

## ORIGINAL ARTICLE

## Value of concomitant endoscopic balloon dilation for intestinal stricture during long-term infliximab therapy in patients with crohn's disease

Yoichiro Ono,<sup>1</sup> Fumihito Hirai,<sup>1</sup> Toshiyuki Matsui,<sup>1</sup> Takahiro Beppu,<sup>1</sup> Yutaka Yano,<sup>1</sup> Noritaka Takatsu,<sup>1</sup> Yasuhiro Takaki,<sup>1</sup> Takashi Nagahama,<sup>1</sup> Takashi Hisabe,<sup>1</sup> Kenshi Yao,<sup>1</sup> Daijiro Higashi<sup>2</sup> and Kitaro Futami<sup>2</sup>

Departments of <sup>1</sup>Gastroenterology and <sup>2</sup>Surgery, Fukuoka University Chikushi Hospital, Fukuoka, Japan

**Aim:** We assessed the long-term outcome of infliximab (IFX) therapy in patients with Crohn's disease (CD) and investigated the efficacy of concomitant endoscopic balloon dilation (EBD) for intestinal stricture during treatment.

**Methods:** The effectiveness of maintenance therapy with IFX was retrospectively evaluated in 185 patients with CD in a single center (median observation period 24 months). IFX effectiveness with and without immunomodulators (IMM) and enteral nutrition (EN), as well as cumulative surgery-free rates, were compared. The efficacy of concomitant EBD in patients with obstructive symptoms and high-level stricture was evaluated.

**Results:** In 185 patients receiving the maintenance therapy, the long-term efficacy rate was 84.9% at 24 months and 79.0% at 48 months. The cumulative surgery-free rate was significantly higher in the maintenance group ( $P < 0.001$ ). Concomitant IMM and EN did not significantly affect the effectiveness of IFX. IFX was discontinued in only 18 cases (7.3%). Symptomatic high-level stricture occurred in 33 patients (17.8%) in the maintenance group and the cumulative surgery-free rate was significantly higher in the EBD combination compared with the non-EBD group ( $P < 0.05$ ). If EBD were considered invasive intervention, the actual cumulative surgery rate in the maintenance group was significantly lower compared with the cumulative invasive intervention rate ( $P < 0.001$ ).

**Conclusion:** Long-term treatment with IFX is highly effective. The surgery-free rate was clearly higher in the maintenance group. Only concomitant EBD for intestinal stricture helped in the avoidance of surgery.

**Key words:** avoidance of surgery, Crohn's disease, endoscopic balloon dilation, infliximab, intestinal stricture.

### INTRODUCTION

Crohn's disease (CD) is an intractable disease in which chronic inflammation progresses, causing complications that include stricture, and fistulas and abscesses of unknown origin occur in the intestinal mucosa and deeper parts. Long-term treatment is required for repeated exacerbations and remissions. Drug therapies that have been used include salazosulfapyridine, corticosteroid, and immunomodulators (IMM) such as azathioprine and 6-mercaptopurine. In Japan, enteral nutrition (EN) with an elemental diet has also been used. Infliximab (IFX) has been demonstrated to exhibit a powerful therapeutic effect, and it provides a novel treatment strategy.

IFX (Remicade; Centocor, Malvern, PA, USA), a chimeric monoclonal antibody to tumor necrosis factor alpha (TNF- $\alpha$ ), is an effective treatment for luminal and fistulizing CD.<sup>1–4</sup> The treatment effect is sustained by repeated re-administration.<sup>2,3,5–9</sup> However, there are few current reports that demonstrate the long-term outcome and safety of IFX treatment.<sup>10,11</sup> In terms of safety, a consensus has not yet been

reached regarding the contribution and effect of IFX to intestinal stenosis, or on recommended measures to treat intestinal stenosis during IFX administration.<sup>12–16</sup>

In the present study, we investigated the long-term outcome of CD upon IFX treatment based on the clinical course of disease, and investigated the efficacy of concomitant endoscopic balloon dilation (EBD) as a measure for intestinal stricture.

### METHODS

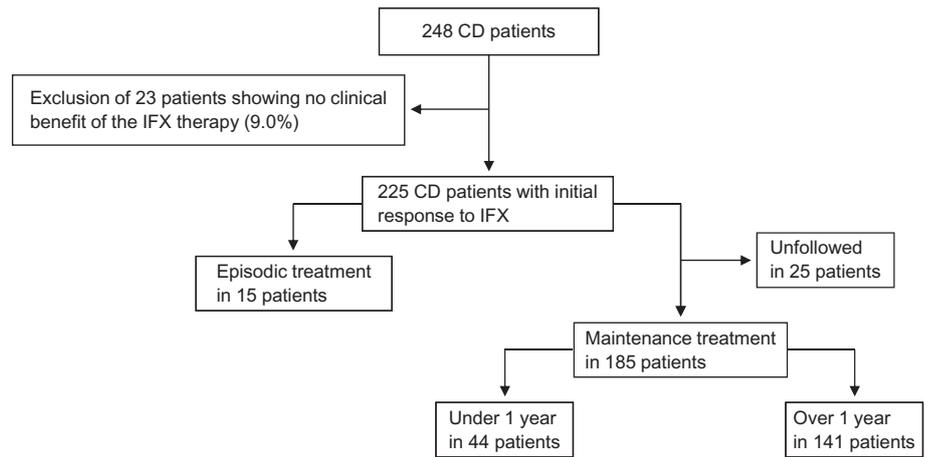
Our subjects comprised 185 evaluable CD patients who had received a maintenance dose of IFX from a total of 248 CD patients who were given IFX (5 mg/kg) in the Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Fukuoka, Japan, prior to January 2011 (Fig. 1). These subjects were retrospectively investigated. Of the 248 total CD patients, 23 (9.3%) were initial non-responders. Of the 225 initial responders, 15 received episodic administration upon recurrence, and 25 patients we could not follow up due to relocation or self-interruption of treatment. Excluding these cases, 185 patients received maintenance treatment and comprised the subjects in our long-term outcome analysis. The total number of CD patients in our department was 770, of whom 24% received an IFX maintenance treatment.

Correspondence: Yoichiro Ono, Department of Gastroenterology, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino, Fukuoka 818-8502, Japan. Email: yono6110@gmail.com

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**Fig. 1.** Subject selection of the present study. CD, Crohn's disease; IFX, infliximab.

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For long-term evaluation, the following definitions, which are similar to those used in an evaluation method that assessed sustained clinical benefit (SCB) by Schnitzler *et al.*<sup>10</sup> and long-term durability by Rudolph *et al.*<sup>11</sup> were used. The good outcome group was defined as the group in which no additional treatment was given, and daily life for these patients was nearly symptom-free. The moderate outcome group was defined as the group that needed additional treatment other than surgical intervention (intestinal resection), but patients could function well in society (inclusive of loss of response in those treated with IFX for a short period). The good and moderate outcome groups were considered to exhibit SCB. The poor outcome group was defined as the group that required surgical intervention (intestinal resection) or hospitalization because of relapse. IFX was considered to be ineffective in the poor outcome group with an end point of performance of intestinal resection or hospitalization because of relapse while receiving IFX.

Among patients with occlusive symptoms from intestinal stricture, those in whom there was improvement with concomitant EBD without intestinal resection were included in SCB. For combination therapies, analyses were carried out to compare the effectiveness of IFX with and without combination therapy: with and without enteral nutrition (EN) in which the patients were given 900–1200 kcal by elemental diet (Elental®; Ajinomoto, Tokyo, Japan) or semi-elemental diet (Ensure®; Abbott Laboratories, Chicago, IL, USA) by oral intake and/or through a self inserted tube,<sup>17</sup> and with and without IMM, respectively.

The surgery-free rate was compared between a total of 38 patients, including 23 initial non-responders and 15 of the episodic administration group, and 185 patients in the maintenance group.

The type and frequency of adverse effects in all 248 subjects who received IFX were identified and assessed with regard to safety.

Subjects with accompanying dilatation of the oral lumen or less than half of the consecutive intestinal lumen were defined as having high-level stricture. High-level stricture was seen in 74 (40%) of the 185 patients in the maintenance group during scrutiny of double contrast small bowel enema.

Nearly half of these 74 patients (33, 45.0%), exhibited obstructive symptoms. The cumulative surgery-free rate of these 33 patients was calculated, and a comparison was made between the EBD combination group and the non-EBD group. The severity of ulcers and stricture at the stricture site at the time of EBD was also evaluated using the ulcer/stenosis score of the Fukuoka index.<sup>18</sup>

More than half of the EBD were carried out for stricture of the ileum, whereas a small number were carried out for stricture of the colon. Using a double balloon endoscope (EN-450T5 medical endoscope; Fujifilm Medical, Tokyo, Japan) or a lower gastrointestinal endoscope (Olympus, Tokyo, Japan), a dilation balloon with a guidewire (CRE™ through-the-scope [TTS] balloon, diameter: 12–15 mm, 15–18 mm, 18–20 mm; Boston Scientific, Natick, MA, USA) was used according to the severity of the stricture. At our hospital, we previously reported the efficacy of EBD and the usefulness of CO<sub>2</sub> insufflation in EBD using double balloon enteroscopy (DBE);<sup>19–22</sup> CO<sub>2</sub> insufflation was used in all cases of EBD, including cases in which a colonoscope was used. Indications for EBD were: (i) small bowel strictures causing obstructive symptoms; (ii) those with a length of ≤5 cm; (iii) those without fistula or abscess; (iv) those without deep ulcer; and (v) those without severe curvature.<sup>22</sup> EBD was added as appropriate in cases of restenosis or reappearance of symptoms.

### Statistical analysis

Long-term analysis was carried out using the Kaplan–Meier method, and comparisons of the efficacy between groups with and without combination therapy, and comparisons according to the content of the combination therapy were carried out using the log–rank test. Similarly, for the cumulative surgery-free rate, calculations were made using the Kaplan–Meier method, and the surgery-free rate exhibited by the different groups was compared using the log–rank test. The level of significance of the log–rank test results was considered to be  $P < 0.05$ . Statistical analysis was conducted using SPSS, version 11.0.

**Table 1.** Patient characteristics

	Total ( <i>n</i> = 185)
Male/Female	131/54
Median age at diagnosis (years, range)	21.0 (8–53)
Median age at first infusion (years, range)	31.0 (12–63)
Median duration of disease prior to first IFX (months, range)	84.0 (1–396)
Median patient follow up of IFX treatment (months, range)	24 (1–103)
Location of CD (%)	
Ileitis	45 (24.3)
Colitis	23 (12.4)
Ileocolitis	117 (63.2)
Concomitant medication at first IFX (%)	
Aminosalicylates	125 (67.6)
Immunomodulator	73 (39.5)
EN	45 (24.3)
EBD (%)	32 (17.3)
Previous major abdominal surgery (%)	113 (61.1)

CD, Crohn's disease; EBD, endoscopic balloon dilation; EN, enteral nutrition; IFX, infliximab.

## RESULTS

### Patient characteristics

The greatest number of cases exhibited a disease type of the small and large intestine, and combination therapy using IMM such as azathioprine (AZA) and 6-mercaptopurine (6MP) was given to 73 patients (39.5%). A majority of patients had a history of intestinal resection (61.1%) (Table 1).

Infusions were given at weeks 0, 2, and 6, and then every 8 weeks. Overall, 141 patients received IFX for more than 1 year, and the median observation period was 24 months.

### Long-term outcome

Based on the Kaplan–Meier survival curve, SCB with the IFX maintenance dose exhibited a survival rate of 84.9% at 24 months and 79.0% at 48 months (Fig. 2).

### Combination therapy

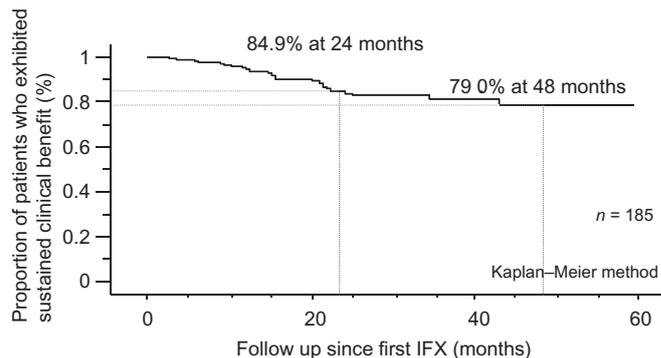
In the same manner as combination therapy, an analysis was carried out based on the Kaplan–Meier survival curve, but no significant differences were seen in SCB, regardless of whether IMM were used (Fig. 3) and whether EN was used.

### Cumulative surgery-free rate

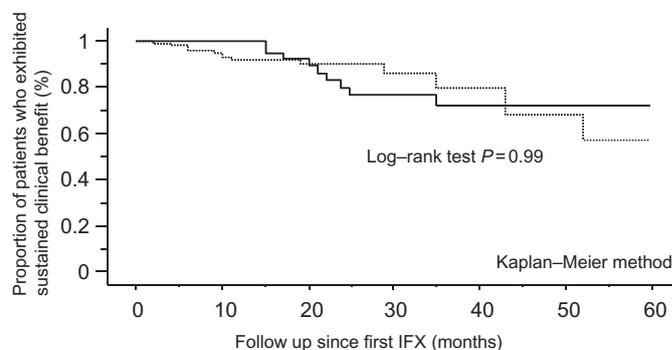
The cumulative surgery-free rate was significantly higher in the maintenance group compared with the initial non-responder and episodic administration group ( $P < 0.001$ , Fig. 4).

### Safety

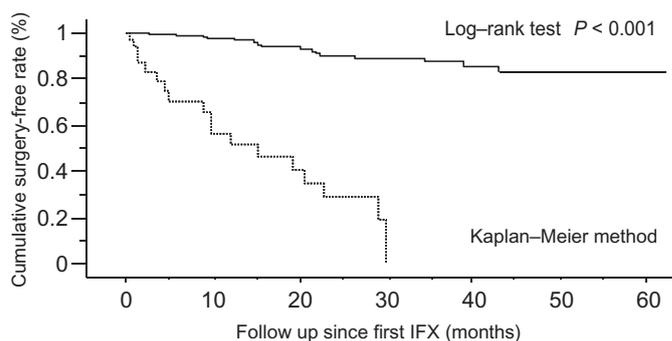
All 248 patients who received IFX were analyzed for safety of the drug. Adverse effects were seen in 87 (35.1%) of the



**Fig. 2.** Proportion of patients who exhibited sustained clinical benefit during maintenance infusion of infliximab using the Kaplan–Meier analysis. In 185 patients in the maintenance group, the long-term efficacy rate was 84.9% at 24 months and 79.0% at 48 months.



**Fig. 3.** Proportion of patients who exhibited sustained clinical benefit during maintenance infusion of infliximab (IFX) with and without immunomodulator. No significant difference was seen between the two groups. —, with immunomodulator ( $n = 73$ ); ·····, without immunomodulator ( $n = 112$ ).



**Fig. 4.** Cumulative surgery-free rate in patients with infusion of infliximab (IFX). The maintenance group was significantly greater than the episodic infusion or non-response group ( $P < 0.001$ ). —, maintenance group ( $n = 185$ ); ·····, episodic infusion or non-response group ( $n = 38$ ).

248 patients. However, IFX was discontinued in 18 (7.3%) patients. In addition to a severe infusion reaction during and after administration in these patients, there was type B hepatitis activation, lupus-like symptoms (antinuclear antibody, anti-DNA antibody positivity), pulmonary cryptococcosis,

**Table 2.** Symptomatic high-level stricture

	<i>n</i> = 33
Location (in case of duplication)	
Ileum	23
Anastomotic site	5
Colon	8
Ascending colon	1
Transverse colon	2
Descending colon	1
Sigmoid colon	2
Rectum	3
EBD (Y/N)	25/8
Mean number of EBD	2.3 ± 1.9
Surgery (Y/N)	5/28

and tuberculosis pleurisy. These reactions were dealt with by discontinuation of IFX.

The appearance of new stricture or progression was confirmed in 14 patients (5.7%) by radiography with double contrast technique, or endoscopic findings. Obstructive symptoms occurred in the majority of cases. The total number of patients with obstructive symptoms during the treatment course, including those experiencing high-level stricture soon after initiation of IFX, was 33 (13.3%) (Table 2). Combination EBD was used as needed in these patients.

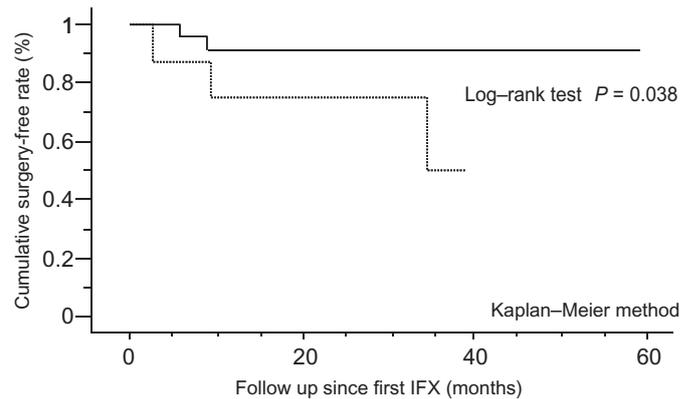
#### Efficacy of concomitant EBD for intestinal stricture

Symptomatic high-level stricture was observed in 33 patients during the follow-up period (Table 2). The site of stricture was the ileum in the majority of patients (23 patients), the intestinal anastomosis in five patients, and the colon in eight patients. Of these, 25 patients in the EBD combination group exhibited a significantly higher cumulative surgery-free period compared with the eight patients in the non-EBD group ( $P < 0.05$ , Fig. 5). EBD was added as appropriate in cases of restenosis or reappearance of symptoms (mean 2.3 times/patient). Of the 33 symptomatic high-level stricture patients, surgery was finally necessary in five (15.2%).

Ulcer and stenosis were evaluated using the Fukuoka index (Fig. 6) in 25 of the patients who underwent EBD. The mean stenosis score was  $2.96 \pm 0.20$  and the mean ulcer score was  $1.73 \pm 1.16$  at the time of initial EBD. Marked stenosis was observed, but the ulcers tended to be nearly healed. As shown in Figure 7, surgery was also needed during the maintenance doses of IFX. EBD was necessary in addition to surgery; however, both can be viewed as invasive interventions. The cumulative surgery rate was significantly lower than the cumulative invasive intervention (EBD or surgery) rate ( $P < 0.001$ ); thus, if EBD were not carried out, the rate of surgery would increase.

## DISCUSSION

In ACCENT I, II,<sup>2,23</sup> and other large-scale trials of IFX, its utility and effectiveness in inducing and maintaining remission in numerous cases of CD have been reported.<sup>1,3-9</sup> However, there are few reports concerning long-term IFX treatment outcomes, and those published show the utility of

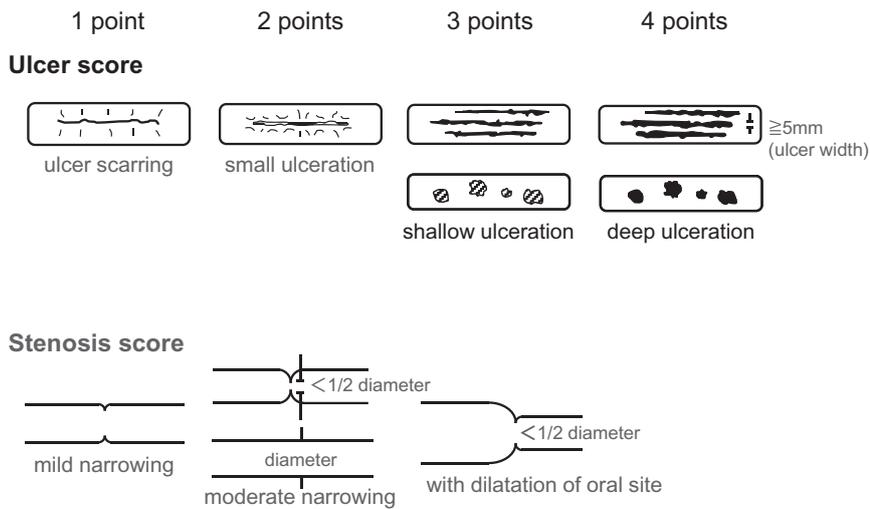


**Fig. 5.** Cumulative surgery-free rate in patients presenting symptomatic bowel obstruction during maintenance infusion of infliximab (IFX). With endoscopic balloon dilation therapy group was significantly greater than without endoscopic balloon dilation therapy group ( $P = 0.038$ ). —, with endoscopic balloon dilation therapy ( $n = 25$ ); ·····, without endoscopic balloon dilation therapy ( $n = 8$ ).

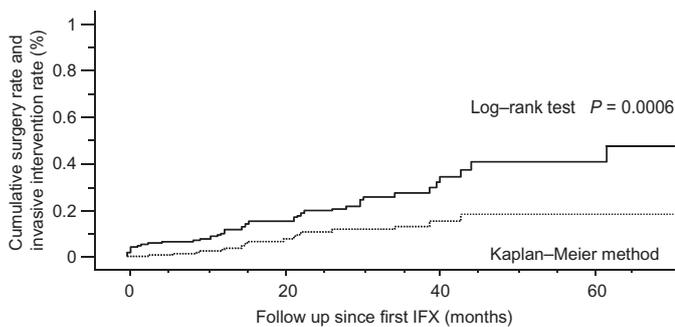
IFX in cases of continuous use over 4 years.<sup>10,11,24</sup> In the present study, the treatment course and efficacy (cases of sustained clinical benefit) with a maintenance dose were analyzed for a comparatively long period of time in a single institution (median observation period, 24 months). In this study, the efficacy rate was high; 84.9% at 24 months and 79.0% at 48 months. Schnitzler *et al.*<sup>10</sup> examined the sustained clinical benefit of IFX in 614 CD patients with an observation period of approximately 5 years, and they reported a sustained clinical benefit that continued over a prolonged period in 63.4% of patients. Rudolph *et al.*,<sup>11</sup> using a similar indicator, investigated the response durability and reported a continuing effect at 72 months in 66.4% of CD patients who exhibited a primary response to IFX. The results of the present study exhibited effectiveness similar to these reports.<sup>10,11</sup> The IFX maintenance dose not only induced remission of CD but was also useful in maintaining clinical benefit over a prolonged period. This is the first report concerning the long-term effectiveness of IFX in Japanese subjects, but it was found to be in concordance with results reported in Western subjects.

Long-term treatment is thought to be necessary for CD. In the 20 years following onset, surgical intervention, namely, intestinal resection, is needed in approximately 75% of patients.<sup>25,26</sup> Moreover, in terms of long-term prognosis, IFX has been reported to lower the rate of hospitalization and surgery.<sup>10,16,26,27</sup> In the present study, the maintenance group also exhibited a significantly higher cumulative surgery-free rate compared with the episodic administration group, and the importance of maintenance IFX administration was confirmed.

Our findings exhibited no significant differences in treatment outcome between with and without combination treatment in spite of the use of IMM and EN. Induction of remission, mucosal healing, and maintenance of remission were observed with IMM in particular.<sup>28,29</sup> In the present study, similar to the report of Schnitzler *et al.*,<sup>10</sup> no significant difference in treatment outcome between with and without the use of IMM was found. The aim of using combination



**Fig. 6.** Schematic illustration of classification of intestinal lesions evaluated by endoscopy (Fukuoka index). As to the ulcer score, ulcer scarring was given 1 point, an open ulcer similar to aphthoid or small ulcer 2 points, a longitudinal ulcer of less than 5 mm in transverse diameter showing an open ulcer or a shallow and broad irregular ulcer 3 points, a longitudinal ulcer of 5 mm or more in transverse diameter showing an open ulcer or a deep and broad irregular but well-demarcated ulcer 4 points. As for the stenosis score, a luminal width of at least half the normal intestinal tract was given 1 point, a luminal width of less than half the normal intestinal tract, but through which an endoscope could be advanced was assigned 2 points, and remarkable stenosis of the lumen such that an endoscope could not be advanced was given 3 points.



**Fig. 7.** Comparison of patients who underwent invasive intervention (surgery or EBD) and patients who underwent surgery ( $n = 18$ ) in the infliximab (IFX) maintenance group. There were 43 patients in the invasive intervention group, comprising surgery ( $n = 18$ ) or EBD ( $n = 25$ ). Cumulative surgery rate and invasive intervention rate in patients during maintenance infusion of IFX with and without endoscopic balloon dilation. Cumulative surgery rate was significantly lower than the invasive intervention rate ( $P < 0.001$ ). —, invasive intervention ( $n = 43$ ) in IFX maintenance; ·····, surgery ( $n = 18$ ) in IFX maintenance.

IMM is to improve the effects of treatment and inhibit infusion reactions during administration and adverse effects, but the risk of developing serious infection or hepatosplenic T-cell lymphoma with combined use of IMM has previously been reported.<sup>30,31</sup> Regardless of whether these background factors were involved, fewer than 40% of patients in the maintenance administration group in our hospital used IMM. This may be due to the possibility that IMM are generally used in more serious cases.

Regarding safety, there are infusion reactions at the time of administration that accompany the antigenicity of the drugs. In patients receiving a maintenance dose, approximately 90% potentially experience some type of adverse event within 1 year.<sup>5,6</sup> In our hospital, adverse effects were seen in approximately 35%, but the majority were mild reactions during administration, and administration could be contin-

ued. Meanwhile, serious adverse effects that lead to discontinuation of administration reportedly occur in 2–9% of patients receiving a maintenance dose.<sup>2,5,32,33</sup> In our hospital, in a manner similar to these reports, severe adverse effects for which the drug had to be discontinued occurred in approximately 7% of cases; among them were cases of serious infection of pulmonary cryptococcosis<sup>34</sup> and tuberculosis pleurisy, but no deaths. Such adverse effects are seen in a small number of cases, but it is thought that they can generally be dealt with conservatively.

Intestinal stenosis is a complication commonly seen in CD, and it is a major factor related to surgical intervention.<sup>26</sup> There have been conflicting views regarding the influence of anti-TNF antibody therapy on stenosis.<sup>35–38</sup> Opinions on the relationship between IFX and stenosis also vary, from the affirmative to the negative.<sup>23,39,40</sup> We previously reported that stenosis advances as ulcers heal during IFX administration.<sup>18</sup> Currently, the effects of anti-TNF therapy in CD patients concerning stenosis remain controversial.<sup>41</sup> Whereas a majority of patients exhibited stricture prior to IFX administration, following IFX administration the stricture progressed or a new stricture appeared in 14 of the 185 patients, or approximately 8%. Obstructive symptoms were seen in 33 (17.8%) of the maintenance group; thus, it appears that stricture progresses as lesions heal in patients receiving IFX. Moreover, the 25 patients in the group with combination EBD exhibited a significantly higher surgery-free rate compared with the eight patients in the non-EBD group. In Figure 7, the cumulative surgery rate and invasive intervention rate rose with time over approximately 4 years from the start of IFX, suggesting that, at least during this time, intestinal stricture could potentially be seen. Therefore, not only regular observation of symptoms but also evaluation with endoscopy or radiography is necessary if severe lesions are observed prior to treatment.

Combined use of IMM or EN did not appear useful, but with the combination including EBD many patients were able to avoid surgery, suggesting that a maintenance treatment is possible. The mean stenosis score was 3.0 and the

mean ulcer score was 1.7 when the stricture site at the time of initial EBD was observed using the Fukuoka index. Marked stenosis was seen, but in many patients the ulcers scarred or showed a healing trend with shallow ulcers remaining. This process suggests that, in reaction, the intestine becomes narrower as the mucosa heals with IFX. Lesions in CD exhibit a non-continuous or multiple distribution and are often accompanied by intestinal stricture, so that surgical intervention is necessary in many cases. However, with the progressive narrowing of the intestine that accompanies the mucosal healing effects of IFX, systematic combination EBD may be a very useful procedure as a future treatment option and as a measure against intestinal stricture when maintenance doses of IFX are given. Therefore, aside from cases with specific contraindications, IFX maintenance administration could potentially be expanded.

### CONCLUSIONS

Infliximab maintenance therapy for CD is a treatment that greatly reduced the surgery rate in the present study. We found no significant differences in treatment outcome between with and without combination treatment in spite of the use of IMM and EN, but combination therapy with EBD for intestinal stricture was useful for avoidance of surgery in many cases, suggesting that maintenance administration is potentially beneficial. The clinical conditions of CD are complex and diverse; thus, it is important to select and combine appropriate treatments that correspond to a patient's background and symptoms.

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