Long-term clinical and real-world experience with Crohn’s disease treated with anti-tumor necrosis factor-α antibodies

Haruka Otake*, Satohiro Matsumoto*, Hirosato Mashima
Department of Gastroenterology, Jichi Medical University Saitama Medical Center, Saitama, Japan

Background/Aims: Although anti-tumor necrosis factor (TNF)-α agents are important therapeutic drugs for Crohn’s disease (CD), data regarding their long-term sustained effects are limited. Herein, we evaluated the long-term loss of response (LOR) to anti-TNF-α agents in patients with CD. Methods: This retrospective study included patients with CD who started treatment with infliximab or adalimumab as a first-line therapeutic approach. The cumulative event-free, retention, and surgery-free rates after the start of biological therapy were analyzed. Secondary LOR was analyzed in patients who achieved corticosteroid-free clinical remission after the start of biological therapy. Cox proportional hazards models were used to analyze the predictive factors of secondary LOR. Results: The cumulative event-free rates at 1, 2, 5, and 10 years were 83.3%, 75.1%, 37.4%, and 23.3%, respectively. The incidence of LOR was 10.6% per patient-year of follow-up. At 12–14 weeks after the start of biological therapy, the proportion of patients with a C-reactive protein to albumin (CRP/ALB) ratio ≥ 0.18 was significantly higher in patients with LOR (P < 0.001). Multivariate analysis indicates that a CRP/ALB ratio ≥ 0.18 (hazard ratio [HR], 5.86; 95% confidence interval [CI], 1.56–22.0; P = 0.009) and upper gastrointestinal tract inflammation (HR, 3.00; 95% CI, 1.26–7.13; P = 0.013) were predictive factors of secondary LOR. Conclusions: Although anti-TNF-α agents contributed to long-term clinical remission of CD, the annual incidence of secondary LOR was 10.6%. The CRP/ALB ratio at 3 months after the start of biological therapy and upper gastrointestinal tract inflammation were identified as predictive factors of secondary LOR. (Intest Res 2022;20:464-474)

Key Words: Crohn disease; Infliximab; Adalimumab; Loss of response; C-reactive protein to albumin ratio

INTRODUCTION

Crohn’s disease (CD) is a refractory inflammatory bowel disease with an unknown etiology. It is a progressive disease because inflammation of the intestinal tract persists even without clinical symptoms and causes intestinal complications such as ulcers, strictures, and fistulae. In Japan, the 2016 Nationwide Epidemiological Survey conducted by the Health and Labour Sciences Research Group reported that the number of registered patients reached 220,000 for ulcerative colitis and 70,000 for CD. Of note, the number of patients with CD is increasing yearly.¹

Biologic agents play an important role in the treatment of CD. In Japan, infliximab (IFX) was approved for the treatment of CD in 2002, followed by adalimumab (ADA) in 2010. These biologics are highly effective, not only for the induction and maintenance of remission but also for mucosal healing. These effects were demonstrated in 2 trials; the ACCENT 1 trial (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long Term Regimen) demonstrated that IFX is effective for maintaining remission for as long as 54 weeks,² and the CHARM trial (Crohn’s Trial of the Fully Human Antibody Adalimumab
for Remission Maintenance) demonstrated the efficacy of ADA for maintaining remission for as long as 54 weeks.\(^3\)

Although anti-tumor necrosis factor (TNF)-\(\alpha\) agents are important therapeutic drugs for inflammatory bowel diseases, the incidence of secondary loss of response (LOR) in some patients is a problem. LOR to anti-TNF-\(\alpha\) agents occurs in 23\% to 46\% of patients,\(^4\) and the annual rates of LOR to IFX and ADA have been reported to be 13\% per patient-year\(^5\) and 20\% per patient-year,\(^6\) respectively. Dose escalation of anti-TNF-\(\alpha\) agents is effective in some patients with LOR and both IFX and ADA have been approved for the treatment of patients who become less responsive to standard TNF-\(\alpha\) therapy in Japan; IFX was approved for dose escalation up to 10 mg/kg in 2011, and ADA was approved for dose escalation to 80 mg with 2-week intervals in 2016. In 2017, the approved dosage of IFX was 5 mg/kg at 4-week intervals. The measurement of blood concentrations of anti-TNF-\(\alpha\) antibodies and anti-drug antibodies contributes to the development of personalized therapeutic strategies appropriate for each patient.\(^7,8\) However, these values cannot be measured in real-world clinical practice in Japan, thus making the prediction of LOR to anti-TNF-\(\alpha\) antibodies an important issue.

In this study, we aimed to evaluate the long-term efficacy of and LOR to IFX and ADA in patients with CD. We also identified the clinical factors affecting secondary LOR to anti-TNF-\(\alpha\) agents and discuss the optimization of anti-TNF-\(\alpha\) therapy.

**METHODS**

**1. Patients**

This is a retrospective single-center study conducted at Saitama Medical Center. Data were obtained through a review of medical records. A total of 119 patients with CD, aged 16 years or older, who started anti-TNF-\(\alpha\) therapy (IFX or ADA) and were regularly followed up at the outpatient clinic of Saitama Medical Center between 2003 and 2020, were enrolled. The exclusion criteria were as follows: (1) patients who had experience of biological CD therapy \((n = 17)\), and (2) patients who had been treated with biologics for postoperative maintenance therapy after intestinal resection \((n = 20)\). This study thus ultimately included 82 patients \((58\) men and 24 women; mean age, 25 ± 10 years at onset; mean disease duration, 7.1 ± 8.3 years).\(^1\)

**2. Treatment Protocol of Biologics Administration**

IFX was administered at 5 mg/kg on weeks 0, 2, and 6, followed by maintenance therapy at 8-week intervals. ADA was administered at 160 mg on week 0, 80 mg on week 2, and 40 mg every 2 weeks thereafter. The concomitant use of thiopurines was allowed if they had already been continuously administered or simultaneously started with biological therapy. Thiopurines were administered at 25–50 mg/day.

**3. Evaluation of the Primary Nonresponse to Biological Therapy**

Clinical symptoms were scored using the Crohn’s Disease Activity Index (CDAI). Clinical remission was defined as a CDAI of less than 150, and patients who achieved this CDAI value and were weaned from steroids were regarded to be in corticosteroid-free clinical remission. The optimal methods or timing of assessment for the primary nonresponse (PNR) to anti-TNF agents has not been clearly defined. There are agreements in clinical trials that PNR to anti-TNF drugs should not be assessed prior to 14 or 12 weeks following initial infusions, respectively, with IFX and ADA.\(^4\) PNR was defined as a failure to achieve a CDAI of less than 150 or a 100-point decrease in the CDAI from baseline to 14 weeks after the start of biological therapy with IFX or 12 weeks after the start of biological therapy with ADA.

**4. Evaluation of the Secondary LOR to Biological Therapy**

The endpoint was the occurrence of events after the start of biological therapy. The patients were followed up until March 2021 and retrospectively analyzed. Events were defined as dose escalation of biologics (dose escalation of IFX to 10 mg/kg and dose escalation of ADA to 80 mg at 2-week intervals); switching to other biologics; the addition of prednisolone or thiopurines; hospitalization because of the exacerbation of CD; surgical treatment; and discontinuation of biologics because of adverse drug reactions to biologics, complications, and comorbidities. Secondary LOR was defined as relapse requiring a dose escalation of biologics, switching to other biologics, the addition of prednisolone or thiopurines, hospitalization because of exacerbation of CD, or surgical treatment during maintenance therapy after achievement of corticosteroid-free clinical remission after the start of biological therapy.

**5. Identification of the Factors Associated with LOR to Biological Therapy**

Only patients who achieved corticosteroid-free clinical remission after the start of biological therapy were divided into 2 groups based on whether they did (LOR group) or did not (non-
LOR group) experience LOR to biologics during maintenance therapy after achievement of corticosteroid-free clinical remission. The patient characteristics and treatment contents were compared and analyzed between these groups. In addition, multivariate analysis was conducted to identify predictive factors of secondary LOR.

6. Evaluation of the Effectiveness of Biologics after Dose Escalation

The patients were followed up until March 2021 for the endpoints of shortening of the dosing interval to a 4-week interval of IFX at 5 mg/kg and those of switching to other biologics after dose escalation of the biologics. These endpoints were retrospectively analyzed.

| Table 1. Baseline Characteristics |
|----------------------------------|
| Characteristics                  | Total (n = 82) | IFX (n = 43) | ADA (n = 39) | P-value |
| Male sex                         | 58 (70.7)      | 32 (74.4)    | 26 (66.7)    | 0.475   |
| Age at onset (yr)                | 25 ± 10 (6–58) | 24 ± 10 (10–55) | 26 ± 11 (6–58) | 0.587   |
| Age at start of biologics (yr)   | 32 ± 13 (15–66) | 32 ± 12 (16–63) | 32 ± 15 (15–66) | 0.993   |
| Duration of disease (yr)         | 7.1 ± 8.3 (0.0–36.3) | 7.8 ± 8.7 (0.2–36.3) | 6.4 ± 8.1 (0.0–29.6) | 0.470   |
| Disease location                 |               |              |              | 0.424   |
| Ileum (L1)                       | 18 (22.0)      | 11 (25.6)    | 7 (17.9)     |         |
| Colon (L2)                       | 16 (19.5)      | 6 (14.0)     | 10 (25.6)    |         |
| Ileum and colon (L3)             | 48 (58.5)      | 26 (60.5)    | 22 (56.4)    |         |
| Upper GI tract inflammation      | 18 (22.0)      | 9 (20.9)     | 9 (23.1)     | 1.000   |
| Disease phenotype                |               |              |              | 0.106   |
| Non-structuring, non-penetrating (B1) | 44 (53.7)      | 20 (46.5)    | 24 (61.5)    |         |
| Strictureing (B2)                | 24 (29.3)      | 12 (27.9)    | 12 (30.8)    |         |
| Penetrating (B3)                 | 14 (17.1)      | 11 (25.6)    | 3 (7.7)      |         |
| Extraintestinal manifestations   | 14 (17.1)      | 4 (9.3)      | 10 (25.6)    | 0.077   |
| Anal fistula                     | 25 (30.5)      | 17 (39.5)    | 8 (20.5)     | 0.092   |
| Prior ileocolonic resection      | 14 (17.1)      | 9 (20.9)     | 5 (12.8)     | 0.389   |
| Current smoking                  | 19 (23.2)      | 11 (25.6)    | 8 (20.5)     | 0.612   |
| Prior treatment                  |               |              |              | 0.004   |
| Immunomodulators                 | 35 (42.7)      | 25 (58.1)    | 10 (25.6)    |         |
| Corticosteroid                   | 57 (69.5)      | 27 (62.8)    | 30 (76.9)    | 0.230   |
| Concomitant treatment            |               |              |              | 0.617   |
| Mesalazine                       | 78 (95.1)      | 40 (93.0)    | 38 (97.4)    |         |
| Immunomodulators                 | 26 (31.7)      | 20 (46.5)    | 6 (15.4)     | 0.004   |
| Corticosteroid                   | 41 (50.0)      | 22 (51.2)    | 19 (48.7)    | 1.000   |
| Enteral nutrition                | 58 (70.7)      | 30 (69.8)    | 28 (71.8)    | 1.000   |
| Clinical examination             |               |              |              |         |
| Hemoglobin (g/dL)                | 12.0 ± 1.8 (7.4–16.5) | 11.9 ± 1.7 (8.4–14.6) | 12.2 ± 1.9 (7.4–16.5) | 0.424   |
| Leukocyte count (10^9/L)         | 7.4 ± 2.5 (1.9–14.6) | 7.3 ± 2.7 (3.0–14.6) | 7.7 ± 2.4 (2.8–13.9) | 0.811   |
| Platelet count (10^9/L)          | 386 ± 108 (171–719) | 408 ± 124 (171–719) | 362 ± 837 (177–603) | 0.055   |
| Albumin (g/dL)                   | 3.5 ± 0.6 (2.2–4.9) | 3.5 ± 0.6 (2.2–4.6) | 3.6 ± 0.5 (2.6–4.7) | 0.260   |
| C-reactive protein (mg/L)        | 20.2 ± 25.9 (0.2–142.1) | 21.4 ± 32.0 (0.2–142.1) | 19.0 ± 17.7 (0.4–51.3) | 0.681   |
| CDAI                             | 206 ± 110 (0–585) | 231 ± 101 (30–585) | 177 ± 115 (0–456) | 0.027   |

Values are presented as number (%) or mean ± standard deviation (range).

IFX, infliximab; ADA, adalimumab; GI, gastrointestinal; CDAI, Crohn’s Disease Activity Index.
7. Ethical Consideration
This study was approved by The Etiological Study Ethical Review Board of Jichi Medical University Saitama Medical Center (IRB No. S21-052). As this study used anonymized data, the requirement for informed consent was waived.

8. Statistical Analysis
Data are expressed as mean ± standard deviation or percentage. The demographic characteristics of the study subjects were compared using the Student t-test and Fisher exact test. The cumulative rates were evaluated by the Kaplan-Meier method and compared using the log-rank test. Predictive factors of LOR were analyzed with multivariate statistics by using Cox regression. The clinically important variables were included in the model. When continuous data were converted to categorical data and analyzed, a receiver operating characteristic curve was used to set a cutoff value for dividing the patients into 2 groups. All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan). Differences at P-values of less than 0.05 were regarded as significant.

RESULTS

1. Patient Characteristics
Table 1 shows the clinical characteristics of the 82 patients in the IFX and ADA groups. The proportion of patients with a history of treatment with immunomodulators was significantly higher in the IFX group (58.1%) than in the ADA group (25.6%, P = 0.004). The concomitant use of immunomodulators was significantly higher in the IFX group (46.5%) than in the ADA group (15.4%, P = 0.004). The 26 patients who were administered immunomodulators concurrently included 24 patients who received azathioprine and 2 patients who received 6-mercaptopurine. The initial dose was 0.75 ± 0.21 mg/kg/day (average, 47 ± 11 mg; range, 25–75 mg) and 0.48 ± 0.03 mg/kg/day (average, 30 mg; range, 30–75 mg), respectively. According to the blood test results at the start of biological therapy, platelet counts tended to be higher in the IFX group (P = 0.055). The CDAI at the start of biological therapy was higher in the IFX group than in the ADA group (231 ± 101 vs. 177 ± 115, P = 0.027).

2. Short-term Efficacy
PNR was evaluated at 14 weeks in the IFX group and at 12 weeks in the ADA group. The proportion of patients with PNR was 7.3% overall; 7.0% in the IFX group and 7.7% in the ADA group (P = 1.000, data not shown). The overall clinical remission rate at 2, 4–6, 12–14, 24, and 52 weeks after the start of biological therapy was 68.3%, 80.0%, 83.3%, 81.8%, and 82.4%, respectively. At the corresponding time points, the clinical remission rate in the IFX group was 73.0%, 76.9%, 81.0%, 75.6%, and 75.0%, respectively, while that in the ADA group were 60.9%, 83.3%, 86.1%, 88.9%, and 91.2%, respectively.

3. Long-term Prognosis and Adverse Events
The cumulative event-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 83.3%, 75.1%, 37.4%, and 23.3%, respectively (Fig. 1A). The cumulative retention rate at 1, 2, 5, and 10 years after the start of biological therapy was 97.4%, 94.7%, 78.3%, and 60.1%, respectively (Fig. 1B). The cumulative dose escalation-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 87.0%, 80.9%, 50.4%, and 32.9%, respectively (Fig. 1C). The cumulative surgery-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 100%, 100%, 97.9%, and 82.5%, respectively (Fig. 1D). There was no significant difference in the cumulative event-free rate, cumulative retention rate, cumulative dose escalation-free rate, or cumulative surgery-free rate between the IFX and ADA groups (Fig. 1E-H). Adverse drug reactions were observed in 3 patients (3.7%), namely peripheral neuropathy in 1 patient, moderate infusion reaction in 1 patient, and psoriasis in 1 patient. All 3 of these patients were in the IFX group. None of these adverse drug reactions were serious. At that time, all 3 patients discontinued the use of biologics.

4. Factors Associated with Secondary LOR to Anti-TNF therapy
Only 78 patients who achieved corticosteroid-free clinical remission after the start of biological therapy were analyzed. The incidence of LOR to anti-TNF therapy was 10.6% per patient-year of follow-up. The average time from biologics initiation to the achievement of corticosteroid-free clinical remission was 2.9 ± 2.3 months (range, 0.8–12.7 months). Table 2 provides details of the patients. The most common disease location was L3 (77.4%), followed by L2 (12.9%) and L1 (9.7%) in the LOR group, whereas the most common disease location in the non-LOR group was L3 (46.8%), followed by L1 (31.9%), and L2 (21.3%), showing a significant difference between the 2 groups (P = 0.021). Upper gastrointestinal (GI) lesions associated with CD were significantly more prevalent in the LOR group (38.7%) than in the non-LOR group (12.8%, P = 0.013). The CDAI at the start of biological therapy tended to be higher in the LOR group.
Fig. 1. (A) Kaplan-Meier analysis of the cumulative event-free rate. (B) Kaplan-Meier analysis of the cumulative retention rate. (C) Kaplan-Meier analysis of the cumulative dose escalation-free rate. (D) Kaplan-Meier analysis of the cumulative surgery-free rate. (E) Kaplan-Meier analysis of the cumulative event-free rate in the infliximab (IFX) group and the adalimumab (ADA) group. (F) Kaplan-Meier analysis of the cumulative retention rate in the IFX group and the ADA group. (G) Kaplan-Meier analysis of the cumulative dose escalation-free rate in the IFX group and the ADA group. (H) Kaplan-Meier analysis of the cumulative surgery-free rate in the IFX group and the ADA group.
The ratio of C-reactive protein to albumin (CRP/ALB ratio) was reported to be a useful biomarker for the evaluation of CD activity; 

therefore, we generated a receiver operating characteristic curve to analyze CRP/ALB ratios at 12 to 14 weeks after the start of biological therapy and set the cutoff value at 0.18 (Fig. 2). The proportion of patients with a CRP/ALB ratio of 0.18 or higher was significantly higher in the LOR group (87.1%) than in the non-LOR group (44.7%, \( P < 0.001 \)). The cumulative relapse-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 88.7%, 81.1%, 53.5%, and 37.9%, respectively (Fig. 3A). In patients with a CRP/ALB ratio of 0.18 or higher, the cumulative relapse-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 84.5%, 75.4%, 41.5%, and 16.9%, respectively. The corresponding rate in patients with a CRP/ALB ratio of less than 0.18 was 96.0%, 91.6%, 76.9%, and 76.9%, respectively (\( P < 0.001 \)) (Fig. 3B). No significant differences in the cumulative relapse-free rates were observed between the IFX and ADA groups, or between patients with and without the concomitant use of thiopurines (Fig. 3C and D). Table 3 shows the results of a multivariate analysis using Cox proportional hazards models. The multivariate analysis identified a CRP/ALB ratio of 0.18 or higher (hazard ratio [HR], 5.86; 95% confidence interval [CI], 1.56–22.0; \( P = 0.009 \)) and upper GI tract inflammation (HR, 3.00; 95% CI, 1.26–7.13; \( P = 0.013 \)) as predictive factors of secondary LOR.

### 5. Long-term Prognosis after Dose-Intensified Anti-TNF Therapy

Among the 36 patients, the doses were escalated in those with (227 ± 97) than in the non-LOR group (187 ± 114, \( P = 0.114 \)). The ratio of C-reactive protein to albumin (CRP/ALB ratio) was reported to be a useful biomarker for the evaluation of CD activity; 

therefore, we generated a receiver operating characteristic curve to analyze CRP/ALB ratios at 12 to 14 weeks after the start of biological therapy and set the cutoff value at 0.18 (Fig. 2). The proportion of patients with a CRP/ALB ratio of 0.18 or higher was significantly higher in the LOR group (87.1%) than in the non-LOR group (44.7%, \( P < 0.001 \)). The cumulative relapse-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 88.7%, 81.1%, 53.5%, and 37.9%, respectively (Fig. 3A). In patients with a CRP/ALB ratio of 0.18 or higher, the cumulative relapse-free rate at 1, 2, 5, and 10 years after the start of biological therapy was 84.5%, 75.4%, 41.5%, and 16.9%, respectively. The corresponding rate in patients with a CRP/ALB ratio of less than 0.18 was 96.0%, 91.6%, 76.9%, and 76.9%, respectively (\( P < 0.001 \)) (Fig. 3B). No significant differences in the cumulative relapse-free rates were observed between the IFX and ADA groups, or between patients with and without the concomitant use of thiopurines (Fig. 3C and D). Table 3 shows the results of a multivariate analysis using Cox proportional hazards models. The multivariate analysis identified a CRP/ALB ratio of 0.18 or higher (hazard ratio [HR], 5.86; 95% confidence interval [CI], 1.56–22.0; \( P = 0.009 \)) and upper GI tract inflammation (HR, 3.00; 95% CI, 1.26–7.13; \( P = 0.013 \)) as predictive factors of secondary LOR.

### 5. Long-term Prognosis after Dose-Intensified Anti-TNF Therapy

Among the 36 patients, the doses were escalated in those with
Table 3. Predictors of the Secondary LOR in Patients with Crohn’s Disease

| Predictive factors                              | HR (95% CI) | P-value |
|-------------------------------------------------|-------------|---------|
| Duration of disease                             | 0.96 (0.91–1.01) | 0.083   |
| Disease location                                |             |         |
| L2 vs. L1                                       | 1.02 (0.23–4.49) | 0.973   |
| L3 vs. L1                                       | 0.64 (0.11–3.46) | 0.606   |
| Upper GI tract inflammation (yes vs. no)        | 3.00 (1.26–7.13) | 0.013   |
| Disease phenotype                               |             |         |
| B2 vs. B1                                       | 1.83 (0.74–4.55) | 0.193   |
| B3 vs. B1                                       | 1.18 (0.37–3.73) | 0.781   |
| Anal fistula (yes vs. no)                       | 1.64 (0.69–3.88) | 0.261   |
| Prior ileocolonic resection (yes vs. no)        | 1.65 (0.49–5.66) | 0.419   |
| CRP/ALB ratio (≥ 0.18 vs. < 0.18)               | 5.86 (1.56–22.0) | 0.009   |

LOR, loss of response; HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; CRP, C-reactive protein; ALB, albumin.

PNR (n = 2), secondary LOR (n = 31), an extraintestinal complication (n = 2), or an elevated CRP level without exacerbation of symptoms (n = 1). The incidence of LOR after dose escalation was 20.8% per patient-year of follow-up. The cumulative event-free rate at 1, 2, and 5 years after dose escalation was 71.0%, 58.4%, and 46.7%, respectively (Fig. 4A). The cumulative event-free rate at 1, 2, and 5 years after dose escalation in the IFX group was 78.0%, 72.0%, and 61.7%, respectively. In the ADA group, the rate at 1 and 2 years after dose escalation was 63.0% and 43.2%, respectively. The incidence of events after dose escalation was significantly lower in the IFX group than in the ADA group (P = 0.039) (Fig. 4B).

**DISCUSSION**

Various randomized controlled trials have investigated the efficacy of biological therapy for patients with CD. Although a meta-analysis has confirmed the superiority of anti-TNF-α
agents over the use of a placebo, no clear conclusion has been reached as to the superiority among the agents. Based on a network meta-analysis of 8 studies evaluating 5 different biologics exclusively in biologic-naive patients, IFX was found to be superior to 4 other biologics (ADA, certolizumab pegol, vedolizumab, and ustekinumab) in remission induction. In our study, although the CDAI at the start of biological therapy tended to be higher in the IFX group than in the ADA group, the clinical remission rate at 2 weeks post-initiation was higher in the IFX group. This suggests that IFX is effective for prompt remission induction, which may be attributable to the route of administration. Intravenous injection is more likely to achieve immediate central distribution, to cause less variability in drug exposure, and to reduce immunogenicity than subcutaneous injection.

Anti-TNF-α agents are highly effective. However, one-third of patients experience PNR, and one-third of or more patients experience secondary LOR. In our study, 7% of patients experienced PNR. Secondary LOR occurred in 40% of patients, corresponding to 11% per patient-year of follow-up. Previous studies have demonstrated that half of the patients with CD experience secondary LOR to IFX. The annual incidence of secondary LOR is 10% per patient-year for IFX and 20.3% per patient-year for ADA. In a study conducted exclusively in Japanese patients with CD, LOR to IFX or ADA was observed in 10% to 20% of the patients annually. In the SONIC study, combination therapy with IFX and immunomodulators also reportedly produced a higher remission rate at 50 weeks than monotherapy with IFX. Although the DIAMOND study did not show a difference in the clinical remission rate between combination therapy and monotherapy at 26 weeks, combination therapy with ADA and thiopurine exhibited a lower proportion of patients positive for anti-ADA antibodies compared to that for monotherapy.

Thiopurine dose adjustments are usually guided by white blood cell count. However, in past cases of this study, the thiopurine doses of several patients were not adequately adjusted; therefore, no significant differences in the cumulative relapse-free rates were observed between patients with and without the concomitant use of thiopurines (Fig. 3D). It has been reported that combination therapy with additional immunomodulators was effective in 42% of patients with CD treated with anti-TNF-α agents. In this study, there were 8 cases in which thiopurine was added because of relapse after the start of biologics. These occurred in the LOR group only. No significant difference in the cumulative relapse-free rate was observed between patients with and without the concomitant use of thiopurines, including these cases (data not shown). In contrast, only a few studies have examined LOR after dose escalation of anti-TNF agents. In our study, the incidence of LOR after dose escalation was 21% per patient-year of follow-up, and the incidence of events after dose escalation of biologics was significantly higher in the ADA group than in the IFX group (Fig. 4). The reasons for this are difficult to explain. The clinical response and clinical remission rates were, respectively, 34% to 90% and 26% to 81% after dose escalation of IFX and 33% to 100% and 15% to 83% after dose escalation of ADA. In patients with secondary LOR to ADA, administering ADA at an escalated dose of 80 mg every 2 weeks or at a dose of 40 mg every week was effective, but 56.8% of patients experienced tertiary LOR.

In recent years, the importance of the treat-to-target strategy
has been emphasized to improve the long-term prognosis of inflammatory bowel disease. According to STRIDE-II (an Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease) initiative of the International Organization for the Study of Inflammatory Bowel Disease, the proposed long-term therapeutic goals are prevention of structural disruption and dysfunction of the intestine, improvement in physical function, and recovery of quality of life, in addition to the conventional therapeutic goals of clinical remission and endoscopic mucosal healing. In CD, prediction of LOR and monitoring using appropriate biomarkers are important to prevent progression to intestinal injury. Our study identified the CRP/ALB ratio at 12 to 14 weeks after the start of biological therapy and upper GI tract inflammation as predictive factors of secondary LOR. Male sex, fistula, stricture, upper GI tract inflammation, a history of surgery, and colorectal lesions have been specified as risk factors for CD-related hospitalization. Age at the time of CD diagnosis, small intestinal lesions, fistulae, strictures, and endoscopically severe ulcers have been specified as risk factors for surgery after the development of CD. In addition, widespread small intestinal lesions, juvenile onset, smoking, and anal lesions have been specified as factors affecting the efficacy of anti-TNF-α agents. Only a few studies have evaluated the role of biomarkers for the prediction of LOR. Hibi et al. have reported that a CRP level of more than 0.5 mg/dL at 14 weeks after the start of IFX therapy is a possible predictive factor of the subsequent incidence of LOR to IFX. As the presence of higher disease activity at the start of biological therapy may lead to the production of a larger amount of anti-drug antibodies, a significant correlation between the CRP level at baseline and the IFX trough level at 2 weeks has been reported. In addition, because low serum ALB levels cause increased clearance of IFX, CRP and serum ALB levels may be involved in the efficacy of anti-TNF-α agents.

In our study, we focused on the CRP/ALB ratio and set the cutoff at 0.18; this cutoff ratio allowed us to predict LOR with a sensitivity of 55.3% and a specificity of 87.1%. In this study, secondary LOR was defined as relapse after the achievement of corticosteroid-free clinical remission after the start of biological therapy. The CRP/ALB ratio decreased when clinical remission was achieved. However, the CRP/ALB ratio at 3 months after the start of biological therapy was a predictor of LOR in long-term prognosis. It is speculated that inflammation may have remained endoscopically or histologically when clinical remission was achieved in cases with a high CRP/ALB ratio at 3 months after the start of biological therapy, that is, cases with high disease activity. We believe that the CRP/ALB ratio can be an important biomarker for predicting LOR in treatment that follows the treat-to-target strategy.

This study has some limitations. First, it is a retrospective cohort study conducted at a single institution. Second, its sample size is small. Third, as described above, there was an 8-year interval between the approval of IFX and ADA for coverage by the National Health Insurance System in Japan. Consequently, dose escalation protocols and shorter dosing schedules for these 2 biologics were approved for coverage at different times. However, because this study was based on real-world data collected over a long period, our findings nevertheless provide valuable insight regarding the efficacy and safety of anti-TNF-α agents.

Although anti-TNF-α agents contributed to long-term clinical remission in CD, secondary LOR occurred at an annual rate of 11%. The annual incidence of LOR after dose escalation of biologics was 21%. The CRP/ALB ratio at 3 months after the start of biological therapy and upper GI lesions were identified as predictive factors of secondary LOR. In clinical practice, attention should be paid to the CRP/ALB ratio. When it is high at 3 months after the start of biological therapy, we need to prepare for the possibility of secondary LOR.

**ADDITIONAL INFORMATION**

**Funding Source**

The authors received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest**

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

**Data Availability Statement**

Not applicable.

**Author Contribution**

Conceptualization, data curation: Otake H, Matsumoto S. Formal analysis: Matsumoto S. Investigation, methodology, project administration: Otake H, Matsumoto S. Supervision: Mashima H. Writing - original draft: Otake H, Matsumoto S. Writing - review & editing: Otake H, Matsumoto S, Mashima H. Approval of final manuscript: all authors.
REFERENCES

1. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol 2021;56:489-526.

2. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn’s disease: the ACCENT I randomised trial. Lancet 2002;359:1541-1549.

3. 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.

4. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFαs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.

5. 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.

6. 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.

7. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNFα treatment: a randomised, controlled trial. Gut 2014;63:919-927.

8. Robin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol 2014;109:1250-1256.

9. Kanda Y. Investigation of the freely available easy-to-use software ‘EZIR’ for medical statistics. Bone Marrow Transplant 2013;48:452-458.

10. Qin G, Tu J, Liu L, et al. Serum albumin and C-reactive protein/albumin ratio are useful biomarkers of Crohn’s disease activity. Med Sci Monit 2016;22:4393-4400.

11. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn’s disease. Aliment Pharmacol Ther 2014;39:1349-1362.

12. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn’s disease. Aliment Pharmacol Ther 2018;48:394-409.

13. 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.

14. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther 2015;41:613-623.

15. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev 2014;13:24-30.

16. Wong U, Cross RK. Primary and secondary nonresponse to infliximab: mechanisms and countermeasures. Expert Opin Drug Metab Toxicol 2017;13:1039-1046.

17. 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.

18. Rudolph SJ, Weinberg DI, McCabe RP. Long-term durability of Crohn’s disease treatment with infliximab. Dig Dis Sci 2008;53:1033-1041.

19. Moroi R, Endo K, Yamamoto K, et al. Long-term prognosis of Japanese patients with biologic-naïve Crohn’s disease treated with anti-tumor necrosis factor-α antibodies. Intest Res 2019;17:94-106.

20. 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.

21. Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn’s disease: a prospective, randomized trial. J Crohns Colitis 2016;10:1259-1266.

22. Macaluso FS, Sapienza C, Ventimiglia M, et al. The addition of an immunosuppressant after loss of response to anti-TNFα monotherapy in inflammatory bowel disease: a 2-year study. Inflamm Bowel Dis 2018;24:394-401.

23. Matteo VY, Basnayake C, Connell WR, et al. Systematic review: efficacy of escalated maintenance anti-tumour necrosis factor therapy in Crohn’s disease. Aliment Pharmacol Ther 2021;54:249-266.

24. Ma C, Huang V, Fedorak DK, et al. Adalimumab dose escalation is effective for managing secondary loss of response in...
Crohn’s disease. Aliment Pharmacol Ther 2014;40:1044-1055.
25. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160:1570-1583.
26. Veloso FT, Ferreira JT, Barros L, Almeida S. Clinical outcome of Crohn’s disease: analysis according to the Vienna classification and clinical activity. Inflamm Bowel Dis 2001;7:306-313.
27. Chow DK, Sung JJ, Wu JC, Tsoi KK, Leong RW, Chan FK. Upper gastrointestinal tract phenotype of Crohn’s disease is associated with early surgery and further hospitalization. Inflamm Bowel Dis 2009;15:551-557.
28. Golovics PA, Lakatos L, Mandel MD, et al. Prevalence and predictors of hospitalization in Crohn’s disease in a prospective population-based inception cohort from 2000-2012. World J Gastroenterol 2015;21:7272-7280.
29. Osamura A, Suzuki Y. Fourteen-year anti-TNF therapy in Crohn’s disease patients: clinical characteristics and predictive factors. Dig Dis Sci 2018;63:204-208.
30. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn’s disease. Gastroenterology 2006;130:650-656.
31. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn’s disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5:1430-1438.
32. Greenstein AJ, Lachman P, Sachar DB, et al. Perforating and non-perforating indications for repeated operations in Crohn’s disease: evidence for two clinical forms. Gut 1988;29:588-592.
33. Louis E, Michel V, Hugot JP, et al. Early development of strictureting or penetrating pattern in Crohn’s disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. Gut 2003;52:552-557.
34. Romberg-Camps MJ, Dagnelie PC, Kester AD, et al. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol 2009;104:371-383.
35. Hibi T, Sakuraba A, Watanabe M, et al. C-reactive protein is an indicator of serum infliximab level in predicting loss of response in patients with Crohn’s disease. J Gastroenterol 2014;49:254-262.
36. 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.
37. 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.