Infliximab therapy intensification based on endoscopic activity is related to suppress treatment discontinuation in patients with Crohn disease
A retrospective cohort study

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Abstract
Administering double doses of infliximab or shortening its dosing interval for patients with Crohn disease who experience a loss of response to treatment is an accepted treatment method; however, the effectiveness and appropriate timing of treatment intensification remain unclear. We examined the treatment outcomes of patients with Crohn disease receiving infliximab therapy intensification.

Among 430 patients with Crohn disease who were seen at our related facilities from July 2002 to July 2018, 46 patients (30 men and 16 women) who were followed up for diminished infliximab effects for >1 year after therapy intensification were included in this study. The relationship between patient background and continuation of therapy intensification was retrospectively examined through a logistic regression analysis.

Among the 46 patients, 67.4% (31 cases) continued therapy intensification for 12 months. The treatment discontinuation rate after 12 months (7.1% vs 43.8%, \( P = .015 \)) and the C-reactive protein levels at the start of therapy intensification (\( P = .0050 \)) were significantly lower in the group in which treatment was strengthened due to remaining endoscopic findings (\( n = 14 \)) than that due to clinical symptoms (\( n = 32 \)). There was no significant difference in the rates of treatment discontinuation after 12 months of treatment strengthening between patients receiving double doses (\( n = 34 \)) and those with shortened dosing intervals (\( n = 12 \)).

Infliximab treatment discontinuation seems to be less likely to occur in patients with Crohn disease who are receiving infliximab treatment intensification based on endoscopic findings of exacerbations than in patients whose treatment is based on clinical symptoms.

 Abbreviations: CI = confidence interval, CRP = C-reactive protein, IBD = inflammatory bowel disease, IFX = infliximab, OR = Odds ratio, \( P \) = probability, TNFα = tumor necrosis factor alpha.

Keywords: Crohn disease, endoscopic finding, infliximab therapy intensification

1 Observational Study

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1. Introduction

Leukocytes are among the immune cells that play pivotal roles in the pathogenesis of inflammatory bowel disease (IBD).[1,2] Macrophages, lymphocytes, fibroblasts, and keratinocytes produce inflammatory cytokine tumor necrosis factor alpha (TNFα) in response to inflammation and infection. Inhibitors of TNFα, such as infliximab (IFX), have revolutionized the treatment of IBD. The efficacy and safety of IFX have been well documented particularly in adult patients with Crohn disease.[3] It has been also well established that IFX is effective in the treatment of fistulizing Crohn disease.[4] However, despite the proven efficacy of these inhibitors, many patients respond only partially or experience a secondary loss of response.[5] A recent meta-analysis showed that the pooled rate of secondary loss of response to IFX therapy was 34%. The potential predictors of loss of response outcomes among patients with Crohn disease included the presence of perianal lesions, younger age at onset of Crohn disease, and involvement of the colon.[6]

The main cause of secondary loss of response to biologics is a decrease in blood IFX concentration. Biological agents other than IFX (eg, vedolizumab and ustekinumab) have been used to treat severe Crohn disease for several years,[7,8] but the exact results of each treatment method remain unknown. IFX dose escalation or shortening is often required and effective for the improvement of clinical symptoms.[9,10] Anti-IFX antibody concentrations can be used to guide treatment intensification in patients with Crohn disease who lose clinical response.[11] However, the effect of these therapy intensifications and their predictors are unknown. We aimed to investigate the outcomes of patients with Crohn disease who received IFX therapy intensification after a secondary loss of response, and to clarify the predictive parameter of IFX therapy intensification.

2. Materials and methods

2.1. Study design and population

This was an observational retrospective study of patients with Crohn disease treated with IFX at the gastroenterology departments of 6 participating tertiary medical centers. All patients were diagnosed with Crohn disease using established endoscopic, radiological, histological, and clinical criteria.[12] Medical records of patients registered in a prospectively collected IBD database of Kagoshima University Hospital and its related hospitals between February 2002 and July 2018 were reviewed: it is a routine practice that our centers follow patients for 1 year or more. This method was based on the previous study.[13] The study was approved by the institutional review board (180152). The Ethics Committee at Kagoshima University Hospital and the related facilities approved the study protocol, and written informed consent was obtained from each participant. The study population included adults and adolescents with Crohn disease who had lost response to maintenance IFX infusions of 5 mg/kg every 8 weeks as per their attending physician’s judgment and who were treated with intensive therapy of IFX. IFX therapy intensification was defined as maintenance IFX infusions of 10 mg/kg every 8 weeks (double doses) or of 5 mg/kg every 4 weeks (shortening the dosing interval). Patients were excluded if they did not use anti-TNFα agents, were treated by other biological products, or observed for <12 months. The patients were also excluded if they underwent surgery due to diminished effects of IFX. Data abstracted included patient demographics, smoking history, term of standard or intensive IFX therapy, concomitant medications, and the reason for IFX therapy intensification.

The primary endpoint was to clarify the predictive parameter of IFX therapy intensification by determining the relation between patient background and continuation of IFX therapy intensification. The patients’ background included sex, age at IFX therapy intensification, terms of standard IFX therapy, terms of IFX therapy intensification, median C-reactive protein (CRP) level, and Crohn disease activity index at baseline and after 12 months of IFX therapy intensification. The secondary endpoint was to determine the relation between IFX therapy intensification reasons and treatment discontinuation rates, as well as the relation between IFX therapy intensification and treatment discontinuation rates in patients receiving double doses and shortened dosing intervals, respectively. We also attempted to find the differences in clinical background between the effective and ineffective groups at 12 months after the start of IFX therapy intensification. Both inpatient and outpatient charts were reviewed. The clinical effect reduction was defined as requiring a treatment change by the attending physician of each facility, after aggravation of clinical symptoms (diarrhea, abdominal pain, and subjective general condition).

2.2. Statistical analysis

Continuous variables of the patient’s background were expressed as mean ± standard deviation. The treatment discontinuation rates after IFX therapy intensification were evaluated using the log-rank test. Comparisons between categorical variables were analyzed using Fisher’s exact test. Odds ratio (OR) and 95% confidence intervals (CIs) were determined for all variables that were compared. The outcomes of this study were analyzed using univariate and multivariate comparisons among all patients with Crohn disease. Multivariate analysis was performed by entering all parameters varying between groups on the univariate analysis with a statistical significance of probability (P) < .10 into a backward logistic regression model. For all tests, a P-value of < .05 was considered statistically significant. The data were analyzed using EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[14] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).

3. Results

3.1. Patients’ characteristics

During the study period, a total of 430 patients with Crohn disease were enrolled in our study. Among these patients, 166 patients were treated with IFX. Forty-six patients with Crohn disease receiving IFX therapy intensification for ≥12 months after a secondary failure of IFX treatment were included in our analysis (Fig. 1). The details of the characteristics of patients included in our analysis are shown in Table 1. Among the 46 patients (30 men and 16 women), 40 patients had Crohn ileocolitis, 2 had Crohn ileitis, and 4 had Crohn colitis; 36 (78.3%) had perianal lesions. The mean duration from disease onset to IFX use was 7.7 years, and the mean effective period from the start of IFX to secondary loss of response was 4.8 years. Thirty-one patients (67.4%) were able to continue IFX therapy intensification for 12 months. Eight patients (21.1%) were exposed to other anti-TNFα agents before IFX treatment. Twenty-five patients (54.3%) were treated with immunomodulators combined with IFX therapy.
intensification. Thirty-two patients (69.6%) received IFX therapy intensification due to the remaining clinical symptoms. Fourteen patients (30.4%) received IFX therapy intensification due to endoscopic findings showing remaining ulcerations and erosions. Thirty-four (73.9%) patients received double doses and 12 patients (26.1%) had shortening of the dosing interval.

3.2. The treatment discontinuation rate at 12 months after the start of IFX therapy intensification

The treatment discontinuation rate at 12 months after the start of IFX therapy intensification was 32.6%. With IFX therapy intensification, 67.4% of the patients were still clinically effective at 12 months after the start of intensification (Fig. 2). The rate of treatment discontinuation at 12 months after IFX therapy intensification due to different reasons is shown in Figure 3. The group receiving intensified treatment with IFX due to the remaining abnormal endoscopic findings had a lower rate of treatment discontinuation than the group receiving intensified treatment with IFX due to worsening clinical symptoms at 12 months after the start of therapy intensification ($P = .015$).

3.3. The differences in clinical background between the effective and ineffective groups at 12 months after the start of IFX therapy intensification

We assessed the differences in clinical background between the effective and ineffective groups at 12 months after IFX therapy...
intensification through univariate and multivariate analyses. As shown in Table 2, treatment continued after 12 months of treatment for significantly more patients in the group receiving therapy intensification due to the remaining endoscopic findings compared to the group with therapy intensification due to worsening clinical symptoms (OR 0.10, 95% CI 0.0022–0.85, \(P = .018\)). However, multivariate analysis revealed that there was a tendency for IFX therapy intensification based on residual endoscopic findings to reduce the treatment discontinuation rate, although there was no significant difference found.

### 3.4. The differences in clinical background according to the reasons for IFX therapy intensification

Next, we assessed the differences in clinical background according to the reasons of IFX therapy intensification, as identified by univariate and multivariate analyses. As shown in Table 3, the univariate analysis demonstrated that the group receiving IFX-therapy intensification based on remaining endoscopic findings had significantly lower CRP levels at the time of treatment intensification than the group receiving IFX therapy.

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**Table 1**

Demographic and clinical characteristics of the included patients.

| Cases of Crohn disease with IFX therapy intensification observed for at least 12 mo (n = 46) |
|---|
| **Age, mean year (range)** | 41.3 (15–78) |
| **Sex (male/female)** | 30/16 |
| **Types of disease (ileocolitis/ileum/colon)** | 40/2/4 |
| **Current smoker (yes/no)** | 10/36* |
| **Anal Crohn disease (yes/no)** | 36/10 |
| **History of use of other anti-TNFα agents before IFX (%)** | 8 (21.1) |
| **History of open surgery before IFX treatment (yes/no)** | 13/33 |
| **Disease duration from onset to IFX use, mean year ± SD** | 7.68 ± 9.11 |
| **Effective period from the start of IFX to secondary loss of response, mean year ± SD** | 4.76 ± 3.68 |
| **Thiopurine at IFX therapy intensification (%)** | 25 (54.3) |
| **CRP level at the start of IFX therapy intensification, mean mg/dL ± SD** | 3.15 ± 2.90* |
| **The methods of IFX therapy intensification (double doses/shortening the dosing interval)** | 34/12 |
| **Reasons for IFX-therapy intensification (exacerbation of clinical symptoms/remaining endoscopic findings)** | 32/14 |

*Anti-TNFα = antitumor necrosis factor alpha, CRP = C-reactive protein, IFX = infliximab, SD = standard deviation.

* The patients whose information was unknown were excluded.

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**Figure 2.** The treatment discontinuation rate at 12 mo after the start of IFX therapy intensification among patients with Crohn disease. IFX = infliximab.
intensification based on clinical symptoms (OR 0.097, 95% CI 0.0090–0.55, P = .0031). The results of the multivariate analysis also revealed that the group receiving IFX therapy intensification based on the remaining endoscopic findings had significantly lower CRP levels at the start of therapy intensification than the group receiving IFX therapy intensification based on clinical symptoms (OR 0.092, 95% CI 0.017–0.49, P = .0050).

3.5. The differences in clinical background according to the methods of IFX therapy intensification

Finally, we assessed the differences in clinical background according to the methods of IFX therapy intensification, as identified by the univariate and multivariate analysis. As shown in Table 4, the univariate analysis demonstrated that there was no
Table 3

The differences in clinical background according to the reasons of IFX therapy intensification as identified by the univariate and multivariate analyses.

| Factors                              | Reasons for IFX therapy intensification | Univariate | Multivariate |
|--------------------------------------|----------------------------------------|------------|--------------|
|                                      | Endoscopic findings (n = 14) Clinical symptoms (n = 32) | OR 95% CI P-value | OR 95% CI P-value |
| Sex (male/female)                    | 9/5 21/11                               | 0.94 0.21–4.51 1.0  | 0.94 0.21–4.51 1.0  |
| Age ≤22.4 yr at diagnosis (yes/no, mean [yr]) | 8/6 (23.3) 16/16 (24.7)  | 0.75 0.17–3.16 0.75  | 0.57 0.11–2.90 0.75  |
| Term of standard IFX therapy ≤99.8 (yes/no, mean [mo]) | 6/8 (119.9) 17/15 (98.6)  | 1.50 0.36–6.58 0.75  | 1.50 0.36–6.58 0.75  |
| Current smoker (yes/no)             | 5/9                                    | 2.81 0.52–15.64 0.24  | 2.81 0.52–15.64 0.24  |
| Prior or current thiopurine use (yes/no) | 10/3 (4) 2/4 (2)                   | 1.11 0.21–7.82 1.0  | 1.11 0.21–7.82 1.0  |
| Thiopurine at IFX therapy intensification (yes/no) | 6/8                                    | 2.12 0.25–45.55 1.0  | 2.12 0.25–45.55 1.0  |
| IFX therapy intensification period of ≤17.1 (yes/no, mean [mo]) | 5/9 (30.8) 18/14 (33.9)      | 2.27 0.54–10.74 0.34  | 2.27 0.54–10.74 0.34  |
| CRP <3.2 at start of IFX therapy intensification (yes/no, mean [mg/dL]) | 12/2 (1.4) 11/20 (3.9)      | 0.097 0.009–0.55 0.0011  | 0.097 0.009–0.55 0.0011  |
| CDAI ≤241 at start of IFX therapy intensification (yes/no, mean) | 5/7 (254) 4/12 (61)         | 1.72 0.36–8.84 0.50  | 1.72 0.36–8.84 0.50  |
| CRP ≤0.20 at 12 mo after the start of IFX therapy intensification (yes/no, mean [mg/dL]) | 6/9 (1.3) 4/12 (2)           | 0.48 0.071–2.57 0.45  | 0.48 0.071–2.57 0.45  |
| CDAI ≤182 at 12 mo after the start of IFX therapy intensification (yes/no, mean) | 6/6 (210) 4/12 (71)      | 1.14 0.19–6.71 1.0  | 1.14 0.19–6.71 1.0  |

CDAI = Crohn disease activity index, CI = confidence interval, CRP = C-reactive protein, IFX = infliximab, OR = odds ratio.
† Fisher exact test.
* The patients whose information was unknown were excluded.



Table 4

The differences in clinical background according to the methods of IFX therapy intensification as identified by the univariate and multivariate analyses.

| Factors                              | Double doses (n = 34) Shortening the dosing interval (n = 12) | Univariate |
|--------------------------------------|-------------------------------------------------------------|------------|
|                                      | OR 95% CI P-value                                          | OR 95% CI P-value |
| Sex (male/female)                    | 22/12 8/4                                                  | 1.99 0.23–6.00 0.001  | 1.99 0.23–6.00 0.001  |
| Age ≤22.4 yr at diagnosis (yes/no, mean [yr]) | 20/14 (23.1) 4/8 (27.0)       | 2.79 0.60–15.29 0.18  | 2.79 0.60–15.29 0.18  |
| Term of standard IFX therapy ≤99.8 (yes/no, mean [mo]) | 15/19 (13.1) 8/4 (62.4)       | 0.40 0.074–1.86 0.31  | 0.40 0.074–1.86 0.31  |
| Current smoker (yes/no)             | 7/26 (39)                                                   | 1.23 1.17–7.02 1.0  | 1.23 1.17–7.02 1.0  |
| Prior or current thiopurine use (yes/no) | 25/8 (3) 9/3                                                | 0.96 0.17–6.85 1.0  | 0.96 0.17–6.85 1.0  |
| Thiopurine at IFX therapy intensification (yes/no) | 20/14 6/6                                                  | 0.71 0.15–3.24 0.74  | 0.71 0.15–3.24 0.74  |
| IFX therapy intensification continued for 6 mo (yes/no) | 24/10 10/2                                                 | 0.49 0.044–2.96 0.47  | 0.49 0.044–2.96 0.47  |
| IFX therapy intensification continued for 12 mo (yes/no) | 23/11 8/4                                                 | 1.04 0.19–5.02 1.0  | 1.04 0.19–5.02 1.0  |
| IFX therapy intensification period of ≤17.1 (yes/no, mean [mo]) | 15/19 (32.0) 8/4 (15.5)     | 0.40 0.074–1.86 0.31  | 0.40 0.074–1.86 0.31  |
| CRP <3.2 at start of IFX therapy intensification (yes/no, mean [mg/dL]) | 15/19 (3.2) 8/4 (3.1)      | 0.42 0.078–1.97 0.31  | 0.42 0.078–1.97 0.31  |
| CDAI ≤241 at start of IFX therapy intensification (yes/no, mean) | 17/11 (233) 8/3 (270)     | 3.97 0.74–28.41 0.082 | 3.97 0.74–28.41 0.082 |
| CRP ≤0.20 at 12 mo after the start of IFX therapy intensification (yes/no, mean [mg/dL]) | 11/10 (0.95) 6/2 (1.9)      | 0.38 0.031–2.80 0.41  | 0.38 0.031–2.80 0.41  |
| CDAI ≤182 at 12 mo after the start of IFX therapy intensification (yes/no, mean) | 11/8 (178) 3/5 (214)      | 2.22 0.32–18.73 0.42  | 2.22 0.32–18.73 0.42  |

CDAI = Crohn disease activity index, CI = confidence interval, CRP = C-reactive protein, IFX = infliximab, OR = odds ratio.
† Fisher exact test.
* The patients whose information was unknown were excluded.

difference in clinical backgrounds between the 2 IFX intensification methods (dosing every 8 weeks [double dose] or regular dose every 4 weeks [shortening the dosing interval]). A multivariate analysis was not performed because no clinical variables had a P-value < .10 in the univariate analysis. There were no differences in treatment discontinuation rates between the 2 IFX therapy intensification methods at 12 months after treatment (Fig. 4).

4. Discussion
Crohn disease can cause various complications, such as fistula, stricture, intraabdominal abscess, and mesenteric fibromatosi
dis. Despite optimal medical management, up to 75% of patients with Crohn disease will require surgery for refractory disease or its complications during the disease course. Although biologics have improved the therapeutic goals for Crohn disease, the problem of diminishing efficacy exists. We performed this study to assess the efficacy of IFX therapy intensification for patients with Crohn disease with secondary loss of response to IFX. We demonstrated that even without subjective symptoms, an intensified treatment based on endoscopic findings may increase the clinical efficacy. The efficacy of maintenance therapy with IFX has been reported to be dependent on the blood trough concentration of...
Moreover, a recent study revealed that IFX has a high clinical response rate in patients with a median blood trough concentration of ≥1 μg/mL, and one of the reasons of secondary loss of response may be due to lower blood trough concentration. A secondary loss of response remains a potential barrier to the long-term efficacy of anti-TNFα therapy in Crohn disease, occurring in up to 61% of anti-TNFα naive patients with ongoing therapy. Although drug switch is also an effective treatment for a secondary loss of response to IFX, it may reduce the treatment options in the future; thus, it should be changed to other anti-TNFα agents if the symptoms are intolerable or particularly severe. As the main cause of secondary loss of response is a decrease in blood IFX concentration, it is considered important to maintain the blood concentration of IFX to avoid diminished effects in the maintenance therapy with IFX. As shown in ACCENT I, in cases where the effect of IFX 5 mg/kg was attenuated by week 54, increasing the dose to 10 mg/kg showed recovery of the drug effects in 90% of cases. Recent studies reported that 8% to 35% of patients had their dose increased within the first year of therapy. There is also evidence to support shortening of the dosing interval as a successful dose intensification strategy, with up to two-thirds of patients regaining response in studies with short-term follow-up.

A previous study showed that, in patients with Crohn disease who underwent enterectomy, the “intervention group” who changed treatment based on the endoscopic findings at 6 months after the operation had a significantly lower endoscopic recurrence rate at 18 months after the operation than the “standard treatment group” who did not undergo endoscopy. In this study, we found that the group receiving IFX therapy intensification based on remaining endoscopic findings had a lower rate of treatment discontinuation than the group receiving therapy intensification based on the nonendoscopic clinical symptoms at least 1 year after the start of therapy intensification. In our findings, IFX therapy intensification based on the exacerbation of or remaining endoscopic lesions, even in the absence of subjective symptoms, may increase the clinical efficacy of IFX. Our results are comparable to the recent study reporting that only strategies based on tight monitoring of objective signs of inflammation, such as mucosal lesions, may have the potential for disease modification. Colonic interaction among chemokines may play a causative role in the inflammation that occurs in chronic colonic diseases including Crohn disease. Chemokine panels such as CD146 and Foxp3 have been reported to be useful in distinguishing inflammatory bowel disease from nonspecific colitis. Fecal calprotectin has also been reported as a suitable tool to assess mucosal inflammation and healing, obviating the need for direct visualization by endoscopy. A previous study reported that there is a significant correlation between fecal calprotectin concentrations and health-related quality of life in patients with Crohn disease. Although we did not consider them in our study, it may be possible to use chemokine panels or fecal calprotectin in the future to confirm the disease condition of Crohn disease, considering the burden on patient’s quality of life.
concentration increases by shortening of the dosing interval, rather than doubling the dose of IFX. However, our study showed that there was no difference in the treatment discontinuation rate at 12 months after the start of IFX therapy intensification, regardless of the treatment intensification strategy. This result may suggest that halving the infusion intervals is not superior to dose-doubling. As reported previously, it may imply that higher peak levels of TNF blockade (as provided by 10 mg/kg/8 weeks) are more biologically relevant than a continuous, yet lower, level of TNF blockade provided by interval halving. Our results may also play a role in the economic burden of treating Crohn disease. While, the introduction of biological drugs has revolutionized the management of IBD, the increasing financial burden of biologics on the health care system is alarming. A previous review showed that the annual direct medical costs for Crohn disease are high and are estimated to be US$4,466 per patient per year. It has been reported that re-induction of anti-TNFα agents may represent an effective and less expensive first-line strategy, avoiding dose-intensification strategies. However, a previous study demonstrated that the risk of infusion reaction was particularly high at the second infusion in the retreatment series. Moreover, the negative anti-IFX antibody results before re-initiation did not rule out infusion reactions. Recently, several biologics other than IFX have become available for insurance coverage. However, for example, treatment of Crohn disease with ustekinumab or vedolizumab after failure of anti-TNFα therapy appears to be cost-effective at a threshold of €31,500. The replacement of the second-line anti-TNFα with ustekinumab/vedolizumab and the course of the disease after discontinuation of biologics are influential drivers for cost-effectiveness. In patients with Crohn disease who do not respond to IFX, it is important to utilize IFX therapy intensification instead of changing the biologic drug easily. In addition, by choosing the double-dose method of IFX therapy intensification, frequent visits to medical centers could be avoided, thereby reducing the economic burden on medical care.

Our study has some limitations. First, this was a retrospective study with a small number of patients analyzed. Although the sample population comprised >400 patients, the number of patients who met the inclusion and exclusion was relatively small. The statistical power was 0.845 for assessing the differences in clinical background according to the reasons for IFX therapy intensification: the required sample size of each group was 22 when we set the statistical power at 0.90. The statistical power for assessing the differences in clinical background according to the IFX therapy intensification strategy was only 0.301 from current patient numbers. These limited sample size underpower the regression analyses. Thus, further studies are needed to assess the generalizability of our results. Second, we could not perform the propensity score matching analysis due to the small number of cases enrolled. Third, we compared the treatment discontinuation rates only at 6 and 12 months after IFX therapy intensification. However, a previous report suggested that future studies on loss of response should aim to report sustained clinical outcomes at a well-defined time point of 12 months post intervention rather than by median follow-up times, thereby facilitating the comparison among studies and among different management strategies. Fourth, given that this study was retrospective, the secondary clinical loss of response was judged by a physician at each facility with subjectivity. However, this judgment was at least based on the categories of Crohn disease activity index. Though blood concentration of IFX and anti-IFX antibodies are the most important factors influencing the long-term efficacy of IFX, these blood tests are not covered by medical insurance and therefore were not measured in each patient. In addition, not all patients underwent endoscopy: the patients who did not undergo endoscopy were included in the group who received IFX therapy intensification due to the worsening clinical symptoms. This might be a cause of selection bias. Fifth, patients with Crohn disease are also known to have a high frequency of Clostridium difficile infections, which affect the flare up symptoms of Crohn disease. However, the data regarding C. difficile infections were unclear in our retrospective cohort. Thus, we could not analyze this variable. Finally, in this study, there was no difference in the treatment discontinuation rate at 12 months after treatment intensification between the 2 intensification methods, but the IFX blood levels could not be measured, as mentioned previously. IFX effects in IBD are related to blood levels. Thus, the correlation between the treatment discontinuation rate and the IFX blood concentration should be examined.

In conclusion, treatment discontinuation seems to be less likely to occur in patients receiving IFX treatment intensification based on remaining endoscopic findings rather than based on clinical symptoms. The differences in treatment intensification strategies do not contribute to the discontinuation of treatment. Although further large studies with longer term evaluation are required to confirm these findings, the results of our study support the use of IFX in the treatment of Crohn disease patients with a loss of response.

Author contributions

YP and FK: analysis of data and drafting of manuscript; AT: analysis of data and approval of manuscript; KY, KK, NN, YS, FS, HO, YN, KT, YS and AI: critical review and approval of manuscript; SK: study concept and design, analysis of data, and writing of manuscript.

References

[1] Sakuraba A, Sato T, Kamada N, et al. Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn’s disease. Gastroenterology 2009;137:1736–45.
[2] Sato T, Kanai T, Watanabe M, et al. Hyperexpression of inducible costimulator and its contribution on lamina propria T cells in inflammatory bowel disease. Gastroenterology 2004;126:829–39.
[3] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn’s disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.
[4] Antakia R, Shorthouse AJ, Robinson K, et al. Combined modality treatment for complex fistulating perianal Crohn’s disease. Colorectal Dis 2013;15:210–6.
[5] Drobne D, Kurtest T, Golob S, et al. Optimised infliximab monotherapy is as effective as optimised combination therapy, but is associated with higher drug consumption in inflammatory bowel disease. Aliment Pharmacol Ther 2019;49:880–9.
[6] Zhang QW, Shen J, Zheng Q, et al. Loss of response to scheduled infliximab therapy for Crohn’s disease in adults: a systematic review and meta-analysis. J Dig Dis 2019;20:65–72.
[7] Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn’s disease. N Engl J Med 2013;369:711–21.
[8] Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn’s disease. N Engl J Med 2016;375:1946–60.
[9] Einarmson TR, Bereza BG, Ying Lee X, et al. Dose escalation of biologics in Crohn’s disease: critical review of observational studies. Curr Med Res Opin 2017;33:1433–49.
[10] Kopylov U, Mantzaris GJ, Katsanos KH, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn’s patients losing response to maintenance dose of infliximab. Aliment Pharmacol Ther 2011;33:349–57.

[11] Dreesen E, Van Stappen T, Ballet V, et al. Anti-infliximab antibody concentrations can guide treatment intensification in patients with Crohn’s disease who lose clinical response. Aliment Pharmacol Ther 2018;47:346–55.

[12] Kannura S, Hamamoto H, Morinaga Y, et al. Fecal human neutrophil peptide levels correlate with intestinal inflammation in ulcerative colitis. Digestion 2016;93:300–8.

[13] Yamada A, Komaki Y, Patel N, et al. Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. Am J Gastroenterol 112 2017;1423–9.

[14] Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013;48:452–8.

[15] Present DH, Rutgeerts P, Targan S, et al. Anti-TNF re-induction is as effective, simpler, and cheaper compared with dose interval shortening for secondary loss of response in Crohn’s disease. J Crohn’s Colitis 2017;12:280–8.

[16] Chang C-W, Wong J-M, Tung C-C, et al. Intestinal stricture in Crohn disease who lose clinical response. Aliment Pharmacol Ther 2019;44:495–507.

[17] Perl D, Waljee AK, Bishu S, et al. Imaging features associated with failure of nonoperative management of intraabdominal abscesses in Crohn disease. Inflamm Bowel Dis 2019;25:1939–44.

[18] Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn’s disease clinical trials. Gut 2016;65:1447–55.

[19] El-Saka AM, Zamzam YA, Haydara T, et al. Immunohistochemical staining with chemokine panel of non-specific colitis predicts future IBD diagnosis. Cytokine 2020;127:154935.

[20] Stothers B, Holick S, Ibsen P, et al. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. Clin Gastroenterol Hepatol 2015;13:1929–36.

[21] Mao J, Wang H, Hu D-M. Rare acute abdominal condition caused by inflammatory bowel disease patients treated preoperatively with vedolizumab. Medicine (Baltimore) 2016;95:e3477.

[22] Castelle NV, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn’s disease. Gut 2015;64:1539–45.

[23] Hofmekler T, Bertha M, McCracken C, et al. Infliximab optimization based on therapeutic drug monitoring in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2017;64:580–5.

[24] Cost-effectiveness analysis of Crohn’s disease treatment with vedolizumab and ustekinumab after failure of tumor necrosis factor-α antagonist. PharmacoEconomics 2018;36:853–63.

[25] Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013;32:2837–49.

[26] Steenholt C, Svenson M, Bendtzen K, et al. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2011;34:51–8.

[27] Holko P, Kawalec P, Pik A. Cost-effectiveness analysis of Crohn’s disease treatment with vedolizumab and ustekinumab after failure of tumor necrosis factor-α antagonist. PharmacoEconomics 2018;36:853–63.

[28] Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013;32:2837–49.

[29] Maharshak N, Barzilay I, Zinger H, et al. Clostridium difficile infection in hospitalized patients with inflammatory bowel disease: Prevalence, risk factors, and prognosis. Medicine (Baltimore) 2018;97:e9772.