TABLE 1. Patient Characteristics

	Patients Who Received a 3rd operation (n = 95)	Patients Who Underwent Only 2nd operations (n = 105)	P-value	Total Number of Patients (n = 200)
Age at diagnosis				
Median	21.1	22.6	$P = 0.439$	22.4
(Range)	(8–49)	(10–53)		(8–53)
Gender			$P = 0.9417$	
Male	71	78		149
Female	24	27		51
Disease location			$P = 0.0006$	
Ileocolic	69	56		125
Small bowel	26	38		64
Colorectal	0	11		11
Type of disease			$P = 0.3032$	
Non-perforating	43	59		102
Perforating	45	40		85
Others	7	6		13
Postoperative medication				
Immunosuppressants			$P = 0.6132$	
+	17	16		106
–	78	89		94
Infliximab			$P = 0.0170$	
+	30	13		48
–	65	87		152
Elemental diet			$P = 0.6175$	
+	56	63		119
–	39	41		80
Others	0	1		1
Disease duration between onset and the first surgery (yrs)				
Median	3.6	4.0	$P = 0.1494$	4.0
(Range)	(0–22.4)	(0–19.8)		(0–22.4)
Disease duration between onset and the second operation (yrs)				
Median	7.8	11.3	$P = 0.0101$	9.8
(Range)	(1.0–27.0)	(1.0–43.2)		(1.0–43.2)
Interval between the first and the second operations (yrs)				
Median	4.0	5.1	$P = 0.0897$	4.7
(Range)	(0.1–26.0)	(0.5–43.2)		(0.1–43.2)

Duration before surgery: duration between diagnosis and the first surgery.
Reoperation: reoperation after the first surgery.

needing a third operation than patients with either colorectal-only disease or small intestine disease. Other factors such as gender, age at diagnosis, preoperative duration of disease, and type of disease did not show any significant correlation with the third operation rate.

Next, we performed a multivariate analysis among the three risk factors that showed a significant impact on the rate of requiring a third operation by univariate analysis (Table 2). In multivariate analysis, the interval between the first and the second operation, and the use of infliximab remained significant risk factors.

Cumulative Rate of Patients Requiring a Third Operation

Cumulative 5-year and 10-year rates of the need for a third operation were significantly higher in patients whose interval between the first and the second operation was 4.7 years or less (P = 0.0069) (Fig. 2). Also patients

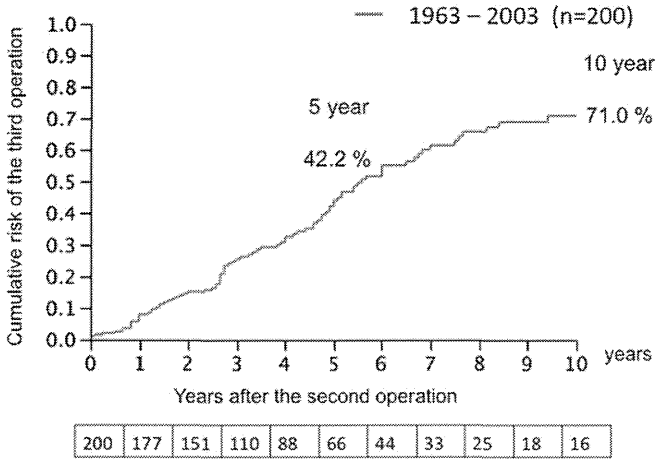


FIGURE 1. The overall 5-year and 10-year cumulative rate of third operations for CD in Japan. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

whose interval was 5.0 years or less showed a higher third operation rate than those with interval more than 5 years (5-year third operation rate; 47.8% versus 35.2%, $P = 0.0232$). Cumulative 5-year and 10-year rates of the need for a third operation were also significantly higher in patients who received infliximab postoperatively than those who did not ($P = 0.0015$) (Fig. 3). With regard to the disease localization, patients with ileocolic disease showed a significantly higher rate of needing a third operation than those with small bowel or colonic disease ($P = 0.0154$) (Fig. 4).

DISCUSSION

The present study showed that the disease interval between the first and the second operation was a significant risk factor for CD patients to need a third operation. A shorter interval was significantly associated with a higher risk of needing a third operation. The 5-year cumulative rate of patients needing the third operation was 47.8% in those with an interval between the first and second surgeries of 5 years or less, while only 35.2% in patients whose interval was more than 5 years ($P = 0.0232$). These results suggest that intensive postoperative adjuvant therapy may be especially important for CD patients who have an interval of 5 years or less between the initial and second surgeries in order to avoid the need for a third operation.

Previous studies demonstrated various risk factors for intestinal operation in CD, however, most of these factors have been focused on predicting the risk of needing the first or second operation.[1,7–13] The risk factors for needing a third operation were unclear. To our knowledge, there has been only one study by Alves et al[14] that evaluated risk factors for a third operation in CD. However, in Alves et al's study, the total number of patients was comparatively small. In their study, there were 28 CD patients who received a second intestinal operation, but since two cases were excluded because of missing data, they only examined a total of 26 CD patients. In the present study, we examined 200 CD patients who underwent a second operation, and to our knowledge, this is the largest number of patients among studies evaluating the risk of needing a third operation for CD. Another difference between Alves et al's study and the present study is the data source. Alves et al's study was based on the data from a single institution. However, a single institution-based study cannot rule out the possibility of patient selection biases. On the other hand, in the present study, we collected data from 13 institutions in Japan and we were able to analyze the risk factors for the third operation based on the multiinstitutional dataset.

Alves et al[14] showed that the third intestinal resection rate was significantly lower in patients treated with immunosuppressive drugs (azathioprine and 6-mercaptopurine, or methotrexate) than in untreated patients (17% versus 58%, $P < 0.02$). However, with regard to the postoperative effect of immunosuppressants in preventing recurrence, previous studies have shown conflicting results.[16–22] For example, Hanauer et al and D'Haens et al[16,18] showed that the postoperative recurrence rate was significantly lower in patients receiving immunosuppressants than in those receiving placebo. A meta-analysis also showed that immunosuppressants are more effective than placebo in preventing both clinical and endoscopic postoperative recurrence in CD.[20] On the other hand, Ardizzone et al[17] reported that there was no difference in the efficacy of immunosuppressants in preventing clinical and surgical relapses after conservative surgery. In the present study, administration of immunosuppressants was not a significant risk factor for needing a third operation. On the other hand, postoperative administration of infliximab was a significant risk factor for the patients needing a third operation in the present study. This is contrary to the results of recent studies, which showed that infliximab is effective for reducing the postoperative recurrence rate.[23–27] In a recent randomized controlled study, Regueiro et al[25] showed that endoscopic (9.1% versus 84.6%, $P = 0.0006$) and histologic (27.3% versus 84.6%, $P = 0.01$) recurrence rates were significantly lower in CD patients who received infliximab after intestinal resective surgery compared to patients who received placebo. One reason for the conflicting results between the present and other studies may be due to a selection bias of the patients who received infliximab. In the present study, patients received infliximab for therapy of recurrent disease. Therefore, there is a possibility that infliximab might have been administered preferably to higher-risk patients for a third operation, while lower-risk patients did not receive these treatments. This patient selection bias may have been responsible for the results indicating infliximab to be a risk factor in the present study.

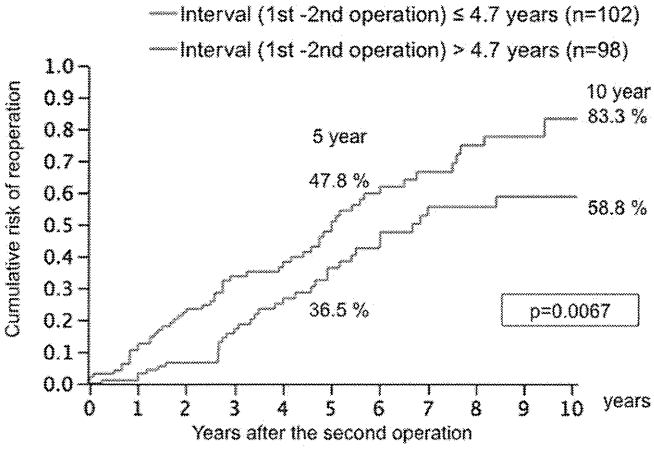
TABLE 2. Results of Univariate and Multivariate Analyses

	Univariate analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Age at diagnosis						
≤22	0.862	0.571–1.295	$P = 0.4747$			
>22						
Gender						
Male	0.772	0.474–1.214	$P = 0.2686$			
Female						
Disease location						
Small bowel, Colorectal	1.749	1.128–2.799	$P = 0.0132$	1.498	0.946–2.413	$P = 0.0859$
Ileocolic						
Type of disease						
Perforating	1.375	0.903–2.098	$P = 0.1370$			
Nonperforating						
Postoperative medication						
Immunosuppressants						
+	1.321	0.752–2.191	$P = 0.3188$			
−						
Infliximab						
+	1.999	1.274–3.068	$P = 0.0030$	1.676	1.054–2.614	$P = 0.0297$
−						
Elemental diet						
+	0.907	0.603–1.377	$P = 0.6413$			
−						
Disease interval between the first and the second operation						
≤4.7	0.566	0.371–0.856	$P = 0.0069$	0.626	0.407–0.953	$P = 0.0287$
>4.7						
Disease duration before the first operation						
≤4.0	1.047	0.691–1.575	$P = 0.8263$			
>4.0						
Disease duration before the second operation						
≤9.8	0.693	0.454–1.045	$P = 0.0802$			
>9.8						

Duration before surgery: duration between diagnosis and the first surgery.
Reoperation: reoperation after the first surgery.

The second reason may be a shorter follow-up period for patients who received infliximab. This is actually one limitation of the present study, because we were unable to evaluate the effect of infliximab with a long enough follow-up period because infliximab did not become available in Japan until 2002. In the present study, more than half of the patients (110 patients) underwent the third operation in or after 2002. Among these patients, the median follow-up period was only 2.8 years. We believe we need to follow patients for a longer period of time to evaluate the true effect of infliximab in the adjuvant setting.

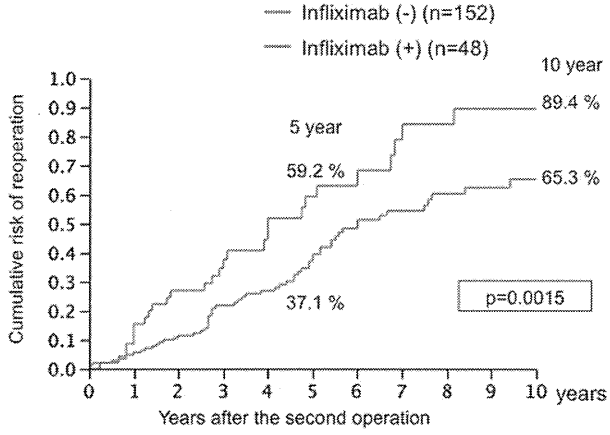
The present study showed that an interval of less than 5 years between the first and the second operation for CD was a significant risk factor for needing a third operation. Previous studies have also shown that there is a correlation between the duration of the disease and a risk of surgery. A number of studies have shown a higher risk of surgery with a shorter history of disease.[28–30] However, these studies examined the relationship between the disease duration before the first operation and this risk of a second operation. None of the previous studies examined the possible role of disease interval on the risk for needing a third operation. We have shown that patients who underwent a second surgery within 5 years of the first operation are at a higher risk of needing a third operation. With regard to the interval between operations, Greenstein et al[11] examined



≤4.7	98	85	72	50	42	33	20	14	10	6	4
>4.7	102	92	79	60	46	33	24	19	15	12	12

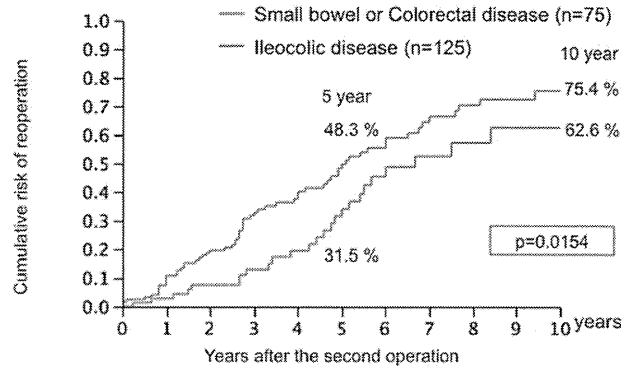
FIGURE 2. The cumulative rate of third operations depends on the interval between the first and the second operations. The cumulative risk of the third operation was significantly higher in patients whose interval between the first and second operations was less than 4.7 years ($P = 0.0067$).

770 patients with CD and reported that third operations occurred faster after second operations than did second operations after the first. Also, in an analysis of CD patients who had undergone multiple operations, Greenstein et al[31] showed that as patients undergo repeated surgical procedures, their postoperative recurrences develop faster after each successive operation. In the present study the mean interval between the second and the third operation (4.4 years) was significantly shorter than that between the



Infliximab (-)	152	137	119	86	72	54	36	28	21	15	13
Infliximab (+)	48	41	33	24	16	12	8	5	3	3	3

FIGURE 3. The cumulative rate of third operations depends on the postoperative administration of infliximab. The cumulative risk of the third operation was significantly higher in patients who received postoperative infliximab ($P = 0.0015$).



Small bowel or Colorectal disease	74	68	59	46	37	28	17	14	9	9	9
Ileocolic disease	125	109	92	64	51	38	27	19	16	11	9

FIGURE 4. The cumulative rate of third operations depends on the localization of the disease. The cumulative risk of the third operation was significantly higher in patients with ileocolic disease ($P = 0.0154$).

first and the second operation (5.8 years) ($P = 0.019$). Our results were in accordance with Greenstein et al's observations.

To our knowledge, the present study was the largest study of CD patients after the second surgery showing the risk of needing a third surgery. These results suggest that patients with a short interval between the first and the second operations need intensive adjuvant therapy postoperatively, such as infliximab. On the other hand, in the present study the disease duration before the first operation was not a significant risk factor for needing a third operation.

Another risk factor for the third operation in the present study was the anatomical site of the disease. Patients who have colorectal involvement will often require a definitive resection with a permanent stoma. In fact, none of the patients with colonic-only disease underwent a third operation in our study. Therefore, we examined patients with small intestine disease and colonic-only disease together against patients with ileocolic disease. By univariate analysis we showed that ileocolic disease was a significantly higher risk factor for needing a third operation, although this did not remain significant by multivariate analysis.

Previously, a number of studies examined the impact of anatomical site of disease on the recurrence, and many studies have demonstrated that the risk of recurrence was highest for ileocolic disease and lowest for colonic-only disease.[32–35] However, most of these studies examined the impact of the anatomical site on the first and/or the second surgery, and therefore, data concerning the need for a third operation with regard to the anatomical site involved is limited. In agreement with previous studies of initial and second surgeries, the present study indicated that there is a significantly higher risk of needing a third operation in

patients with ileocolic disease. The present study shows ileocolic disease to be a risk factor, not only for the first or the second operation, but also for the third operation for CD.

Another unique factor that might affect the risk of needing surgery in Japanese CD patients is the use of the elemental diet (ED) therapy. In Japan, ED, rather than corticosteroid therapy, is considered to be effective in the primary remission-induction therapy for active intestinal inflammation.[36–38] A Japanese randomized controlled trial showed that a "half elemental diet" therapy regimen, in which half of the daily calorie requirement is provided by an elemental diet and the remaining half by a free diet, is effective in reducing the relapse rate compared with patients eating purely a free diet (relapse rate; 34.6% versus 64.0%).[36] However, in the present study ED was not a significant factor for needing a third operation.

One of the limitations of the present study is that we could not examine the association between the third operation and several well-established risk factors including smoking, steroid use, and perianal disease, since they were not available in retrospective review.[7,9,10,12,13] Although these factors are known to be associated with the operation rate, it still remains unclear how these factors affect the risk of the third operation. We believe further studies are necessary to clarify this point. Another important issue is the endpoint of the present study. In the present study we included both intestinal resections and strictureplasties as an intestinal operation. Ideally these two procedures need to be analyzed separately. However, some patients receive both intestinal resections and strictureplasties at the same time, and furthermore the number of each procedure differs between each individual. Therefore, in the present study we did not divide patients according to each procedure. However, we believe that each procedure as well as the number of procedures needs to be evaluated separately. Lastly, although we examined multiple factors in association with the risk of third operation, the number of patients was comparatively small. Therefore, in order to clarify these issues we believe that a prospective study with a large number of patients is necessary.

In conclusion, to our knowledge, the present study is the first to show that a shorter interval between the first and the second operations is a significant risk factor for needing a third operation. Patients whose interval between initial and second surgeries is 5 years or less are at a higher risk of recurrence and, therefore, should receive postoperative adjuvant therapy to prevent the need for a third operation. However, to further confirm this we need to prospectively evaluate CD patients with a longer follow-up period. This is particularly important because the use of infliximab, which is generally thought to reduce disease symptoms and recurrence, was a risk factor for the third operation in our study. However, due to the retrospective nature of the present study, this was considered to be due to a bias, because these drugs might have been administered more frequently to higher-risk patients. Nevertheless, further studies are needed to confirm whether this is indeed the case.

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ORIGINAL ARTICLE

Retrieval of Serum Infliximab Level by Shortening the Maintenance Infusion Interval Is Correlated with Clinical Efficacy in Crohn's Disease

Toshifumi Hibi, MD, PhD,[1] Atsushi Sakuraba, MD,[1] Mamoru Watanabe, MD, PhD,[2] Satoshi Motoya, MD, PhD,[3] Hiroaki Ito, MD, PhD,[4] Kenta Motegi, MD,[5] Yoshitaka Kinouchi, MD, PhD,[6] Masakazu Takazoe, MD,[7] Yasuo Suzuki, MD, PhD,[8] Takayuki Matsumoto, MD, PhD,[9] Kazuhiko Kawakami, MD,[10] Takayuki Matsumoto, MD, PhD,[11] Ichiro Hirata, MD, PhD,[12] Shinji Tanaka, MD, PhD,[13] Toshifumi Ashida, MD, PhD,[14] and Toshiyuki Matsui, MD, PhD[15]

Background: Infliximab has shown beneficial effects in the treatment of Crohn's disease (CD). The aim of this study was to assess 1) the clinical efficacy of shortening the infusion interval from 8 to 4 weeks when patients had shown loss of response during maintenance therapy, and 2) the association between the serum trough level and clinical efficacy.

Methods: This was an open-label prospective multicenter study. Infliximab was administered at 5 mg/kg to patients with active CD at weeks 0, 2, and 6. Week 10 responders received infliximab every 8 weeks thereafter. In those with loss of response after week 14 the interval was switched to every 4 weeks. Co-primary endpoints were the rate of patients achieving clinical response and remission at week 54. Serum level of infliximab was measured at each visit.

Results: Fifty-seven patients who responded to induction treatment received maintenance therapy after week 14. Thirty-seven patients continued at the 8-week interval and 20 patients were switched to a 4-week interval. The overall clinical response and remission rates at week 54 were 82.5% and 61.4%, respectively. For those with loss of response, treatment at the 4-week interval resulted in clinical response and remission rates of 83.3% (15/18) and 55.6% (10/18), respectively, at week 54. A correlation between clinical efficacy and serum trough level was found ($P < 0.01$, overall).

Conclusions: A treatment strategy with an option of shortening the dosing interval of infliximab retrieves its trough level and may be useful for maintaining its efficacy.

(Inflamm Bowel Dis 2011;000:000–000)

Key Words: Crohn's disease, infliximab, maintenance, serum level, dosing interval

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that is characterized by inflammation at various sites in the gastrointestinal tract, often resulting in complications such as stenosis and fistula that requires surgery.[1] Therefore, maintaining a prolonged remission is an important issue in the treatment of CD.[2]

The pathogenesis of CD remains unclear, but inflammatory cytokines[3] including tumor necrosis factor (TNF)-α has been suggested to play an important role.[4–6] Infliximab, an antihuman TNF-α monoclonal antibody, binds to human TNF-α, neutralizing its bioactivity and inducing apoptosis of TNF-α-producing cells.[7] Clinical studies have

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From the [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan, [3]Inflammatory Bowel Diseases Center, Sapporo-kosei General Hospital, Sapporo, Japan, [4]Department of Molecular Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan, [5]Department of Gastroenterology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan, [6]Health Administration Center, Center for the Advancement of Higher Education, Tohoku University, Sendai, Japan, [7]Inflammatory Bowel Diseases Center, Social Insurance Central General Hospital, Tokyo, Japan, [8]Department of Internal Medicine, Toho University Sakura Medical Center, Sakura, Japan, [9]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Japan, [10]Matsuda Hospital Colo-Proctological Institute, Shizuoka, Japan, [11]Department of Lower Gastroenterology, Hyogo College of Medicine, Hyogo, Japan, [12]Department of Gastroenterology, Fujita Health University, Aichi, Japan, [13]Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan, [14]Third Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan, [15]Department of Gastroenterology, Fukuoka University Chikushi Hospital, Fukuoka, Japan.

Reprints: Toshifumi Hibi, MD, PhD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan (e-mail: thibi@sc.itc.keio.ac.jp).

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demonstrated the therapeutic effect of infliximab in CD.[8–12] Based on the results of the ACCENT I study, 5 mg/kg of infliximab at 8-week intervals is considered the standard therapy for maintenance of remission of CD.[10] In clinical practice, we have often encountered patients in whom the therapeutic effect did not persist for 8 weeks. In these cases the dose should be escalated or the interval shortened.[13] However, no clinical study has yet examined the efficacy of the recommended treatment, and the ACCENT I study only clarified the efficacy of episodic administration with increased dosing at the time of loss of response.

In the current study, 5 mg/kg infliximab was administered as standard therapy to active CD patients at 8-week intervals. Patients showing loss of response continued infliximab by shortening the dosing interval to 4 weeks. We aimed to assess whether this treatment strategy is useful for maintaining remission in CD and investigated the association between the clinical efficacy of infliximab and its serum trough level.

PATIENTS AND METHODS

Patients

This multicenter, open-label, controlled study was conducted at 18 institutions from July 2004 until May 2006. The protocol was approved by each Institutional Review Board and the study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice. Prior to registration, written informed consent was obtained from all patients.

Patients included in the study had CD for more than 6 months, with a score of Crohn's Disease Activity Index (CDAI) between 220 and 400, despite conventional treatments. Exclusion criteria were: 1) age $\leq$15 years; 2) marked stenosis of the bowel, short bowel syndrome, ostomy, abscess, or marked internal fistula; 3) previous treatment with any biologic targeting TNF-α; 4) use of parenteral nutrition, total enteral nutrition, or cyclosporine/tacrolimus/corticosteroids (intravenous) within 4 weeks before the start of the observation period; 5) leukocytapheresis within 3 months before the start of the observation period; 6) serious/opportunistic infection, tuberculosis, active hepatitis B/C, and human immunodeficiency virus (HIV) infection within 6 months before the start of the observation period, and chronic infectious disease of any kind.

Combination of nutritional and/or drug therapies at a stable dose were allowed as follows: 1) azathioprine/mercaptopurine had to be started at least 16 weeks before and maintained at a stable dose from 8 weeks before the start of the observation period; 2) corticosteroids and 5-aminosalicylates had to be started at least 8 weeks before and maintained at a stable dose from 4 weeks before the start of the observation period; 3) enteral nutrition therapy (elemental diet/nutritional supplement) had to be maintained at a stable dose from 4 weeks before the start of the observation period; and 4) metronidazole and ciprofloxacin had to be maintained at a stable dose from 2 weeks before the start of the observation period. The doses of corticosteroids, metronidazole, and ciprofloxacin could be decreased or discontinued.

Study Design

Patients were screened for eligibility 2 weeks before enrolment. Patients who met the inclusion criteria were enrolled and received 5 mg/kg intravenous infusion of infliximab at weeks 0, 2, and 6. Responders were defined as those who achieved at least a 25% reduction and a decrease of 70 points or more from the baseline CDAI score on at least one occasion, and subsequently not ever meeting the below loss of response criteria during the initial 10 weeks. Responders received 5 mg/kg of infliximab at 8-week intervals until week 46. For those who met the criteria for dosing interval switching at weeks 14, 22, 30, 38, or 46, 5 mg/kg infliximab was administered at 4-week intervals from that point until week 50. Loss of response was defined as follows: 1) patients with a CDAI score of at least 175, a CDAI score increase of 35% or more, and a CDAI score increase of 70 points or more in comparison with the CDAI score that fulfilled the clinical response criteria for the first time, and patients who met these conditions again at least once on the succeeding two evaluation days; 2) those in whom a contraindicated medication was newly used or the dose of medications used for CD was increased; 3) those who underwent surgery for CD; and 4) those who discontinued the study because of insufficient efficacy. In patients who met criterion (1), the point at which they initially met the criterion was regarded as the time to loss of response, and thereafter they were given infliximab at 4-week interval. In those meeting criteria (2–4), the earliest point was regarded as the time to loss of response, infliximab was discontinued, and alternative treatment was chosen. Patients with no response by week 10 were regarded as dropouts and subjected to alternative treatments.

Outcome Measures

CDAI was assessed at weeks 0, 2, and 6, and then at 4-week intervals until week 54. The IBD Questionnaire (IBDQ) and the number of draining fistulas were assessed at weeks 0, 10, 30, and 54.

Adverse events were ascertained until week 54 (in those who discontinued: 12 weeks after the final administration). An infusion reaction was defined as any adverse event that occurred during or within 2 hours after the infusion.

To assess the serum levels of infliximab, blood samples were obtained before each infusion at weeks 0, 2, and 6, and then every 4 weeks until week 54. The serum infliximab concentration was measured by enzyme-linked immunosorbent assay using anti-infliximab monoclonal antibody (Centocor Ortho Biotech, Horsham, PA) at Mitsubishi Tanabe Pharma (Osaka, Japan). The minimum detectable infliximab concentration was 0.1 μg/mL. The association between clinical efficacy and serum trough level of infliximab was analyzed in patients in whom both results were obtained at week 14.

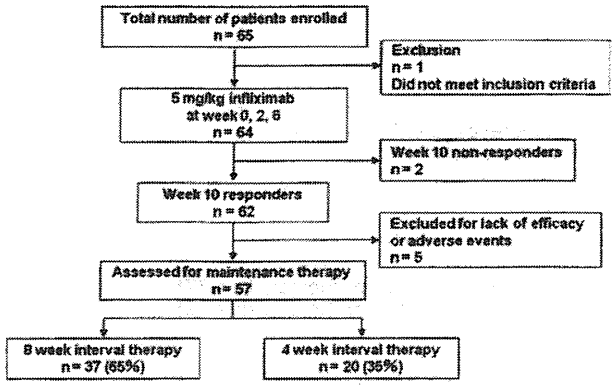

FIGURE 1. Flow chart of patients enrolled in the study.

Statistical Analysis

Efficacy was assessed in the full analysis set by the last observation carried forward approach. Patients who did not receive infliximab after week 14 were excluded from analysis. Analysis was done on an intention-to-treat basis.

The primary endpoints were the proportion of patients showing a clinical response (reduction in CDAI of 25% or more and 70 points or more from baseline) and remission (CDAI: less than 150 points) at week 54 in the week 10 responder group. These data were expressed as values with 95% confidence intervals (CI). The secondary endpoints were the proportion of patients showing a clinical response and remission at each point, the time to loss of response, the median IBDQ score, the doses and withdrawal rates of oral corticosteroids, and the number of draining fistulas. Fisher's exact test was used for the analysis between the proportion of patients showing clinical response and remission in the 8- and 4-week interval therapy group.

The duration of efficacy was expressed as the cumulative sustained efficacy rate and the median time to loss of response, which was calculated by the life table analysis system using the week in which a clinical response was initially observed as the starting point. When the cumulative sustained efficacy rate exceeded 0.5 after week 52, it was impossible to estimate the median time to loss of response; therefore, it was considered 52 weeks or more.

Regarding oral corticosteroids, the mean dose for 7 days prior to the date of evaluation was measured, and the point at which it reached 0 mg was regarded as the discontinuation point. The dosages of corticosteroids are expressed as mean ± standard error of the mean (SEM) and were compared with that at baseline using the Wilcoxon signed rank test. The proportions of patients with a closure of 50% or more or a closure of 100% of draining fistulas observed during the observation period were defined as the fistula response or complete fistula closure rates.

Correlation between clinical responses and serum trough level of infliximab was analyzed by Spearman's rank correlation coefficient using the data collected at week 14, so that it could be assessed 8 weeks after the previous dosing in all subjects. In patients who were switched to a 4-week interval, the median serum trough level at each point was calculated, considering the time of interval switching as baseline.

Patients who received at least one dose of infliximab were assessed in the safety analysis. Incidences of adverse events between the 8- and 4-week interval group were compared. The former group included one patient who met the criteria for interval switching, but did not undergo any subsequent treatment.

RESULTS

Patients

Of the 65 patients enrolled, 64 received 5 mg/kg of infliximab at weeks 0, 2, and 6 (Fig. 1). One patient did not meet the inclusion criteria and was excluded. The characteristics of the patients are shown in Table 1.

Of the 62 that met the response criteria during the initial 10 weeks, 57 received infliximab after week 14 as maintenance therapy and five withdrew from the study because of insufficient efficacy or adverse events. Thirty-seven patients completed the study at 8-week intervals. In 20, the interval was switched to 4 weeks, thus demonstrating an annual switching rate of ≈35%. Treatment was switched at weeks 14, 22, 30, and 38, in 10 (50%), 5 (25%), 4 (20%), and 1 (5%) patient, respectively, indicating that shortening the interval occurred at an early stage.

Efficacy

The overall clinical response and remission rates of both groups (95% CI) at week 14 were 84.2% (72.1–92.5)

TABLE 1. Baseline Patient Characteristics ($n = 64$)

Gender (male: female)	49: 15
Age (years), median (IQR)	29.0 (24.5–36.0)
Disease duration (years), median (range)	5.8 (0.5–27.0)
Disease location (ileum: colon: ileocolonic)	14: 15: 35
Patients with previous surgery for Crohn's disease, *n* (%)	31 (48.4)
Resection: stricturoplasty	23: 8
Smoker, *n* (%)	21 (32.8)
Patients with concomitant medication, *n* (%)	
Corticosteroids	21 (32.8)
5-Aminosalicylates	62 (96.9)
Immunomodulators	10 (15.6)
Metronidazole/ciprofloxacin	12 (18.8)
Enteral nutrition	40 (62.5)
Crohn's Disease Activity Index, median (IQR)	285.0 (249.0–337.0)
Inflammatory Bowel Disease Questionnaire, median (IQR)	146.5 (129.5–163.5)
Draining fistulas (none: 1: 2: 3 or more)	56: 4: 3: 1
C-reactive protein (mg/dL), median (IQR)	1.7 (0.7–4.3)

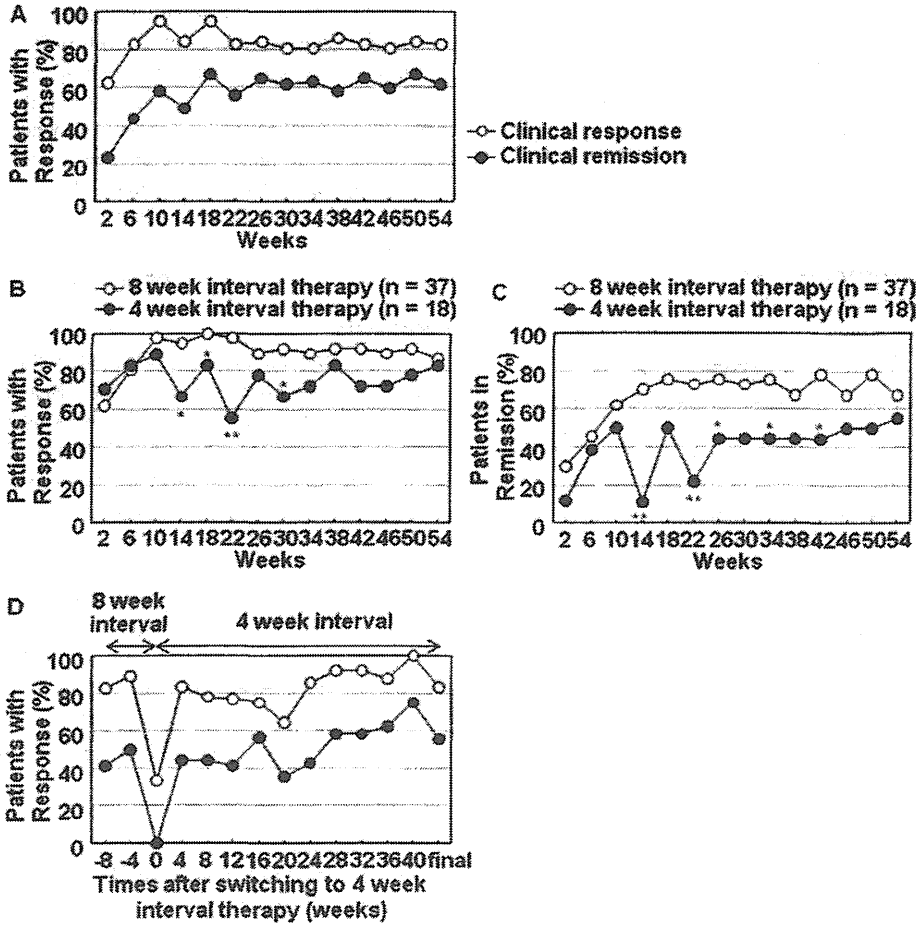

FIGURE 2. Time courses of clinical response and remission induced by maintenance therapy of infliximab. Fifty-seven out of 62 week-10 responders completed the study, at either 8- or 4-week intervals. (A) Time courses of clinical response and remission in the overall group. The overall clinical response and remission rates of both groups (95% CI) at week 14 were 84.2% (72.1–92.5) and 49.1% (35.6–62.7), respectively. At week 54 they were 82.5% (70.1–91.3) and 61.4% (47.6–74.0), respectively, similar to those at week 14. (B,C) Time courses of clinical response (B) and remission (C) for 8- and 4-week interval therapy group. Thirty-seven patients completed the study with infusions at 8-week intervals and 18 patients required switching to a 4-week interval. $^{*}P < 0.05$, $^{**}P < 0.01$ (8-week vs. 4-week interval therapy, calculated by Fisher exact test). (D) Clinical efficacy of infliximab in patients switched to 4-week interval therapy. Of the 18 patients, clinical response was achieved in 15 (83.3%) and clinical remission in 10 (55.6%) at 54 weeks.

and 49.1% (35.6–62.7), respectively. At week 54 they were 82.5% (70.1–91.3) and 61.4% (47.6–74.0), respectively, similar to those at week 14 (Fig. 2A). This suggests that the clinical responses and remissions obtained by week 14 could be sustained over 1 year, confirming the usefulness of the standard regimen and, furthermore, the option of shortening the dosing interval to 4 weeks in patients who have lost response.

When comparing the clinical response and remission rates in the 8- and 4-week interval therapy groups, the efficacy was also sustained after week 14 in the former and clinical response and remission rates were 86.5% (32/37) and 67.6% (25/37), respectively (Fig. 2B). On the other hand, in the latter these rates decreased transiently between 14 to 30 weeks, but recovered to almost similar levels to the former at week 54 (Fig. 2C).

Figure 2D shows the clinical response and remission rates of patients in the 4-week interval therapy group, considering the switching point to 4-week interval as the starting point. Of the 20 patients who were switched to 4-week interval, two were excluded due to lack of sufficient data at some timepoint during the study. At the switching point, the clinical response and remission rates were 33.3% (6/18) and 0% (0/18), respectively. Treatment at the 4-week interval resulted in clinical response and remission rates of 83.3% (15/18) and 55.6% (10/18), respectively, at week 54. This suggests that shortening the dosing interval to 4 weeks could retrieve clinical response and remission.

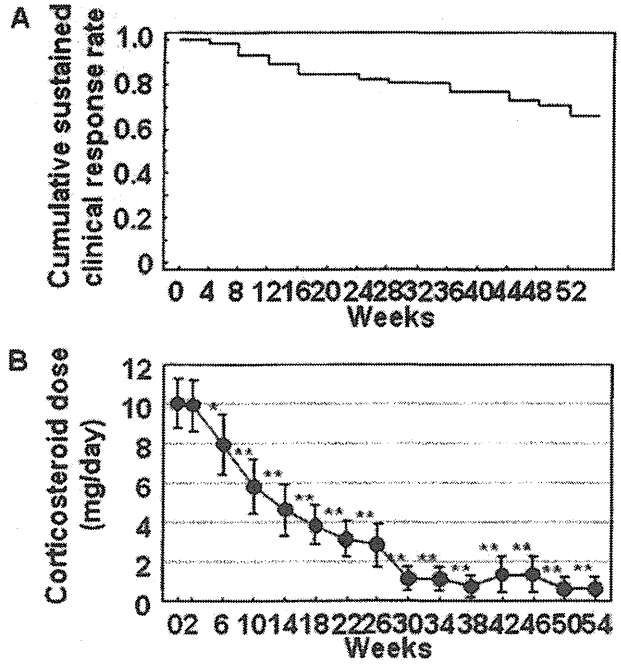

FIGURE 3. (A) Effect of infliximab on sustained clinical response. The median duration of efficacy in the overall 57 patients using life table analysis was 52 weeks or more. (B) Changes in the mean daily oral corticosteroid dose. Data are shown as the means ± SEM of prednisolone of the 18 patients who were taking oral corticosteroids at baseline. Statistical differences as compared with dosage at baseline were calculated by the Wilcoxon signed rank test (*P < 0.05, **P < 0.01).

The median duration of efficacy was 52 weeks or more (Fig. 3A), suggesting that the efficacy of infliximab could be sustained over a year.

The median IBDQ score at week 0 was 152, and this increased to 180 at week 10, showing early improvement in the quality of life (QOL) (data not shown). At weeks 30 and 54 the median IBDQ scores were 185 and 180, respectively. This suggests that maintenance treatment with infliximab sustains improvement in QOL over a period of 1 year.

Corticosteroids were administered to 18 patients (31.6%) at baseline. Changes in the doses of corticosteroids, which were converted to prednisolone, in these patients are shown in Figure 3B. The mean values of doses at weeks 0, 10, 30, and 50 were 10.0, 5.8, 1.1, and 0.6 mg, respectively. Maintenance infliximab sequentially increased the number of patients achieving withdrawal from corticosteroids to 72.2% (13/18) at week 54.

The numbers of draining fistulas before the study were as follows: 1 in 4 patients, 2 in 3, and 4 in 1. The fistula response rates at weeks 10 and 54 were 62.5% (5/8) and 75.0% (6/8), respectively, and complete closure of fistulas were obtained in 50.0% (4/8) and 62.5% (5/8), respectively (data not shown).

Relationship Between Efficacy and Serum Infliximab Concentration

The median serum trough levels of infliximab at week 14 were 0.80 μg/mL in 9 patients with no response, 1.10 μg/mL in 19 patients with a clinical response (not in remission), and 3.40 μg/mL in 29 patients in remission, respectively, thus showing a significant correlation (P < 0.01, overall; Fig. 4A). Of the patients whose serum trough level of infliximab was below its detection limit (0.1 μg/mL), 33% were nonresponders and no patient achieved clinical remission (Fig. 4B). On the other hand, the number of patients showing a clinical response/remission increased depending on the serum trough level. Of the patients with a serum trough level of 5 μg/mL or more, clinical response/remission was observed in 89%, thus showing a significant correlation between the clinical efficacy and serum trough level (P < 0.05, overall).

Figure 4C shows the serum trough level of infliximab in those patients in whom the dosing interval was switched to 4 weeks, considering the time of switching as the starting point. The clinical response and remission rates at the time of switching were 33.3% (6/18) and 0% (0/18), respectively, and the median serum trough level was 0.8 μg/mL. Administration at 4-week intervals increased both the clinical response and remission rates, and the serum trough levels to the range of 4.9–8.9 μg/mL. In patients receiving maintenance therapy at 8-week intervals, the efficacy also persisted after week 14, and the median serum trough levels 8 weeks after each dosing until week 54 ranged between 2.0–3.1 μg/mL.

Safety

All 64 patients treated with infliximab were included in the safety evaluation. The rate of patients experiencing at least one adverse event, including any minor ones, during the 54-week study period was 63/64 (98.4%) (Table 2). The incidence of serious adverse events was 18.8%. The most frequent serious adverse event was exacerbation of CD, occurring in 12.5%. No patient showed any fatal adverse reaction.

The incidences of adverse events and infections were similar between the patients receiving 8- and 4-week interval therapy. The incidence of serious adverse reactions in the latter was slightly higher than that in the former. In the latter, infection developed in two patients (tonsillitis: one, venereal wart: one). Tonsillitis resolved with antibiotic treatment without the discontinuation of infliximab. Venereal wart appeared after 14 weeks of the study. Administration of infliximab was continued but resection was selected and, after all, infliximab therapy was discontinued.

DISCUSSION

The current study assessed the efficacy and safety of the standard maintenance therapy of infliximab at 5 mg/kg every 8 weeks, and the option of shortening the interval to

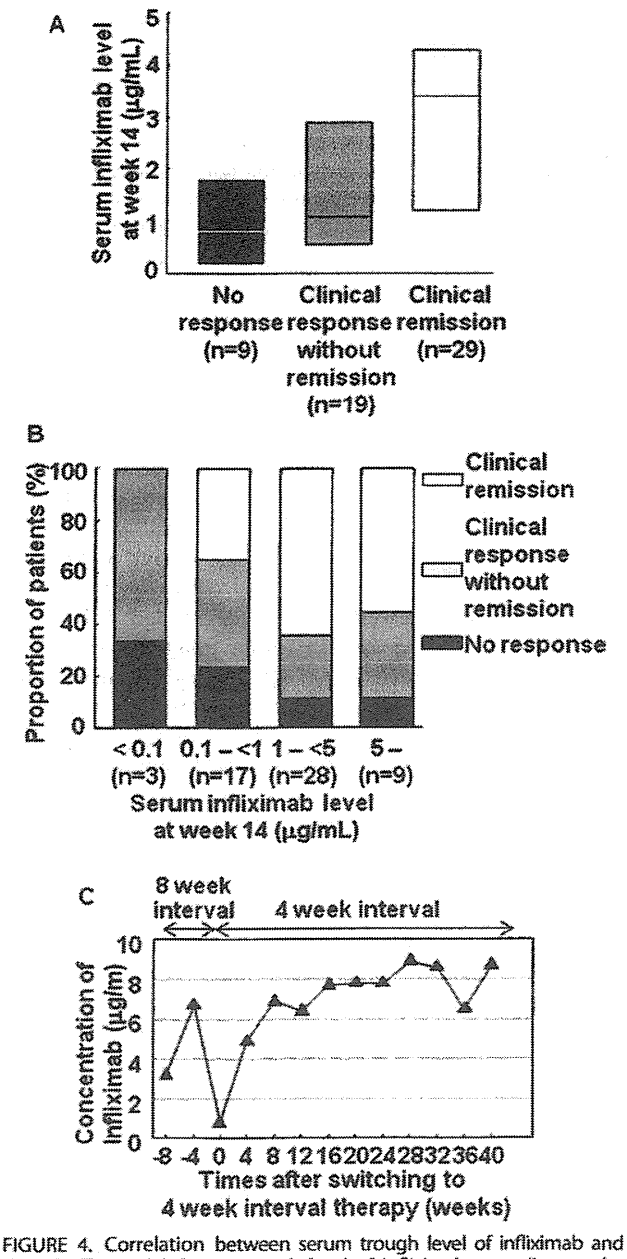

FIGURE 4. Correlation between serum trough level of infliximab and clinical efficacy. (A) Serum trough level of infliximab according to the clinical efficacy at week 14. Results are shown as median (IQR). Significant correlation between serum trough level and efficacy was seen ($P < 0.01$, overall). (B) Proportion of patients in clinical remission, clinical response without remission, and no response at different trough levels. In patients with a serum trough level below its detection limit (0.1 μg/mL), 33% were nonresponders and no patient achieved clinical remission. In those with a serum trough level of 5 μg/mL or more, no response was observed in 11%, whereas clinical response without remission was observed in 33% and clinical remission was achieved in 56%. There was a significant correlation between the clinical efficacy and serum trough level ($P < 0.05$, overall). (C) Changes in the median serum trough level of infliximab in patients switched to a 4-week interval. The serum trough level of infliximab increased compared to the timepoint of switching (week 0 on graph) after switching to a 4-week interval.

4 weeks in patients who have lost response in CD. We have shown that patients who have lost response to the standard regimen will recover response when their infusion interval was shortened to 4 weeks. This was accompanied by an increase in the serum trough level of infliximab and the threshold of its clinical efficacy was ≈1 μg/mL.

The clinical response and remission rates after 54 weeks were 82.5% and 61.4%, respectively, in the whole treatment group. In ACCENT I, they were 43% and 28%, respectively, for patients treated with 5 mg/kg infliximab.[10] The duration of efficacy was >52 weeks in our study and 38 weeks in ACCENT I. The two studies cannot be compared directly; however, our results suggest that the treatment strategy including administration at a 4-week interval will result in reachieving response.

Few studies have investigated the association between the efficacies of infliximab in CD with its serum trough level. Maser et al[14] reported that remission and endoscopic improvement were achieved in CD patients in whom the serum trough level was maintained at a higher level. Afif et al[15] assessed the usefulness of measuring infliximab and human antichimeric antibody concentrations in patients with inflammatory bowel disease, in a retrospective fashion, and showed that in those with subtherapeutic infliximab concentrations, dose escalation was associated with complete or partial clinical response in more than 80% of patients. They also demonstrated that concurrent immunosuppressive therapy was significantly associated with therapeutic infliximab concentrations. In the current study we showed that the efficacy of infliximab correlated with its serum trough level. The median serum trough levels in patients with a clinical response and in nonresponders were 1.10 and 0.80 μg/mL, respectively. In addition, the trough level at the time of switching was 0.80 μg/mL in patients in whom the interval was shortened. These findings suggest that the threshold of trough levels of infliximab to obtain clinical efficacy is ≈1 μg/mL. Loss of response was possibly due to insufficient serum trough levels, and shortening the interval increased the serum trough levels leading to sustained effect. Studies in rheumatoid arthritis indicated that more potent effects were achieved at a higher serum trough levels and that the threshold of the clinical responses was 1 μg/mL,[16,17] similar to our study. In our study the concurrent use of immunomodulators showed trends toward increased time until loss of response, higher trough levels at week 14, and more likelihood to maintain clinical response with 8-week interval treatment (data not shown). None of these were significantly different when compared to patients not on immunomodulators, which may have been due to the relatively small number of patients included in our study, eight on concurrent and 49 on no immunomodulators. The concurrent use of steroids also showed a trend toward higher trough levels at

TABLE 2. Summary of Safety Data

Patients Involved in Maintenance Treatment	All Patients	Total Patients	8 Week Interval	4 Week Interval
Patients, *n*	64	57	38	19
Adverse events, *n* (%)	63 (98.4)	56 (98.2)	37 (97.4)	19 (100.0)
Infections, *n* (%)	49 (76.6)	43 (75.4)	29 (76.3)	14 (73.7)
Infusion reactions, *n* (%)	9 (14.1)	8 (14.0)	6 (15.8)	2 (10.5)
Serious adverse events, *n* (%)	12 (18.8)	7 (12.3)	4 (10.5)	3 (15.8)
Worsening of Crohn's disease	8 (12.5)	4 (7.0)	3 (7.9)	1 (5.3)
Nausea	1 (1.6)	1 (1.8)	1 (2.6)	
Ileus	1 (1.6)	1 (1.8)	1 (2.6)	
Peritonitis	1 (1.6)			
Tonsillitis	1 (1.6)	1 (1.8)		1 (5.3)
Venereal wart	1 (1.6)	1 (1.8)		1 (5.3)
Pneumonia	1 (1.6)			
Serious infection, *n* (%)	6 (9.4)	4 (7.0)	2 (5.3)	2 (10.5)
Serious infusion reaction, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

week 14 (data not shown) at levels that were comparable to immunomodulators.

We chose to shorten the infusion interval of infliximab from 8 weeks to 4 weeks to achieve sufficient trough levels; however, we assume that similar levels may be achieved by infusion intervals of around 6 weeks in some patients. Other reasonable options that may also achieve sufficient trough levels include dose escalation or another induction therapy (0, 2, 6 weeks). We suggest that, depending on the patient condition and available options, the interval may be tailored according to the measured trough level, or the infusion interval may be gradually reduced until sufficient trough level and/or clinical efficacy is achieved. We are also aware that our study lacks a control group, which ideally should be a placebo-treated population or a group that was continuously treated at an 8-week interval.

In summary, we performed a standard maintenance therapy with 5 mg/kg of infliximab for CD at 8-week intervals and in patients showing loss of response the dosing interval was shortened to 4 weeks. This strategy led to high serum trough level of infliximab, which was accompanied by retrieval of clinical response, and, in some, clinical remission. Shortening the infusion interval of infliximab and monitoring its trough level may be useful and safe for maintaining long-term efficacy of infliximab in patients who have lost response to it.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Effects of family history on inflammatory bowel disease characteristics in Japanese patients

Erika Kuwahara · Keiko Asakura · Yuji Nishiwaki · Nagamu Inoue · Mamoru Watanabe · Toshifumi Hibi · Toru Takebayashi

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Abstract
Background Although the prevalence of inflammatory bowel disease (IBD) is reported to have reached a plateau in Western countries, it is increasing in Asia. The etiology of IBD is still under investigation. We performed an epidemiological study to clarify the characteristics of IBD in Japan, focusing on patients' family history.
Methods We obtained clinical data on ulcerative colitis (UC) (46,114 cases) and Crohn's disease (CD) (11,305 cases) in 2007 from an electronic database maintained under the Japanese Ministry of Health, Labour and Welfare's nationwide registry system, and analyzed the differences in disease characteristics between patients with IBD who had a family history of the disease and those who did not.
Results A total of 2.7% of the patients with UC and 2.6% of those with CD had a family history. The present age and age at disease onset were lower among the patients with UC who had a family history than among those without (present age: $p < 0.001$; age at disease onset: $p < 0.001$; Mann–Whitney *U*-test), but no similar trend was observed in the patients with CD. Disease severity was worse among both the UC and CD patients with a family history. The clinical course of patients with UC was not affected by family history. Levels of independence in daily life were associated with family history among CD patients, whereas age was associated with levels of independence in daily life among UC patients.
Conclusion Disease characteristics of IBD vary in some aspects according to the presence or absence of a family history.

Keywords Inflammatory bowel disease · Family history · Japan

E. Kuwahara (✉) · K. Asakura · T. Takebayashi
Department of Preventive Medicine and Public Health, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: erika_yano@mail.goo.ne.jp

Y. Nishiwaki
Department of Environmental and Occupational Health, Faculty of Medicine, Toho University, Tokyo, Japan

N. Inoue · T. Hibi
Division of Gastroenterology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

M. Watanabe
Department of Gastroenterology and Hepatology, School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Introduction

Inflammatory bowel disease (IBD) includes 2 chronic diseases that cause inflammation of the intestines: ulcerative colitis (UC) and Crohn's disease (CD). A complex interplay of environmental, genetic, and immunologic factors are involved in the development of IBD [1]. The incidence of IBD is higher in developed countries than in developing countries and among white populations than among non-white populations [2]. However, it is reported that the incidence of IBD has reached a plateau in the northern part of the world [3]. Meanwhile, its prevalence is steadily increasing in Asian countries in spite of improvements in IBD treatment [4]. Environmental change, modernization, and Westernization of lifestyle could be partly responsible for the rising incidence [4], but increasing awareness of IBD among physicians and the availability of better diagnostic tools must also be playing a part in the increasing number of reported cases in Asia [4].

Furthermore, improved socioeconomic conditions have led to a decline in the incidence of infectious colitis, and particularly tuberculosis, in many parts of Asia, which has allowed physicians to diagnose IBD with more confidence [4]. However, the precise reasons for the increasing incidence of IBD have not been fully elucidated.

Since 1972, the Japanese Ministry of Health, Labour and Welfare (MHLW) has been conducting a nationwide investigation to clarify the etiologies of and establish better treatments for patients with any of 45 intractable diseases who satisfy certain criteria [3]. UC and CD have been included in the list since 1975 and 1976, respectively. Patients in whom UC or CD is diagnosed on the basis of the specified diagnostic criteria are required to register annually with their local prefectural government, and each patient's attending doctor is required to supply detailed information about the patient's condition in the registration form. The submitted forms are evaluated by specialists on each prefecture's Committee on Measures for Intractable Diseases, and those patients who pass this screening become eligible for financial aid for their treatment. A pilot study performed in 2004 found that 67.2% of patients claiming aid for UC treatment, and 76.7% of those claiming aid for CD were subsidized via this system (this result was reported in the annual report of the IBD Research Committee [in Japanese]). Since 2001, the prefectural governments have been making efforts to convert the data from the paper registration forms into electronic form. In 2009, Asakura et al. [5] used the electronic data to investigate the prevalence, age and sex distribution, and degree of IBD in Japan.

These electronic forms contain a wide range of data on patients with UC and CD: sex, age, age at onset, location of residence, family history (FH), clinical examination data, symptoms, and signs. The forms also provide data on a large number of patients (more than 40,000 patients with UC and more than 10,000 with CD), making them suitable for descriptive epidemiological analysis. FH is known to be a risk factor for IBD [3], and previous studies have indicated an association between FH and UC severity [6, 7], but no association between FH and CD severity [8, 9]. This large electronic database allowed us to carry out a more detailed investigation of IBD data to clarify the proportion of patients with an FH and the differences in disease characteristics between those with and without an FH of IBD.

Methods

Data source and questionnaire

We used the electronic data on IBD patients for the year 2007 furnished by the Japanese MHLW. Detailed information about the data available from the MHLW has been reported by Asakura et al. [5]. In short, the paper registration forms submitted by IBD patients are collected and converted into electronic form by their local prefectural governments each year. The conversion rates vary with the prefecture, but they range from around 40–60% every year. After the electronic data are anonymized, the MHLW makes them available for medical research. In 2007, 96,994 UC patients and 27,384 CD patients submitted registrations, of which 46,114 (47.5%) and 11,305 (41.3%), respectively, were converted into electronic form. We used only the electronic data for analysis.

Using these data, we examined the distribution of present age, age at disease onset, clinical course, severity of illness, and level of independence in daily life, paying particular attention to patients' FH of IBD. Invalid data were excluded from the analysis. Attending doctors are required to supply details of FH of IBD in the registration forms. The registration forms include questions about FH of UC and CD for both UC and CD patients. We focused on UC patients' FH of UC, and on CD patients' FH of CD.

Clinical course is classified in the registration form according to the appearance of symptoms: one attack only; relapse-remitting; chronic continuous; acute fulminating; or unknown type. Patients are categorized as having the chronic continuous type if their symptoms continue for more than 6 months after the first attack. Acute fulminating type is applied to those whose symptoms are acute and severe with complications such as toxic megacolon, perforation, and septicemia. Classification as acute fulminating type indicates an extremely poor prognosis. Independence in daily life is classified into 5 categories: normal; some inconvenience; in need of partial support; in need of total support; and unknown. Classification is made on the basis of patients' self-assessments and their doctors' subjective opinions.

Statistical analysis

Continuous variables and categorical variables were analyzed with Fisher's exact test or the χ^2 test, as appropriate. All statistical analyses were performed with SPSS statistical software, version 18.0J (SPSS, Chicago, IL, USA); $p < 0.05$ was considered statistically significant.

Ethical considerations

Before filling out a registration form, the patients are asked by their attending doctors whether they consent to their clinical information being used for medical research. If the patients decline, the information is not recorded in the electronic data list. All data provided by the MHLW are anonymous, and researchers cannot access personal information such as the name or address of any patients.

Results

No record of sex was included in the data on 1 of the 46,114 patients registered as having UC and 1 of the 11,305 with CD; these 2 patients were excluded from the study. Table 1 shows that 2.7% of the UC patients and 2.6% of the CD patients had FH; 2.4% of the male UC patients had FH, as compared with 3.2% of the female UC patients. The male ($n = 542$) to female ($n = 611$) ratio of these patients was 0.89, while the M: F ratio of the UC patients without FH was 1.19 (male 22,330; female 18,708) ($p < 0.001$). On the other hand, among the 11,304 patients with CD, the data show no difference in the M: F ratio between patients with or without FH.

For 42,190 UC patients and 11,014 CD patients there was information about both their present age and FH. The peak age of the group without FH [FH (−) group] was 35–39 years among UC patients; in the group of patients with FH [FH (+) group], the peak age was lower than that of the FH (−) group: 30–34 years (Fig. 1). The present age was significantly lower among the patients with UC who had an FH than among those without an FH ($p < 0.001$; Mann–Whitney *U*-test). A secondary weak peak was observed at 55–59 years in both groups. Among the CD patients, the peak age in both the FH (+) and FH (−) groups was 30–34 years. No secondary peak in present age was observed in the FH (−) group, but there was a weak peak at 50–59 years in the FH (+) group.

Figure 2 shows the distribution of age at disease onset. Information about both age at onset and FH was provided by 37,282 of the patients with UC and by 9,673 of those with CD. Among the UC patients, the peak onset age was 25–29 years in the FH (−) group. In the FH (+) group, the peak onset age was lower and the range was broader: 15–25 years. Age at disease onset was lower among the UC patients with FH than among those without FH ($p < 0.001$; Mann–Whitney *U*-test). The median age of CD onset in the FH (−) group was 24 years, and that of the FH (+) group was 25 years. The peak onset age was the same in both groups: 20–24 years.

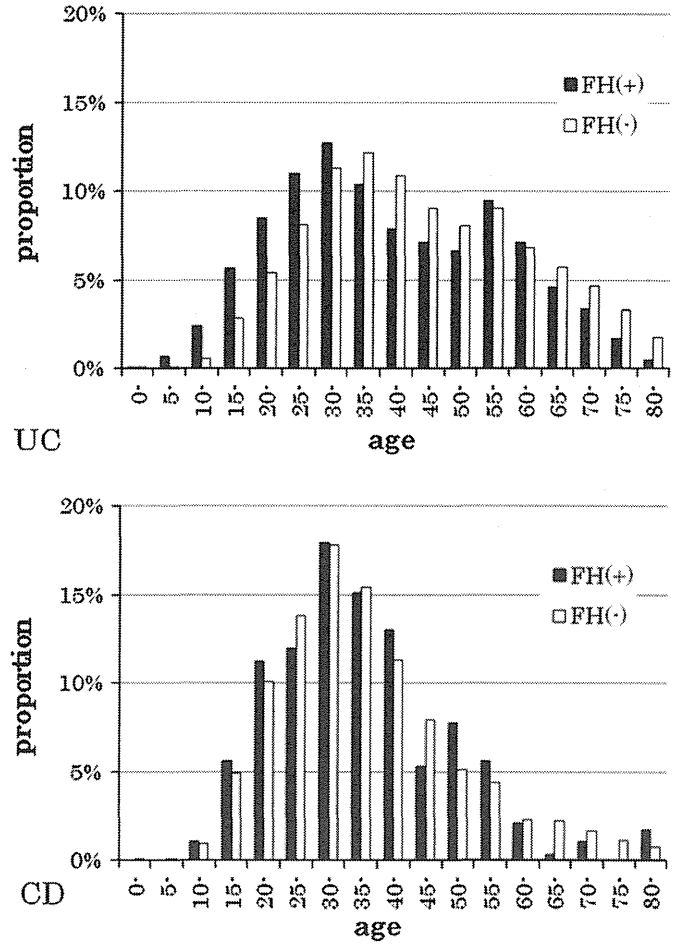


Fig. 1 Age distribution according to the presence or absence of family history (*FH*). *Vertical bars* show (number of patients in each age group divided by total number of patients) ×100. *CD* Crohn's disease, *UC* ulcerative colitis

Disease severity was graded according to Truelove and Witts' criteria for UC [10], and according to the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) score for CD [11]. After excluding data

Table 1 Numbers and percentages of UC and CD patients with and without a family history of the disease (2007)

	UC			CD		
	Total (%)[a]	Male (%)	Female (%)	Total (%)[a]	Male (%)	Female (%)
FH[b] (+)	1,153 (2.7)	542 (2.4)	611 (3.2)	284 (2.6)	195 (2.5)	89 (2.6)
FH[b] (−)	41,038 (97.3)	22,330 (97.6)	18,708 (96.8)	10,730 (97.4)	7,458 (97.5)	3,272 (97.4)
UK[c]	3,922	2,066	1,856	290	198	92
Total	46,113	24,938	21,175	11,304	7,851	3,453

The numbers in parentheses are percentages calculated after excluding unknown (UK) cases

FH family history, *FH (+)* with FH, *FH (−)* without FH, *CD* Crohn's disease, *UC* ulcerative colitis

[a] Sum of numbers of male and female patients

[b] Patients for whom valid information on FH was recorded in the registered data

[c] Patients for whom valid information on FH was not recorded in the registered data

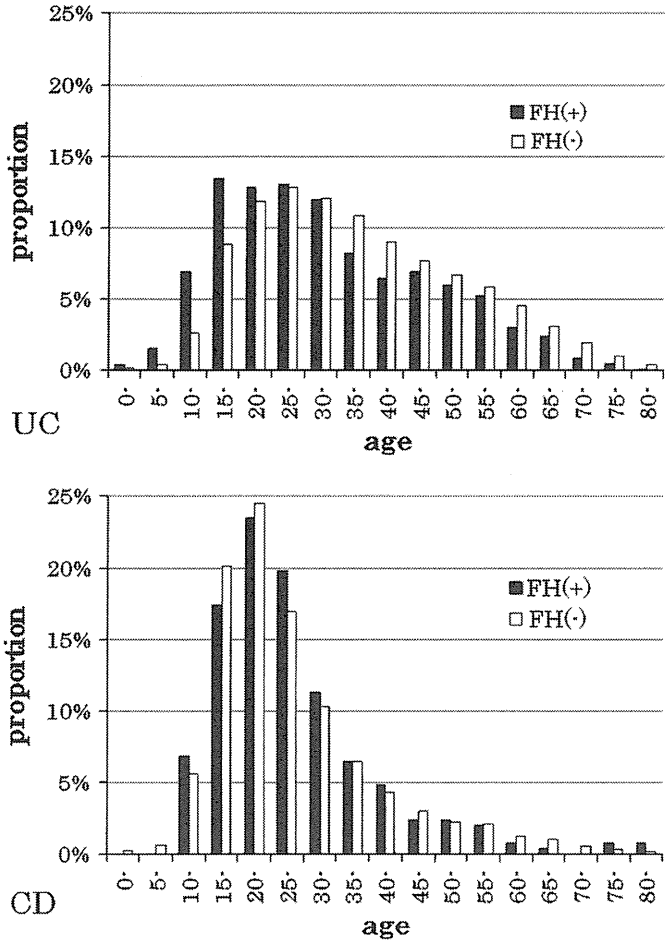
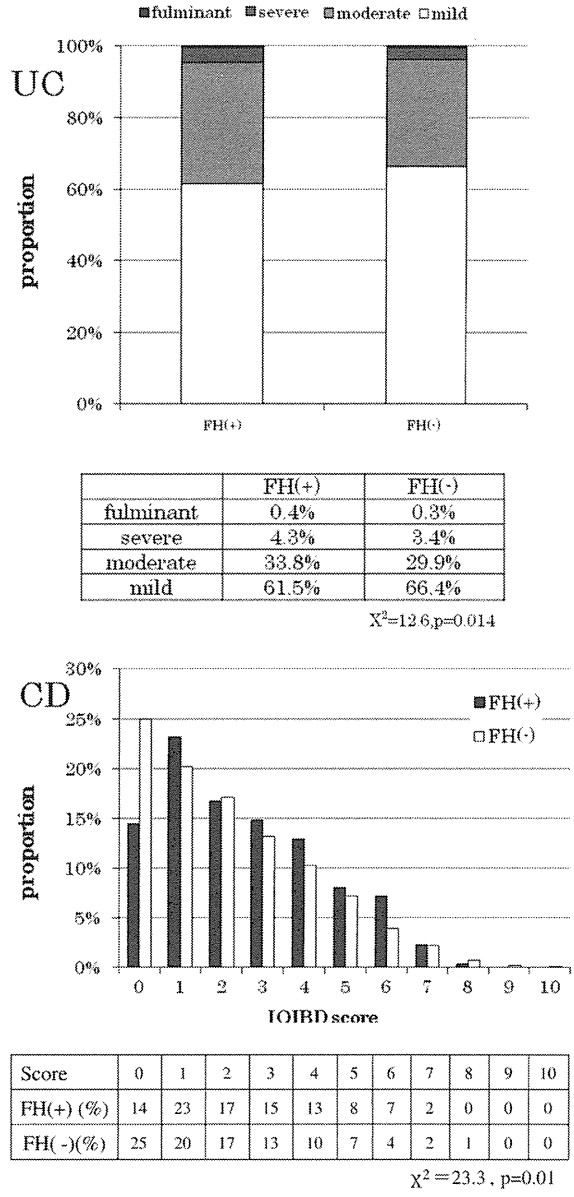


Fig. 2 Distribution of age at disease onset. *FH* family history. *Vertical bars* show (number of patients in each age group divided by total number of patients) ×100



	FH(+)	FH(-)
fulminant	0.4%	0.3%
severe	4.3%	3.4%
moderate	33.8%	29.9%
mild	61.5%	66.4%

X^2=12.6,p=0.014

Score	0	1	2	3	4	5	6	7	8	9	10
FH(+) (%)	14	23	17	15	13	8	7	2	0	0	0
FH(-)(%)	25	20	17	13	10	7	4	2	1	0	0

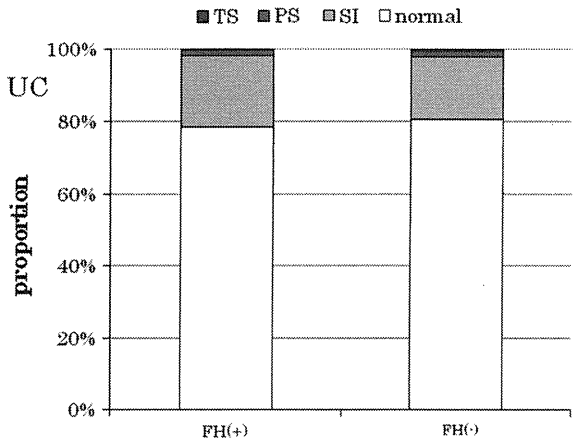
χ^2 = 23.3, p=0.01

Fig. 3 Distribution of disease severity. *UC* Truelove and Witts' criteria, modified, *CD* International Organization for the Study of Inflammatory Bowel Disease (IOIBD) score, *FH* family history

on patients who had not responded to the questions about disease severity and/or FH, those who responded that they did not know ("unknown"), and those who provided invalid information (e.g., an IOIBD score of over 10), we compared disease severity in patients with and without FH. Of the UC patients, 40,297 provided valid information about both disease severity and FH, and 9,091 CD patients provided information about both IOIBD scores and FH. In 33.3% of the UC patients without FH and 38.1% of those with FH, disease severity was moderate or severe (Fig. 3). Among the CD patients without FH, the largest group (24.9%) had an IOIBD score of 0; the largest group among the patients with FH (23.2%) had a score of 1. The differences in disease severity between the FH (+) and FH (−) groups showed statistical significance, using the χ^2 test ($\chi^2 = 12.6$, $p = 0.014$ for UC, $\chi^2 = 23.3$, $p = 0.010$ for CD). Therefore, it can be concluded that patients with FH generally have greater disease severity than patients without FH.

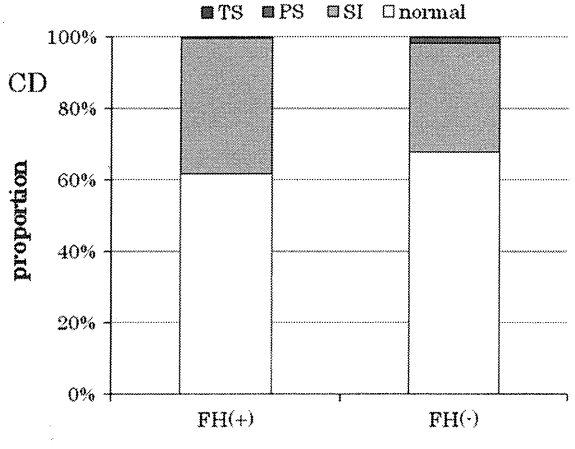
Only the registration form for UC patients included a section concerning clinical course, which was classified as: one attack only; relapse-remitting; chronic continuous; acute fulminating; or unknown type. We excluded those who did not answer the question about clinical course (946 patients, 21 of whom reported FH, and 925 of whom reported no FH) and those whose answer was "unknown", (859 patients, 28 of whom reported FH, and 831 of whom reported no FH). About 20% of the remaining patients were in the one-attack-only group, nearly 50% were in the relapse-remitting group, and nearly 25% were in the chronic continuous group. There was no significant difference in distribution between the FH (+) and FH (−) groups.

We analyzed the patient's level of independence in daily life in association with FH, age, and severity of disease. Valid data on independence in daily life, age, and FH were available for 39,375 patients with UC and 10,313 with CD. First, we compared the levels of independence in daily life



	FH(+)	FH(-)
TS	0.1%	0.3%
PS	1.6%	1.6%
SI	19.9%	17.7%
normal	78.4%	80.4%

X^2=5.28,p=0.15

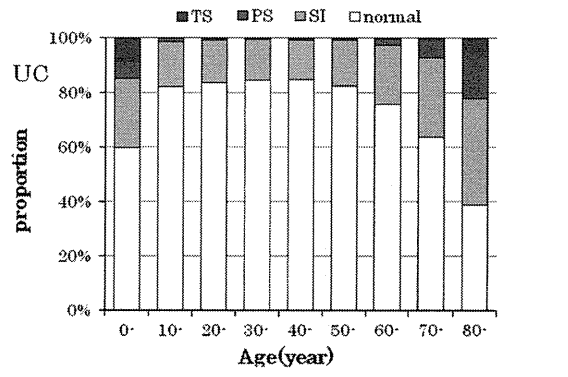


	FH(+)	FH(-)
TS	0.0%	0.2%
PS	0.4%	1.6%
SI	37.9%	30.4%
Normal	61.7%	67.8%

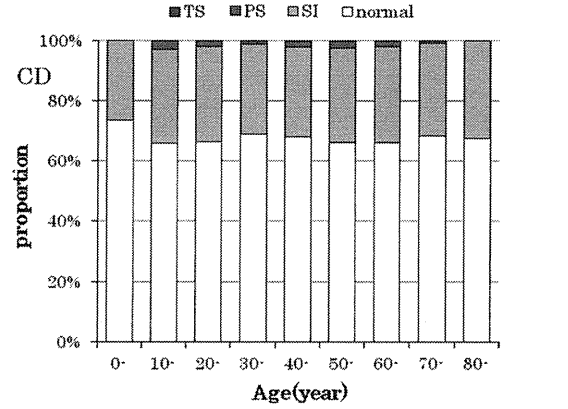
X^2=9.04,p=0.029

Fig. 4 Level of independence in daily life according to family history. *SI* some inconvenience, *PS* in need of partial support, *TS* in need of total support

between the FH (+) and FH (−) groups (Fig. 4). Among the UC patients, there was no difference in the distribution of independence levels between the 2 groups: about 80% of the patients in both groups were able to lead normal daily lives. Among the CD patients, 61.7% of the patients with FH were able to lead normal lives; the corresponding figure for the patients without FH was 67.8% ($\chi^2 = 9.04$, $p = 0.029$). Contrary to our expectations, we found no statistically significant FH-related differences in independence levels among the UC patients. However, among the patients with CD, independence levels differed between the FH (+) and FH (−) groups. Next, we analyzed the patients'



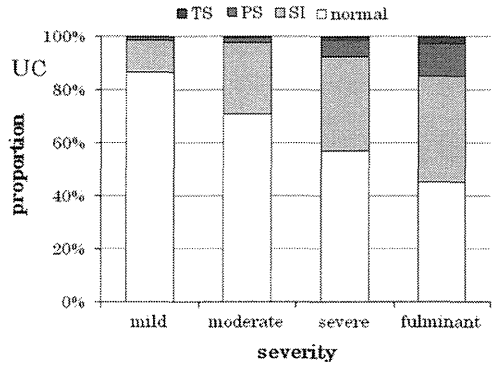
age	0-	10-	20-	30-	40-	50-	60-	70-	80-
TS(%)	8.3	0.1	0.1	0.1	0.1	0.2	0.3	1.1	4.0
PS(%)	6.3	1.3	0.5	0.5	0.6	0.6	1.9	5.5	15.4
SI(%)	25.0	15.5	14.7	13.6	13.3	15.3	20.1	26.5	34.0
normal(%)	58.3	77.2	77.2	77.7	77.9	75.5	69.0	57.8	33.6



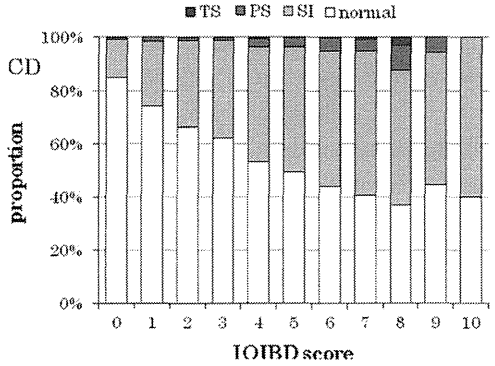
age	0-	10-	20-	30-	40-	50-	60-	70-	80-
TS(%)	0.0	3.0	1.9	0.9	1.9	2.1	1.9	1.1	0.0
PS(%)	26.7	31.2	31.5	30.2	29.8	31.2	32.1	30.6	32.5
SI(%)	73.3	65.8	66.4	68.8	68.0	66.2	66.0	68.3	67.5
normal (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Fig. 5 Level of independence in daily life according to patients' age. *SI* some inconvenience, *PS* in need of partial support, *TS* in need of total support

levels of independence in daily life according to age. Figure 5 shows that about 80% of the UC patients in their teens through 50s led normal lives, but those in their 60s and over gradually encountered difficulties in daily life ($p < 0.001$). On the other hand, about 60% of the CD patients were able to lead consistently normal lives regardless of age, whereas about 25% of them experienced some inconvenience. As shown in Fig. 6, in both the UC and CD patients, difficulties in daily life increased in line with disease severity ($p < 0.001$ in both UC and CD). About 80% of the patients with mild UC were able to lead normal lives, whereas only about 40% of those with severe UC were able to do so. Similarly, about 80% of the CD patients with IOIBD scores of 0 lived normal lives, compared with about 30% of those with IOIBD scores of 10. Thus, the independence levels were lower among the CD patients than among the UC patients, especially among the young and middle-aged CD patients with FH.



severity	mild	moderate	severe	fulminant
TS(%)	0.2	0.4	1.4	2.5
PS(%)	1.3	1.8	6.1	12.5
SI(%)	12.1	26.8	35.7	40.0
normal(%)	86.4	70.9	56.9	45.0



score	0	1	2	3	4	5	6	7	8	9	10
TS(%)	0.0	0.0	0.3	0.2	0.4	0.3	0.3	0.9	2.7	0.0	0.0
PS(%)	0.7	1.5	0.3	0.9	3.1	3.3	4.7	4.1	9.6	5.6	0.0
SI(%)	14.3	24.4	32.7	37.0	43.2	47.2	51.2	54.3	50.7	50.0	60.0
normal(%)	85.0	74.1	66.2	62.0	53.3	49.3	43.9	40.6	37.0	44.4	40.0

Fig. 6 Level of independence in daily life according to disease severity. *SI* some inconvenience, *PS* in need of partial support, *TS* in need of total support

Discussion

Several studies have investigated FH in relation to IBD. In China, for example, 1.48% of UC patients were found to have an FH [12], and a Korean study showed that 2.01% of UC patients and 1.51% of CD patients had first-degree FH [13]. It is difficult to compare our data directly with those of other epidemiological studies, because different collection methods were used. However, in Western countries, FH has been reported in 5–18% of IBD patients [8, 14–21], which is a much higher rate than that found in Asian studies, including ours. This may reflect the fact that genetic factors are related to IBD development. Of course the existence of FH does not mean directly that the patient has a certain gene or genetic characteristics, because people in the same family have similar lifestyles; namely, family members of IBD patients are exposed to environmental factors similar to those of the IBD patients. However, there are several studies that found genetic mutations specific for IBD and they are probably inherited by family members. We should consider that genetic factors are partly associated with the development of IBD. For example, according to some previous studies, gene mutations differed between different ethnic groups. The HLA-DRB1 alleles associated with UC differ between Asian and Western populations [22–27], and whereas the NOD-2 mutation is not associated with CD in Japanese [28], Chinese [29], or Koreans [30], an association has been identified in Western populations [31, 32]. Thus, the etiology of IBD appears to differ partially between Asian and Western populations. Also, it has been reported that the familial aggregation of IBD is greater among relatives of CD patients than among relatives of UC patients in Western populations [14–21]. In contrast, our study indicates that similar numbers of Japanese UC and CD patients have FHs. Further studies are needed to clarify this discrepancy between Western and Japanese populations.

In the present study, we investigated the differences in IBD characteristics between patients with and without FHs. A previous Japanese study found that 1.9% of UC patients and 1.5% of CD patients had FHs [33]; these rates are slightly lower than those found in the present study. One possible reason for this difference in rates is that improved diagnostic skills in the 15 years since the previous study was carried out have led to a higher rate of diagnosis. Also, family members of patients diagnosed with IBD might be inclined to view the appearance of gastrointestinal symptoms in themselves as a matter requiring quick medical consultation. Another possible reason for the discrepancy in the FH rates found between the previous and present studies may be the relationship between genetic factors and environmental factors, both of which are significant in the development of IBD. It is possible that IBD symptoms appear only when people with certain genetic make-ups are exposed to environmental factors that might cause IBD, such as Westernized dietary habits and better sanitation, both of which have been becoming more prevalent in Japanese society.

Our data correspond with those of Kitahora et al. [6], who reported that disease onset occurs earlier in UC patients with an FH than in those without an FH. Our data also agree with those presented in another report that showed no relation between FH and onset age in Japanese children with CD [7].

Few of the preceding studies mentioned differences in disease severity between adult patients with and without FH, although two indicated that FH had no impact on disease severity [8, 9]. However, we found that IBD patients with an FH tended to experience more severe symptoms than those without an FH. That we were able to detect this tendency may be because we examined data on a larger number of patients.