material.

### 4. Treatment regimen

Patients received 5 mg/kg infliximab infusion at weeks 0, 2, and 6 as the induction therapy and weeks 14, 22, and 30 as the maintenance therapy. Concomitant medications as oral 5-aminosalicylic acids or conventional immunomodulators (i.e., azathioprine, 6-mercaptopurine, or methotrexate) administered at week 0 had to be maintained with a stable dose throughout the study period. Oral corticoste-

roids at week 0 were maintained with a stable dose during induction therapy. However, if clinical response was observed during the maintenance therapy, these agents were tapered and discontinued. Initiation of any concomitant therapy for intestinal BD was not allowed throughout the study, except premedications for management of infusion reactions.

### 5. Assessments/measurements

The DAIBD consists of eight different intestinal BD-related variables: fever, abdominal mass, abdominal tenderness, intestinal complications, EIMs, general well-being, abdominal pain, and the total number of liquid stools.<sup>12</sup> Clinical response was defined as a decrease of 20 points or more in the mean DAIBD score from week 0. Clinical remission was defined as a DAIBD score of  $\leq 19$ .<sup>13</sup> The CDAI consists of eight different Crohn's disease-related variables: EIMs, abdominal mass, weight, hematocrit, use of anti-diarrhea drug(s) and/or opiates, the total number of liquid stools, abdominal pain/cramping, and general well-being.<sup>14</sup> CDAI-70 responder was defined as patients with a reduction of  $\geq 70$  points in the CDAI score from week 0. Mucosal healing was assessed using ileocolonoscopy by measuring the longest diameter of the largest open ulcer of the ileum and/or colon. Mucosal healing was evaluated by the central review committee with still images captured from the ileocolonoscopy video, and improvement according to ulcer size was classified into four grades: mucosal healing (grade 0), marked improvement (reduction to  $\leq 1/4$ , grade 1), improvement (reduction to  $\leq 1/2$  and  $>1/4$ , grade 2), and no change or worse (reduction less than  $1/2$  or expansion, grade 3).<sup>7</sup>

Safety was evaluated by monitoring AEs including infusion reactions, infections, tuberculosis assessment, concomitant medications, and abnormalities determined using clinical laboratory tests, vital signs, physical examinations, or electrocardiogram. The relatedness of AEs with infliximab was assessed by the investigators.

### 6. Statistical analyses

Two analyses were planned with the modified intention-to-treat using a fixed sequence to control multiplicity for each therapy phase (Fig. 2). With a sample size of approximately 31 patients and using a two-sided, one-sample t-test for both timepoints with an alpha level of 0.05, the power was more than 99%.

Missing data were imputed with the last observation carried forward for the post-week 0 DAIBD, CDAI, or CRP values. Efficacy analyses were performed using the modified intention-to-treat of each therapy. Safety analyses included all patients receiving at least one administration

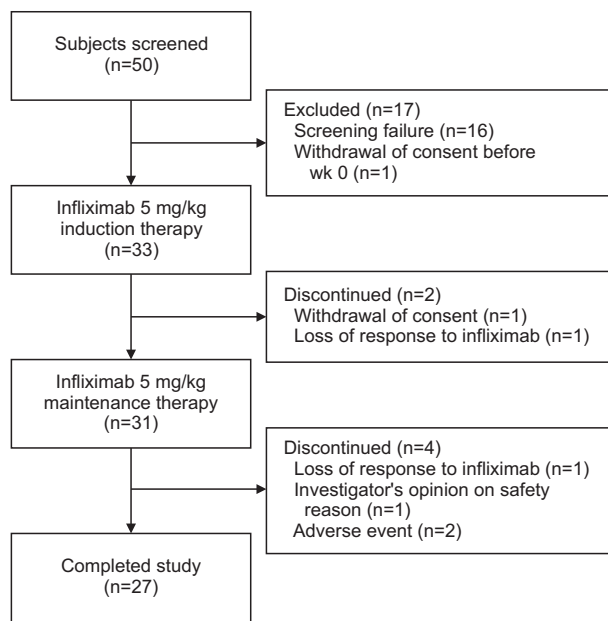


Fig. 2. Patient flowchart.

for induction therapy and maintenance therapy each. Continuous and dichotomous variables are summarized with descriptive statistics.

Two one-sample t-tests were performed for the coprimary endpoints. For exploratory purposes, *post hoc* statistical testing for differences in CDAI, CRP, and the proportion of EIMs between weeks 0 to 8 and 32 was performed using paired t-test or Wilcoxon signed-rank test for continuous variables and McNemar test for categorical variables, as appropriate. Analyses were performed using the statistical software package SAS 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### 1. Patients

Of the 50 patients screened, 33 patients were enrolled for the induction therapy, 31 (93.9%) continued to receive maintenance therapy regardless of the response to the induction therapy, and 27 completed the study (Fig. 2). Of the 31 patients who received the infliximab maintenance therapy, five patients who did not respond to the induction therapy were excluded from the maintenance therapy analysis. Thus, 26 patients who responded to the infliximab induction therapy were included in the maintenance therapy analysis. The demographics and characteristics of the patients at week 0 of each therapy are listed in Table 1.

At the screening, all 33 patients were found to have typical ulcers located in their terminal ileum/ileocecal valves

Table 1. Patient Demographics and Clinical Characteristics

Characteristics	Induction therapy (n=33)	Maintenance therapy (n=26)
Age, yr	50.8±12.3	52.2±12.7
Male sex	18 (54.5)	16 (61.5)
Body mass index, kg/m <sup>2</sup> *	22.5±3.3	22.3±3.6
Disease duration, yr	5.4±4.8	6.7±5.5
Ulcer of intestinal BD		
Typical ulcers	33 (100)	26 (100)
Atypical ulcers	0	0
Type of intestinal BD		
Definite	26 (78.8)	19 (73.1)
Probable	7 (21.2)	7 (26.9)
Pre-study therapy related to intestinal BD <sup>†</sup>		
Immunomodulators <sup>‡</sup>	29 (87.9)	24 (92.3)
5-ASA	29 (87.9)	22 (84.6)
Corticosteroids	22 (66.7)	18 (69.2)
Concomitant medication		
Immunomodulators+5-ASA	14 (42.4)	10 (38.5)
5-ASA	9 (27.3)	8 (30.8)
Immunomodulators	3 (9.1)	3 (11.5)
5-ASA+corticosteroids	3 (9.1)	2 (7.7)
Immunomodulators+corticosteroids	2 (6.1)	2 (7.7)
Immunomodulators+5-ASA+corticosteroids	2 (6.1)	1 (3.8)
Immunomodulators+5-ASA	14 (42.4)	10 (38.5)
DAIBD	90.8±40.1	94.2±37.8
CDAI	244.8±96.2	250.3±97.3
C-reactive protein, mg/L	20.1±36.1	20.7±40.4
Ulcer location		
Terminal ileum or ileocecal valve	33 (100)	26 (100)
Cecum	3 (9.1)	3 (11.5)
Ascending colon	2 (6.1)	2 (7.7)
Transverse colon	1 (3.0)	1 (3.8)
Left-sided colon or rectum	0	0
Diameter of the largest open ulcer, cm	3.3±1.9	3.0±1.8

Data are presented as mean±SD or number (%). The disease duration, DAIBD, CDAI, and C-reactive protein are reported as the values at week 0; others values are from the screening.

BD, Behçet's disease; 5-ASA, 5-aminosalicylic acid; DAIBD, disease activity index for intestinal BD; CDAI, Crohn's Disease Activity Index.

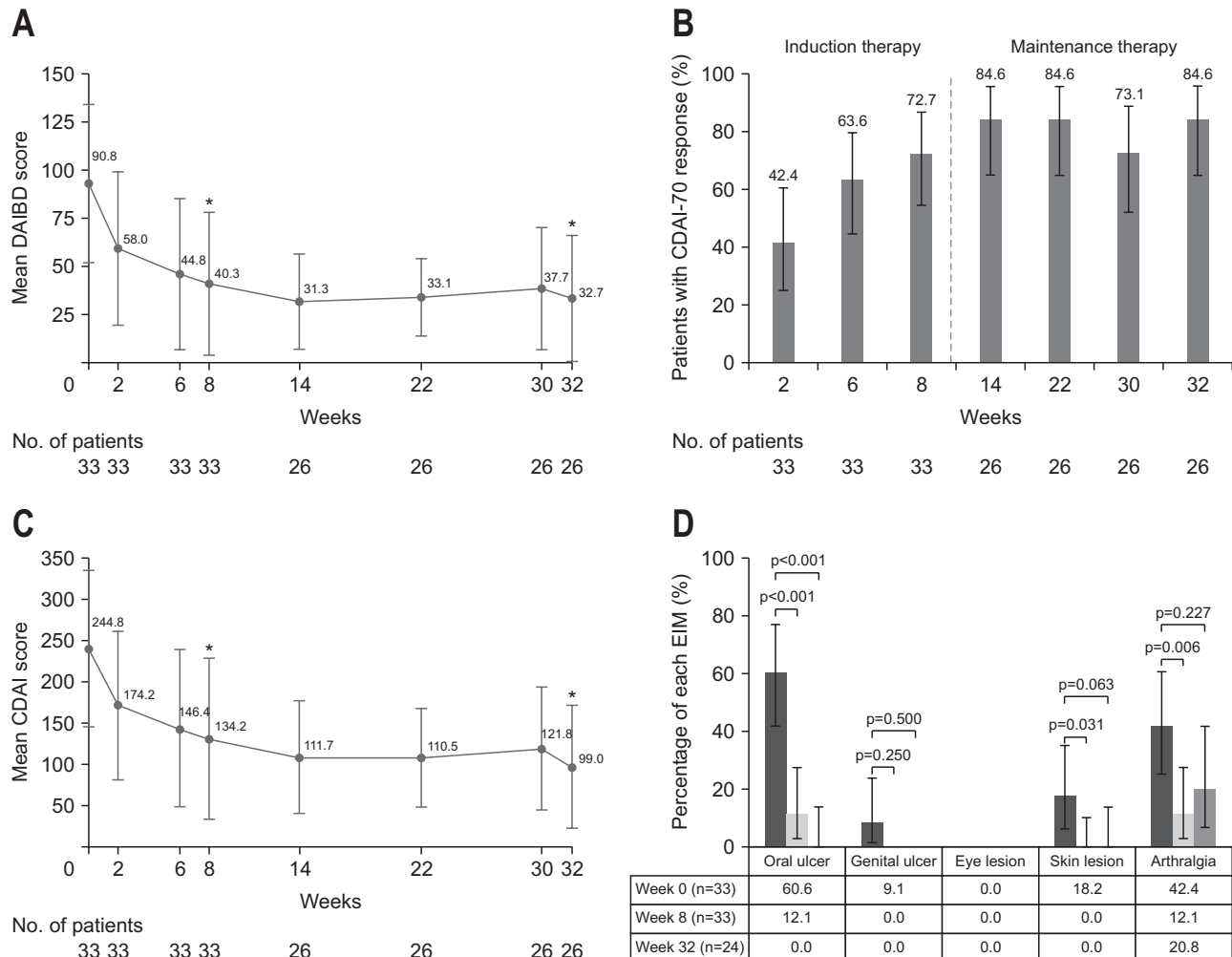
\*Body mass index was based on the height at screening and weight at week 0; <sup>†</sup>Pre-study therapies for intestinal BD were therapies that were administered up to 3 months before the first dose of infliximab; <sup>‡</sup>Immunomodulators include azathioprine, 6-mercaptopurine or methotrexate.

that were relatively large, with the mean diameter of the largest ulcer being 3.3±1.9 cm. The mean CDAI value was 244.8±96.2, and the mean CRP level was 20.1±36.1 mg/L, showing moderate-to-severe clinical symptoms and a high level of inflammation. The most common primary EIM was the oral ulcer, reflecting the general feature of BD.<sup>15</sup>

## 2. Efficacy

The mean decrease in the DAIBD score of the induction therapy was more than 20, from 90.8±40.1 (week 0) to 40.3±36.4 (week 8), with a statistically significant mean change of 50.5±36.4 (95% confidence interval, 37.5 to 63.4;  $p<0.001$ ) (Table 1, Fig. 3A). The proportion of patients with clinical response was 75.8% and 78.8%, and the proportion of patients with clinical remission was 15.2% and 30.3% at weeks 2 and 8, respectively. At week 8, the percentage of CDAI-70 responders was 72.7% (Fig. 3B) and the mean change in the CDAI score from week 0 was 110.7±87.9 ( $p<0.001$ ) (Fig. 3C). The mean change in the CRP concentration was 15.7±34.3 mg/L. The percentage of patients with at least one EIM was 81.8% at week 0, which decreased to 24.2% at week 8. The most common EIM, oral ulcer, found in 60.6% of the patients at week 0, decreased to 12.1% at week 8 (Fig. 3D).

Maintenance therapy demonstrated a sustained clinical response in 26 patients who responded to the induction therapy. The mean DAIBD score changed from 94.2±37.8 (week 0) to 32.7±32.1 (week 32) with a statistically significant mean change of 61.5±38.5 (95% confidence interval, 46.0 to 77.1;  $p<0.001$ ) (Table 1, Fig. 3A). The proportion of patients with clinical response was 92.3% at both weeks 14 and 32, and that of patients with clinical remission was 30.8% and 38.5% at weeks 14 and 32, respectively. The mean time to achieve the first clinical remission was 65.4±62.2 days after the first infliximab administration. At week 32, the percentage of CDAI-70 responders was 84.6% (Fig. 3B), the mean change in CDAI score from week 0 was 151.3±83.3 ( $p<0.001$ ) (Fig. 3C), and the mean change in CRP concentration was 16.1±35.7 mg/L ( $p<0.001$ ). The percentage of patients with at least one EIM decreased to 20.8% at week 32, during which all EIMs disappeared, ex-



**Fig. 3.** Changes in the mean DAIBD and CDAI scores and EIMs. (A) DAIBD score (mean±SD) after visits. (B) Percentage (95% confidence interval) with a CDAI-70 response after the visit. (C) Changes in the mean CDAI score after the visits. (D) Changes in EIMs.

DAIBD, disease activity index for intestinal Behçet's disease; CDAI, Crohn's Disease Activity Index; EIMs, extraintestinal manifestations. \*Statistical testing was performed at weeks 8 and 32. Both are  $p<0.001$ .

cept arthralgia (Fig. 3D).

Regarding the mucosal healing of the 24 patients with ileocolonoscopy results in the maintenance therapy, the mean diameters of the largest open ulcer at weeks 0 and 32 were  $3.0 \pm 1.8$  cm and  $0.9 \pm 1.0$  cm, respectively, in the terminal ileum/ileocecocol valve (Table 1). The mean reduction ratio of open ulcers from weeks 0 to 32 was  $0.7 \pm 0.4$ . According to the predefined mucosal healing grades, 37.5% of the 24 patients achieved mucosal healing (Fig. 4A). Representative endoscopic images of the terminal ileum/ileocecocol valve of a patient who achieved mucosal healing are presented in Fig. 4B.

### 3. Safety

Overall, infliximab therapy was generally well-tolerated without any new safety issues (Table 2). Treatment-related AEs were reported in 45.5% and 45.2% of patients during the induction and maintenance therapies, respectively. There were no serious AEs related to infliximab observed during both induction and maintenance therapies. Two patients experienced infusion reactions, such as pruritus, rash, paresthesia, and dyspnea. Six patients had infections including nasopharyngitis, anal abscess, and cystitis, which were not considered related to infliximab. Two patients withdrew from the study due to AEs as follows: pruritus as an infusion reaction and detection of breast cancer. The latter was assessed to have an improbable association with infliximab therapy.

## DISCUSSION

In this study, we showed that infliximab considerably reduced DAIBD and CDAI scores in patients with moderate-to-severe active intestinal BD refractory to conven-

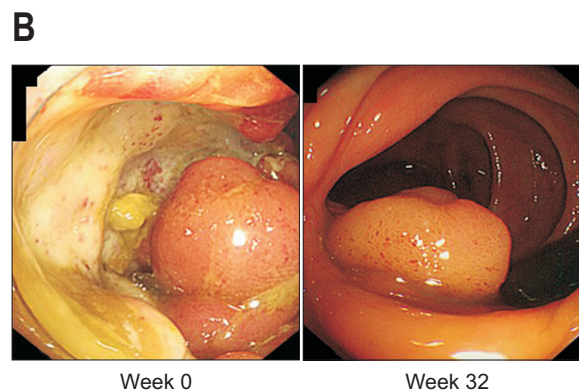
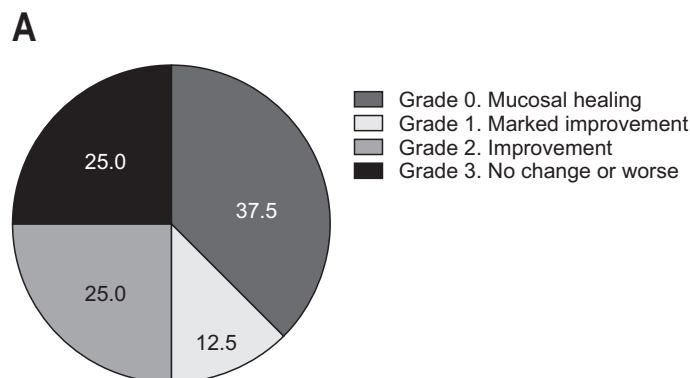
tional therapies. Intestinal BD is frequently associated with severe symptoms, such as abdominal pain, perforation, and bleeding.<sup>16</sup> A considerable number of patients fail to

**Table 2.** Adverse Events

Adverse events	Induction therapy (n=33)	Maintenance therapy (n=31)
Treatment-emergent adverse events*	15 (45.5)	14 (45.2)
Adverse events considered related to infliximab	1 (3.0)	5 (16.1)
Treatment-emergent serious adverse events	2 (6.1)	4 (12.9)
Abdominal pain	1 (3.0)	3 (9.7)
Asthenia	1 (3.0)	0
Angina pectoris	0	1 (3.2)
Breast cancer	0	1 (3.2)
Serious adverse events considered related to infliximab	0	0
Adverse events leading to early discontinuation	0	2 (6.5)
Infusion reactions	0	2 (6.5)
Pruritus	0	1 (3.2)
Rash	0	1 (3.2)
Paresthesia	0	1 (3.2)
Dyspnea	0	1 (3.2)
Infections	3 (9.1)	6 (19.4)
Onychomycosis	1 (3.0)	0
<i>Clostridium difficile</i> infection	1 (3.0)	0
Nasopharyngitis	1 (3.0)	4 (12.9)
Anal abscess	0	1 (3.2)
Cystitis	0	1 (3.2)

Data are presented as number (%).

\*A treatment-emergent adverse event was defined as any event that was not present prior to the initiation of infliximab or any already-present event that worsened in either intensity or frequency following exposure to infliximab, regardless of its relationship to infliximab.



**Fig. 4.** Grade of endoscopic improvement and representative endoscopic images with mucosal healing. (A) Proportion of patients with endoscopic improvement at week 32. Twenty-four patients with ileocolonoscopy results obtained both in the screening phase and at week 32 were included for the mucosal healing evaluation. (B) Representative ileocolonoscopy still images of the terminal ileum/ileocecocol valve of a patient who achieved mucosal healing during the study. At week 0, the diameter of the largest open ulcer was 2.0 cm. At week 32, no ulcer was observed.

respond to conventional treatments, such as corticosteroids and/or immunomodulatory agents, including thiopurines and methotrexate. Currently, no treatment is recognized as the standard of care for such patients because the acquisition of robust data on therapeutic options has been limited by the rarity of the disease and lack of well-designed studies. However, mounting evidence shows that anti-TNF- $\alpha$  therapy may be efficacious in intestinal BD.<sup>6</sup> In a retrospective study of 28 Korean patients with moderate-to-severe active intestinal BD, infliximab demonstrated a rapid clinical response, which was maintained until 54 weeks.<sup>13</sup> Additionally, the first phase 3 study of infliximab in 11 Japanese patients with intestinal BD (a total of 18 patients with BD) showed complete response without clinical symptoms.<sup>10</sup> The above findings suggested that infliximab is a potent treatment option for intestinal BD and merited additional study.

Here, significant symptomatic improvement was observed as early as week 2, the first evaluation after the first infusion of infliximab (Fig. 3A and C). The induction therapy demonstrated a significant mean decrease of 50.5 in the DAIBD score, with 78.8% of patients exhibiting clinical response and 30.3% exhibiting clinical remission. These significant clinical improvements were maintained during additional 24 weeks of maintenance therapy, with a mean decrease of 61.5 in the DAIBD score, 92.3% of patients showing a clinical response, and 38.5% of patients showing clinical remission. Moreover, this rapid and sustained improvement was also observed in terms of CDAI and CRP throughout the study. The considerable reduction of CRP level, as a biomarker for inflammation level and disease prognosis for intestinal BD, was comparable with previous findings from studies with TNF- $\alpha$  inhibitors including infliximab in patients with intestinal BD.<sup>7,17-20</sup>

EIMs occur frequently in patients with inflammatory bowel disease over the course of the disease, with a major impact on the quality of life, the incidence of morbidities, and disability.<sup>21,22</sup> Previous studies reported that these EIMs are mostly responsive to anti-TNF- $\alpha$  agents.<sup>23</sup> As a multisystemic disease, intestinal BD is associated with various EIMs similar to inflammatory bowel disease; however, related studies are very limited. In our study, the number of EIMs per patient and the proportion of patients with EIMs were reduced significantly following induction therapy and the response was well maintained via the maintenance therapy. The most common EIM among patients with intestinal BD was oral ulcer at week 0, and no patients reported oral ulcer after 32 weeks of infliximab treatment. Our study showed that infliximab therapy improved EIMs significantly, suggesting that infliximab can be an effective treatment for systemic BD. This was also proven in a previ-

ous study of Japanese patients with intestinal, neurological, and vascular BD.<sup>10</sup>

Recently, mucosal healing has been widely accepted as an important treatment goal in the management of inflammatory bowel disease because it can predict a higher chance of maintaining clinical remission and a lower rate of inflammatory bowel disease-related hospitalization.<sup>24</sup> It is also suggested as an ultimate therapeutic goal in the management of intestinal BD as an independent factor predictive of long-term prognosis.<sup>25</sup> According to the ileo-colonoscopy outcomes in this study, mucosal healing was observed in 37.5% of patients following the 32-week infliximab treatment, suggesting that infliximab can induce mucosal healing, leading to a favorable long-term prognosis in patients with intestinal BD.

Infliximab was well-tolerated in the present study and exhibited a safety profile similar to that established in other approved indications, including Crohn's disease and ulcerative colitis.<sup>26</sup>

The limitations of this study include small sample size and single-arm design. However, considering the rare prevalence of intestinal BD, conducting of a large-scale study with a control arm is technically not feasible. Moreover, it is considered unethical to have a control arm in the absence of standard treatment for patients with moderate-to-severe intestinal BD who failed oral corticosteroids or immunomodulators. Second, although DAIBD is currently the only validated index for clinical disease activity and response evaluation following medical therapy in intestinal BD,<sup>12</sup> the optimal index remains undetermined. To complement, we evaluated CDAI as a secondary outcome and found that CDAI was well correlated with DAIBD.

In summary, infliximab was generally well-tolerated and efficacious in moderate-to-severe active intestinal BD in Korean patients who showed an inadequate response to prior treatments with at least one oral corticosteroid, azathioprine, 6-mercaptopurine, or methotrexate. Infliximab treatment demonstrated a fast and robust improvement in clinical response based on the DAIBD score, CDAI score, and CRP levels as early as 2 weeks following the first infusion. The rapid clinical response was well maintained throughout the 32 weeks of study. Moreover, infliximab showed clinical improvement in EIMs, and mucosal healing through endoscopic outcomes. Such consistent and definitive evidence demonstrates that both infliximab induction and maintenance therapies are effective in moderate-to-severe active intestinal BD.

## CONFLICTS OF INTEREST

This work was supported by Janssen Korea Ltd.

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.H.C., W.H.K. Data acquisition: all authors. Data analysis and interpretation: all authors. Drafting of the manuscript: J.H.C., Y.L. Critical revision of the manuscript for important intellectual content: J.H.C., Y.L. Approval of final manuscript: all authors.

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## SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at <https://doi.org/10.5009/gnl220278>.

## REFERENCES

- Cheon JH, Kim WH. An update on the diagnosis, treatment, and prognosis of intestinal Behçet's disease. *Curr Opin Rheumatol* 2015;27:24-31.
- Park YE, Cheon JH. Updated treatment strategies for intestinal

- Behçet's disease. *Korean J Intern Med* 2018;33:1-19.
- Gül A. Behçet's disease: an update on the pathogenesis. *Clin Exp Rheumatol* 2001;19(5 Suppl 24):S6-S12.
- Kaneko S, Suzuki N, Yamashita N, et al. Characterization of T cells specific for an epitope of human 60-kD heat shock protein (HSP) in patients with Behçet's disease (BD) in Japan. *Clin Exp Immunol* 1997;108:204-212.
- Yamashita N, Kaneoka H, Kaneko S, et al. Role of gamma-delta T lymphocytes in the development of Behçet's disease. *Clin Exp Immunol* 1997;107:241-247.
- Park J, Cheon JH. Anti-tumor necrosis factor therapy in intestinal Behçet's disease. *Gut Liver* 2018;12:623-632.
- Tanida S, Inoue N, Kobayashi K, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. *Clin Gastroenterol Hepatol* 2015;13:940-948.
- Park Y, Cheon JH. Update on the treatment of Behçet's disease of the small bowel with biologic agents. *Curr Gastroenterol Rep* 2020;22:24.
- Suzuki Y, Hagiwara T, Kobayashi M, Morita K, Shimamoto T, Hibi T. Long-term safety and effectiveness of adalimumab in 462 patients with intestinal Behçet's disease: results from a large real-world observational study. *Intest Res* 2021;19:301-312.
- Hibi T, Hirohata S, Kikuchi H, et al. Infliximab therapy for intestinal, neurological, and vascular involvement in Behçet disease: efficacy, safety, and pharmacokinetics in a multicenter, prospective, open-label, single-arm phase 3 study. *Medicine (Baltimore)* 2016;95:e3863.
- Cheon JH, Kim ES, Shin SJ, et al. Development and validation of novel diagnostic criteria for intestinal Behçet's disease in Korean patients with ileocolonic ulcers. *Am J Gastroenterol* 2009;104:2492-2499.
- Cheon JH, Han DS, Park JY, et al. Development, validation, and responsiveness of a novel disease activity index for intestinal Behçet's disease. *Inflamm Bowel Dis* 2011;17:605-613.
- Lee JH, Cheon JH, Jeon SW, et al. Efficacy of infliximab in intestinal Behçet's disease: a Korean multicenter retrospective study. *Inflamm Bowel Dis* 2013;19:1833-1838.
- Best WR, Beckett JM, Singleton JW, Kern F Jr. Development of a Crohn's Disease Activity Index: National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439-444.
- Shin SJ, Lee SK, Kim TI, et al. Chronological changes in the systemic manifestations of intestinal Behçet's disease and their significance in diagnosis. *Int J Colorectal Dis* 2010;25:1371-1376.
- Jung YS, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Long-term clinical outcomes of Crohn's disease and intestinal Behçet's disease. *Inflamm Bowel Dis* 2013;19:99-105.
- Ma D, Zhang CJ, Wang RP, Wang L, Yang H. Etanercept in the treatment of intestinal Behçet's disease. *Cell Biochem Biophys* 2014;69:735-739.

18. Inoue N, Kobayashi K, Naganuma M, et al. Long-term safety and efficacy of adalimumab for intestinal Behçet's disease in the open label study following a phase 3 clinical trial. *Intest Res* 2017;15:395-401.
19. Lopalco G, Emmi G, Gentileschi S, et al. Certolizumab pegol treatment in Behçet's disease with different organ involvement: a multicenter retrospective observational study. *Mod Rheumatol* 2017;27:1031-1035.
20. Vitale A, Emmi G, Lopalco G, et al. Long-term efficacy and safety of golimumab in the treatment of multirefractory Behçet's disease. *Clin Rheumatol* 2017;36:2063-2069.
21. Juillerat P, Manz M, Sauter B, Zeitz J, Vavricka SR; Swiss IBDnet, an Official Working Group of the Swiss Society of Gastroenterology. Therapies in inflammatory bowel disease patients with extraintestinal manifestations. *Digestion* 2020;101 Suppl 1:83-97.
22. Keller R, Mazurak N, Fantasia L, et al. Quality of life in inflammatory bowel diseases: it is not all about the bowel. *Intest Res* 2021;19:45-52.
23. Greuter T, Rieder F, Kucharzik T, et al. Emerging treatment options for extraintestinal manifestations in IBD. *Gut* 2021;70:796-802.
24. Yim SM, Kim DH, Lee HJ, et al. Mucosal healing predicts the long-term prognosis of intestinal Behçet's disease. *Dig Dis Sci* 2014;59:2529-2535.
25. Park JJ, Kim WH, Cheon JH. Outcome predictors for intestinal Behçet's disease. *Yonsei Med J* 2013;54:1084-1090.
26. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis* 2015;9:806-815.