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Case Proceedings

Efficacy of Calcineurin Inhibitors for Induction of Remission in Intestinal Behçet's Disease

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Background: The efficacy of calcineurin inhibitors (CNIs) for induction of remission in intestinal Behçet's disease (intestinal BD) has not been explored.

Methods: A multicenter retrospective case series study of patients with active intestinal BD treated with CNIs (cyclosporin and tacrolimus) was conducted.

Results: Of 16 patients, 12 (75%) showed a clinical response and 5 (31.3%) achieved clinical remission after 2 weeks of CNI treatment. Similar efficacy of CNIs was observed even in 7 patients refractory to antitumor necrosis factor-alpha therapies. Endoscopic improvement was observed in 11 of 12 patients.

Conclusions: CNIs may be promising treatment options for refractory intestinal BD.

Lay Summary

Our multicenter retrospective case series study showed the short-term efficacy of calcineurin inhibitors (cyclosporin and tacrolimus) in patients with active intestinal Behçet's disease who were refractory to conventional therapies including corticosteroids and antitumor necrosis factor-alpha antibodies.

Key Words: intestinal Behçet's disease, calcineurin inhibitor, cyclosporin, tacrolimus

Introduction

Behçet's disease (BD) is a chronic, relapsing multisystemic inflammatory disorder of unknown etiology.[1] Intestinal BD is a specific subtype of BD, characterized by punched-out ulcers typically in the ileocecal region. Deep gastrointestinal ulcers in intestinal BD can cause life-threatening complications such as perforative peritonitis, abscess, and massive bleeding.[2] Intractable and penetrating ulcers of intestinal BD require urgent surgical resection, but the postoperative recurrence rate is high.[2] Nevertheless, current therapeutic options for intestinal BD are limited, especially for rapid induction of remission to avoid severe complications or the need for surgery. Although high-dose corticosteroids and antitumor necrosis factor-alpha (TNF-α) antibody agents are recommended for moderate-to-severe intestinal BD,[2,3] these therapies often fail to achieve remission. There remains an unmet need to improve the prognosis and mortality in patients with intestinal BD.

Calcineurin inhibitors (CNIs) including cyclosporin A (CsA) and tacrolimus (Tac) are strong and fast-acting immunosuppressants. Despite the positive results of CNIs in the treatment of BD uveitis,[4] their efficacy for intestinal BD remains to be elucidated.[2,3,5,6] Therefore, we aimed to evaluate the efficacy of CNIs as a novel therapy for the induction of remission in patients with intestinal BD.

Methods

Study Design

This was a multicenter retrospective case series study to investigate the short-term efficacy of CNIs for patients with active intestinal BD. Patients with intestinal BD who had received CNI treatment [continuous intravenous CsA (CsA-iv), peroral CsA (CsA-po), or peroral Tac] from April 2005 to October 2020 were searched in the databases of 3 referral centers for inflammatory bowel diseases in Japan: Keio University Hospital, Tokyo Yamate Medical Center, and Tokyo Women's Medical University Hospital. All identified patients were confirmed to meet the diagnostic criteria of intestinal BD proposed by the Japanese Ministry of Health, Labour and Welfare's research team on BD[2] and to rule out the possibility of other inflammatory bowel

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Table 1. Characteristics of 16 patients with intestinal BD treated with calcineurin inhibitors.

	Total (n = 16)	CsA-iv (n = 9)	CsA-po (n = 5)	Tac (n = 2)
Sex (male), n (%)	10 (62.5%)	7 (77.8%)	1 (20.0%)	2 (100%)
Age, y, mean ± SD	43.3 ± 14.2	36.2 ± 10.8	59.6 ± 6.6	34.0 ± 3.0
Duration of intestinal BD, y, mean ± SD	5.6 ± 5.2	7.3 ± 6.0	3.0 ± 1.8	4.0 ± 3.0
Body weight, kg, mean ± SD	45.8 ± 8.8	45.4 ± 6.6	45.4 ± 12.9	48.5 ± 1.5
Body mass index, kg m^{-2}, mean ± SD	17.6 ± 3.0	17.1 ± 1.9	17.9 ± 4.5	19.4 ± 1.5
Other BD lesions, n (%)				
Recurrent oral ulcer	15 (93.8%)	8 (88.9%)	5 (100%)	2 (100%)
Ocular lesion	1 (6.3%)	1 (11.1%)	0 (0%)	0 (0%)
Skin lesion	14 (87.5%)	8 (88.9%)	4 (80.0%)	2 (100%)
Recurrent genital ulcer	6 (37.5%)	3 (33.3%)	2 (40.0%)	1 (50.0%)
Arthritis	10 (62.5%)	6 (66.7%)	3 (60.0%)	1 (50.0%)
Vascular lesion	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neurological lesion	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Past medications, n (%)				
5-Aminosalicylates	13 (81.3%)	7 (77.8%)	5 (100%)	1 (50.0%)
Prednisolone	13 (81.3%)	8 (88.9%)	3 (60.0%)	2 (100%)
Anti-TNF-α antibodies	8 (50.0%)	6 (66.7%)	1 (20.0%)	1 (50.0%)
Infliximab/adalimumab/both	5/2/1	4/2/0	1/0/0	0/0/1
Colchicine	7 (43.8%)	6 (66.7%)	0 (0%)	1 (50.0%)
Thiopurines	7 (43.8%)	4 (44.4%)	2 (40.0%)	1 (50.0%)
Methotrexate	1 (6.3%)	0 (0%)	0 (0%)	1 (50.0%)
Thalidomide	1 (6.3%)	1 (11.1%)	0 (0%)	0 (0%)
History of ileocecal resection, n (%)	4 (25.0%)	3 (33.3%)	0 (0%)	1 (50.0%)
Concomitant medications, n (%)				
5-Aminosalicylates	12 (75.0%)	9 (100%)	2 (40.0%)	1 (50.0%)
Prednisolone	11 (68.8%)	8 (88.9%)	1 (20.0%)	2 (100%)
Anti-TNF-α antibodies	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Colchicine	2 (12.5%)	2 (22.2%)	0 (0%)	0 (0%)
Thiopurines	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Methotrexate	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalidomide	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DAIBD score, mean ± SD	88.8 ± 39.5	88.9 ± 42.3	88.0 ± 41.5	90.0 ± 10.0
Blood tests				
Total protein, g dL^{-1}, mean ± SD	6.5 ± 0.8	6.6 ± 0.7	6.6 ± 0.8	5.5 ± 0.5
Albumin, g dL^{-1}, mean ± SD	3.2 ± 0.5	3.3 ± 0.4	3.3 ± 0.6	2.5 ± 0.1
WBC, $\times 10^3$ μL^{-1}, mean ± SD	8.6 ± 3.1	9.5 ± 3.5	8.6 ± 1.6	4.7 ± 0.7
Hemoglobin, g dL^{-1}, mean ± SD	11.6 ± 1.4	11.9 ± 0.9	11.5 ± 1.5	10.3 ± 2.2
Platelets, $\times 10^4$ μL^{-1}, mean ± SD	32.8 ± 13.1	34.3 ± 14.7	34.3 ± 9.4	22.0 ± 6.0
CRP, mg dL^{-1}, median (min–max)	1.1 (0.1–12.0)	1.1 (0.1–8.6)	0.9 (0.8–12.0)	5.0 (1.0–9.0)
Location of ulcers, n (%)				
Ileum	2 (12.5%)	1 (11.1%)	1 (20.0%)	0 (0%)
Ileocecum	11 (68.8%)	6 (66.7%)	5 (100%)	0 (0%)
Colon and rectum	9 (56.3%)	6 (66.7%)	2 (40.0%)	1 (50.0%)
Ileocecal anastomosis site	4 (25.0%)	2 (22.2%)	1 (20.0%)	1 (50.0%)
Depth of main ulcer, n (%)				
Shallow	1 (6.3%)	0 (0%)	1 (20.0%)	0 (0%)
Deep	15 (93.8%)	9 (100%)	4 (80.0%)	2 (100%)
Morphology of main ulcer, n (%)				
Oval	1 (6.3%)	0 (0%)	1 (20.0%)	0 (0%)
Geographic	9 (56.3%)	6 (66.7%)	2 (40.0%)	1 (50.0%)
Volcano	6 (37.5%)	3 (33.3%)	2 (40.0%)	1 (50.0%)

Table 1. Continued

	Total (n = 16)	CsA-iv (n = 9)	CsA-po (n = 5)	Tac (n = 2)
Size of main ulcer, n (%)				
<2 cm	3 (18.8%)	1 (11.1%)	2 (40.0%)	0 (0%)
≥2 cm	13 (81.3%)	8 (88.9%)	3 (60.0%)	2 (100%)
Number of ulcers, n (%)				
1	7 (43.8%)	3 (33.3%)	3 (60.0%)	1 (50.0%)
2–4	2 (12.5%)	2 (22.2%)	0 (0%)	0 (0%)
≥5	7 (43.8%)	4 (44.4%)	2 (40.0%)	1 (50.0%)
Dose of CNI, mg kg^{-1} day^{-1}, mean ± SD		3.1 ± 0.8	4.4 ± 1.1	0.14 ± 0.08
Serum trough level of CNI, ng mL^{-1}, mean ± SD		600 ± 139	145 ± 35	13.2 ± 1.3

Abbreviations: BD, Behçet's disease; CNI, calcineurin inhibitor; CRP, C-reactive protein; CsA-iv, intravenous cyclosporin; CsA-po, peroral cyclosporin; DAIBD, disease activity index for intestinal BD; Tac, peroral tacrolimus; TNF, tumor necrosis factor; WBC, white blood cells.

diseases such as Crohn's disease, ulcerative colitis, intestinal tuberculosis, cytomegalovirus enteritis, drug-induced enteritis, malignancy, and myelodysplastic syndrome-related enteritis. We reviewed the medical records of patients and collected the data of their demographics, characteristics, medical history, types of CNIs, serum concentration of CNIs, concomitant drugs, clinical symptoms, hematological examinations results, endoscopic findings before and after 2 weeks of CNI treatment, and adverse events during CNI treatment.

Assessment of Efficacy and Safety of CNI Treatment

To assess the clinical activity of intestinal BD, we used a validated clinical index, the disease activity index for intestinal BD (DAIBD).[7] The DAIBD scores were calculated from 8 variables (general well-being, fever, extraintestinal manifestations, abdominal pain, abdominal mass, abdominal tenderness, intestinal complications, and number of liquid stools) and patients with DAIBD scores <19, 20–39, 40–74, and ≥75 were considered to have remission, mild, moderate, and severe disease activities, respectively. Clinical response was defined as a decrease in DAIBD score by 20 points or more from baseline, or a DAIBD score of 19 points or less. Clinical remission was defined as a DAIBD score of 19 points or less. Endoscopic improvement was defined as a decrease in the size or depth of the main ulcers after 2 weeks of CNI treatment compared with just before CNI treatment. The findings of endoscopy performed more than 2 weeks after the end of 2-week CNI treatment were excluded from the assessment. Adverse events were determined from the abnormalities identified in the chart review. Mild adverse events were defined as temporary and acceptable symptoms or laboratory changes, and serious adverse events were defined as severe impairments that made it difficult to continue administration of CNIs.

Study Endpoints

The primary endpoint of this study was the clinical response at 2 weeks after CNI administration. Secondary endpoints were clinical remission at 2 weeks after CNI administration, changes in DAIBD scores and serum C-reactive protein (CRP) levels between baseline and 2 weeks after CNI administration, and adverse events related to CNI treatment. For subgroup analyses, clinical response rate in patients who had been refractory to anti-TNF-α antibody therapy, changes in dose of corticosteroids in patients treated with corticosteroids during CNI treatment, and changes in endoscopic findings in patients who underwent endoscopic examinations before and after CNI treatment were evaluated. To determine which factors were associated with response to CNI treatment, univariate analyses comparing CNI responders with nonresponders were performed.

Statistical Analysis

Descriptive statistics were calculated as percentages for categorical variables, and as the mean with SD or the median with interquartile range (IQR) for continuous variables, as appropriate. Comparative analyses were performed using paired t-test or Wilcoxon signed rank test, and univariate analyses were performed using Fisher's exact test for categorical variables and unpaired t-test or Mann–Whitney U-test for continuous variables, as appropriate. The missing data were omitted, and the rest of the data were analyzed. All tests were performed with a 2-sided significance level of 5%.

Ethical Considerations

This study complied with the Declaration of Helsinki (revised in 2013) and the Guidelines for Medical Research Involving Human Subjects (Japanese Ministry of Health, Labour and Welfare). The protocol of this study (IRB number 20200250) was reviewed and approved by the institutional review board of each participating center. All data were collected anonymously.

Results

Sixteen patients with intestinal BD treated with CNIs were identified (Table 1). All patients were refractory to conventional therapies and 4 patients had undergone ileocecal resection. At baseline, 15 (93.8%) patients had moderate-to-severe disease activity and 14 (87.5%) patients had geographic- or volcanic-shaped deep intestinal ulcers. Of the 16 patients, all were hospitalized due to worsening symptom of intestinal BD, and 9, 5, and 2 patients received CsA-iv, CsA-po, and Tac for at least 2 weeks, respectively. CsA-iv treatment was applied to patients on total parenteral nutrition support. Doses of CNI were adjusted by monitoring their serum trough levels in accordance with the CNI therapy for ulcerative colitis. During CNI treatment, concomitant medications including

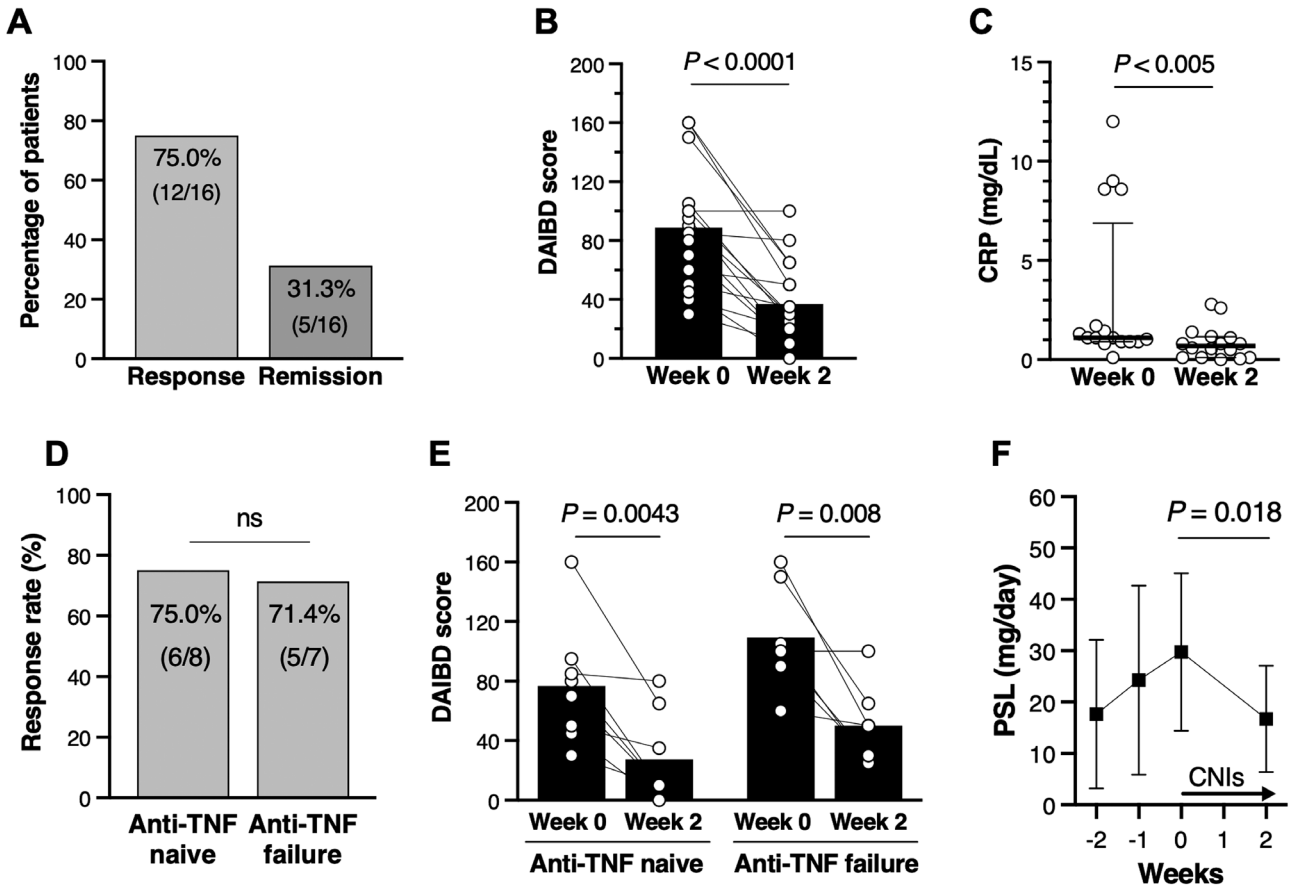

Figure 1. Clinical efficacy of 2-week CNI induction therapy in 16 patients with active intestinal BD. (A) Response and remission rates at week 2. Decrease in mean DAIBD score (B) and median serum CRP level (C) between baseline and week 2. Error bars, interquartile range. (D and E) Comparison of the response rates of CNIs between patients naive (n = 8) to and refractory (n = 7) to anti-TNF-α antibody therapy (D) and decreased mean DAIBD scores (E). (F) Mean dose of concomitant PSL before and after the start of CNI treatments. Error bars, SD. Statistical analyses were performed using paired t-test in (B), (E), and (F), Wilcoxon signed rank test in (C), and Fisher's exact test in (D). Abbreviations: BD, Behçet's disease; CNI, calcineurin inhibitor; CRP, C-reactive protein; DAIBD, disease activity index for intestinal BD; PSL, prednisolone; TNF, tumor necrosis factor.

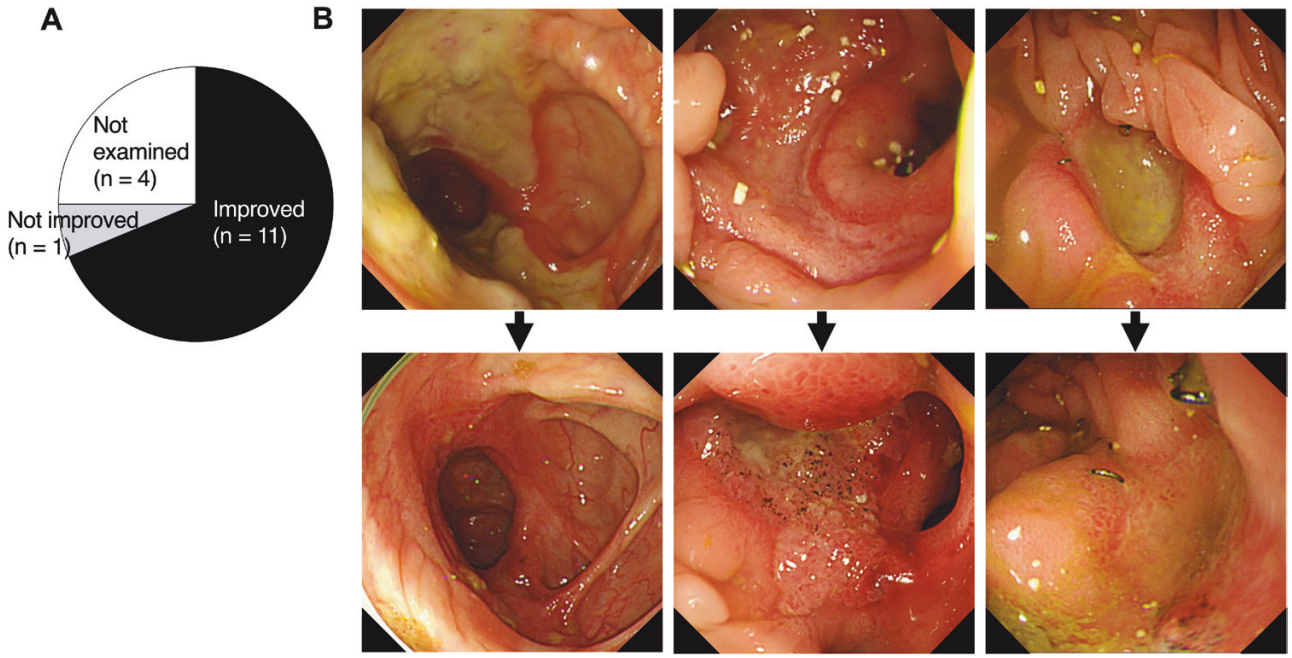

Figure 2. Endoscopic improvement of intestinal BD after CNI induction therapy. (A) Percentage of patients with improved endoscopic findings after 2 weeks of CNI treatment. (B) Three representative cases of improved intestinal ulceration (top: before CNI treatment; bottom: after CNI treatment). Abbreviations: BD, Behçet's disease; CNI, calcineurin inhibitor.

corticosteroids, 5-aminosalicylates, and colchicine were continued, but no other medications were given.

After 2 weeks of CNI treatment, 75.0% (n = 12) of patients showed a clinical response and 31.3% (n = 5) of patients achieved clinical remission (Figure 1A). The mean DAIBD score significantly decreased from 88.8 ± 39.5 to 36.9 ± 28.0 (P < .0001) (Figure 1B) and the median serum CRP decreased from 1.10 mg dL^{-1} (IQR, 0.09–6.88) to 0.70 mg dL^{-1} (IQR, 0.10–1.15) (P < .005) (Figure 1C). Notably, 71.4% of patients who had failed to respond to anti-TNF-α antibody therapy responded to CNIs (Figure 1D), with a decreased mean DAIBD score from 109.3 ± 32.1 to 50.0 ± 24.3 (P = .008) (Figure 1E) and median serum CRP from 1.10 mg dL^{-1} (IQR, 0.90–8.60) to 0.60 mg dL^{-1} (IQR, 0.10–1.17) (P = .047). These results were comparable to patients naive to anti-TNF-α antibody therapy. Of the 12 patients who underwent endoscopy at 2 weeks after CNI treatment, 11 (91.7%) patients showed an improvement in ulcer size and depth (Figure 2A and B).

Comparing the baseline characteristics of 12 CNI responders with 4 CNI nonresponders, the effectiveness of CNIs was not correlated with disease severity but was significantly correlated with previous prednisolone (PSL) use (P = .007) and tended to correlate with concomitant PSL use (P = .06) (Table 2). In 11 patients who received PSL for 2 weeks CNI treatment, the mean PSL dose was reduced from 29.7 ± 14.6 to 16.7 ± 9.8 mg day^{-1} (P = .018) (Figure 1F). In 6 patients who received unchanged PSL doses for 2 weeks prior to CNI treatment, the mean DAIBD score significantly

Table 2. Comparison of baseline characteristics of responders versus nonresponders.

	Responders (n = 12)	Nonresponders (n = 4)	P
Sex (male), n (%)[a]	8 (66.7%)	2 (50.0%)	.60
Age, y, mean ± SD[b]	39.8 ± 12.6	53.5 ± 13.9	.11
Duration of intestinal BD, y, mean ± SD[b]	6.5 ± 5.5	2.8 ± 2.4	.24
Body mass index, kg m^{-2}, mean ± SD[b]	17.1 ± 3.0	19.3 ± 2.2	.24
Age, y, mean ± SD[b]	39.8 ± 12.6	53.5 ± 13.9	.11
Past medications, n (%)[a]			
5-Aminosalicylates	9 (75.0%)	4 (100%)	.53
Prednisolone	12 (100%)	1 (25.0%)	.007
Anti-TNF-α antibodies	6 (50.0%)	2 (50.0%)	>.99
Thiopurines/methotrexate	6 (50.0%)	1 (25.0%)	.58
Colchicine	6 (50.0%)	1 (25.0%)	.58
History of ileocecal resection, n (%)[a]	3 (25.0%)	1 (25.0%)	>.99
Concomitant medications, n (%)[a]			
Prednisolone	10 (83.3%)	1 (25.0%)	.06
5-Aminosalicylates	10 (83.3%)	2 (50.0%)	.24
Colchicine	2 (16.7%)	0 (0%)	>.99
DAIBD score at baseline, mean ± SD[b]	93.8 ± 43.0	73.8 ± 19.8	.41
Blood tests at baseline[b]			
Total protein, g dL^{-1}, mean ± SD	6.3 ± 0.5	7.0 ± 1.2	.18
Albumin, g dL^{-1}, mean ± SD	3.2 ± 0.5	3.2 ± 0.5	>.99
WBC, $\times 10^3$ μL^{-1}, mean ± SD	9.1 ± 3.3	7.1 ± 1.9	.28
Hemoglobin, g dL^{-1}, mean ± SD	11.8 ± 1.3	10.9 ± 1.6	.25
Platelets, $\times 10^4$ μL^{-1}, mean ± SD	34.6 ± 14.0	27.2 ± 7.0	.36
CRP, mg dL^{-1}, median (min–max)[c]	1.2 (0.1–9.0)	1.0 (0.8–1.7)	.25
Endoscopic findings, n (%)[a]			
Extend beyond ileocecal area	8 (66.7%)	2 (50.0%)	.60
Deep ulcer	12 (100%)	3 (75.0%)	.25
Volcanic-shaped ulcer	3 (25.0%)	3 (75.0%)	.12
Size of ulcer ≥2 cm	9 (75.0%)	4 (100%)	.53
Number of ulcers ≥5	5 (41.7%)	2 (50.0%)	>.99
Type of CNI, n (%)[a]			
CsA-iv	8 (66.7%)	1 (25.0%)	.26
CsA-po	3 (25.0%)	2 (50.0%)	.55
Tac	1 (8.3%)	1 (25.0%)	.45

Abbreviations: BD, Behçet's disease; CNI, calcineurin inhibitor; CRP, C-reactive protein; CsA-iv, intravenous cyclosporin; CsA-po, peroral cyclosporin; DAIBD, disease activity index for intestinal BD; Tac, peroral tacrolimus; TNF, tumor necrosis factor; WBC, white blood cells.
[a]Fisher's exact test.
[b]Unpaired t-test.
[c]Mann–Whitney U-test.

Table 3. Adverse events of CNI treatments.

	Number of cases (%)
Mild adverse events	5[a] (31.2%)
Hyperkalemia	2 (12.5%)
Tremor	2 (12.5%)
Stomachache	1 (6.3%)
Elevated serum creatinine	1 (6.3%)
Elevated serum transaminase	1 (6.3%)
Elevated serum GGT	1 (6.3%)
Serious adverse events	0 (0%)

Abbreviations: CNI, calcineurin inhibitor; GGT, gamma-glutamyl transferase.
[a]Hyperkalemia, tremor, and elevated serum creatinine occurred in the same patient, and hyperkalemia and headache in another patient.

decreased from 70.8 ± 24.2 to 28.3 ± 36.6 (P = .012) after 2 weeks of CNI treatment.

During 2 weeks of CNI treatment, no serious adverse events were observed but 31.3% of patients experienced mild adverse events (Table 3). After 2 weeks of CNI therapy, 10 patients (5 CsA-iv, 4 CsA-po, and 1 Tac) continued to receive CNIs orally and 6 patients (4 CsA-iv, 1 CsA-po, and 1 Tac) switched to anti-TNF-α treatments. Two patients underwent surgery at 4 and 11 weeks after CNI induction therapies (1 continued oral CsA and 1 switched to anti-TNF-α).

Discussion

This is the first case series study of the efficacy of CNIs for intestinal BD and showed that CNIs are clinically, serologically, and endoscopically effective in moderate-to-severe intestinal BD. Since intestinal BD is a relatively rare disorder, evidence from large studies demonstrating the short-term efficacy of induction in remission therapies including corticosteroid and anti-TNF-α agents in patients with intestinal BD remains scarce. Park et al reported in a retrospective study of patients with moderate-to-severe intestinal BD treated with systemic corticosteroids that the complete remission rate was 46.3% and the partial remission rate was 42.6% 1 month after the first course of corticosteroids.[8] In a Korean multicenter retrospective study for patients with intestinal BD treated with infliximab, the clinical response rate was 75.0% and the clinical remission rate was 32.1% at week 2.[9] In a Japanese multicenter, open-label, uncontrolled study evaluating the efficacy of adalimumab in patients with intestinal BD refractory to corticosteroid and/or immunomodulator therapies, 40% of patients showed marked improvement and 15% achieved complete remission at 8–12 weeks.[10] When considered in comparison with these results, the short-term efficacy of CNI therapy in our study (clinical response rate of 75.0% and remission rate of 31.3% at week 2) is comparable to corticosteroid therapy and anti-TNF-α therapy.

CNIs are strong immunosuppressants that suppress interleukin-2 production in T lymphocytes by inhibiting the calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells (NF-AT).[11] Recent studies further revealed that CNIs modulate not only adaptive immunity but also innate immunity.[12] Although the etiology of BD has not been fully elucidated, dysregulation of both innate and adaptive immune responses to environmental and self-antigens are thought to be involved in the pathogenesis of BD.[13] The dual effects of CNIs on innate and adaptive immunity may explain the rapid improvement in refractory intestinal BD. In addition, the results of a univariate analysis suggested that the combination of CNIs and corticosteroids may synergize their efficacy in the treatment of intestinal BD by modulating a broader range of immunity.

A limitation of our study is that it is based on a retrospective single-arm study design with a small sample size, but our observations that CNI treatment improved the disease activity in patients with intestinal BD refractory to anti-TNF-α therapies, reduced the need for concomitant corticosteroids use, and improved the disease activity in patients receiving constant doses of corticosteroids support the efficacy of CNI itself for intestinal BD.

Conclusions

CNIs are a class of drugs that can be promising treatment options for active intestinal BD. Our results provide preliminary evidence of the efficacy of CNIs for intestinal BD via clinically relevant endpoints, which is a strong rationale for future prospective studies with a large number of subjects.

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Authors' Contributions

T. Kawaguchi planned and initiated the study, collected and analyzed the data, and drafted the manuscript. M.F. and T.O. collected the data and edited and revised the manuscript. H.K., S.S., K.N., T.S., and Y.M. designed the study and edited and revised the manuscript. T. Kanai supervised the study and edited and revised the manuscript. All authors approved the final draft.

Conflicts of Interest

None declared.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

References

1. Sakane T, Takeno M, Suzuki N, et al. Behçet's disease. *N Engl J Med*. 1999;341(17):1284–1291.
2. Watanabe K, Tanida S, Inoue N, et al. Evidence-based diagnosis and clinical practice guidelines for intestinal Behçet's disease 2020 edited by Intractable Diseases, the Health and Labour Sciences Research Grants. *J Gastroenterol*. 2020;55(7):679–700.
3. Park YE, Cheon JH. Updated treatment strategies for intestinal Behçet's disease. *Korean J Intern Med*. 2018;33(1):1–19.

4. Esatoglu SN, Hatemi G. Update on the treatment of Behçet's syndrome. *Intern Emerg Med*. 2019;14(5):661–675.
5. Matsumura K, Nakase H, Chiba T. Efficacy of oral tacrolimus on intestinal Behcet's disease. *Inflamm Bowel Dis*. 2010;16(2):188–189.
6. Bayraktar Y, Ozaslan E, Van Thiel DH. Gastrointestinal manifestations of Behcet's disease. *J Clin Gastroenterol*. 2000;30(2):144–154.
7. 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(2):605–613.
8. Park JJ, Cheon JH, Moon CM, et al. Long-term clinical outcomes after the first course of corticosteroid therapy in patients with moderate to severe intestinal Behçet's disease. *Gastroenterology*. 2010;138(Suppl_1):S698–S699.
9. 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(9):1833–1838.
10. 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.e3.
11. Park YJ, Yoo SA, Kim M, et al. The role of calcium-calcineurin-NFAT signaling pathway in health and autoimmune diseases. *Front Immunol*. 2020;11:195.
12. Bendickova K, Fric J. Roles of IL-2 in bridging adaptive and innate immunity, and as a tool for cellular immunotherapy. *J Leukoc Biol*. 2020;108(1):427–437.
13. Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: a comprehensive review. *J Autoimmun*. 2015;64:137–148.