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Long-term prognosis of Japanese patients with biologic-naïve Crohn's disease treated with anti-tumor necrosis factor-α antibodies

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Background/Aims: Few reports have described the long-term treatment outcomes of the anti-tumor necrosis factor-α antibody for Japanese Crohn's disease (CD) patients. The aim of this study was to evaluate them and clarify the clinical factors that affect the long-term prognosis of the anti-tumor necrosis factor-α treatments. **Methods:** This was a retrospective, observational, single-center cohort study. Japanese CD patients treated with either infliximab or adalimumab as a first-line therapy were analyzed. The cumulative retention rates of the biologics, relapse-free survival, and surgery-free survival were analyzed using Kaplan-Meier methods. The clinical factors associated with the long-term outcomes were estimated by both the log-rank test and Cox proportional hazard model. **Results:** The cumulative retention rate was significantly higher in the group with a concomitant elemental diet of ≥900 kcal/day, baseline C-reactive protein (CRP) levels <2.6 mg/dL, and baseline serum albumin levels ≥3.5 g/dL, respectively. The baseline serum albumin levels were also associated with both relapse-free and surgery-free survival. The lack of concomitant use of an elemental diet ≥900 kcal/day was identified as the only independent risk factor for the withdrawal of the biologics. **Conclusions:** Baseline CRP levels and serum albumin levels could affect the long-term outcomes in CD patients. Concomitant elemental diet of ≥900 kcal/day could have a positive influence on clinical treatment course. **(Intest Res 2019;17:94-106)**

Key Words: Crohn disease; Infliximab; Adalimumab; Long-term prognosis

INTRODUCTION

Crohn's disease (CD) is a chronic IBD with unknown etiology. In recent years, Asian countries have had increasing numbers of CD patients.[1] Japanese patients with CD are also increasing, and the evaluation of the long-term prognosis of recent patients should be required. During long-term disease durations, many of the CD patients experience relapse and develop other GI complications, such as stenosis, fistula, or perforation, which often require surgery.[2] As for the Japanese CD patients, the rates of cumulative operations for the primary diagnosis of CD were reported at 50% to 66.4% at 10 years.[3,4] Repeated surgeries or hospitalizations usually lower the quality of life of the patient. Since there is not currently a curative treatment for CD, the key for improving long-term prognosis is to perform effective maintenance treatments after remission.

Anti-TNF-α antibodies, such as infliximab (IFX) or adalim-

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umab (ADA), provide dramatic induction of remission efficacy for CD.[5,6] These biologics are regarded as key drugs for refractory CD with moderate to severe disease activities, especially for induction of remission. After the induction of remission treatment with anti-TNF-α antibodies, a following maintenance treatment with the same biologics is standard. Although large-scale clinical trials, such as the ACCENT study[5,7] and the CHARM trial,[8] revealed the 1-year treatment outcomes after IFX and ADA administration, the long-term prognosis from maintenance treatment with these biologics is yet to be clarified. Recently, several studies using retrospective data from Western countries have revealed prognosis data for CD patients on maintenance therapies for more than 1 year.[9-14] These studies reported that, despite the maintenance biologics treatments, CD relapse rates increased year by year, indicating that both IFX and ADA had a loss of response (LOR) during the scheduled administrations. The LOR rates of IFX and ADA were estimated as 13% per patient-year and 20.3% per patient-year, respectively.[15,16]

In Japan, maintenance treatments for CD with IFX and ADA were officially approved from 2007 and 2010, respectively. However, there are still few studies, which evaluated the long-term prognosis of anti-TNF-α treatments for Japanese patients. Because the clinical[17,18] and genetic[19] backgrounds of Asian CD patients are different from those of Western patients, it is quite important to evaluate the prognosis of anti-TNF-α treatments in Japanese patients. The factors, which are associated with the long-term outcomes of anti-TNF-α treatment, are also unknown for Japanese patients. Moreover, whether concomitant treatments, such as thiopurine or elemental diet, also affect maintenance efficacy is still controversial. In order to optimize biologic, maintenance treatments and improve the prognosis of Japanese CD patients, these issues should be investigated.

In the present study, we aimed to evaluate the long-term prognosis of Japanese CD patients who were treated with either IFX or ADA as a first biologic. We also aimed to identify the clinical factors for the concomitant treatments, which affect the long-term prognosis of CD, and to discuss the best optimization for maintenance treatment with anti-TNF-α antibodies, in Japanese patients.

METHODS

1. Study Design

The present study was a retrospective, observational, cohort study at a single-center.

2. Patients

We enrolled consecutive Japanese patients, who were treated with either IFX (Mitsubishi-Tanabe Pharma, Tokyo, Japan) or ADA (EA pharma, Tokyo, Japan) as a first biologic, from Tohoku University Hospital between March 2003 and December 2016. We excluded the patients who did not receive the scheduled maintenance treatment within 8 weeks due to either primary non-response or intolerance for the agents. Primary non-response was defined as the case with stopping the biologics within induction phase (first three times administration) due to no or less response for the agents. The intolerance was defined as the case with stopping the biologics due to the adverse events. We also excluded the patients who received the biologics as a postoperative maintenance therapy. The study protocol was reviewed and approved by the Tohoku University Ethics Committee (IRB No. 2018-1-138). Written informed consent was obtained from all patients.

3. Protocol of Anti-TNF-α Antibodies Administration

The anti-TNF-α antibodies treatments were performed for the CD patients with moderate to severe disease activities, who had active luminal disease or active perianal disease. For the patients with perianal fistula with abscess, biologics were administrated only after surgical drainage. There was no indication of anti-TNF-α antibodies for the CD patients who had severe strictures or internal fistulas. During the induction phase of IFX treatment, 5 mg/kg of the drug was administered at weeks 0, 2, and 6. Subsequently, as maintenance therapy, 5 mg/kg of IFX was administered every 8 weeks. Regarding the induction phase of ADA treatment, 160 mg of the drug was injected subcutaneously at week 0. At week 2, a dose of 80 mg was administered subcutaneously. After week 4, ADA at a dose of 40 mg was administered every 2 weeks subcutaneously. The patients who were administered with either biologic dose escalation or on a shortened time interval were excluded, because such cases were judged as LOR. Concomitant thiopurine and elemental diet were defined as simultaneous usage of these at the start of the biologics. Starting thiopurine or elemental diet after biologics administration was regarded as relapse. As for thiopurines, the doses were 25 to 50 mg/body in most of the cases. The dose optimizations of thiopurine were performed by monitoring the white blood cell counts that should be adjusted within 3,000 to 4,000/μL. In the several cases, the dose was increased up to 100 mg/body. Both thio-

purine and elemental diet were basically continued during the biologics administration unless the adverse events occurred.

4. Evaluations of the Long-Term Prognosis of Maintenance Treatment

We reviewed the medical records of all enrolled patients and evaluated the cumulative retention rates of the biologics (end point: discontinuation of biologics), the cumulative relapse-free survival (end point: clinical relapse), and the surgery-free survival (end point: operation), using the Kaplan-Meier method. Following the preceding study,[11] clinical relapse was defined as the necessity of additional, internal treatment (e.g., steroids, thiopurine, dose escalation or a switching of the biologics), hospitalization due to the worsening of CD, or surgery. Discontinuation of biologics contained the cases with LOR and adverse events. Most of the patients administered biologics visited our hospital every month, and we assessed the disease status of the patients at that time.

5. Identification of the Factors Associated with Long-Term Outcomes

Association between clinical factors and the long-term prognosis was analyzed using a log-rank test. The estimated clinical factors were as follows; gender, age at diagnosis (<20 or ≥20 years), durations of disease at the start of anti-TNF therapy (<3 or ≥3 years), location of the lesion (ileal, ileocolonic, or colonic), disease condition (inflammation, stenosis, or fistula), presence of anal lesions (such as perianal fistulas and abscess, anal ulcers and anal stenosis), history of intestinal resection, concomitant elemental diet (<900 or ≥900 kcal/day), concomitant thiopurine, CRP levels at the start of the anti-TNF therapy, and serum albumin levels at the start of the anti-TNF therapy. As for the cutoff values of both CRP and serum albumin levels, the values showing the most significant differences in log-rank tests were adopted. We also perform a multivariate analysis using Cox proportional hazard model, to identify the independent risk factors that affect withdrawal of the biologics, relapse, or surgery.

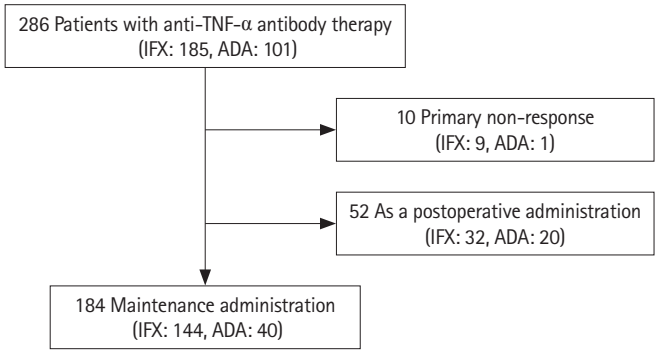

Fig. 1. Diagram of the patients administered biologics. Two hundred and eighty-six patients were enrolled and 62 patients were excluded due to several reasons such as primary non-response and postoperative maintenance. IFX, infliximab; ADA, adalimumab.

6. Statistics

Survival was estimated using the Kaplan-Meier method. The comparisons of survival between the 2 groups were analyzed using the log-rank test. Multivariate analysis, to identify the factors associated with long-term prognosis, was performed using Cox proportional hazard model. The threshold for statistical significance was P-values <0.05. All analyses were performed using JMP Pro11 (SAS institute, Tokyo, Japan) software.

RESULTS

1. Patient Characteristics

In this study, we first enrolled 286 patients. Ten primary non-response cases and 52 postoperative maintenance cases were excluded. Finally, the long-term outcomes were analyzed in the 184 cases; IFX (144 patients, 78.3%), ADA (40 patients,

Table 1. Clinical Characteristics of Study Population (n=184)

Characteristic	No. (%)
Sex (male/female)	125 (67.9)/59 (32.1)
Age at diagnosis (<20/≥20 yr)	74 (40.2)/110 (59.8)
Disease duration at the start of the biologics (<3/≥3 yr)	73 (39.7)/111 (60.3)
Disease location (ileal/ileocolonic/colonic)	26 (14.1)/125 (67.9)/ 33 (17.9)
Disease behavior (inflammatory/stricture/ fistula)	85 (46.2)/62 (33.7)/ 37 (20.1)
Anal disease (no/yes)	67 (36.4)/117 (63.6)
Previous intestinal resection (no/yes)	100 (54.3)/84 (45.7)
Concomitant elemental diet (<900/≥900 kcal/day)	154 (85.1)/27 (14.9)
Concomitant thiopurine (no/yes)	151 (82.1)/33 (17.9)
CRP levels at the baseline (<2.6/≥2.6 mg/dL)	140 (78.2)/39 (21.8)
Serum albumin levels at the baseline (<3.5/≥3.5 g/dL)	78 (43.6)/101 (56.4)
Anti-TNF-α (infliximab/adalimumab)	144 (78.3)/40 (21.7)

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21.7%) (Fig. 1). The baseline characteristics of the patients are summarized in Table 1. As for the disease duration, 111 patients (60.3%) had more than a 3-year history at the start of the anti-TNF-α treatment. Twenty-seven patients (14.9%) con-

Table 2. A Comparison of Backgrounds between ED Group and Non-ED Group

Characteristic	ED (≥900 kcal/day) groups (n=27)	Non-ED (<900 kcal/day) groups (n=154)	*P*-value
Sex (male/female)	22 (81.5)/5 (18.5)	101 (65.6)/53 (34.4)	0.1209
Age at diagnosis (<20/≥20 yr)	12 (44.4)/15 (55.6)	60 (39.0)/94 (61.0)	0.6713
Disease duration at the start of the biologics (<3/≥3 yr)	11 (40.7)/16 (59.3)	62 (40.3)/92 (59.7)	1.0000
Observation period (yr)	5.93 (2.08–7.63)	3.66 (1.69–6.44)	0.1272
Disease location (ileal/ileocolonic/colonic)	4 (14.8)/19 (70.4)/4 (14.8)	21 (13.6)/104 (67.5)/29 (18.8)	0.9023
Disease behavior (inflammatory/stricture/fistula)	11 (40.7)/14 (51.9)/2 (7.4)	73 (47.4)/46 (29.9)/35 (22.7)	0.0494
Anal disease (no/yes)	10 (37.0)/17 (63.0)	55 (35.7)/99 (64.3)	1.0000
Previous intestinal resection (no/yes)	16 (59.3)/11 (40.7)	83 (53.9)/71 (46.1)	0.6781
Concomitant thiopurine (no/yes)	24 (88.9)/3 (11.1)	125 (81.2)/29 (18.8)	0.4217
CRP levels at the baseline (<2.6/≥2.6 mg/dL)	22 (81.5)/5 (18.5)	116 (77.8)/33 (22.2)	0.8027
Serum albumin levels at the baseline (<3.5/≥3.5 g/dL)	7 (25.9)/20 (74.1)	70 (47.0)/79 (53.0)	0.0570
Anti-TNF-α (infliximab/adalimumab)	21 (77.8)/6 (22.2)	120 (77.9)/34 (22.1)	1.0000

Values are presented as number (%) or median (interquartile range).
ED, elemental diet.

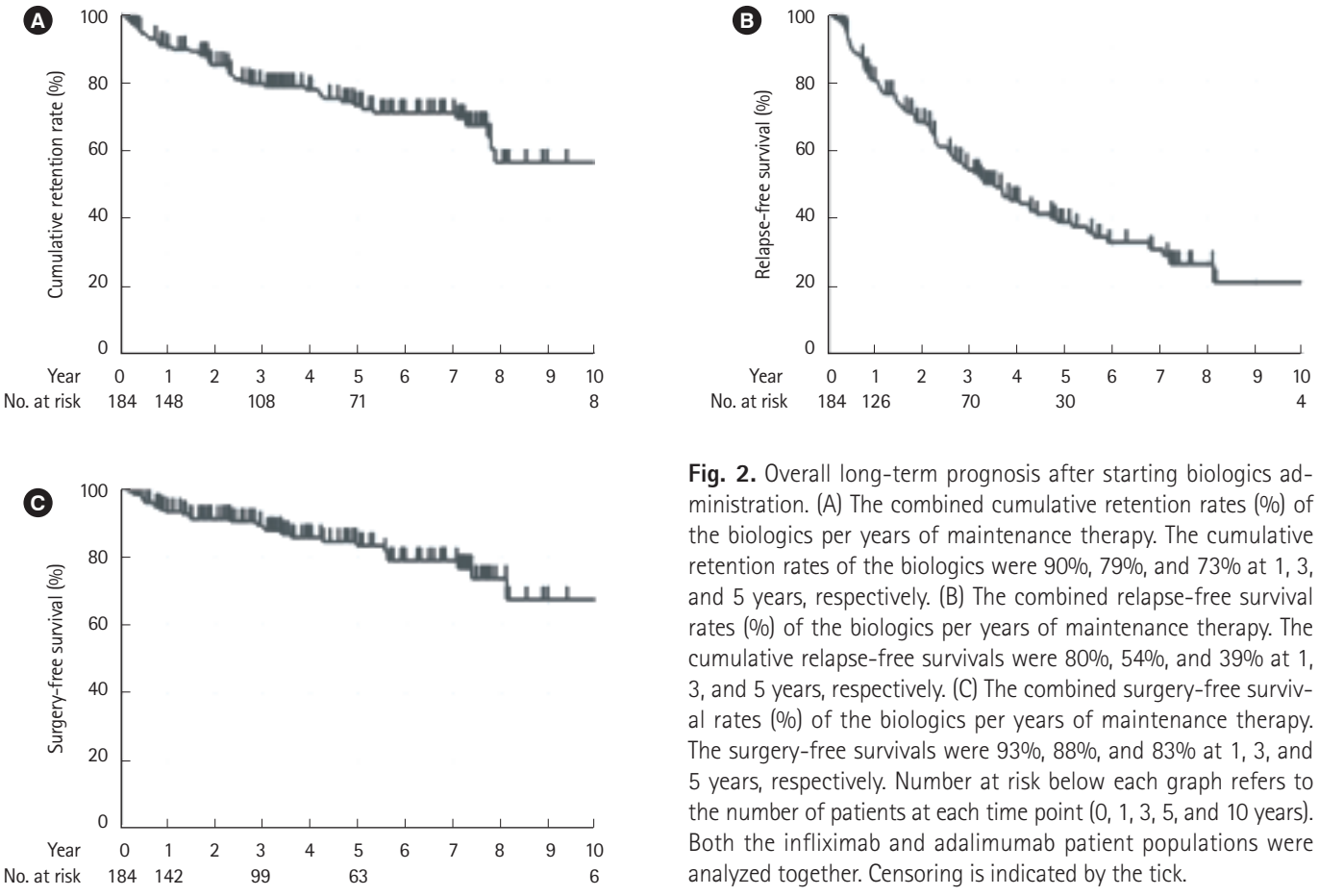


Fig. 2. Overall long-term prognosis after starting biologics administration. (A) The combined cumulative retention rates (%) of the biologics per years of maintenance therapy. The cumulative retention rates of the biologics were 90%, 79%, and 73% at 1, 3, and 5 years, respectively. (B) The combined relapse-free survival rates (%) of the biologics per years of maintenance therapy. The cumulative relapse-free survivals were 80%, 54%, and 39% at 1, 3, and 5 years, respectively. (C) The combined surgery-free survival rates (%) of the biologics per years of maintenance therapy. The surgery-free survivals were 93%, 88%, and 83% at 1, 3, and 5 years, respectively. Number at risk below each graph refers to the number of patients at each time point (0, 1, 3, 5, and 10 years). Both the infliximab and adalimumab patient populations were analyzed together. Censoring is indicated by the tick.

sumed an elemental diet of ≥900 kcal/day, and 33 patients (17.9%) were treated with concomitant thiopurine. In 39 patients (21.8%), the serum CRP levels were ≥2.6 mg/dL at the baseline. In 78 patients (43.6%), the serum albumin concentrations were <3.5 g/dL at the baseline. The median observational period was 3.74 years. There were no differences of baseline disease activity and patient backgrounds between elemental diet ≥900 kcal/day group and <900 kcal/day group (Table 2).

2. Overall Long-Term Prognosis and Adverse Events

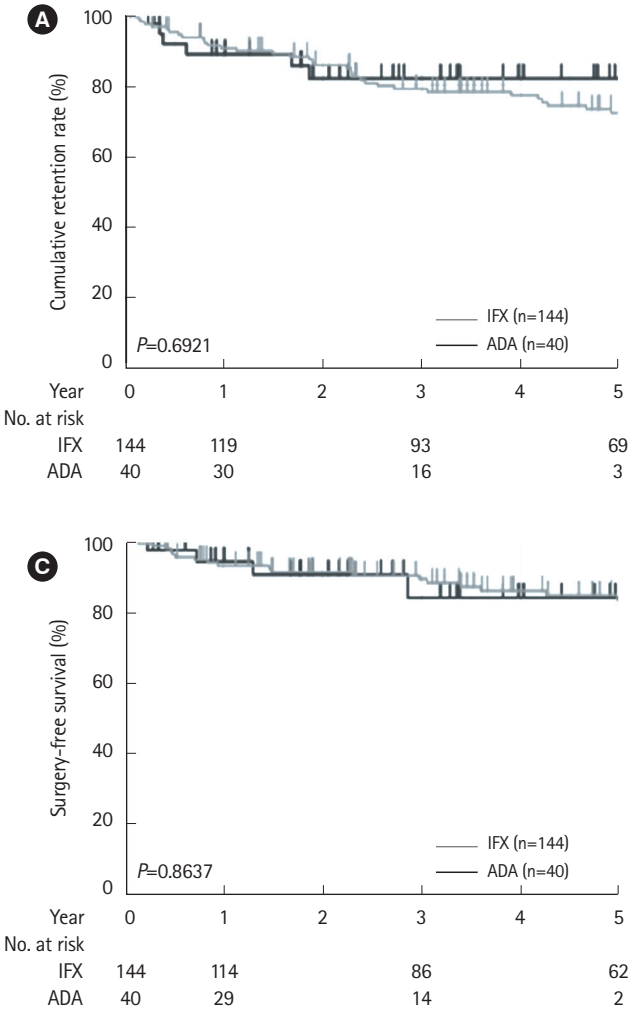
The rates of the cumulative retention of the biologics, the cumulative relapse-free survival, and the surgery-free survival are shown in Fig. 2. The cumulative retention rates of biologics were 90%, 79%, and 73% at 1, 3, and 5 years, respectively. The cumulative relapse-free survivals were 80%, 54%, and 39% at 1, 3, and 5 years, respectively. The surgery-free survivals were 93%, 88%, and 83% at 1, 3, and 5 years, respectively (Supplementary Fig. 1).

There were no differences between the IFX and ADA patient groups in the rates of the cumulative retention of the biologics, the cumulative relapse-free survival or the surgery-free survival (Fig. 3).

The adverse events of biologics were observed in 41 cases. The number of each event was as follows (including duplication), infusion reaction: 12 cases, exanthema: 10 cases, joint pain: 6 cases, muscle pain: 3 cases, labial herpes: 3 cases, ileus: 3 cases, headache: 3 cases, and others: 14 cases. The frequency of adverse events was 5.4 patients/year exposure. A total of 93 cases resulted in the biologics discontinuation due to LOR and a total of 19 cases resulted in the biologics discontinuation due to the adverse events (Supplementary Fig. 2).

3. Factors Associated with Long-Term Outcomes

The association between clinical factors and long-term outcomes, analyzed using the log-rank test, are summarized in



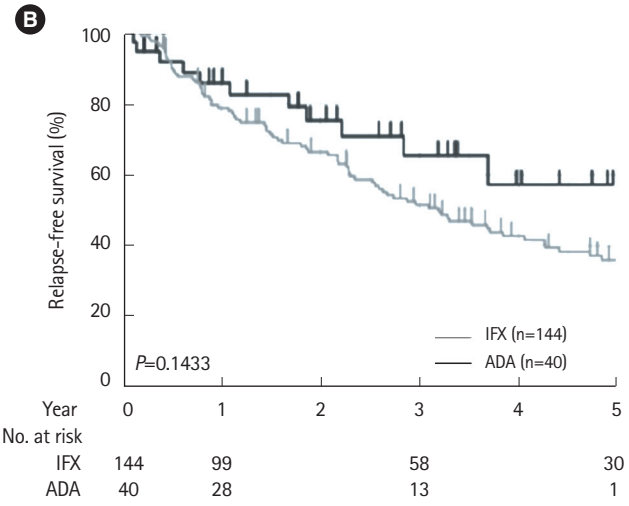


Fig. 3. The comparisons of long-term outcomes between infliximab (IFX) and adalimumab (ADA) treatments. (A) The cumulative retentions rates (%) of each biologic per years of maintenance therapy. (B) The relapse-free survival rates (%) of each biologic per years of maintenance therapy. (C) The surgery-free survival rates (%) of each biologic per years of maintenance therapy. Below each graph is the number of patients at each time point (0, 1, 3, 5, and 10 years), for each treatment. There were no differences between IFX (n=144) and ADA (n=40) in the cumulative retention rates of biologics, the cumulative relapse-free survival and the surgery-free survival. Censoring is indicated by the tick.

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Table 3. Summary of the Association between Clinical Factors and Long-Term Outcomes (Univariate Analysis)

Clinical factor	No. of patients	Cumulative retention rate	Cumulative relapse-free survival	Cumulative surgery-free survival
		P-value[a]		
Sex				
Male	125	0.0497[b]	0.4373	0.5842
Female	59			
Age at diagnosis (yr)				
<20	74	0.7545	0.8738	0.5752
≥20	110			
Disease duration at the start of the biologics (yr)				
<3	73	0.9513	0.6801	0.4236
≥3	111			
Disease location				
Ileal	26	0.2624	0.8271	0.2010
Ileocolonic	125			
Colonic	33			
Disease behavior				
Inflammatory	85	0.1904	0.7333	0.0510
Stricture	62			
Fistula	37			
Anal disease				
No	67	0.2823	0.8176	0.4921
Yes	117			
Previous intestinal resection				
No	110	0.7862	0.9922	0.1886
Yes	84			
Concomitant elemental diet (kcal/day)				
<900	154	0.0430[b]	0.9012	0.6003
≥900	27			
Concomitant thiopurine				
No	151	0.1837	0.8918	0.7960
Yes	33			
CRP levels at the baseline (mg/dL)				
<2.6	140	0.0098[b]	0.0837	0.2189
≥2.6	39			
Serum albumin levels at the baseline (g/dL)				
<3.5	78	0.0274[b]	0.0257[b]	0.0292[b]
≥3.5	101			
Anti-TNF-α antibody				
Infliximab	144	0.6921	0.1433	0.8637
Adalimumab	40			

[a]Log-rank test.
[b]Statistical significance ($P \leq 0.05$).

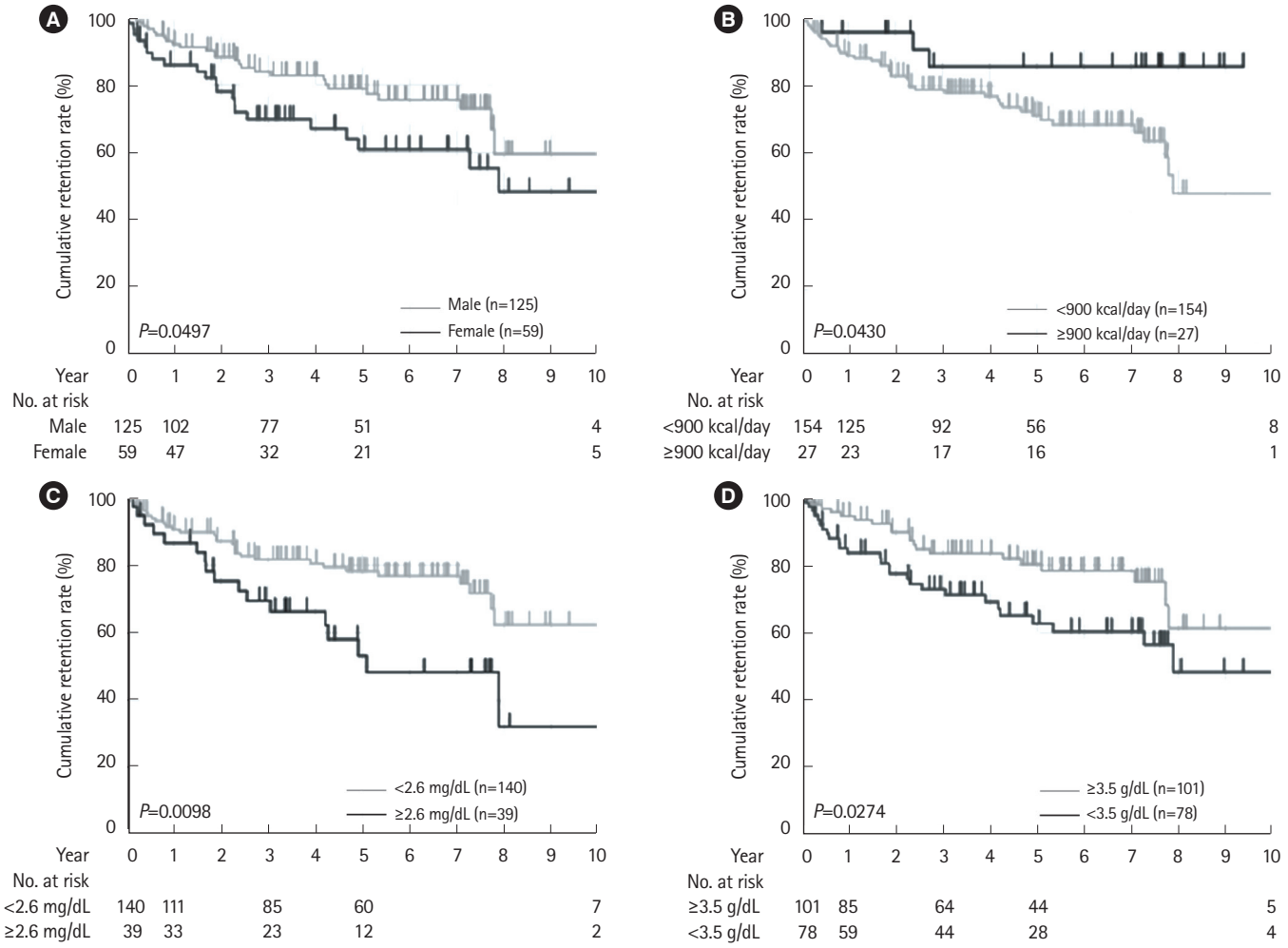

Fig. 4. The differences of cumulative retention rates for each clinical factor. (A) The combined cumulative retention rates (%) of the biologics per years of maintenance therapy separated by sex. The cumulative retention rate was significantly higher in the male group (vs. female, *P*=0.0497). (B) The combined cumulative retention rates (%) of the biologics per years of maintenance therapy separated by concomitant elemental diet. The cumulative retention rate was significantly higher in the group with concomitant elemental diet of ≥900 kcal/day (vs. <900 kcal/day, *P*=0.0430). (C) The combined cumulative retention rates (%) of the biologics per years of maintenance therapy separated by baseline CRP levels. The cumulative retention rate was significantly higher in the group with the baseline CRP levels <2.6 mg/dL (vs. ≥2.6 mg/dL, *P*=0.0098). (D) The combined cumulative retention rates (%) of the biologics per years of maintenance therapy separated by baseline serum albumin levels. The cumulative retention rate was significantly higher in the group with the baseline serum albumin levels ≥3.5 g/dL (vs. <3.5 g/dL, *P*=0.0274). Number at risk below each graph refers to the number of patients at each time point (0, 1, 3, 5, and 10 years), separated by factor. Both the infliximab and adalimumab patient populations were analyzed together. Censoring is indicated by the tick.

Table 3. The cumulative retention rates of the biologics were different when associated with gender, concomitant elemental diet, CRP levels at the baseline and serum albumin levels at the baseline.

The differences in the Kaplan-Meier curves of the cumulative retention rate of the biologics, for each clinical factor are shown in Fig. 4. The cumulative retention rate was significantly higher in the male group (vs. female, $P=0.0497$), in the group with a concomitant elemental diet of ≥900 kcal/day (vs. <900 kcal/day, $P=0.0430$), in the group with baseline CRP levels <2.6 mg/dL (vs. ≥2.6 mg/dL, $P=0.0098$), and in the group with baseline serum albumin levels ≥3.5 g/dL (vs. <3.5 g/dL, $P=0.0274$).

The differences in cumulative relapse-free survival and surgery-free survival rates between the 2 groups, divided by the baseline albumin levels, are shown in Fig. 5. The group with

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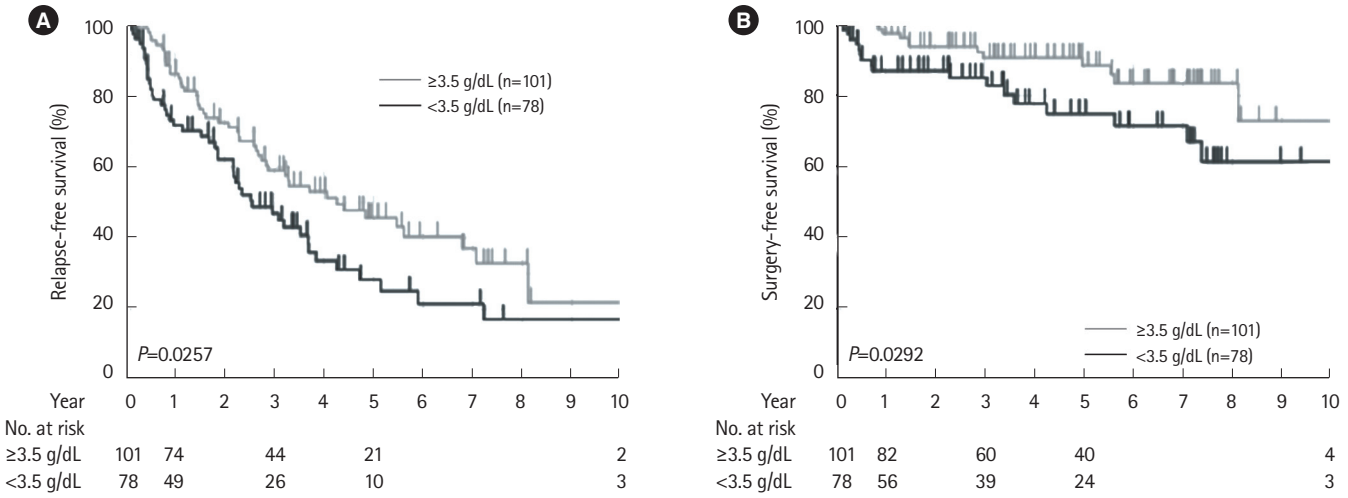

Fig. 5. The differences in cumulative relapse-free and surgery-free survival rates depending on baseline albumin levels. (A) The combined relapse-free survival rates (%) and (B) the combined surgery-free survival rates (%) of the biologics per years of maintenance therapy depending on baseline albumin levels. The group with baseline serum albumin levels ≥3.5 g/dL showed significantly higher relapse-free and surgery-free survival rates than the group with baseline serum albumin levels <3.5 g/dL (P=0.0257 and P=0.0292, respectively). Number at risk below each graph refers to the number of patients at each time point (0, 1, 3, 5, and 10 years), for each albumin level group. Both the infliximab and adalimumab patient populations were analyzed together. Censoring is indicated by the tick.

baseline serum albumin levels ≥3.5 g/dL showed significantly higher relapse-free survival and surgery-free survival rates than the group with baseline serum albumin levels <3.5 g/dL (P=0.0257 and P=0.0292, respectively).

The results of the multivariate analysis using Cox proportional hazard model are summarized in Table 4. The lack of concomitant use of an elemental diet ≥900 kcal/day was identified as the only independent risk factor for the withdrawal of the biologics (HR, 3.19, 95% CI, 1.02–13.89; P=0.045).

DISCUSSION

In this study, we investigated the long-term prognosis of Japanese patients with biologic-naïve CD treated with either IFX or ADA. It is well known that the genetic backgrounds of CD patients are different among races, especially between the Asian and the Western patients.[19] Since, the disease phenotype, clinical course, the response to the treatment including the biologics could be also different among races.[17,18] Although several studies from the West reported the long-term prognosis of biologics, there have been few reports from the Asian countries. Therefore, it is worth evaluating the long-term outcomes of biologics in the Japanese population. Previous studies on Western CD patients revealed that, during the maintenance of remission treatment with IFX or ADA, the LOR rates gradually increased year by year.[9,11,15,16,20,21] The LOR rates of both IFX and ADA were estimated as 13% per patient-year and 20.3% per patient-year, respectively.[15,20] The present study, which included only Japanese patients, also showed that 10% to 20% of the patients relapsed per year while receiving a maintenance treatment with either IFX or ADA. These data indicated that LOR rates in the maintenance of remission treatment with anti-TNF-α antibodies did not differ between Western and Japanese patient populations. In this study, there were no differences between IFX and ADA treatments for long-term prognosis. These results were consistent with the recent, observational, cohort study from Australia and New Zealand.[21]

In the present research, we also investigated the factors associated with the long-term outcomes of anti-TNF-α therapies. There were few reports, which described the association between either baseline CRP levels or albumin levels and the long-term treatment outcomes with anti-TNF-α antibodies for CD. In general, higher CRP levels reflect a higher disease activity. It has been reported that a higher disease activity during the induction phase of the biologics could lead to the production of greater amounts of anti-drug antibodies.[22-25] Therefore, higher CRP levels at the baseline could indicate a worse long-term treatment outcome, due to an elevated immune response to the treatment drugs, which could cause increased LOR. Serum albumin levels are also known to affect the pharmacokinetics of the biologics. It has been reported that low se-

Table 4. Risk Factors Associated with Log-Term Prognosis (Multivariate Analysis)

Risk factor	No. of patients	Withdrawal of the biologics		Relapse		Surgery	
		HR (95% CI)	*P*-value[a]	HR (95% CI)	*P*-value[a]	HR (95% CI)	*P*-value[a]
Sex							
Male	125	1	0.0787	1	0.7359	1	0.5631
Female	59	1.81 (0.93–3.51)		1.09 (0.65–1.81)		1.30 (0.53–3.13)	
Age at diagnosis (yr)							
<20	74	1	0.5888	1.10 (0.69–1.76)	0.6840	1	0.5704
≥20	110	1.21 (0.62–2.44)		1		1.29 (0.54–3.24)	
Disease duration (yr)							
<3	73	1.19 (0.55–2.57)	0.6541	1.02 (0.60–1.73)	0.9501	1	0.8994
≥3	111	1		1		1.07 (0.40-3.01)	
Disease location							
Ileal	26	1	0.2235	1.24 (0.54–2.78)	0.8546	4.57 (0.89–34.50)	0.1586
Ileocolonic	125	2.10 (0.71–8.98)		1.15 (0.64–2.20)		3.15 (0.83–20.73)	
Colonic	33	1.16 (0.30–5.70)		1		1	
Disease behavior							
Inflammatory	85	1	0.0521	1	0.6233	1	0.2251
Stricture	62	2.02 (0.81–4.88)		1.20 (0.63–2.29)		2.04 (0.59–7.25)	
Fistula	37	3.84 (1.30–11.29)		1.46 (0.67–3.10)		3.42 (0.85–14.09)	
Anal disease							
No	67	1.43 (0.70–2.86)	0.3244	1.11 (0.67–1.82)	0.6879	1.35 (0.55–3.18)	0.4999
Yes	117	1		1		1	
Previous intestinal resection							
No	100	2.20 (0.84–6.00)	0.1091	1.11 (0.48–1.66)	0.7429	1.15 (0.36–3.79)	0.8161
Yes	84	1		1		1	
Combined elemental diet (kcal/day)							
<900	154	3.15 (1.02–13.89)	0.0454[b]	1	0.9297	1.14 (0.36–4.52)	0.8339
≥900	27	1		1.03 (0.60–2.07)		1	
Combined thiopurine							
No	151	1	0.1921	1	0.8787	1	0.5427
Yes	33	1.66 (0.76–3.39)		1.05 (0.57–1.80)		1.37 (0.47–3.57)	
CRP level (mg/dL)							
<2.6	140	1	0.0804	1	0.1564	1	0.1618
≥2.6	39	1.97 (0.92–4.16)		1.50 (0.85–2.58)		2.04 (0.74–5.27)	
Serum albumin level (g/dL)							
<3.5	78	1.24 (0.63–2.43)	0.5377	1	0.0832	1.88 (0.78–4.57)	0.1566
≥3.5	101	1		1.50 (0.95–2.37)		1	
Anti-TNF-α antibody							
Infliximab	144	1.47 (0.62–4.08)	0.3948	1.78 (0.91–3.82)	0.0924	1	0.9719
Adalimumab	40	1		1		1.02 (0.27–3.02)	

[a]Cox proportional hazard model.
[b]Statistical significance ($P \leq 0.05$).

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rum albumin levels increase the clearance of IFX.[22,26] Thus, the concentration of the biologics could be decreased in the patients with low serum albumin levels. Furthermore, lower drug concentrations at the induction phase could lead to the generation of greater amounts of anti-drug antibodies by inhibiting the immunological tolerance.[27] According to these possible mechanisms, it is reasonable that both higher CRP and lower albumin levels at baseline could indicate worse the long-term treatment outcomes.

The results of the present study showed that the cumulative retention rate was significantly higher in the group with a concomitant elemental diet of ≥900 kcal/day group. Elemental diet has been known to improve the nutritional status and reduce the inflammation of intestine in CD patients. Because of its excellent safety, it is regarded as one of the first-line treatments for adult CD patients in Japan. The previous randomized control study, which did not include patients treated with biologics, confirmed that the maintenance treatment with an elemental diet of ≥900 kcal/day, called "half-ED," independently prevented the relapse of CD.[28] Recently, the patients treated with ED alone are decreasing because of the progress in medicine including the biologics. However, ED treatment is still considered to be an important treatment combined with drug therapy both in induction and maintenance of remission. The results of our study indicated that half-ED could be effective in improving the long-term prognosis of CD patients treated with anti-TNF-α antibodies, by extending the cumulative retention efficacy of the treatments. Indeed, several retrospective studies from Japanese institutions have reported that the patients, who were treated with IFX and a concomitant elemental diet, exhibited better long-term outcomes than those who were treated with IFX alone.[29-33] The present study strongly supports this previous evidence of the increase in IFX efficacy. Our data, including the patients treated with ADA, suggested that the concomitant half-ED could also be effective in the maintenance treatment of ADA. Concerning ADA treatment, concomitant half-ED therapy reduced ADA-LOR in IFX-intolerant or refractory CD patients.[34] Our present study results support these findings. In the present study, there were no patients with full ED. The long-term outcomes were not different among 3 groups (no elemental diet, concomitant elemental diet of <900 kcal/day, concomitant elemental diet of ≥900 kcal/day) (data are not shown). However, half- ED (ED ≥900 kcal/day) group had significantly better cumulative retention rate than the ED <900 kcal/day group which included no-ED cases. We think that concomitant ED at least ≥900 kcal/day would be quite important to improve the long-term outcomes according to these results.

Another discussion point is the discrepancy in the results of elemental diet. Significant effectiveness of ED was found only in the cumulative retention rates, but neither in the relapse-free survivals nor cumulative surgery-free survivals. The definition of relapse of the present study was the necessity of additional, internal treatment, hospitalization, or surgery. The relapse cases included various disease severities or clinical courses. We considered that picking up the recurrence cases widely could make it difficult to detect the efficacy of ED treatment in the relapse-free survivals. On the other hands, the number of the surgery cases was relatively small. We considered that the efficacy of ED treatment in the surgery-free survivals could not be proved because of the sample size.

Determining the mechanism for the combination effect seen when combining elemental diet and the treatment with anti-TNF-α biologics is important to improving long-term outcomes in CD patients. Here, we propose 3 possible hypotheses concerning the effects of concomitant half-ED and anti-TNF-α biologics for improving the long-term outcomes of the biologics. The first is the direct add-on effect of half-ED in reducing bowel inflammation. The second is the indirect effect of lowering the disease activity, which could result in less production of anti-drug antibodies.[27] The third is the indirect effect of improving of serum albumin levels, which could inhibit the clearance of the biologics.[22,26] To clarify both the necessity of a concomitant elemental diet with either IFX or ADA treatment, and its mechanisms in improving the long-term outcomes in CD patients more thoroughly, a prospective, randomized control trial is required. It is also important to know whether the concomitant elemental diet affect the concentration of anti-drug antibodies and the trough value of serum biologics concentration in the future study.

In this study, concomitant thiopurine use did not affect the long-term prognosis. A previous study described significantly improved outcomes in the combination treatment of IFX and thiopurines, both in the induction phase,[35] and in the maintenance phase.[21] A subanalysis of the DIAMOND study revealed that higher 6-thioguanin nucleotide levels tended to be negative for anti-ADA antibodies.[36] The efficacy of concomitant thiopurine use in the maintenance treatment with ADA is still controversial. We consider that this interpretation of our results is difficult because of the small patient population size, and the selection bias due to the retrospective study design. Further prospective studies are required to determine wheth-

er the combination therapy of thiopurine with anti-TNF-α antibodies is superior to the mono-therapy in Japanese CD patients.

The limitations of the present study include: the retrospective study design, use of patients from a single-center, and the imbalance in the patient numbers between the IFX and ADA treatments. Important clinical factors, such as the CD activity index, BMI and smoking habits were not analyzed in the present study, because of lacking data due to the retrospective nature of the research. It was also an important limitation in that 160 out of 184 patients of the present study were administered biologics before dose intensification became available in Japan. The sample number would be too small to analyze if we exclude the patients administered biologics before dose intensification became available. Sinse we did not limit the time span of patient enrollment regardless of dose intensification available. Overfitting of our study could be problematic since we performed several multivariate analyses. The use of 3 outcomes (the rates of cumulative retention of biologics, cumulative relapse-free survival and surgery-free survival) makes it difficult to identify the true factor that affects the long-term prognosis. However, we believe that we need to conduct a prospective study to identify the true factor that affects long-term prognosis, from the clinical factors we detected in the present study.

In conclusion, both the baseline CRP levels and serum albumin levels could affect the long-term outcomes when treating with anti-TNF-α biologics for CD. Additionally, concomitant half-ED could improve the long-term retention rates of these biologics.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Conceptualization: Endo K, Kakuta Y, and Kinouchi Y. Methodology: Moroi R, Yamamoto K, Endo K, Naito T, and Kuroha M. Formal analysis: Moroi R, Yamamoto K, Onodera M, Kanazawa Y, and Kimura T. Writing–original draft: Moroi R, Yamamoto K, and Endo K. Writing–review and editing: Masamune A and Shimosegawa T. Approval of the final manuscript: All authors.

REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46-54.e42.
2. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012; 380:1590-1605.
3. Oriuchi T, Hiwatashi N, Kinouchi Y, et al. Clinical course and longterm prognosis of Japanese patients with Crohn's disease: predictive factors, rates of operation, and mortality. J Gastroenterol 2003;38:942-953.
4. Sato Y, Matsui T, Yano Y, et al. Long-term course of Crohn's disease in Japan: incidence of complications, cumulative rate of initial surgery, and risk factors at diagnosis for initial surgery. J Gastroenterol Hepatol 2015;30:1713-1719.
5. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-1549.
6. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006; 130:323-333.
7. Sands BE, Blank MA, Patel K, van Deventer SJ; ACCENT II Study. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol 2004;2:912-920.
8. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.
9. Eshuis EJ, Peters CP, van Bodegraven AA, et al. Ten years of infliximab for Crohn's disease: outcome in 469 patients from 2 tertiary referral centers. Inflamm Bowel Dis 2013;19:1622-1630.
10. Stein DJ, Ananthakrishnan AN, Issa M, et al. Impact of prior irregular infliximab dosing on performance of long-term infliximab maintenance therapy in Crohn's disease. Inflamm Bowel Dis 2010;16:1173-1179.
11. Sprakes MB, Ford AC, Warren L, Greer D, Hamlin J. Efficacy, tolerability, and predictors of response to infliximab therapy

for Crohn's disease: a large single centre experience. J Crohns Colitis 2012;6:143-153.
12. Bouguen G, Trouilloud I, Siproudhis L, et al. Long-term outcome of non-fistulizing (ulcers, stricture) perianal Crohn's disease in patients treated with infliximab. Aliment Pharmacol Ther 2009;30:749-756.
13. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492-500.
14. Orlando A, Renna S, Mocciaro F, et al. Six year adalimumab efficacy in steroid-dependent Crohn's disease patients: a prospective single-center real life study. Dig Liver Dis 2016;48:1314-1317.
15. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011;106:674-684.
16. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol 2009;104:760-767.
17. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018;390:2769-2778.
18. Vegh Z, Kurti Z, Lakatos PL. Epidemiology of inflammatory bowel diseases from west to east. J Dig Dis 2017;18:92-98.
19. Fuyuno Y, Yamazaki K, Takahashi A, et al. Genetic characteristics of inflammatory bowel disease in a Japanese population. J Gastroenterol 2016;51:672-681.
20. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:2118-2124.
21. Doecke JD, Hartnell F, Bampton P, et al. Infliximab vs. adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study. Aliment Pharmacol Ther 2017;45:542-552.
22. Ordás I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012;91:635-646.
23. Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. Aliment Pharmacol Ther 2015;41:1094-1103.
24. Buurman DJ, Maurer JM, Keizer RJ, Kosterink JG, Dijkstra G. Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice. Aliment Pharmacol Ther 2015;42:529-539.
25. Steenholdt C, Bendtzen K, Brynskov J, Ainsworth MA. Optimizing treatment with TNF inhibitors in inflammatory bowel disease by monitoring drug levels and antidrug antibodies. Inflamm Bowel Dis 2016;22:1999-2015.
26. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946-964.
27. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol 2013;9:164-172.
28. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: a randomized-controlled trial. Aliment Pharmacol Ther 2006;24:1333-1340.
29. Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease. J Gastroenterol 2010;45:24-29.
30. Sazuka S, Katsuno T, Nakagawa T, et al. Concomitant use of enteral nutrition therapy is associated with sustained response to infliximab in patients with Crohn's disease. Eur J Clin Nutr 2012;66:1219-1223.
31. Hirai F, Ishihara H, Yada S, et al. Effectiveness of concomitant enteral nutrition therapy and infliximab for maintenance treatment of Crohn's disease in adults. Dig Dis Sci 2013;58:1329-1334.
32. Kamata N, Oshitani N, Watanabe K, et al. Efficacy of concomitant elemental diet therapy in scheduled infliximab therapy in patients with Crohn's disease to prevent loss of response. Dig Dis Sci 2015;60:1382-1388.
33. Nguyen DL, Flores S, Sassi K, Bechtold ML, Nguyen ET, Parekh NK. Optimizing the use of anti-tumor necrosis factor in the management of patients with Crohn's disease. Ther Adv Chronic Dis 2015;6:147-154.
34. Sugita N, Watanabe K, Kamata N, et al. Efficacy of a concomitant elemental diet to reduce the loss of response to adalimumab in patients with intractable Crohn's disease. J Gastroenterol Hepatol 2018;33:631-637.
35. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-1395.
36. Nakase H, Motoya S, Matsumoto T, et al. Significance of mea-

surement of serum trough level and anti-drug antibody of adalimumab as personalized pharmacokinetics in patients with Crohn's disease: a subanalysis of the DIAMOND trial. Aliment Pharmacol Ther 2017;46:873-882.

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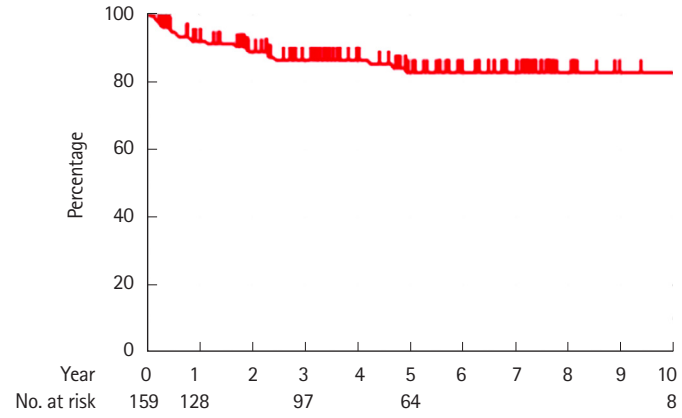
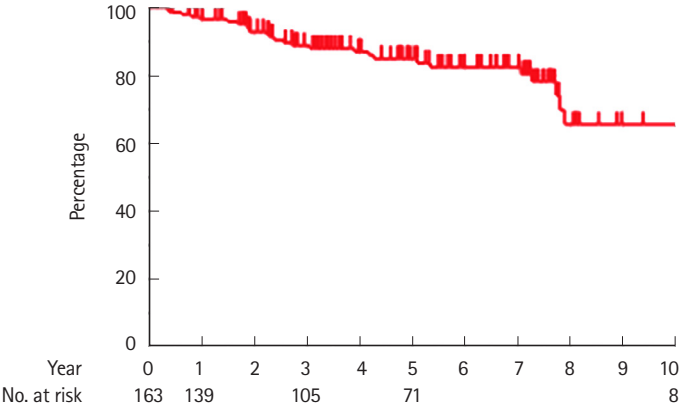
See "Long-term prognosis of Japanese patients with biologic-naïve Crohn's disease treated with anti-tumor necrosis factor-α antibodies" on page 94-106.



Supplementary Fig. 1. Cumulative retention rate (exclude loss of response).



Supplementary Fig. 2. Cumulative retention rate (exclude adverse effects).