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Original Article

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Long-Term Response Durability of Infliximab for Pediatric Inflammatory Bowel Disease in Japan: A Single Center Experience

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ABSTRACT

Purpose: The long-term efficacy and safety of infliximab (IFX) in Japanese children with inflammatory bowel disease (IBD) remain unclear. This study aimed to examine the long-term outcomes of IFX treatment in Japanese children with IBD.
Methods: We retrospectively recruited patients aged <16 years who were diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) at Kurume University Hospital in Japan between 2011 and 2022 and examined the effectiveness and safety of IFX. We characterized the responses to IFX as primary response, primary nonresponse (PNR), secondary loss of response (sLOR), or still receiving IFX.
Results: Among the 77 enrolled patients with UC (median age, 10 years) and 48 with CD (median age, 12 years), 55 (27 with UC and 28 with CD) received IFX treatment. IFX treatment was significantly more common in patients with CD (58.3%) than in those with UC (35.1%; p=0.016). The PNR was significantly greater in patients with UC (18.5%) than in those with CD (0.0%; p=0.023), as was the sLOR (UC, 51.9%; CD, 21.4%; p=0.026). The likelihood of continuing IFX treatment during follow-up (median, 38 months) was significantly higher in patients with CD (71.4%) than in those with UC (29.6%; p=0.003). Adverse events resulting in the discontinuation of IFX occurred in 3.6% of the patients; one patient with CD developed leukemia, and the other had a serious infusion reaction.
Conclusion: The long-term durability of IFX in Japanese pediatric patients with IBD was inadequate in UC compared with CD. Serious adverse events in 3.6% of patients required discontinuation.

Keywords: Inflammatory bowel disease; Pediatrics; Infliximab; Remission; Treatment outcome

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic noninfectious inflammation of the gastrointestinal tract, mainly ulcerative colitis (UC) and Crohn's disease (CD) [1,2]. Patients with both UC and CD commonly present with abdominal pain and diarrhea. Rectal

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Conflict of Interest

The authors have no financial conflicts of interest.

bleeding occurs more frequently in UC than in CD, and patients with CD often experience weight loss and perianal disease [3]. At the turn of the 21st century, IBD has become a global health problem, with increasing numbers of patients in Asia and South America as societies and diets have become more westernized [4]. In Japan, the incidence of IBD has increased tenfold over the past 20 years, affecting 220,000 and 70,000 patients with UC and CD, respectively [5].

Pediatric-onset IBD is characterized by extensive intestinal involvement and rapid progression, with a more severe course than in adults, relatively poor therapeutic responses to corticosteroids and immunosuppressive drugs, and a higher likelihood of the need for biological agents [6]. In Japan, seven biologics are currently approved for the treatment of IBD; however, only infliximab (IFX) and adalimumab (ADA) for UC and IFX for CD have been approved for pediatric use [7-9].

IFX is a chimeric immunoglobulin G-1 monoclonal antibody directed against tumor necrosis factor alpha (TNF-α) [10]. IFX is a key drug for the treatment of moderate-to-severe pediatric IBD. Hyams et al. [11,12] reported the efficacy and safety of IFX treatment in pediatric patients with IBD in North America; however, few reports have examined the long-term efficacy and safety of IFX in Japanese pediatric patients with IBD [13]. The present study aimed to clarify the long-term effectiveness and safety of IFX in pediatric patients with IBD treated at a single center in Japan.

MATERIALS AND METHODS

Design and ethical matters

This retrospective observational study was conducted at Kurume University. The study protocol complied with the ethical guidelines of the Declaration of Helsinki (2021 revision) and was approved by the Ethics Committee of Kurume University (approval no. 22113). The research content was published by the Ethics Committee of the Kurume University website, and participants were given the opportunity to refuse to participate in this study (opt-out method) because this retrospective observational study for academic research was based on their medical records.

Study subjects

We retrospectively examined the medical records of children aged <16 years who were newly diagnosed with UC or CD at Kurume University Hospital between January 2011 and December 2022 and evaluated their clinical course until December 2023. Patients who were transferred to another hospital during the study period were also included, with the follow-up period defined as the end of their last visit to our hospital. Patients who were followed up for <22 weeks after the initiation of IFX were excluded. IBD was diagnosed on the basis of the revised Porto criteria [14]. We excluded patients with IBD-unclassified or monogenic IBD. We analyzed the patient characteristics, IBD lesion location, disease activity, treatments including IFX, effectiveness and safety of IFX, duration from IFX initiation to corticosteroid-free management, and long-term outcomes. The clinical course of IFX treatment was compared between patients with UC and those with CD. Sites of IBD activity were recorded according to the Paris classification [15]. In assessing the disease activity of IBD, we used the Pediatric Ulcerative Colitis Activity Index (PUCAI) for UC and the Pediatric Crohn's Disease Activity Index (PCDAI) for CD [16,17]. In UC, remission, mild activity, and moderate to

severe activity are represented by PUCAI scores below 10 points, 10–35 points, and over 35 points, respectively [16]. In CD, remission, mild activity, and moderate to severe activity are represented by PCDAI scores below 10 points, 10–30 points, and over 30 points, respectively [17]. Responsiveness to IFX treatment was assessed as primary response, primary nonresponse (PNR), secondary loss of response (sLOR), or continuation of IFX treatment. Primary response was defined as the achievement of clinical remission (PUCAI or PCDAI <10) or sufficient improvement (PUCAI or PCDAI decrease by more than 20 points and 50% compared with before IFX treatment) at 14 weeks after initiation of IFX (week 14) without increasing the prednisolone (PSL) dose before IFX treatment. PNR was defined as failure to respond to IFX treatment by week 14; these patients did not achieve clinical remission or sufficient improvement and discontinued IFX. sLOR was defined as the discontinuation of IFX due to IBD relapse after a primary response, including the discontinuation of IFX maintenance therapy after dose escalation (dose increase or shortened interval between doses). The reasons for discontinuing IFX were categorized as PNR, sLOR, or serious adverse events (SAE). Combination treatment with IFX and thioprine was defined as receiving the combination for more than 14 weeks.

Use of IFX

Enrolled patients with UC or CD received an IFX induction regimen (5 mg/kg) at weeks 0, 2, and 6. After this regimen, patients who achieved a primary response received a maintenance regimen of IFX (5 mg/kg every 8 weeks (q8w). Patients with CD with reduced IFX effectiveness during the maintenance regimen underwent IFX dose escalation at a dose of 10 mg/kg q8w or a shorter interval of 5 mg/kg q4w. All patients receiving IFX treatment also received intravenous hydrocortisone (3–5 mg/kg/dose; maximum dose, 200 mg) as premedication before each IFX infusion.

Statistical analysis

Continuous variables are expressed as medians with minimum and maximum values, and categorical variables are expressed as percentages. Fisher's exact test and Mann–Whitney U-test were used, as appropriate. Tests were two-sided. The significance of p-value was set at $p<0.05$.

RESULTS

Study population

We enrolled 125 patients with IBD (UC, 77; CD, 48). Nine patients with unclassified IBD and two with monogenic IBD were excluded. Fifty-five patients (UC, 27; CD, 28) received IFX (**Fig. 1**). The proportion of patients treated with IFX was significantly higher in the CD group (58.3%) than in the UC group (35.1%; $p=0.016$). The characteristics of all enrolled patients and those treated with IFX are shown in **Tables 1** and **2**, respectively.

Effectiveness of IFX treatment

The frequency of PNR was significantly higher in patients with UC (18.5%) than in those with CD (0.0%; $p=0.023$), whereas sLOR was significantly higher in UC (51.9%) than in CD (21.4%; $p=0.026$). The median follow-up period for patients with sLOR was 16 months (range, 4 to 84). The proportion of patients who continued IFX treatment during the follow-up period (median, 38 months; range, 5–113 months) was significantly higher in the CD group (71.4%) than in the UC group (29.6%; $p=0.003$; **Fig. 2**).

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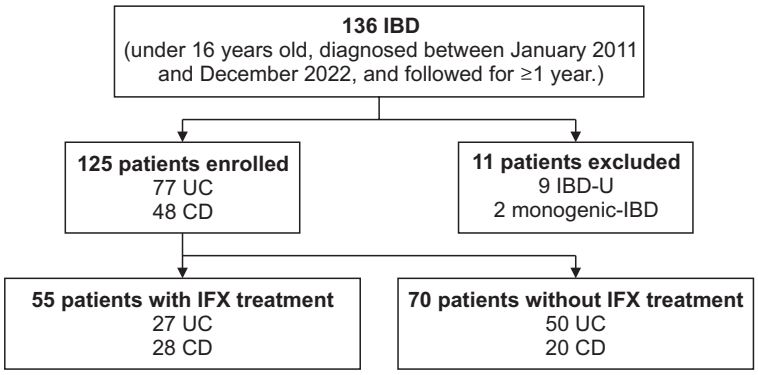

Fig. 1. Patient disposition.
IBD: inflammatory bowel disease, IBD-U: inflammatory bowel disease unclassified, UC: ulcerative colitis, CD: Crohn's disease, IFX: infliximab.

Table 1. Characteristics of enrolled patients

	Ulcerative colitis			Crohn's disease		
	Total	IFX (+)	IFX (–)	Total	IFX (+)	IFX (–)
Number of subjects	77	27	50	48	28	20
Male	43 (55.8)	16 (59.3)	27 (54.0)	35 (72.9)	20 (71.4)	15 (75.0)
Age at diagnosis (yr)	10 (1–15)	10 (2–15)	11 (1–15)	12 (3–15)	12 (8–15)	12 (3–15)
Age at diagnosis (yr)						
Below 6	18 (23.4)	7 (25.9)	11 (22.0)	1 (2.1)	0 (0.0)	1 (5.0)
Between 6 and 9	11 (14.3)	3 (11.1)	8 (16.0)	8 (16.7)	3 (10.7)	5 (25.0)
Between 10 and 16	48 (62.3)	17 (63.0)	31 (62.0)	39 (81.3)	25 (89.3)	14 (70.0)
Disease location	E1/E2/E3/E4	E1/E2/E3/E4	E1/E2/E3/E4	L1/L2/L3/L4	L1/L2/L3/L4	L1/L2/L3/L4
	2/5/2/68	0/0/0/27	2/5/2/41	7/6/33/2	3/0/24/1	4/6/9/1
Disease activity at diagnosis		PUCAI			PCDAI	
Score	45 (5–85)	60 (20–85)	40 (5–80)	37.5 (7.5–65)	36.25 (10–65)	37.5 (7.5–65)
Remission (below 10)	1 (1.3)	0 (0.0)	1 (2.0)	1 (2.1)	0 (0.0)	1 (5.0)
Mild (between 10 and 30 [35 in UC])	25 (32.5)	4 (14.8)	21 (42.0)	15 (31.3)	9 (32.1)	6 (30.0)
Moderate to severe (over 30 [35 in UC])	51 (66.2)	23 (85.2)	28 (56.0)	32 (66.7)	19 (67.9)	13 (65.0)

Values are presented as number only, number (%), or median (range). Categories for age at diagnosis and disease location were delineated using the Paris classification.
IFX: infliximab, IFX (+): infliximab treatment, IFX (-): no infliximab treatment, E3: extensive (hepatic flexure distally), E4: pancolitis (proximal to the hepatic flexure), L1: ileal, L2: colonic, L3: ileocolonic, and L4: upper disease (modifier), PUCAI: Pediatric Ulcerative Colitis Activity Index, PCDAI: Pediatric Crohn's Disease Activity Index, UC: ulcerative colitis.

Time from initiation of IFX to corticosteroid discontinuation

Eighty-one percent of all patients with UC (22/27), 81.8% of patients with UC who did not experience PNR (18/22), and 35.7% of patients with CD (10/28) received PSL at the time of IFX initiation. All patients without PNR attained freedom from PSL after a median of 9 weeks (range, 3–60 weeks) in the UC group and 6 weeks (range, 2–19 weeks) in the CD group. Although patients with CD were able to discontinue PSL somewhat sooner, the times were not significantly different (p=0.27).

Combination treatment of IFX and thioprine

Excluding patients with PNR or SAE, 54.0% (26/48) of the patients (15 with UC and 11 with CD) received azathioprine (AZA), but none received 6-mercaptopurine. The proportion of patients receiving both IFX and AZA did not significantly differ between the UC (67.9%) and CD (42.0%; p=0.089) groups. Among patients with UC, 71.4% (5/7) and 60.0% (9/15) experienced sLOR with IFX alone and IFX plus AZA, respectively; the difference was not significant (p=1.0). Similarly, 26.7% (4/15) and 18.2% (2/11) of patients with CD showed sLOR with IFX alone and a combination of IFX and AZA, respectively, without a significant difference (p=1.0).

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Table 2. Characteristics of patients with IFX treatment

	Ulcerative colitis	Crohn's disease	*p*-value
Number of subjects	27	28	
Age at initiation of IFX therapy (yr)	12 (2–16)	12.5 (8–16)	0.207
Duration of observation from initiation of IFX to last visit (mo)	44 (13–132)	48 (5–137)	0.78
Age at initiation of IFX therapy (yr)			
Below 6	4 (14.8)	0 (0.0)	0.123
Between 6 and 9	4 (14.8)	4 (14.3)	
Between 10 and 16	19 (70.4)	24 (85.7)	
Disease activity before IFX therapy	PUCAI	PCDAI	
Score	55 (15–85)	30 (5–65)	0.002
Remission (below 10)	0 (0.0)	1 (3.6)	0.072
Mild (between 10 and 30 [35 in UC])	7 (25.9)	14 (50.0)	
Moderate to severe (over 30 [35 in UC])	20 (74.1)	13 (46.4)	
Medications before initiation of IFX therapy			
5-ASA	27 (100.0)	28 (100.0)	
PSL	27 (100.0)	17 (60.7)	
AZA or 6-MP	26 (96.3)	20 (71.4)	
TAC	8 (29.6)	0 (0.0)	
ADA	4 (14.8)	1 (3.6)	
Initiation order of IFX in biologics			
1st	23 (85.2)	27 (96.4)	
2nd	4 (14.8)	1 (3.6)	

Values are presented as number only, median (range), or number (%).
IFX: infliximab; min, minimum; max, maximum, PUCAI: Pediatric Ulcerative Colitis Activity Index, PCDAI: Pediatric Crohn's Disease Activity Index, UC: ulcerative colitis, 5-ASA: 5-aminosalicylic acid, PSL: prednisolone, AZA: azathioprine, TAC: tacrolimus, ADA: adalimumab.

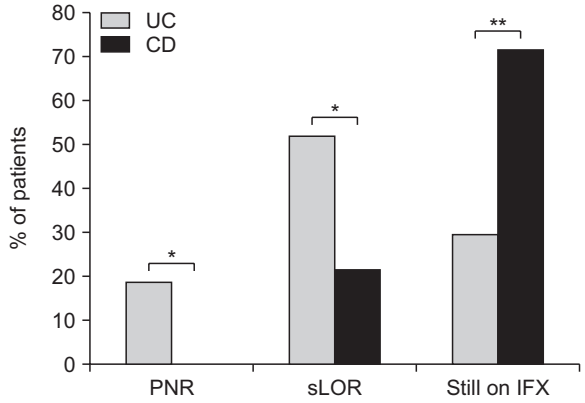

Fig. 2. Outcome of infliximab therapy. The proportion of patients with PNR was significantly greater in UC (5/27, 18.5%) than in CD (0/28; 0.0%; p=0.023), whereas sLOR to IFX was significantly more frequent in UC (14/27; 51.9%) than in CD (6/28; 21.4%; p=0.026). The duration of IFX treatment during the follow-up period (median, 37.5 months; range, 3–113 months) was significantly longer in the CD group (20/28, 71.4%) than in the UC group (8/27, 29.6%; p=0.003). $^{*}p<0.05$; $^{**}p<0.01$.
UC: ulcerative colitis, CD: Crohn's disease, PNR: primary nonresponse, sLOR: secondary loss of response.

Safety

Considering the entire IFX-treated population (n=55), two patients with CD (3.6%) discontinued IFX due to SAE. One of these patients discontinued the IFX treatment after being diagnosed with T-cell acute lymphoblastic leukemia at 17 years of age. CD was diagnosed at the age of 12 years, and remission was achieved with 5-aminosalicylic acid (5-ASA) and a partial elemental diet. Subsequently, the patient was administered IFX and AZA, beginning at the age of 14 years, to treat CD relapse. Three years after the initiation of IFX and AZA, leukemia developed, and CD remission continued. The leukemia went into remission with chemotherapy, and at present, at 20 years of age, the patient has completed treatment

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for leukemia. He received 5-ASA and a partial elemental diet for CD, while maintaining remission from both leukemia and CD.

Another patient with CD experienced a serious infusion reaction (IR) including flushing, chest discomfort, nausea, and rash, resulting in the discontinuation of IFX. He had been in remission from CD while receiving ADA and AZA for more than 4 years. Altogether, IR occurred in three patients (5.5%) in the present study; however, the other two patients were able to continue IFX.

Long-term outcome after IFX failure

Twenty-seven patients (19 with UC and 8 with CD) failed IFX treatment. After IFX failure against UC, the Chinese herbal medicine Qing-Dai was most used (57.9%), followed by vedolizumab (VDZ; 31.6%), ustekinumab (UST; 26.3%), and ADA (15.8%); after failure against CD, ADA was most commonly chosen (62.5%), followed by UST (25.0%). Among patients with UC at the end of the observation period, Qing-Dai was the most common treatment (47.4%), followed by VDZ (26.3%), UST (15.8%), and ADA (5.3%). In CD, ADA was the most common (62.5%), followed by UST (25.0%). One patient with UC who was not successfully treated with IFX, AZA, UST, VDZ, or Qing-Dai underwent total colectomy. No mortalities occurred during the study period (**Table 3**).

DISCUSSION

In the present study, examining the long-term durability of IFX for the treatment of Japanese pediatric patients with IBD, it was found to be inadequate for UC compared to CD. Severe adverse events resulting in the discontinuation of IFX treatment occurred in 3.6% of patients.

IFX treatment showed dramatic effectiveness against severe CD that is resistant to steroids and immunomodulators, as reported in 1993 [18]. IFX was approved in the United States

Table 3. Treatments and prognosis after IFX treatment failure

	Ulcerative colitis	Crohn's disease
Number of subjects	19	8
Treatment and prognosis after IFX treatment failure		
ADA	3 (15.8)	5 (62.5)
GLM	1 (5.3)	0 (0.0)
UST	5 (26.3)	2 (25.0)
VDZ	6 (31.6)	0 (0.0)
Chinese herbal medicine (Qing-Dai)	11 (57.9)	0 (0.0)
Total colectomy	1 (5.3)	0 (0.0)
Others	0 (0.0)	1* (12.5)
Treatment at the end of observational period		
ADA	1 (5.3)	5 (62.5)
GLM	0 (0.0)	0 (0.0)
UST	3 (15.8)	2 (25.0)
VDZ	5 (26.3)	0 (0.0)
Chinese herbal medicine Qing-Dai	9 (47.4)	0 (0.0)
Total colectomy	1 (5.3)	0 (0.0)
Others	0 (0.0)	1* (12.5)
Occurrence of death	0 (0.0)	0 (0.0)

Values are presented as number only or number (%).
IFX: infliximab, ADA: adalimumab, GLM: golimumab, UST: ustekinumab, VDZ: vedolizumab.
*This patient developed leukemia and was in remission after chemotherapy. Currently, he has completed treatment for leukemia and has received 5-aminosalicylic acid and a partial elemental diet for Crohn's disease. The patient maintained Crohn's disease remission without reinitiation of IFX.

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in 1998 as the first biological agent for treating CD [19]. Subsequently, IFX was approved in Japan for adults with CD in 2002 and UC in 2010 and for children aged 6 years and older with UC and CD in 2017 [7,9].

In the present study, the outcomes of IFX treatment in UC were 18.5%, 51.9%, and 29.6% for PNR, sLOR, and IFX, respectively, and those in CD were 0%, 21.4% and 71.4%, respectively. Rutgeerts et al. [20] reported that in adults with moderate-to-severe active UC, IFX treatment showed a primary response rate of 66% at 8 weeks, with 35% remaining in remission at 54 weeks. Hyams et al. [11] reported that in pediatric patients with moderate-to-severe UC, 27% experienced PNR by week 8, and the remission rate at week 54 for 8-week responders was 38%. Among 20 Japanese pediatric patients with UC treated with IFX, 40%, 35%, and 25% experienced PNR, sLOR, and successful continuation of IFX, respectively [13]. The frequency of PNR in UC has varied among previous reports, which has been attributed to differences in study designs, such as the number of weeks considered in the evaluation and concomitant medications. No major differences, such as race or age, were evident between patients remaining on IFX and others, and factors, such as race or age conferred no major differences in the remission maintenance effectiveness of IFX for moderate to severe UC. Targan et al. [19] reported that in a group of adults with moderate to severe active CD, PNR was evident at 4 weeks in 35%, and Gisbert and Panés [21] reported an occurrence of sLOR of 37%, with an annual risk of sLOR of 13% per patient-year. In an evaluation of the long-term efficacy of IFX in pediatric CD, Hyams et al. [12] reported that PNR occurred in 1% of cases, and the continuation of IFX occurred in 67% of cases. Tajiri et al. [9] reported that in a Japanese pediatric CD study with a 54-week observation period, 14 patients treated with IFX experienced 0%, 7%, and 86% occurrences of PNR, sLOR, and continuation of IFX, respectively. Children showed fewer PNR occurrences than expected in adults, suggesting that the effectiveness of IFX may be age-dependent. In the present study, as in previous pediatric reports, few patients with CD experienced PNR, and maintenance of remission was better in patients with CD than in patients with UC. Thus, IFX appears to have a higher likelihood of effectiveness and long-term continuation rate in pediatric patients with CD than in pediatric patients with UC.

A combination of IFX and thioprine was reported to decrease the risk of IBD flare-ups [22,23]. One reported benefit of combining IFX and thioprine is that fewer antibodies develop against IFX, even in pediatric patients [24,25]. However, we found no thioprine-related decrease in the frequency of sLOR, which may have resulted from antibodies against IFX even when a combination of IFX and thioprine was administered. This was a retrospective observational study in which the decision to concomitantly use AZA was made on a case-by-case basis. Because AZA may have been administered in more severe cases, a selection bias may have resulted.

One of the most common adverse events of IFX treatment is IR, which has been reported in 5–23% of patients with IBD participating in large randomized controlled trials involving IFX [11,20,22,26-28]. Choquette et al. [29] enumerated the most frequent manifestations of IR as pruritus (19.9% of all reported reactions), followed by flushing (9.9%), dyspnea (6.2%), chest discomfort (5.9%), hypertension (5.9%), myalgia (5.0%), nausea (4.7%), urticaria (4.7%), headache (4.0%), rash (3.4%), and dizziness (2.8%). Premedication with IV hydrocortisone prevents IR [30]. In our study, IR was observed in three patients (5.5%), a lower frequency than that generally reported, possibly because patients with IBD treated with IFX in our study were premedicated with intravenous hydrocortisone.

An increased risk of malignancy, such as lymphoma has been reported with the combination of IFX and thioprine; however, IFX alone has not been associated with an increased risk of malignancy in pediatric IBD [31-34]. Louis et al. [35] reported that in patients with CD in sustained corticosteroid-free remission treated with a combination of IFX and thioprine, the withdrawal of IFX significantly increased relapses, whereas withdrawal of thioprine did not increase relapses. In the present study, one patient with CD, treated with a combination of IFX and thioprine, developed leukemia. We need to determine the best time to consider thioprine withdrawal for patients with IBD in sustained remission.

The present study has some limitations. In a retrospective study conducted at a single pediatric center, selection bias must be considered. This study included only a small number of subjects limited to Japanese children. In addition, no restrictions were imposed concerning concomitant medications, including corticosteroids, which may have affected the efficacy assessments and caused an underestimation of the PNR and sLOR. Moreover, we did not consider the possible influence of IFX dose escalation (dose increase or shortened intervals). Enrolled patients with UC were more severely affected than those with CD, and the amount of IFX used was only 5 mg/kg in UC due to insurance coverage.

In conclusion, we found that the long-term durability of IFX in Japanese pediatric patients with IBD was inadequate for UC compared with CD. The frequency of adverse events that resulted in discontinuation of IFX treatment was 3.6%. To the best of our knowledge, this is the first report to clarify the long-term durability of IFX in Japanese pediatric patients with UC or CD. Thus, IFX appears to have a higher likelihood of effectiveness and long-term continuation rate in pediatric patients with CD than in those with UC. The present study suggests that after new biologics other than TNF-α inhibitors are approved for pediatric IBD, treatment strategies may differ between UC and CD.

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