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 of ≥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(1):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-
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-\(\alpha\) Antibodies Administration
The anti-TNF-\(\alpha\) 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 administered only after surgical drainage. There was no indication of anti-TNF-\(\alpha\) 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 severe cases, the dose was increased up to 100 mg/body. Both thio-

Methods

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

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 (76.9)/33 (19.7) |
| 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) |

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.
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.
sisted 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 retention 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.
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<sup>a</sup> |
|----------------------------------------|-----------------|---------------------------|---------------------------------|---------------------------------|---------------------|
| Sex                                    |                 |                           |                                 |                                 |                     |
| Male                                   | 125             | 0.049<sup>b</sup>         | 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<sup>b</sup>        | 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<sup>b</sup>        | 0.0837                          | 0.2189                          |                     |
| ≥2.6                                   | 39              |                           |                                 |                                 |                     |
| Serum albumin levels at the baseline (g/dL) |             |                           |                                 |                                 |                     |
| <3.5                                   | 78              | 0.0274<sup>a</sup>        | 0.0257<sup>a</sup>              | 0.0292<sup>a</sup>              |                     |
| ≥3.5                                   | 101             |                           |                                 |                                 |                     |
| Anti-TNF-α antibody                    |                 |                           |                                 |                                 |                     |
| Infliximab                             | 144             | 0.6921                    | 0.1433                          | 0.8637                          |                     |
| Adalimumab                             | 40              |                           |                                 |                                 |                     |

<sup>a</sup>Log-rank test.

<sup>b</sup>Statistical significance (P<0.05).
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 $\geq 900$ kcal/day (vs. $< 900$ kcal/day, $P=0.0430$), in the group with baseline CRP levels $< 2.6$ mg/dL (vs. $\geq 2.6$ mg/dL, $P=0.0098$), and in the group with baseline serum albumin levels $\geq 3.5$ 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...
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. Since, the disease phenotype, clinical course, the response to the treatment including the biologics could be also different among races. 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. The LOR rates of both IFX and ADA were estimated as 13% per patient-year and 20.3% per patient-year, respectively. 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.

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. 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 HR (95% CI) | P-value<sup>a</sup> | Relapse HR (95% CI) | P-value<sup>a</sup> | Surgery HR (95% CI) | P-value<sup>a</sup> |
|------------------------------|-----------------|----------------------------------------|----------------------|---------------------|----------------------|---------------------|---------------------|
| **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)                       | 1.29 (0.54–2.24)     |                     |                      |                     |                     |
| **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)     |                     |                      |                     |                     |
| Colonic                      | 33              | 1.16 (0.30–5.70)                       | 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<sup>b</sup>   | 1                   | 0.9297               | 1.14 (0.36–4.52)    | 0.8339              |
| ≥900                         | 27              | 1                                      | 1.03 (0.60–2.07)     |                     |                      |                     |                     |
| **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)    |                      |                     |                     |

<sup>a</sup>Cox proportional hazard model.  
<sup>b</sup>Statistical significance (P<0.05).
rum albumin levels increase the clearance of IFX.\textsuperscript{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.\textsuperscript{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 $\geq 900$ kcal/day group. Elemental diet has been known to improve the nutritional status and reduce the inflammation in 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 $\geq 900$ kcal/day, called “half-ED,” independently prevented the relapse of CD.\textsuperscript{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-$\alpha$ 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.\textsuperscript{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.\textsuperscript{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 $\geq 900$ kcal/day) (data are not shown). However, half-ED (ED $\geq 900$ 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 $\geq 900$ 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-$\alpha$ 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-$\alpha$ 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.\textsuperscript{27} The third is the indirect effect of improving of serum albumin levels, which could inhibit the clearance of the biologics.\textsuperscript{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,\textsuperscript{35} and in the maintenance phase.\textsuperscript{36} A subanalysis of the DIAMOND study revealed that higher 6-thioguanin nucleotide levels tended to be negative for anti-ADA antibodies.\textsuperscript{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. Since 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.

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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).