Gut and Gastroenterology

RESEARCH ARTICLE

Evaluation of Loss of Response to Anti-Tumor Necrosis Factor-α Biologic Agents in Patients with Crohn's Disease: A Multicenter, Retrospective Study

Tomoya Sugiyama[1] MD, Makoto Sasaki[1]* Prof D, Shoko Nakagawa[1] MD, Kazunori Adachi[1] MD, Takashi Yoshimine[1] MD, Yoshiharu Yamaguchi[1] MD, Shinya Izawa[1] MD, Mari Mizuno[1] MD, Sayuri Yamamoto[1] MD, Masahide Ebi[1] MD, Yasushi Funaki[1] MD, Naotaka Ogasawara[1] Prof D, Yusuke Inoue[2] MD, Masayuki Endo[3] MD, Yoshihide Kimura[4] MD, Tomonori Yamada[5] MD, Yoshikazu Hirata[6] MD, Tsutomu Mizoshita[7,8] MD, Hiromi Kataoka[7] Prof D, Kunio Kasugai[1] Prof D

[1]Department of Gastroenterology, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan
[2]Department of Gastroenterology, Japan Community Health Care Organization Chukyo Hospital, 1-1-10 Sanjo, Minami-ku, Nagoya 457-8510, Japan
[3]Department of Gastroenterology, Japan Organization of Occupational Health and Safety Asahi Rosai Hospital, 61, Hirako-cho, Owariasahi, Aichi 488-8585, Japan
[4]Department of Gastroenterology, Nagoya City West Medical Center, 1-1-1, Hirate-cho, Kita-ku, Nagoya 462-8508, Japan
[5]Department of Gastroenterology, Japanese Red Cross Nagoya Daini Hospital, 2-9 Myoken-cho, Syowa-ku, Nagoya 466-8650, Japan
[6]Department of Gastroenterology, Kasugai Municipal Hospital, 1-1-1 Takaki-cho, Kasugai, Aichi 486-8510, Japan
[7]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
[8]Department of Gastroenterology, Toyokawa City Hospital, 23-Noji, Yawata-Cho, Toyokawa, Aichi 442-0857, Japan

Abstract

Study background: Anti tumor necrosis factor-α is thought to play an important role in the treatment of Crohn's disease. However, loss of response to anti tumor necrosis factor-α remains problematic. We aimed to assess loss of response to anti tumor necrosis factor-α in the treatment of Crohn's disease and clarify factors associated with loss of response.

Methods: We analyzed loss of response in 128 patients with Crohn's disease from multiple centers. All the patients were naïve to anti tumor necrosis factor-α at the time of the initial treatment. The Kaplan-Meier method, Rank test, and Cox regression analyses were used in the statistical analyses.

Results: Twenty-five percent of the patients were women, and the median age of the patients was 31 years (interquartile range 22.0-43.2 years). Loss of response to infliximab and adalimumab treatments was recognized in 26 (28.8%) of 90 patients and in 7 (18.4%) of 38 patients, respectively. In the multivariate Cox regression analysis, the presence of an ileitis lesion and a high C-reactive protein level (≥2.25 mg/dL) before treatment induction were identified as independent risk factors for predicting loss of response (hazard ratio=2.563, $p<0.05$ and hazard ratio=5.317, $p<0.05$, respectively).

Conclusion: The C-reactive protein level of the patients prior to anti tumor necrosis factor-α therapy is an important factor to consider when predicting loss of response in anti tumor necrosis factor-α naïve patients.

Keywords: Crohn's disease, Tumor necrosis factor-alpha, Biologic medicines, Multicenter study

Abbreviations: CD; Crohn's disease, IFX; infliximab, ADA; adalimumab, TNF-α; tumor necrosis factor alpha, LOR; loss of response, CRP; C-reactive protein, AZA; azathioprine, IQRs; interquartile ranges, ROC; receiver-operating characteristic.

Introduction:

Crohn's disease (CD) is a chronic and refractory inflammatory disorder of the gastrointestinal tract with an unknown etiology. Complications, such as stenosis, fistulas, and perforations, can occur over time with disease progression [1]. Between 30% and 60% of patients with CD require intestinal tract resection within 5 years of disease onset [2, 3]. TNF-α is thought to play an important role in the treatment of CD [4]. In Japan,

***Correspondence to:** Prof Makoto Sasaki D, Department of Gastroenterology, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan Tel: +81-561-62-3311, Fax: +81-561-62-6690; E-mail: msasaki@aichi-med-u.ac.jp

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infliximab (IFX) and adalimumab (ADA), two anti tumor necrosis factors (TNF-α), were approved for the treatment of CD in 2002 and 2010, respectively. However, loss of response (LOR) to anti TNF-α agent remains problematic. Previous reports have shown that early treatment of CD with anti TNF-α agents is more effective compared to conventional management strategies [5], and the use of concomitant immunomodulators, pre-treatment with a corticosteroid, and early dose optimization prevent LOR [6]. It has also been reported that C-reactive protein (CRP) levels are useful in predicting LOR [7].

Nevertheless, the best way to prevent LOR is still unclear, and many patients require repeated intestinal tract resections. In this study, we assessed LOR to anti TNF-α agents in the treatment of CD and aimed to clarify the factors associated with LOR.

Methods:

Patients and study design: In this multicenter, retrospective cohort study, we enrolled 134 CD patients who were initially treated with anti TNF-α agents (IFX or ADA) as remission treatment induction and maintenance therapies between May 2004 and July 2016. All the patients were naïve to anti TNF-α agents at the time therapy began. IFX was infused at a dose of 5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter as a maintenance therapy. ADA was administered at doses of 160 and 80 mg at weeks 0 and 2, respectively, and at 40 mg every 2 weeks thereafter as a maintenance therapy. We excluded 6 patients who were primary non-responders (patients who experienced no clinical benefit during the first 8 weeks after the TNF-α therapy began). Ultimately, we analyzed the risk factors for LOR in 128 CD patients. The observation period was between May 2004 and April 2018. This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional ethics boards of each hospital.

Outcome measures and definitions: LOR was defined as the need to switch from anti TNF-α to another therapy, an increase of the anti TNF-α dose, the addition of other drugs (corticosteroids and azathioprine [AZA]) for remission induction, the addition of cytapheresis, or a need for surgery. We divided the 128 patients into two groups by sex, disease behavior (perforating, penetrating type, or neither), disease duration (≥3 years or <3 years), disease location (ileitis, ileocolitis, or colitis), history of ileocolonic resection, type of anti TNF-α (IFX or ADA) treatment, use of a corticosteroid before treatment induction, the presence of a perianal disease, concomitant treatment with AZA, or CRP level (≥2.25 mg/dL or <2.25 mg/dL) before treatment induction. We then analyzed the cumulative LOR ratios between the two groups. Data from the patients who could not continue anti TNF-α therapy because of adverse events, other diseases, childbirth, or unknown reasons were censored at the last date of follow-up.

Statistical analyses: Age, disease duration before anti TNF-α treatment, and follow-up period after treatment are expressed as medians and interquartile ranges (IQRs). The cumulative LOR ratios were calculated using the Kaplan-Meier method, and differences in the cumulative ratios between the two groups were compared using the log-rank test. The optimal cut-off for the CRP level before treatment induction was determined by a receiver-operating characteristic (ROC) analysis. Cox regression analysis (multivariate stepwise logistic regression analysis) was performed to identify the risk factors for LOR. The factors investigated were female sex, age, disease behavior, disease duration, disease location, history of ileocolonic resection, type of anti TNF-α, use of a corticosteroid before treatment induction, the presence of a perianal disease, concomitant treatment with AZA, and CRP level before treatment induction. A p-value of <0.05 was considered significant. All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results:

Patients: One-hundred twenty-eight patients with CD were analyzed in this study. The baseline characteristics of the patients are shown in Table 1. Twenty-five percent of the patients were women. The median age of the patients was 31 years (IQR 22.0-43.2 years), the median duration before the anti TNF-α treatment was 1.7 years (IQR 0.2-9.3 years), and

Table 1: Patients' baseline characteristics (N=128).

	Data
Female sex (%)	25
Median age at induction therapy (years) (IQR)	31 (22.0-43.2)
Median duration before anti-TNF-α therapy (years) (IQR)	1.7 (0.2-9.3)
Median follow-up period after anti-TNF-α therapy (years) (IQR)	2.9 (1.0-5.1)
Type of first anti-TNF-α (n)	
IFX	90
ADA	38
Disease location (n)	
Ileal	35
Ileocolonic	60
Colonic	33
Type of disease behavior (n)	
Inflammatory	58
Stenotic	50
Penetrating	19
Unknown	1
History of intestinal tract resection (%)	20.3
Perianal disease (%)	30.7
Concomitant treatment with AZA (%)	32.7
Use of a corticosteroid before induction (%)	20

IQR: interquartile range; TNF-α: tumor necrosis factor-α; IFX: infliximab; ADA: adalimumab; AZA: azathioprine.

the median follow-up period after the treatment was 2.9 years (IQR 1.0-5.1 years). LOR to IFX and ADA treatments was recognized in 26 (28.8%) of 90 patients and 7 (18.4%) of 38 patients, respectively. Twelve (46.1%) of the 26 patients with LOR to the IFX treatment required an infusion dose escalation to 10 mg/kg. Eleven of the IFX treatment patients (42.3%) were switched to ADA, and 3 (11.6%) underwent intestinal tract resection. On the other hand, 2 (28.6%) of the 7 patients with LOR to the ADA treatment required a dose escalation to 80 mg at 2 weeks, and 5 (71.4%) of the patients receiving ADA treatment were switched to IFX. Two (1.5%) of the 128 total patients stopped receiving anti TNF-α treatments because of another disease; one of these patients required treatment for breast cancer, and the other required a corticosteroid for nephrotic syndrome. Additionally, 1 patient stopped receiving treatment because of delivery of an infant. Adverse events leading to the discontinuation of treatment were seen in 7 patients (5.4%); of these, arthralgia was reported in 2 patients treated with IFX, anaphylaxis was reported in 1 patient treated with IFX, and the adverse events were unknown in the other 4 patients.

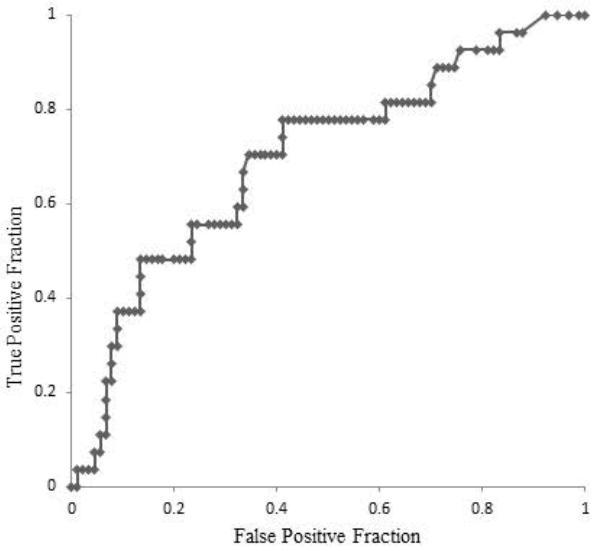

Figure 1: Receiver operating characteristic curve of the C-reavtive protein level before treatment induction

Cut-off level for CRP: In this study, a ROC analysis of the CRP level before treatment induction indicated that the best CRP cut-off level for predicting LOR was ≥2.25 mg/dL, with a sensitivity of 70.3% and a specificity of 65.6% **(Fig. 1)**. The area under the curve was 0.69 (95% confidence interval [CI], 0.58-0.81).

Cumulative LOR ratios: Figures 2a-j show the Kaplan-Meier curves for the cumulative LOR ratios of anti TNF-α therapy based on multiple factors. There were no significant differences among the cumulative LOR ratios according to sex, disease behavior, disease location, history of ileocolonic resection, type of first anti TNF-α, use of a corticosteroid

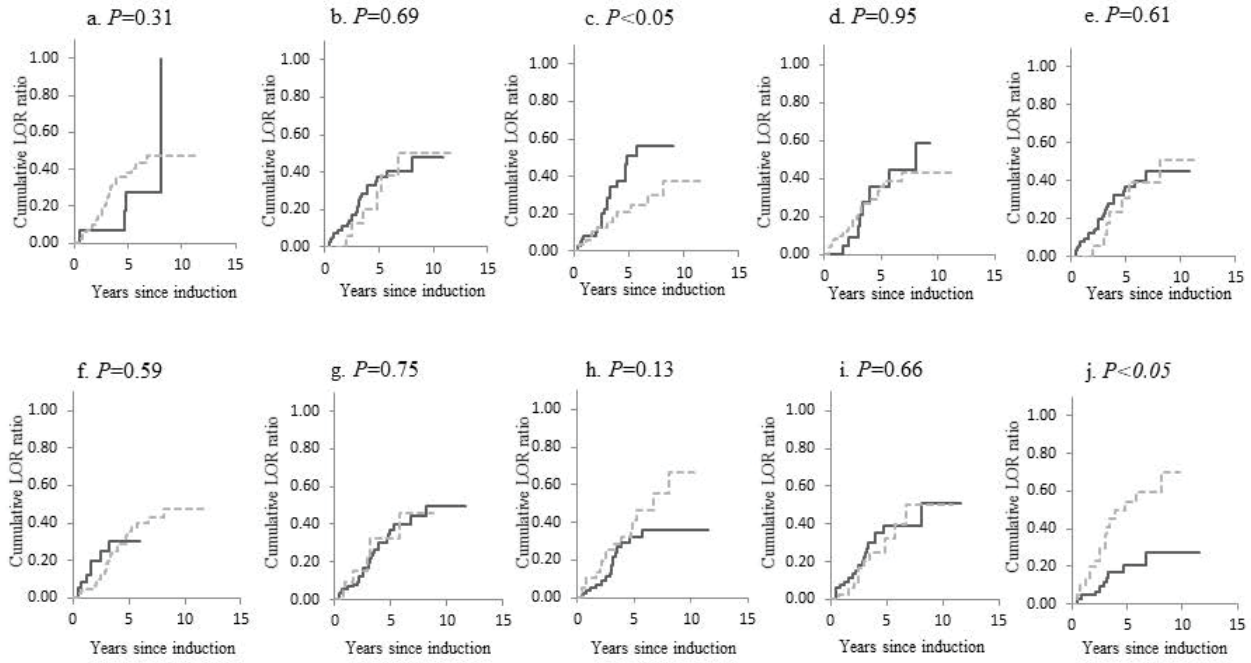

Figure 2: Kaplan-Meier curves for the cumulative loss of response (LOR) ratios by (a) sex (–female sex [n=32], male sex [n=96]), (b) disease behaviour (–non-perforating, penetrating type [n=108], perforating, penetrating type [n=19]), (c) disease duration (–<3 years [n=71], ≥3 years [n=54]), (d) disease location (–colitis [n=33], ileitis and ileocolitis [n=95]), (e) history of ileocolonic resection (–without resection [n=102], with resection [n=26]), (f) type of anti tumour necrosis factor-α (–adalimumab [n=38], infliximab [n=90]), (g) use of a corticosteroid before treatment induction (–with a corticosteroid [n=25], without a corticosteroid [n=100]), (h) the presence of a perianal disease (–without perianal disease [n=88], with a perianal disease [n=39]), (i) concomitant treatment with azathioprine (AZA) (–without AZA [n=78], with AZA [n=38]), and (j) C-reactive protein level before induction (–<2.25 mg/dL [n=69], ≥2.25 mg/dL [n=48]).

Table 2: Risk factors for loss of response in the multivariate Cox regression analysis (n=109).

Variable	HR	95% CI	p-value
Ileitis and ileocolitis	2.563	1.020-6.436	0.045
Perforating and penetrating types	0.331	0.093-1.173	0.086
C-reactive protein (≥2.25 mg/dL)	5.317	2.237-12.633	<0.001

CI: confidence interval; HR: hazard ratio.

before treatment induction, the presence of perianal disease, or concomitant treatment with AZA. However, the cumulative LOR ratios were significantly higher in the group with a disease duration <3 years than in the group with a disease duration ≥3 years (Fig. 2c). Moreover, the cumulative LOR ratios were significantly higher in the group with a high CRP level (≥2.25 mg/dL) than in the group with a low CRP level (<2.25 mg/dL) (Fig. 2j).

Risk factors for predicting LOR: In the multivariate Cox regression analysis, the presence of both an ileitis lesion and a high CRP level before treatment induction were identified as independent risk factors for predicting LOR (Table 2).

Discussion:

To the best of our knowledge, this is one of the few studies that have investigated the effects of IFX or ADA treatments in naïve CD patients only. In this study, we showed that the cumulative LOR ratios in the short disease duration group and the high CRP level group were higher than those of the long disease duration group and the low CRP level group, respectively. Moreover, the results of our multivariate analysis showed that the presence of an ileitis lesion and a high CRP level before treatment induction were both independent risk factors for predicting LOR.

Gisbert et al. [8] reported that the mean percentage of patients with LOR to IFX was 37%. In the ADJUST study [9], LOR was recognized in 44.1% of the patients who received ADA treatment. In our study, LOR was recognized in 28.8% (IFX treatment) and 18.4% (ADA treatment) of the patients. We believe that the LOR ratios in our study were lower than those seen in previous studies because we investigated only anti TNF-α naïve patients. In the ADJUST study [9], previous use of IFX was reported as a risk factor for discontinuation of ADA treatment.

Otake et al. [10] reported that there was no significant difference in the cumulative LOR ratios between IFX and ADA. Ma et al. [11] also reported that the proportions of patients with LOR were similar for both the IFX and ADA treatments. In accordance with these studies, we found that there was no significant difference in the type of anti TNF-α (IFX or ADA) administered first.

In our study, the LOR ratio was higher in the short disease duration group than in the long disease duration group. However, in the CHARM trial, Colombel et al. [12] reported that starting ADA therapy earlier in the disease course increases the probability of achieving deep remission. In general, CD is a progressive disease, and early anti TNF-α therapy has been shown to be effective. Here, we showed that a high CRP level before treatment induction is an independent risk factor for predicting LOR. Therefore, the significantly higher CRP level in the short disease duration group than in the long disease duration group was likely the reason why the LOR ratio was high for the short disease duration group.

Previous studies have shown that several factors are predictors of LOR. Hibi et al. [7] reported that the CRP level was a predictor of LOR to IFX treatments. Furthermore, in the ADJUST study [9], Tanaka et al. reported that female sex, perianal disease, CRP level, low albumin level, previous use of IFX, and concomitant treatment with a steroid were prognostic factors associated with the discontinuation of ADA. In addition, Gutierrez et al. [13] reported that smoking at the time of diagnosis was significantly and independently associated with the risk of LOR to IFX. In our study, the presence of an ileitis lesion and a high CRP level before induction were identified as independent risk factors for predicting LOR. The disease location was not statistically significant in the univariate analysis; however, the presence of an ileitis lesion was identified as an independent risk factor for predicting LOR in the multivariate analysis. We suggest that the difference in these results was caused by the different number of patients between the univariate and multivariate analyses. Sex, disease behavior, disease duration, history of ileocolonic resection, type of first anti TNF-α (IFX or ADA), use of a steroid before treatment induction, presence of a perianal disease, and concomitant treatment with AZA were not significant risk factors for predicting LOR. We believe that this result was caused by the fact that, unlike previous studies, we only analyzed naïve anti TNF-α patients, and patients who received both IFX and ADA treatments were not included in this study. To prevent LOR, we suggest that some form of treatment is necessary to reduce the patient's CRP level before anti TNF-α therapy should begin. In our study, the use of a steroid before treatment induction was not a significant risk factor for predicting LOR. To the best of our knowledge, no studies have investigated the association between reducing the CRP level before anti TNF-α therapy and LOR. Therefore, further studies are needed.

There are some limitations in our study. Firstly, it had a retrospective design, therefore it lacked data and we could not analyze the data from all the patients. Moreover, we did not investigate the CD Activity Index score, serum TNF-α levels, TNF-α antibody levels, and patients' lifestyle habits. Therefore, a prospective study of the risk factors for predicting LOR is needed. Secondly, the sample size was small; thus, a large-scale multicenter study is also needed.

In conclusion, our study shows that the CRP level prior to anti TNF-α therapy is an important factor for predicting LOR in anti TNF-α naïve patients. CRP level could potentially be used to plan treatment for patients with CD. Further studies

are needed to confirm whether reducing the CRP level before starting anti TNF-α therapy can prevent LOR in patients with CD.

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Conflict of interest

K.K. received lecture fees from Daiichi Sankyo Co., Ltd., Astra Zeneca Co., Ltd., EA Pharma Co., Ltd., Mylan Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., and Takeda Pharmaceutical Co., Ltd. K.K. received research grants from Astellas Co., Ltd., Daiichi Sankyo Co., Ltd., EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., and Takeda Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to declare.

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