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The effect of early trough level of infliximab on subsequent disease course in patients with Crohn disease

A prospective cohort study

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Abstract

Decreased trough level of infliximab (TLI) is associated with diminished efficacy in patients with Crohn disease (CD). We examined whether TLI at 14 weeks subsequent to the start of infliximab (IFX) treatment would impact long-term clinical course.

Serum IFX levels and antibodies to IFX (ATI) at 14 and 54 weeks after IFX administration were measured in 12 patients with mild to moderate CD. We examined patient background, clinical severity, blood test values, and the relationship between ATI and TLI up to 108 weeks.

We compared the group with TLI < 3 μg/mL at 14 weeks (TLI(14) < 3 group) the group with TLI > 3 μg/mL (TLI(14) ≥ 3 group). Patients in the TLI(14) ≥ 3 group were significantly more likely to use immunomodulators before IFX treatment induction ($P = .01$). At 54 weeks, 2 cases of ATI production were observed in the TLI(14) < 3 group, but no ATI production was observed in the TLI(14) ≥ 3 group. TLI in the TLI(14) ≥ 3 group at 54 weeks was significantly higher than in the TLI(14) < 3 group (6.5 μg/mL vs 1.0 μg/mL; $P < .01$). Although CD activity index and serum albumin values in the TLI(14) ≥ 3 group at 14, 54, and 108 weeks significantly improved compared to baseline, these improvements were not observed in the TLI(14) < 3 group. The remission maintenance rate at 108 weeks evaluated with the Kaplan–Meier method was significantly higher in the TLI(14) ≥ 3 group than the TLI(14) < 3 group (100% vs 33.3%; $P = .02$).

The TLI 14 weeks after IFX treatment in patients with CD affects long-term outcome.

Abbreviations: Alb = albumin, ATI = antibodies to infliximab, CD = Crohn disease, CDAI = Crohn disease activity index, Hb = hemoglobin, IBD = inflammatory bowel disease, IFX = infliximab, IM = immunomodulator, IQR = interquartile range, PSL = prednisolone, SES-CD = simplified endoscopic activity score for Crohn disease, TLI = trough level of infliximab, TNFα = tumor necrosis factor alpha.

Keywords: antibody to infliximab, anti-tumor necrosis factor agent, Crohn disease, immunomodulators, trough level of infliximab

1. Introduction

Overproduction of inflammatory cytokines, particularly tumor necrosis factor alpha (TNFα), plays an important role in the pathogenesis of inflammatory bowel disease (IBD). Anti-TNFα therapy has revolutionized the treatment of inflammatory bowel disease.[1] Anti-TNFα therapy is also effective against Crohn disease (CD), which has dramatically changed the therapeutic strategy across all stages, from induction of the disease through maintenance therapy.[2] Infliximab (IFX), an anti-TNFα drug, is effective against luminal and fistulizing CD.[3,4] However, IFX is not effective for all patients with CD, and primary nonresponse and loss of response with poor therapeutic efficacy continues to be a clinical limitation.[5,6] An analysis of past clinical studies reported an IFX secondary failure rate in CD of 37% on average.[7] One of the suspected causes for the loss of response during anti-TNFα therapy is the appearance of antibodies against anti-TNFα medications (e.g., IFX) and a resultant decrease in the blood trough concentration. In support of this theory, a higher rate of clinical remission was reported in a group of patients with CD with a higher trough level of IFX (TLI) when compared to those with undetectable levels of TLI.[8]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The human body may produce antibodies to IFX (ATI), and ATIs attenuate the effects of IFX by reducing the blood concentrations of the drug.[9,10] Meta-analyses have shown that a loss of response occurs when ATIs are produced.[11] Thus, it is hypothesized that the therapeutic effects of anti-TNFα preparations are substantially linked to the pharmacokinetics of the medication in the body and factors that ameliorate this response (e.g., IFX). To attenuate this loss of response, 2 measures have been recommended clinically,[12] which include a double dose administration of IFX, shortening administration period and a combined use of immunomodulators (IMs).[13,14] However, TLI after IFX administration varies among patients, and it is not clear what factors affect TLI. In addition, the impact of TLI after a short period of IFX treatment on the subsequent clinical course has not yet been determined.

In this study, we analyzed what factors impact TLI in patients with CD who had a measurable TLI and ATIs. Additionally, we examined the effect of TLI on the subsequent clinical course of CD after a short period of IFX treatment.

2. Methods

2.1. Patients

Twelve patients with CD at Hamamatsu University School of Medicine who began IFX treatment between April 2014 and March 2016 were included in this study. All patients provided informed consent prior to enrollment in this study. Patients for whom consent was not obtained were excluded from the study. Patients with ulcerative colitis and Behçet disease, those with other IBDs (such as indeterminate colitis), and patients using biologics other than IFX were also excluded. Cases in which an additional IM was implemented concurrently with or after IFX or cases in which IFX treatment was discontinued or the dose altered were also excluded. Preadministration of prednisolone (PSL) was performed at the discretion of the attending physician. However, patients who had an alteration in the dose of PSL during the observational period were also excluded from this study. Although this study was a prospective study, the judgment regarding the addition and change of treatment was entrusted to the attending physician, and patients whose treatments were changed after IFX administration were excluded from the study. And the result of ATI was not known to the attending physician.

2.2. Data collection

The TLI was measured at 14, 54, and 108 weeks after IFX treatment began. We measured ATI at 14 and 54 weeks after IFX treatment began. Serum samples were collected within 3 hours prior to IFX administration and stored at −20°C until being sent to the laboratory for analysis. Serum C-reactive protein (CRP) and serum albumin (Alb) levels were measured for the assessment of CD activity and nutritional status of the patients. These clinical measurements were performed at the laboratory test department of Hamamatsu University School of Medicine.

2.3. Measurement of TLI and ATI

Measurement of TLI and ATIs was performed in the laboratory facility through solid-phase enzyme-linked immunosorbent assay using an iMark microplate reader (Bio-Rad Laboratories, Inc). An accepted and standardized cut-off value for TLI in the assessment of CD has not yet been determined. In this study, we defined the TLI concentration cut-off value as 3 μg/mL, based on previous reports.[15,16]

2.4. Assessment of CD

The CD activity was assessed based on the CD activity index (CDAI).[17] In this study, a mild disease condition was defined as a CDAI of 150 to 220, a moderate disease condition was defined as CDAI of 220 to 450, and a severe disease condition was defined as CDAI of 450 or more. Remission maintenance rate was evaluated by establishing a CDAI cut-off value of 150. CDAI was assessed before IFX induction and at the time of TLI measurement. The endoscopic finding of CD was evaluated with simplified endoscopic activity score for CD (SES-CD).[18]

2.5. Ethical consideration

This study was approved by the Ethics Committee of Hamamatsu University School of Medicine (Registration number 15-221). Full verbal and written explanation of this study was provided to the patients with CD, and written informed consent was obtained from each patient. This study was conducted in accordance with Good Clinical Practice principles in adherence to the Declaration of Helsinki.

2.6. Statistics

Statistical analysis was performed using statistical software (SPSS for Windows, Version 16.0). Data are expressed as mean ± standard deviation. Chi-squared or Fischer exact test were used in 2 group comparisons. Remission maintenance rate was expressed using the Kaplan–Meier method and a significant difference was shown by the Log-rank test. $P < .05$ was considered as statistically significant.

3. Results

3.1. Patient characteristics

The baseline characteristics of the patients are shown in Table 1. Of the 12 patients with CD, 9 (75.0%) were males. The median disease duration was 1 year (interquartile range: 0.5–34). The average of CDAI was 184.9 (71–340). No patients were treated with adalimumab previously. Six patients (50.0%) had an operation history for CD. Patients who received PSL during IFX induction were excluded. Five patients (41.7%) used IMs in this study. The mean TLI 14 weeks after IFX treatment induction (TLI (14)) in 12 patients with CD was 3.9 μg/mL.

3.2. The influence of IMs on 14-week trough values

We compared the group with TLI ≥ 3 μg/mL (TLI(14) ≥ 3 group) and the group with TLI < 3 μg/mL (TLI(14) < 3 group) at 14 weeks after IFX treatment induction (Table 2). Although there were 6 patients in each group, 1 patient in the TLI(14) ≥ 3 group dropped out during the study course for moving. Age at IFX induction, disease duration, and CDAI at the time of IFX induction were not significantly different between these 2 groups. Regarding treatment for CD, no significant difference was shown between the 2 groups for either 5-aminosalicylate or enteral diet. Four patients used IMs in the TLI(14) ≥ 3 group, whereas no IMs were used in the TLI(14) < 3 group ($P = .01$), indicating that IMs may be a factor in serum IFX levels. Based on these results, we

Table 1

Baseline characteristics of included Crohn disease.

Patients characteristics	N = 12
Age at IFX induction, yrs	39.6 (16–65)
Male/female, %	9 (75)/3 (25)
Median disease duration, yrs	1 (0.5–34)
CDAI, mean (IQR)	184.9 (71–340)
Previous treatment with ADA	0
Age at diagnosis; A1 below16 yrs, A2 between 17 and 40 yrs, A3 above 40 yrs (%)	
A1/A2/A3	1 (8.3)/9 (75.0)/2 (16.7)
Current disease location; L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease, %	
L1/L2/L3/L4	5 (41.7)/0 (0)/7 (58.3)/0 (0)
Current disease behavior; B1 nonstricturing, nonpenetrating, B2 stricturing, B3 penetrating, %	
B1/B2/B3	7 (58.3)/2 (16.7)/3 (25.0)
B1/B2 + B3	7 (58.3)/5 (41.7)
Active perianal fistula, %	4 (33.3)
Previous surgery, %	6 (50.0)
Treatment at IFX induction, %	
5-Aminosalicylate	10 (83.3)
Prednisolone	0 (0)
Immunomodulators	5 (41.7)
Enteral nutrition	8 (66.7)
Preadministration of prednisolone	6 (54.5)

ADA = adalimumab, CDAI = Crohn disease activity index, IFX = infliximab, IQR = interquartile range.

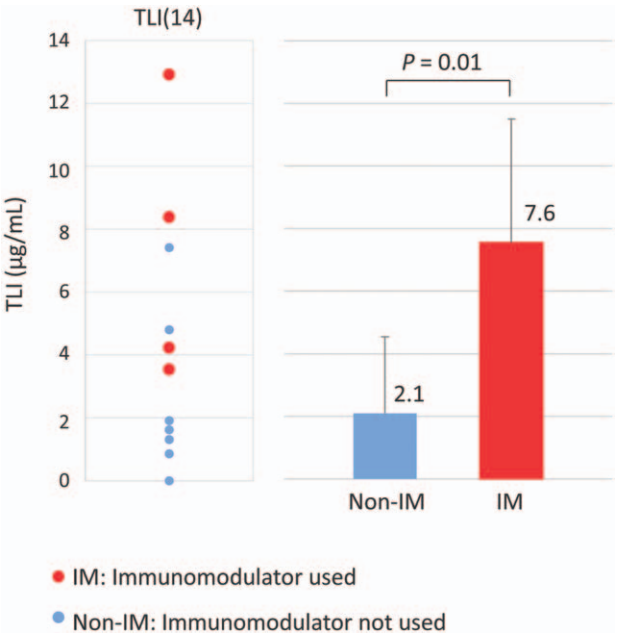

Figure 1. Comparison of trough level of infliximab (IFX) at week 14 (TLI(14)) with or without the use of immunomodulators (IMs). Distribution map shows the trough level of IFX (TLI, μg/mL). Four patients used IMs at the induction of IFX treatment. The mean TLI(14) of Crohn disease patients who were treated with IMs was 7.6 μg/mL, and the mean TLI(14) of those treated without IMs was 2.1 μg/mL.

examined the TLI at 14 weeks with or without the use of IMs (Fig. 1). Of the 12 total patients with CD, all those who were treated with IMs (IM group) had a TLI of more than 3 μg/mL. The mean TLI(14) of the group without IM treatment (non-IM group) was 2.1 μg/mL, and the mean TLI(14) of the IM group showed a significantly high value of 7.6 μg/mL compared to the non-IM group ($P = .01$).

3.3. The influence of the week 14 trough level on the week 54 trough level

The TLI at weeks 14 and 54 are shown in Figure 2. ATI was positive at 54 weeks in 2 cases and both of these had a TLI of 0 μg/mL at week 54. In these 2 cases, 1 case had a TLI of 1.31 μg/mL at week 14, and the other had a TLI of 0 μg/mL at week 14. The mean TLI at week 54 was significantly higher in the TLI(14) ≥ 3 group than in the TLI(14) < 3 group (6.5 μg/mL vs 1.0 μg/mL; $P = .01$).

3.4. The influence of week 14 trough level on CDAI, CRP, and Alb at up to 108 weeks

We examined changes in the levels of CDAI, serum CRP, and serum Alb before IFX treatment induction and at weeks 14, 54, and 108 after IFX treatment induction. CDAI of the TLI(14) < 3

Table 2

Comparison of baseline demographic variables of trough level of IFX at 14 weeks (TLI(14)) ≥ 3 μg/mL and TLI(14) < 3 μg/mL groups.

	TLI(14) ≥ 3 (n = 6)	TLI(14) < 3 (n = 6)	*P* value
Age at IFX induction, yrs	39.8 ± 17.7	39.5 ± 19.8	.98
Male/female, %	4 (66.7)/2 (33.3)	5 (83.3)/1 (16.7)	.51
Disease duration, yrs	14.5 ± 14.5	6.8 ± 8.8	.29
CDAI, mean (IQR)	182.5 (120–264)	187.3 (71–340)	.91
Age at diagnosis; A1 below 16 yrs, A2 between 17 and 40 yrs, A3 above 40 yrs, %			
A1/A2/A3	0 (0)/6 (100.0)/0 (0)	1 (16.7)/3 (50.0)/2 (33.3)	.14
Current disease location; L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease, %			
L1/L2/L3	3 (50.0)/0 (0)/3 (50.0)	2 (33.3)/0 (0)/4 (66.7)	.14
Current disease behavior; B1 nonstricturing, nonpenetrating, B2 stricturing, B3 penetrating, %			
B1/B2/B3	3 (50.0)/0 (0)/3 (50.0)	4 (66.7)/2 (33.3)/0 (0)	.08
Treatment at IFX induction, %			
5-Aminosalicylate	6 (100)	4 (80.0)	.25
Immunomodulators	4 (66.7)	0 (0)	.01
Enteral nutrition	4 (66.7)	2 (33.3)	.56
Preadministration of prednisolone	3 (50.0)	1 (16.7)	.22

CDAI = Crohn disease activity index, IFX = infliximab, IQR = interquartile range.

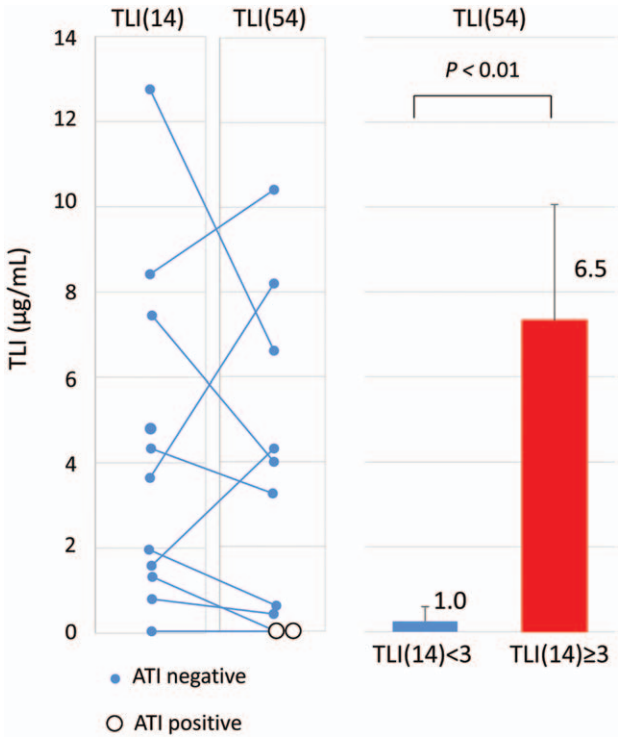

Figure 2. Changes in the trough level of infliximab (TLI) from week 14 to week 54. The mean infliximab (IFX) trough concentrations at week 54 in the TLI(14) ≥ 3 (trough level of IFX at week 14 > 3 μg/mL) group and TLI(14) < 3 (trough level of IFX at week 14 < 3 μg/mL) group were 6.5 and 1.0 μg/mL, respectively. ATI = antibodies to infliximab.

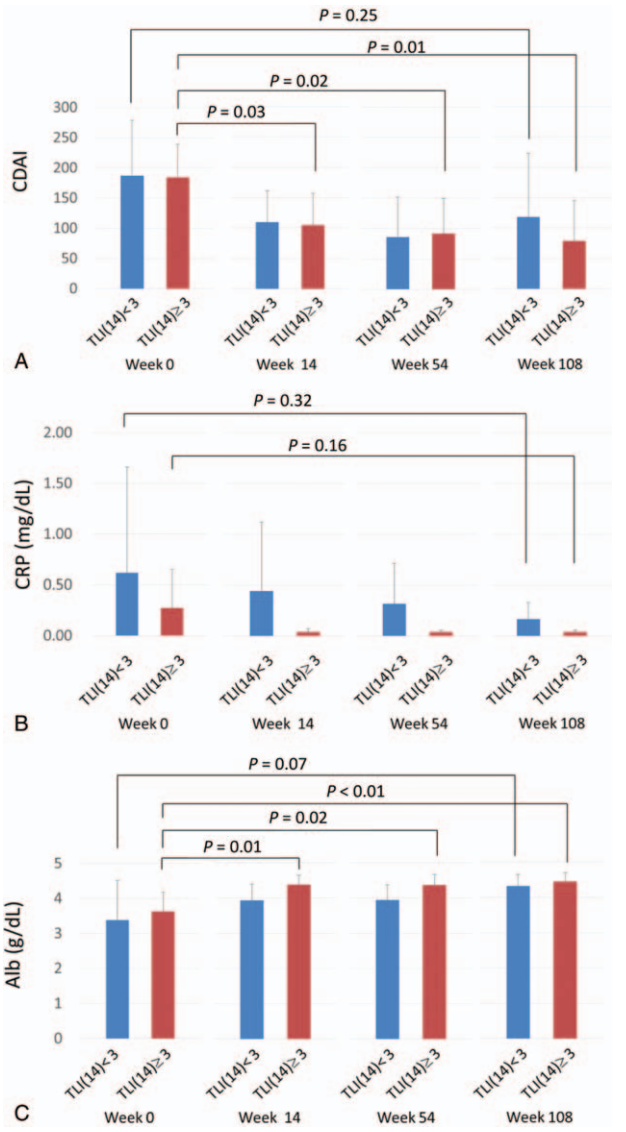

Figure 3. The influence of trough level of infliximab at week 14 (TLI(14)) on the subsequent pathologic course. Crohn disease activity index (CDAI) (A), C-reactive protein (CRP) concentration (mg/dL) (B), and serum albumin (Alb) concentration (g/dL) (C). TLI(14) ≥ 3 and TLI(14) < 3 mean, TLI(14) ≥ 3 μg/mL and TLI(14) < 3 μg/mL, respectively.

group showed no significant difference between before and 108 weeks after IFX treatment, and CDAI of patients in this group did not significantly improve upon treatment with IFX ($P = .25$) (Fig. 3A). In contrast, in the group of TLI(14) ≥ 3, CDAI at week 14 ($P = .03$), week 54 ($P = .02$), and week 108 ($P = .01$) showed a significant decrease compared to CDAI at week 0. CRP values of the TLI(14) < 3 and TLI(14) ≥ 3 groups showed no significant differences between before and 108 weeks after IFX treatment ($P = .32$ and $P = .16$, respectively) (Fig. 3B). The serum Alb concentration of the TLI(14) < 3 group showed no significant difference between before and 108 weeks after IFX treatment ($P = .07$) (Fig. 3C). The serum Alb concentration of the TLI(14) ≥ 3 group was shown to be significantly increased after IFX treatment at week 14 ($P = .01$), week 54 ($P = .02$), and week 108 ($P < .01$) (Fig. 3C). The serum Alb concentration of the TLI(14) ≥ 3 group was shown to be significantly increased after IFX treatment at week 14 ($P = .01$), week 54 ($P = .015$), and week 108 ($P < .01$) (Fig. 3C). The TLI(14) < 3 group showed a significant difference between the SES-CD at 0 and 108 weeks ($P = .03$), whereas the TLI(14) ≥ 3 group showed no significant difference ($P = .05$; Fig. 4).

3.5. The influence of the week 14 trough on the clinical course up to week 108

We evaluated the remission maintenance rate using the Kaplan–Meier method (Fig. 5). The remission maintenance rate of the TLI (14) ≥ 3 group was maintained at 100% even at week 108. The remission maintenance rate of the TLI(14) < 3 group declined to 33.3% at week 108. Evaluation with the Log-rank test of these 2 groups showed a significant difference in the remission maintenance rate ($P = .02$). In addition, we examined whether the value of TLI(14) affected the subsequent treatment course (Fig. 6). Four patients were forced to change to other treatments (e.g., change to a double dose of IFX, shortened the IFX administration period, or changed to alternate biologic products) after IFX treatment induction, of which all of these patients were in the TLI(14) < 3 group. TLI in cases in which IFX could be continued without alteration were significantly higher than those in cases in which other treatments were introduced ($P = .03$).

4. Discussion

Measurements of both TLI and ATIs are important in the treatment of CD, as the therapeutic effect of IFX in CD is

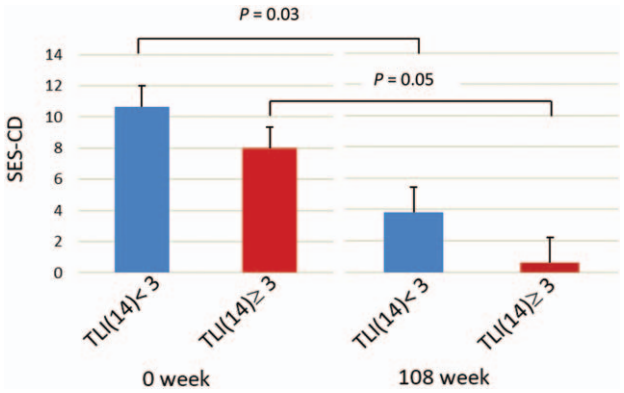

Figure 4. The influence of trough level of infliximab at week 14 (TLI(14)) on the subsequent course of endoscopic status evaluated with simplified endoscopic activity score for Crohn disease (SES-CD).

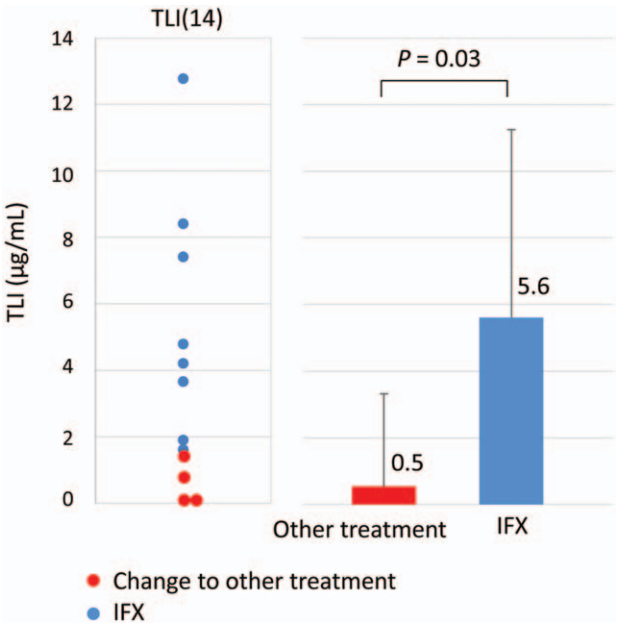

Figure 6. The influence of trough level of infliximab (IFX) at week 14 (TLI(14)) on the subsequent pathologic course. This figure shows the IFX trough concentration of Crohn disease patients who either continued IFX therapy or those who changed to other forms of treatment.

critically influenced by these factors. Further, there is substantial interindividual variability in the values of TLI and the appearance of ATIs in patients with CD. As such, quantifying and evaluating these differences enables more efficacious treatment of CD in individual patients. In fact, therapeutic drug monitoring aimed at treat-to-target can effectively and safely use anti-TNFα preparations.[19–21] It has been reported that achieving a high TLI value after a short period of IFX treatment can induce subsequent high remission maintenance rates.[22–27] However, these reports only followed and evaluated patients up to approximately 50 weeks, and there are few reports examining the affects early TLI levels have on the long-term course of CD.

In this study, we examined how TLI at 14 weeks affected clinical activity, blood biomarkers, and the subsequent treatment course of CD up to 108 weeks. While there have been some reports suggesting a TLI cut-off for CD, no definite clinical value has been accepted or standardized at present. As such, we defined the TLI cut-off value as 3 μg/mL in reference to prior study designs and divided the TLI(14) group into a <3 μg/mL (TLI(14) < 3) group and a >3 μg/mL (TLI(14) ≥ 3) group.[15,16] When comparing several background factors between the TLI(14) ≥ 3 and TLI(14) < 3 groups, we found that only the use of IMs before IFX treatment induction showed a significant difference between these groups. While there were 4 patients (66.7%) who used IMs before IFX treatment induction in the TLI(14) ≥ 3 group, there were no patients who used IMs in the TLI(14) < 3. Therefore, IM use prior to IFX treatment induction could be considered as a factor influencing TLI. In support of these findings, IMs have been previously reported to be involved in IFX trough concentration and the appearance of ATIs.[28–31] Moreover, TLI is reported to be

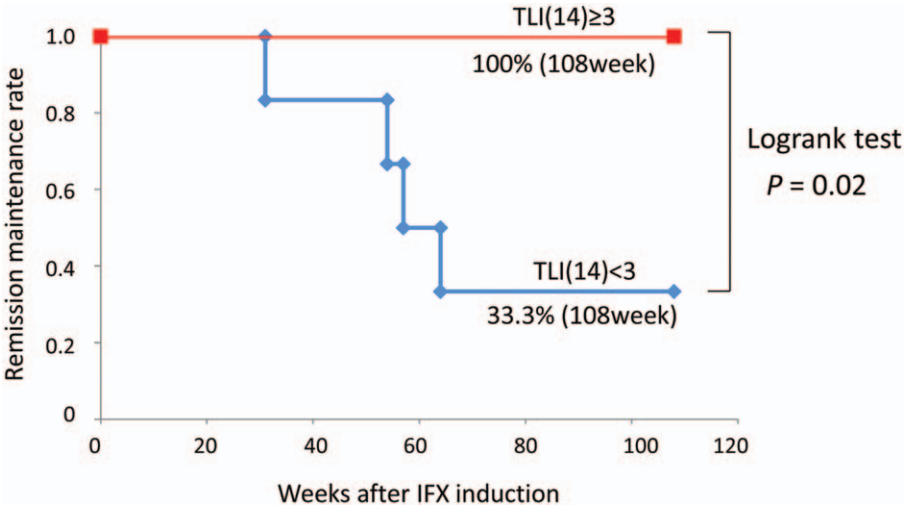

Figure 5. The Kaplan–Meier estimator graph of trough level of infliximab (IFX) at week 14 (TLI(14) ≥ 3) and TLI(14) < 3 groups showing the remission maintenance rate. TLI(14) ≥ 3 and TLI(14) < 3: mean TLI(14) ≥ 3 μg/mL and TLI(14) < 3 μg/mL, respectively. The significant difference was determined by a log-rank test.

correlated with the concentration of 6-thioguanine nucleotide, which is one of the thiopurine metabolites.[32]

We evaluated TLI at week 54 in the TLI(14) < 3 and TLI(14) ≥ 3 groups. The mean TLI at week 54 was significantly higher in the TLI(14) ≥ 3 group than in the TLI(14) < 3 group. This suggests that TLI after a short period of IFX treatment may affect long-term TLI values and that a high TLI value at week 14 can predict subsequent positive long-term effects of IFX therapy. In support of this finding, we also noted that cases in which IMs were used at the time of IFX treatment induction also presented with a maintenance of TLI at >3 μg/mL, and ATIs were not detected in these individuals. Indeed, IMs have a previously identified mechanism capable of suppressing the production of anti-TNFα antibodies, which we suggest could have suppressed the production of ATIs in this study.[33] In both the TLI(14) ≥ 3 and TLI(14) < 3 groups, the changes in CDAI, CRP, and Alb from week 14 to week 108 were evaluated. While CRP was not significantly different between 14 and 108 weeks in both groups, CDAI and Alb showed significant differences between weeks 14 and 108 in the TLI(14) ≥ 3 group. That is, a higher TLI at 14 weeks contributed to improvements in clinical biomarkers (CDAI and Alb) at 108 weeks. Significant improvement of CRP was not obtained with IFX therapy at week 108. Most of the patients in this study had relatively mild to moderate pathology, and the mean CRP values of the TLI(14) ≥ 3 and TLI(14) < 3 groups at the time of treatment induction were 0.615 and 0.273 mg/dL, respectively. This relatively low level at 14 weeks was likely the reason CRP did not decrease significantly at week 108. Regarding the SES-CD in the TLI (14) < 3 group, the SES-CD at the beginning of the IFX therapy was not very high, so it was considered that no significant endoscopic improvement was obtained at 108 weeks.

Evaluation using the Kaplan–Meier method showed that the remission maintenance rate at 108 weeks was significantly lower in the TLI(14) < 3 group compared to the TLI(14) ≥ 3 group, which was maintained at 100%. Further, 4 cases (66.7%) in the TLI(14) < 3 group switched from IFX to another form of CD treatment. As described above, we therefore suggest that IFX trough concentration (TLI) in the early phase of IFX treatment can predict subsequent clinical prognosis.

Next, we examined which factors influence IFX blood concentration at the early phase of IFX treatment induction. Factors affecting the pharmacokinetics of anti-TNFα preparations include sex, body mass index, blood TNFα concentration before drug administration, drug leakage into feces, clearance through the reticulum, and the presence of antidrug antibodies.[34–36]

Although these factors may affect TLI in the early phase of IFX treatment, it is difficult to evaluate all of these factors accurately in clinical practice. Therefore, it would be a good idea to construct a long-term CD treatment strategy with reference to TLI after a short period of IFX induction while predicting the subsequent treatment effect of IFX.

We hypothesize that the results of the present study are connected to clinical treatment as follows: First, if the condition of CD is not stable and IFX is likely to be required in the future, IMs should be administered in advance. Further, a greater IFX dose should be given if the patient's condition seems to be deteriorating. The order of this treatment is important, and it has been reported in the past that the re-remission rate is only 18.4% even with addition of IMs during a loss of response case treated with only a single administration of IFX.[37] Therefore, the use of IMs prior to IFX administration is important in long-term treatment strategies and in preventing a loss of response. Second, our 1st measurement of TLI was made at week 14. Given a loss of response is likely if the TLI at week 14 is low, the frequency of endoscopy should be increased in these low TLI patients. Further, CD activity should be evaluated carefully using a variety of relevant biomarkers. Moreover, if exacerbation of disease activity is expected, an increase in IFX concentration, a decreased time period between IFX administration, or a change to other biologic agents should be considered. Although the small number of patients in this study is a limitation, we suggest the findings of this prospective study are important. Specifically, we identified several challenges associated with the use of IFX in a real clinical setting, and as such, our results may lead to improved long-term patient care.

In conclusion, the TLI in patients with CD at 14 weeks after IFX treatment induction had a significant influence on the long-term course of CD pathology. Therefore, we suggest long-term therapeutic strategies in patients with CD should be based on early phase TLI measurements.

Author contributions

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