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Original Article

Factors Predicting a Favorable Disease Course Without Anti-TNF Therapy in Crohn's Disease Patients

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Determining factors that predict a favorable disease course without anti-tumor necrosis factor (TNF) agents would help establish a more cost-effective strategy for Crohn's disease (CD). A retrospective chart review was performed for CD patients with disease durations > 10 years who had not received anti-TNF agents as first-line therapy. Patients were divided into 2 groups: those who received neither anti-TNF agents nor bowel resection (G1), and those who had received an anti-TNF agent and/or bowel resection (G2). The patient backgrounds, therapies and clinical courses were compared between the groups. A total of 62 CD patients met the inclusion criteria (males: 71%; median duration of follow-up: 19 years). Six patients were included in G1; they were significantly less likely to have upper gastrointestinal lesions than G2 ($p = 0.007$). A multivariate analysis revealed that the significant factors for avoidance of bowel resection without anti-TNF treatment were non-stricturing and non-penetrating behaviors, and absence of upper gastrointestinal lesions at the diagnosis (hazard ratios 0.41 and 0.52; $p = 0.004$ and 0.04, respectively). In consideration of the long treatment course of CD, patients with non-stricturing and non-penetrating behaviors and no upper gastrointestinal lesions should not be treated with anti-TNF agents as first-line therapy.

Key words: Crohn's disease, anti-TNF agent, upper gastrointestinal lesion, bamboo joint-like appearance

Crohn's disease (CD) is a chronic and progressive disease characterized by periods of remission and clinical relapses. CD patients often require bowel resection and urgent hospitalization due to unexpected complications such as stenosis or abscess, which greatly reduce their quality of life. In clinical practice, many CD patients experience disabling courses despite the provision of specific treatments; in contrast, 10-25% of the patients enjoy a favorable disease course without any complications [1-3]. Before the era of biologics, although corticosteroid therapy was practically the only effective treatment option for moderate to severe CD, 28-57% of patients with newly developed CD did not require corticosteroids throughout their lives [4]. Thus, the disease courses of CD can vary widely among patients.

The first anti-tumor necrosis factor (TNF) agent was approved by the U.S. Food and Drug Administration in 1998, and anti-TNF agents have since become a mainstay treatment for CD. Although a number of researchers and clinicians consider so-called "top-down ther-

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apy" to be the best strategy for treating CD patients, many physicians have found that CD patients do not always require anti-TNF agent treatment at the time of the diagnosis or during their long disease course. Additionally, because anti-TNF agents are more expensive than oral corticosteroids or immunomodulators, the indiscreet use of these agents results in a substantial economic burden for both patients and the medical community. Given the recent increase in the numbers of CD patients globally and the development of new "high-cost" biologics, it is important to differentiate high-risk CD patients who will need aggressive treatment with biologics from CD patients who can tolerate the step-up strategy without needing biologics.

Although several studies have identified factors that affect the disease course in CD patients [5-7], the requirement of anti-TNF agents has not been counted as a risk factor or a consequence of severe or disabling disease courses. Therefore, to identify CD patients who absolutely do not require an anti-TNF agent, we investigated factors predicting a favorable disease course without anti-TNF treatment in CD patients with a disease duration exceeding 10 years.

Methods

Patients. We performed a retrospective chart review for all CD patients with disease onset from January 1983 to December 2006 who had been followed at Okayama University Hospital until May 2016. Patients who were not given a full examination (including esophagogastroduodenoscopy [EGD]) for intestinal lesions were excluded.

None of the patients had received an anti-TNF agent as the first-line therapy because infliximab, the first anti-TNF agent approved in Japan, only became available at our institute in 2007. We divided the patients into 2 groups: those who were not treated with an anti-TNF agent and did not undergo bowel resection (G1), and those who were treated with an anti-TNF agent and/or underwent bowel resection (G2) during their disease course until the last follow-up. The patients' backgrounds, clinical manifestations, therapies, and disease courses during the long-term follow-up were investigated and compared. We sought to identify any factors that could be used to predict a favorable disease course, *i.e.*, disease courses with no bowel resection and without the use of anti-TNF agents. We defined the length of favorable disease courses as 2 different periods: 10 years and 5 years (Fig. 1A, B).

This retrospective analysis was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 1506-046). There were no conflicts of interest or sponsors of this study.

Diagnosis and classification of CD. The diagnosis of CD was based on a combination of conventional criteria that included clinical symptoms and the findings obtained by endoscopy, histopathology, and/or radiography. We have routinely given patients diagnosed with CD several examinations before starting their treatment: a blood examination, EGD, total colonoscopy including observation of the terminal ileum, abdominal computed tomography, and small-bowel follow-through. The disease locations and disease behavior were classified according to the Montreal classification [8]. In addition, the presence/absence of upper gastrointestinal (GI) lesions was determined according to the EGD findings. Upper GI lesions included both ulcers and erosions in the antrum and erosions and notched signs in the duodenum [9-12]. A bamboo joint-like appearance (BLA) was also regarded as a characteristic upper GI finding of CD [13]. A BLA is characterized by longitudinal folds with traversing erosive fissures or linear furrows, often found in the lesser curvature of the gastric body and cardia, and sometimes observed in the bulb of the duodenum [14, 15] (Fig. 2).

Treatment policy for CD including the administration of anti-TNF agents. All CD patients were treated with the step-up policy, based on the guidelines published by the British Society of Gastroenterology, the European Crohn's and Colitis Organization, and the American College of Gastroenterology [1-3]. In general, if tolerated, a sufficient dose of 5-aminosalicylate (ASA) and an elemental diet were administered to patients with mild to moderate activity. CD patients with severe activity or those refractory to 5-ASA or an elemental diet were considered to be indicated for corticosteroid. In the patients with steroid-refractory or steroid-dependent courses, an immunomodulator was started.

None of the patients were administered anti-TNF agents before December 2006, even when they underwent intestinal resections or experienced repeated flare-ups. We started to use the anti-TNF agents for remis-

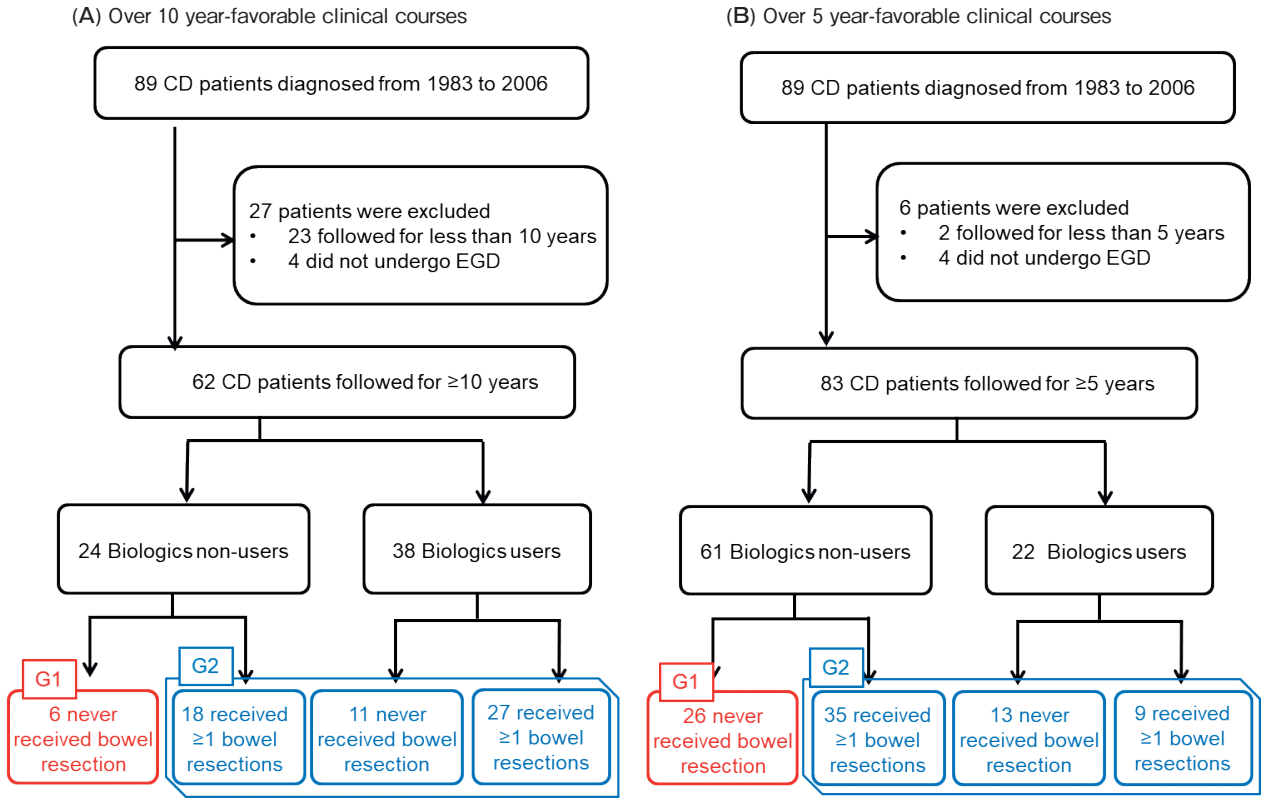

Fig. 1 Patient flow chart. **A**, Over 10 year-favorable clinical courses; **B**, Over 5 year-favorable clinical courses.

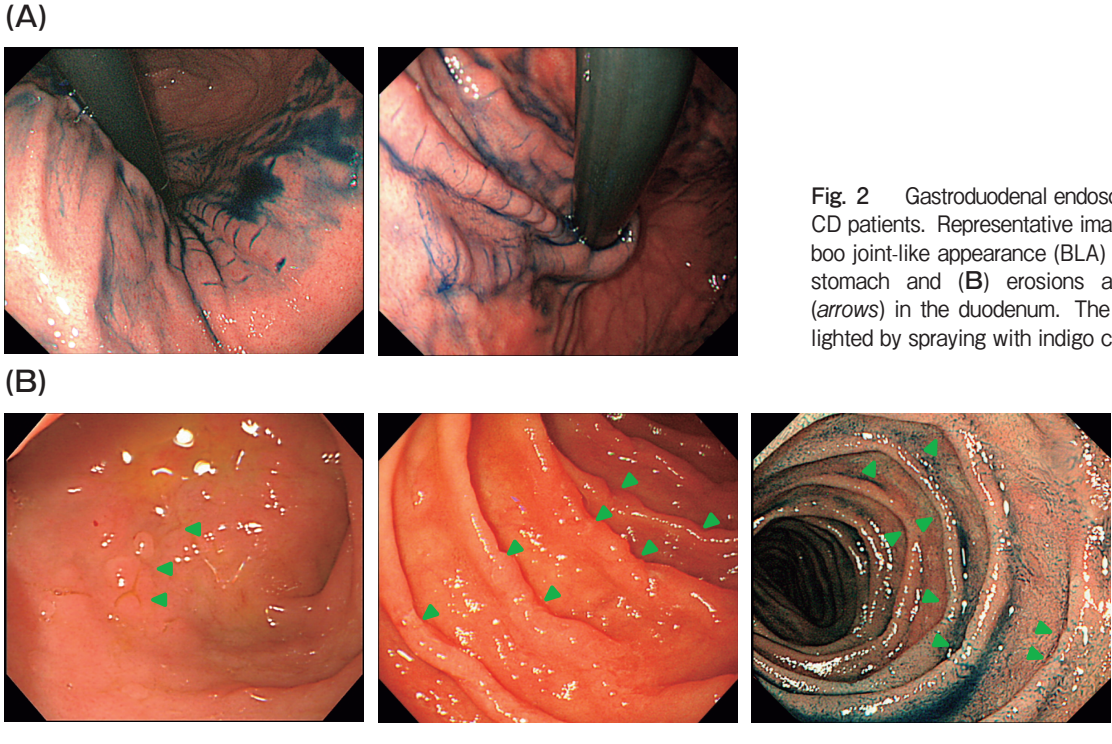

Fig. 2 Gastroduodenal endoscopic findings of the CD patients. Representative images of (**A**) the bamboo joint-like appearance (BLA) in the cardia of the stomach and (**B**) erosions and notched signs (*arrows*) in the duodenum. The lesions were highlighted by spraying with indigo carmine dye.

sion induction and maintenance therapy if appropriate, only after the Ministry of Health, Labor and Welfare in Japan approved infliximab as maintenance therapy for CD in January 2007. At our institute, the indications for the administration of anti-TNF agents were as follows: (1) failure to respond to standard treatments, including elemental diet, 5-ASA, corticosteroids and immunomodulators; and (2) a moderate to severe symptoms score >150 on the Crohn's Disease Activity Index (CDAI) despite existing treatments and being at high risk for intestinal failure (*i.e.*, having a <2 m length of residual small intestine after bowel resection and/or polysurgery).

Statistical analyses. The patient characteristics were compared using the chi-squared test, Fisher's exact test, and the Mann-Whitney *U*-test. Univariate and multivariate analyses using a Cox proportional hazards regression model were conducted to identify variables associated with avoiding both the use of anti-TNF agents and bowel resection. Variables with *p*-values <0.10 in a univariate analysis were further tested in a multivariate analysis. The hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The rates of using anti-TNF agents or undergoing a bowel resection after the CD diagnosis were analyzed by the Kaplan-Meier method. A statistical comparison was carried out by the log-rank test. *P*-values <0.05 were considered significant. All of the statistical analyses were performed using the JMP pro software program, ver. 12 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Eighty-nine patients were diagnosed with CD from 1983 to 2006 at Okayama University Hospital. Of these, as indicated in Fig. 1A, we excluded the 23 patients who were lost to follow-up before 10 years and the 4 patients who had not undergone an EGD examination at the diagnosis. Among the remaining 62 patients, all of whom had maintained steroid-free remission at the last visit of the study period, 38 patients received anti-TNF agents during their ≥10-year disease course, and the other 24 patients did not. Of the 24 patients without treatment with an anti-TNF agent, 18 underwent bowel resections at least once, and only the remaining 6 patients had favorable clinical courses without bowel resection (G1). In G1, only one patient had both stricturing and an upper GI lesion and had been in remission with an immunomodulator and elemental diet for 20 years. Among the 38 biologic users, 11 patients had never undergone bowel resections, and the other 27 patients had undergone at least one bowel resection. The 56 patients who were treated with anti-TNF agents and/or bowel resections once or more during their disease courses were classified as G2 according to their treatment history of anti-TNF agents and bowel resections.

When we redefined the length of a favorable clinical course as 5 years, 83 patients were included between 1983 and 2006 (Fig. 1B). In this redefined group, 61 patients were biologics non-users during their 5-year disease course, and 26 patients who had never undergone bowel resections for ≥5 years were included in G1. The remaining 57 patients comprised G2.

The clinical characteristics of the analyzed patients over the 10-year favorable clinical courses are summarized in Table 1. The average duration of follow-up was 19 years. The patients in G1 were significantly less likely to have upper GI lesions than those in G2 (1 [17%] vs. 40 [67%], $p=0.007$). None of the other factors (including the Montreal classification and medications received during the follow-up) differed significantly between the 2 groups. In the analysis of the redefined groups over the 5-year favorable clinical courses, there were no significant differences between G1 and G2 (data not shown).

Factors associated with bowel resection and/or use of anti-TNF agents. We investigated the factors predicting a favorable clinical course for 10 years among the patients who had never undergone bowel resections and did not use anti-TNF agents—*i.e.*, the factors for inclusion in G1. The multivariate analysis revealed that (1) the absence of upper GI lesions and (2) non-stricturing and non-penetrating behavior in the Montreal classification were significant factors: HR 0.52, 95%CI: 0.27-0.98 and HR 0.41, 95%CI: 0.22-0.75, respectively (Table 2). When the minimum period for a favorable clinical course was limited to 5 years, non-stricturing and non-penetrating behavior was the only significant factor: HR 0.01, 95%CI: 0-0. 01 (Table 3).

Ratios of patients with neither bowel resections nor anti-TNF agent treatments. We performed a Kaplan-Meier analysis to examine the ratios of patients with neither bowel resections nor the use of anti-TNF agents in the total patient series. The time to bowel resection or use of anti-TNF agents according to the predictive factors for a 10 year-favorable disease course

Table 1 Patients' background characteristics in G1 and G2 groups

Total (n=62)	G1 (n=6)	G2 (n=56)	*p*-value
Gender (Male)	4 (67%)	40 (71%)	0.81
Age at diagnosis (year)*	29 (20–38)	24 (18–30)	0.22
Follow-up periods (year)*	16 (12–24)	19 (14–26)	0.41
Age at diagnosis**			
A1/A2/A3	1 (17%)/5 (83%)/0 (0%)	3 (5%)/48 (86%)/5 (9%)	0.62
Location at diagnosis†			
L1/L2/L3	1 (17%)/3 (50%)/2 (33%)	15 (27%)/6 (11%)/35 (63%)	0.61
Behavior at diagnosis‡			
B1/B2/B3	5 (83%)/1 (17%)/0 (0%)	34 (61%)/17 (30%)/5 (9%)	0.25
Perianal disease	0 (0%)	14 (25%)	0.13
Smoking (Yes)	2 (33%)	11 (20%)	0.43
Upper gastrointestinal lesions	1 (17%)	40 (67%)	0.007
Medications during follow-up			
Biologics	0 (0%)	38 (68%)	0.001
Corticosteroids	1 (17%)	19 (34%)	0.39
Immunomoduators	3 (50%)	36 (64%)	0.49
Elemental diet	3 (50%)	29 (52%)	1.00

*Median (IQR)
**A1, <16 years; A2, 17–40 years; A3, >40 years.
†L1, ileal lesion; L2, colonic lesion; L3, ileocolonic lesion.
‡B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating.

Table 2 A multivariate analysis of predictive factors associated with a 10-year favorable disease course

Risk Factors	Univariate	Multivariate	
	p-value	HR (95% C.I.)	*p*-value
Age ≥40 years at diagnosis	0.21		
Sex (female)	0.43		
Disease duration	0.45		
Montreal classification			
Location (L1/L2+L3)†	0.47		
Behavior (B1/B2+B3)‡	0.052	0.41 (0.22–0.75)	0.004
Perianal disease (−)	0.059	0.51 (0.27–1.03)	0.060
Smoking habit (−)	0.14		
Upper gastrointestinal lesions (−)	0.096	0.52 (0.27–0.98)	0.042
Treatment during follow-up			
Immunomodulators (−)	0.25		
Corticosteroids (−)	0.79		

†L1, ileal lesion; L2, colonic lesion; L3, ileocolonic lesion.
‡B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating.

is shown in Figure 3. The patients without upper GI lesions were less likely to undergo a bowel resection or be treated with anti-TNF agents compared to the patients with such lesions, although a log-rank test did not reveal significance (Fig. 3A; $p=0.10$). In contrast, the patients without stricturing and penetrating behavior were significantly less likely to undergo bowel resections or be treated with anti-TNF agents (Fig. 3B; $p=0.04$, log-rank test).

The additional prognostic curves showed that the patients without stricturing and penetrating behavior and without upper GI lesions had the lowest risk of bowel resection or anti-TNF agent administration, whereas those with stricturing or penetrating behavior plus upper GI lesions were the most highly likely to undergo bowel resections or anti-TNF agents. The

Table 3 A multivariate analysis of the predictive factors associated with a 5-year favorable disease course

Risk factors	Univariate	Multivariate	
	p-value	HR (95% C.I.)	*p*-value
Age ≥40 years at diagnosis	0.59		
Sex (female)	0.51		
Disease duration	0.22		
Montreal classification			
Location (L1/L2+L3) †	0.20		
Behavior (B1/B2+B3) ‡	0. 03	0.01 (0–0.01)	0.025
Perianal disease (−)	0.086	0.30 (0.82–13.5)	0.071
Smoking habit (−)	0.33		
Upper gastrointestinal lesions (−)	0.38		
Treatment during follow-up			
Immunomodulators (−)	0.15		
Corticosteroids (−)	0.99		

† L1, ileal lesion; L2, colonic lesion; L3, ileocolonic lesion.
‡ B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating.

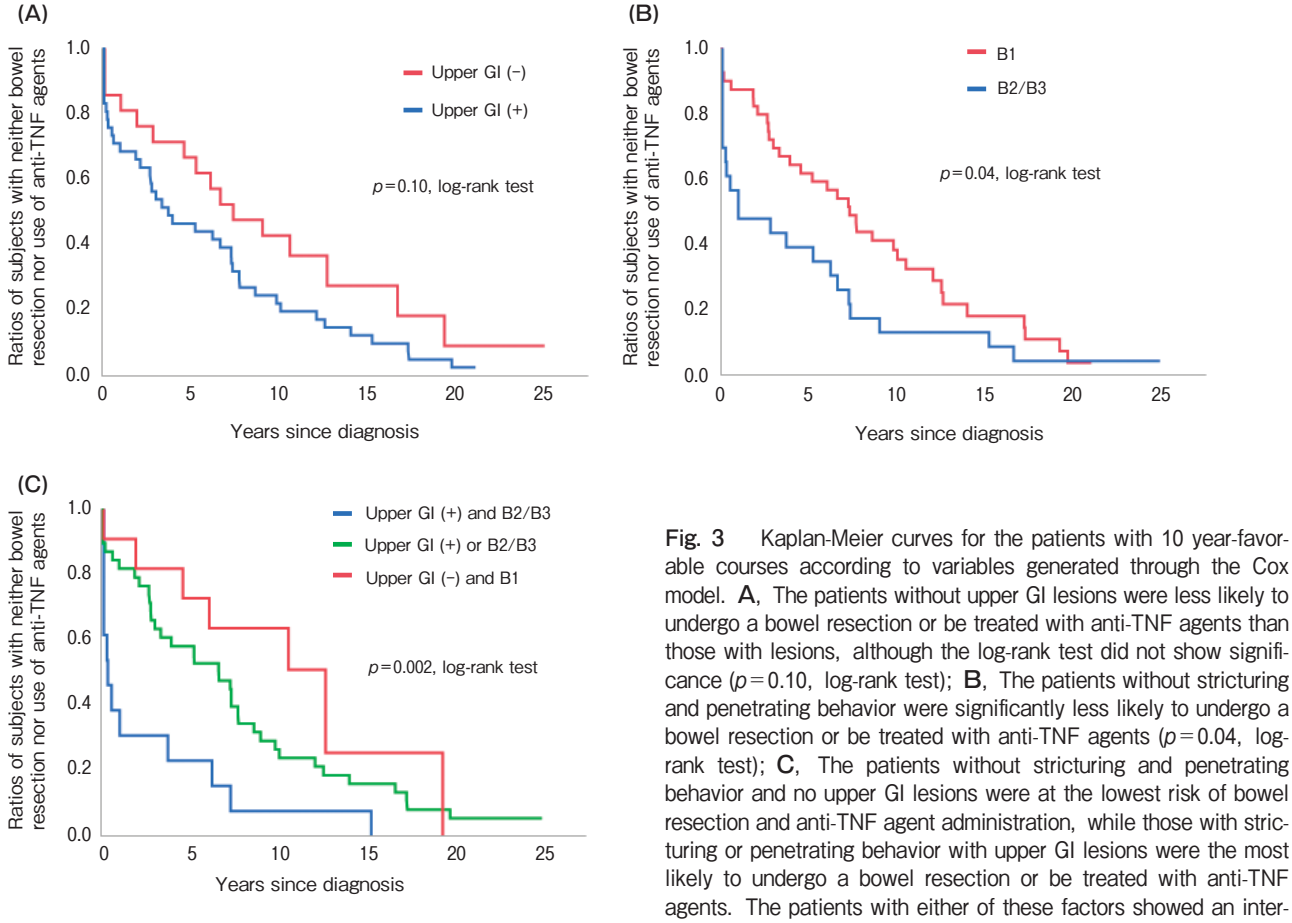

Fig. 3 Kaplan-Meier curves for the patients with 10 year-favorable courses according to variables generated through the Cox model. **A**, The patients without upper GI lesions were less likely to undergo a bowel resection or be treated with anti-TNF agents than those with lesions, although the log-rank test did not show significance ($p=0.10$, log-rank test); **B**, The patients without stricturing and penetrating behavior were significantly less likely to undergo a bowel resection or be treated with anti-TNF agents ($p=0.04$, log-rank test); **C**, The patients without stricturing and penetrating behavior and no upper GI lesions were at the lowest risk of bowel resection and anti-TNF agent administration, while those with stricturing or penetrating behavior with upper GI lesions were the most likely to undergo a bowel resection or be treated with anti-TNF agents. The patients with either of these factors showed an intermediate risk ($p=0.002$, log-rank test).

patients with either factor showed an intermediate risk of bowel resection or anti-TNF agent treatment (Fig. 3C: $p = 0.002$, log-rank test). These results suggest that the disease behavior and the presence of upper GI lesions at the diagnosis affect the prognosis of CD patients.

Discussion

We investigated factors that could predict a favorable disease course in CD patients who have not been treated with anti-TNF agents. The results of our analyses showed that non-stricturing and non-penetrating behavior and the absence of upper GI lesions at the diagnosis were factors associated with no bowel resection and no anti-TNF agents over both the short-term and long-term disease courses. A novel finding of this study is that the presence of upper GI lesions including a BLA is a prognostic factor for CD patients during their long-term disease courses.

Several studies have reported factors predicting the disease course of CD [5,6,16-19]. However, few reports have identified the factors associated with not using anti-TNF agents. Although anti-TNF agents are potent medications for CD, there are several drawbacks, including severe adverse events, frequent losses of response, and extremely high cost. It can also be difficult to discontinue maintenance treatment with these agents due to the risk of relapse and safety concerns regarding re-administration. Although some investigators emphasize the importance of top-down therapy, it is apparent that not all CD patients require treatment with anti-TNF agents. It would thus be quite useful to know which factors can be used to identify CD patients who will not need treatment with anti-TNF agents. Our findings in this report, therefore, appear to be unique and helpful in the treatment of CD in clinical practice.

Several research groups have used a variety of definitions for favorable or disabling disease courses in attempts to identify predictive factors in CD. For example, Beaugerie *et al.* defined a disabling course as a requirement of more than 2 steroid courses, steroid dependence, hospitalization for disease flare or complication, disabling chronic symptoms for a cumulative time > 12 months, and the need for immunosuppressive therapy, intestinal resection or surgery for perianal disease [5]. The definitions of complicated disease courses determined by other researchers have included single or multiple surgeries, stricturing and penetrating behavior, hospitalization and/or postoperative recurrences [6,17-27]. In contrast, Kruis *et al.* defined mild CD status as receiving no therapy other than 5ASA throughout the follow-up, or 5ASA in combination with a single short (< 12 week) course of low-dose (≤ 40 mg/day) corticosteroids at the start of the treatment [16].

In contrast to these reports, we defined a favorable disease course rather simply, as no bowel resection and not using an anti-TNF agent during ≥ 10 years' follow-up, since the use/non-use of such agents in CD patients is a great concern in clinical practice. Although we initially planned to include "steroid-free remission" and "absence of adverse effects of corticosteroids" in the definition of a favorable disease course, all of the patients met these criteria at the time of the last follow-up. Therefore, the patients classified in G1 experienced disease courses with no bowel resection, without the use of anti-TNF agents and without complications associated with corticosteroids — which a majority of inflammatory bowel disease specialists would accept as a definition of a favorable disease course in CD.

Beaugerie *et al.* showed that age at onset, perianal lesions, and the requirement for steroids to control the first flare were predictive factors of disabling disease [5]. In our study as well, a lack of perianal disease was nearly significant as a predictor for avoiding anti-TNF agents or bowel resection ($p = 0.06$). Corticosteroid use was not a factor affecting the disease courses in our patients, due to the extremely low rate of corticosteroid use in the patients with a favorable disease course. The preference in Japan for an elemental diet over corticosteroids for patients with relatively mild CD may have contributed to this result.

In their retrospective study of patients followed for > 15 years, Cosnes *et al.* observed that younger age at the diagnosis, a smoking history, and short duration of disease in CD were associated with disease severity when they defined severe status as one of the following: active disease for > 3 consecutive years, more than one intestinal surgery, the establishment of a permanent stoma, death related to CD, and complications of CD or CD treatment [7]. Although the definition of non-severe status in that study differs from the favorable disease course definition that we used herein, our analyses indicated that the age at the diagnosis, smoking habit and duration of disease were not significant factors. These factors have been shown to be associated

with a poor prognosis or aggravation of the disease status in CD in other studies [5, 17-28], but in real-world data, these are not always detected as risk factors, because CD is generated by multiple factors including genetics, intestinal flora, and the patient's living environment, with great heterogeneity [29, 30].

Although the patients in G1 were defined clearly and the predicting factors for G1 were identified, G2 patients had various disease courses and treatments, and this diversity made it difficult to determine the factors predicting the CD patients' prognosis. In fact, 61% of G2 was non-stricturing and non-penetrating at diagnosis, and 33% had not received ant-TNF agents for 10 years. The diversity of G2 confirms that the disease courses of CD patients are often heterogeneous and are determined by various factors.

Focusing on upper GI lesions in CD, Wolters *et al.* reported that CD patients with lesions were at an increased risk for the first recurrence [27]. To the best of our knowledge, their study referred to upper GI lesions as a significant predictive factor of CD for the first time. Unfortunately, however, a clear definition of upper GI lesions was not provided in that study, and it was not stated whether a BLA was included. The BLA is a stable landmark for CD regardless of the disease activity or use of anti-TNF agents, and the inter-observer agreements for a BLA are higher than those for other upper GI findings such as gastric lesions or duodenum notched signs and erosions [31, 32]. We have previously focused on the BLA as a specific finding of CD and found that the incidence rate of BLA in CD patients was significantly higher than that in patients with ulcerative colitis or gastroesophageal reflux disease (CD, 44%; ulcerative colitis, 5%; gastroesophageal reflux disease, 0%) [33]. In the present study, 41 (66%) patients had upper GI lesions, and 26 (42%) had a BLA. In particular, 17 (28%) patients had only a BLA as the findings in the upper GI tract, and this prevalence is consistent with that of previous reports [15, 28, 32-37]. Collectively, these results indicate that the meticulous observation of upper GI lesions, including a BLA revealed by EGD, is relevant in the determination of treatment strategies for CD.

In our analysis limited to a 5-year course, upper GI lesions were not a significant factor in the multivariate analysis of the predictive factors associated with a favorable disease course, despite their significance in the 10-year analysis. Although CD has a chronic progressive disease course which often makes intestinal lesions such as stenosis and fistulas irreversible, it sometimes takes a long time to progress to intestinal lesions that need bowel resection or anti-TNF agents and not all patients require anti-TNF agents or bowel resections immediately after their diagnosis. Therefore, we considered that the clinical importance of upper GI lesions became more clear with a longer follow-up period.

Given our results, we propose the following clinical management strategy for patients with newly developed CD: first, of course, thorough examinations of the GI tract, including EGD examination, should be performed. On EGD, a BLA should be noted as a relevant finding. Patients without stricturing and penetrating behavior and showing the absence of upper GI lesions should be treated with the step-up strategy without immediate use of anti-TNF agents. In contrast, for patients with stricturing or penetrating behavior plus upper GI lesions, prompt use of anti-TNF agents should be considered as a treatment option. The treatment strategy for the remaining patients (not included in either type) should be considered based on the patient's status, including the disease behavior and the patient's desires. For those patients, however, the top-down strategy cannot be recommended, as other safer and lower-cost treatments may be effective.

Our study has several limitations, including its retrospective design, small number of patients, and single-center setting. However, it is impractical to perform a prospective study with an observation period exceeding 10 years. In the treatment of CD, not only short-term but long-term perspectives are necessary. We investigated factors that could be associated with a favorable disease course over both the short and long terms, *i.e.*, 5 years and 10 years. Moreover, the condition that no CD patients receive an anti-TNF agent as the first-line therapy could not be enforced going forward prospectively. Nonetheless, the results of our retrospective analysis, despite its relatively small scale, will be valuable for the considerations of current and future treatment strategies for CD.

In conclusion, our long-term follow-up study revealed that in CD patients not treated with an anti-TNF agent, the absence of stricturing and penetrating behavior and the absence of upper GI lesions (including BLA) were predictors of a favorable disease course. Anti-TNF agents are potently effective but are not an

essential medication for CD. Our findings will help determine more efficient and cost-effective treatment strategies for patients with CD.

References

1. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S and IBD Section of the British Society of Gastroenterology: Guidelines for the management of inflammatory bowel disease in adults. Gut (2011) 60: 571–607.
2. K Lichtenstein GR, Hanauer SB, Sandborn WJ and Practice Parameters Committee of American College of Gastroenterology: Management of Crohn's disease in adults. Am J Gastroenterol (2009) 104: 465–483.
3. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF and Travis SP: The Second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis (2010) 4: 28–62.
4. Gollop JH, Phillips SF, Melton LJ 3rd and Zinsmeister AR: Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943–1982. Gut (1988) 29: 49–56.
5. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP and Cosnes J: Predictors of Crohn's disease. Gastroenterol (2006) 130: 650–656.
6. Loly C, Belaiche J and Louis E: Predictors of severe Crohn's disease. Scand J Gastroenterol (2008) 43: 948–954.
7. Cosnes J, Bourrier A, Nion-Larmurier I, Sokol H, Beaugerie L and Seksik P: Factors affecting outcomes in Crohn's disease over 15 years. Gut (2012) 61: 1140–1145.
8. Satsangi J, Silverberg MS, Vermeire S and Colombel JF: The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut (2006) 55: 749–753.
9. Nugen FW, Richmond M and Park SK: Crohn's disease of the duodenum. Gut (1977) 18: 115–120.
10. Nugent FW and Roy MA: Duodenal Crohn's disease: an analysis of 89 cases. Am J Gastroenterol (1989) 84: 249–254.
11. Rutgeerts P, Onette E, Vantrappen G, Geboes K, Broeckaert L and Talloen L: Crohn's disease of the stomach and duodenum: a clinical study with emphasis on the value of endoscopy and endoscopic biopsies. Endoscopy (1980) 12: 288–294.
12. Annunziata ML, Caviglia R, Papparella LG and Cicala M: Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. Dig Dis Sci (2012) 57: 1618–1623.
13. Yokota K, Saito Y, Einami K, Ayabe T, Shibata Y, Tanabe H, Watari J, Ohtsubo C, Miyokawa N and Kohgo Y: A bamboo joint-like appearance of the gastric body and cardia: possible association with Crohn's disease. Gastrointestinal Endoscopy (1997) 466: 268–272.
14. Hokama A, Nakamura M, Ihama Y, Chinen H, Kishimoto K, Kinjo F and Fujita J: Notched sign and bamboo-joint-like appearance in duodenal Crohn's disease. Endoscopy (2008) 40: E151.
15. Hirokawa M, Shimizu M, Terayama K, Tamai M, Takeda M, Iida M and Manabe T: Bamboo-joint-like appearance of the stomach: a histopathological study. APMIS (1999) 107: 951–956.
16. Kruis W, Katalinic A, Klugmann T, Franke GR, Weismüller J, Leifeld L, Ceplis-Kastner S, Reimers B and Bokemeyer B: Predictive factors for an uncomplicated long-term course of Crohn's disease: a retrospective analysis. J Crohns Colitis (2013) 7: e263–270.
17. Lazarev M, Huang C, Bitton A, Cho JH, Duerr RH, McGovern DP, Proctor DD, Regueiro M, Rioux JD, Schumm PP, Taylor KD, Silverberg MS, Steinhart AH, Hutfless S and Brant SR: Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. Am J Gastroenterol (2013) 108: 106–112.
18. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR and Loftus EV Jr: Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterol (2010) 139: 1147–1155.
19. van der Heide F, Dijkstra A, Weersma RK, van der Logt EM, Faber KN, Sluiter WJ, Kleibeuker JH and Dijkstra G: Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis (2009) 15: 1199–1207.
20. Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J, Moum B and Lygren I: Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol (2007) 5: 1430–1438.
21. Lakatos L, Kiss LS, David G, Pandur T, Erdelyi Z, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E and Lakatos PL: Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002–2006. Inflamm Bowel Dis (2011) 17: 2558–2565.
22. Lakatos PL, Vegh Z, Lovasz BD, David G, Pandur T, Erdelyi Z, Szita I, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E, Golovics PA, Mandel M, Horvath A, Szathmari M, Kiss LS and Lakatos L: Is current smoking still an important environmental factor in inflammatory bowel diseases? Results from a population-based incident cohort. Inflamm Bowel Dis (2013) 19: 1010–1017.
23. Bernell O, Lapidus A and Hellers G: Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg (2000) 231: 38–45.
24. Schaefer ME, Machan JT, Kawatu D, Langton CR, Markowitz J, Crandall W, Mack DR, Evans JS, Pfefferkorn MD, Griffiths AM, Otley AR, Bousvaros A, Kugathasan S, Rosh JR, Keljo DJ, Carvalho RS, Tomer G, Mamula P, Kay MH, Kerzner B, Oliva-Hemker M, Kappelman MD, Saeed SA, Hyams JS and Leleiko NS: Factors that determine risk for surgery in pediatric patients with Crohn's disease. Clin Gastroenterol Hepatol (2010) 8: 789–794.
25. Peyrin-Biroulet L, Harmsen WS, Tremaine WJ, Zinsmeister AR, Sandborn WJ and Loftus EV Jr: Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970–2004). Am J Gastroenterol (2012) 107: 1693–1701.
26. Greenstein AJ, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD and Aufses AH Jr: Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. Gut (1988) 29: 588–592.
27. Wolters FL, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L, Langholz E, Politi P, Qasim A, Koutroubakis I, Tsianos E, Vermeire S, Freitas J, van Zeijl G, Hoie O, Bernklev T, Beltrami M, Rodriguez D, Stockbrügger RW and Moum B: Phenotype at diagnosis predicts recurrence rates in Crohn's disease. Gut (2006) 55: 1124–1130.
28. van der Heide F, Dijkstra A, Weersma RK, Albersnagel FA, van der Logt EM, Faber KN, Sluiter WJ, Kleibeuker JH and Dijkstra G: Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis (2009) 15: 1199–1207.

29. Lichtenstein GR: Emerging prognostic markers to determine Crohn's disease natural history and improve management strategies: a review of recent literature. Gastroenterol Hepatol (2010) 6: 99–107.
30. Kwon J, Im JP, Ye BD, Cheon JH, Jang HJ, Lee KM, Kim YS, Kim SW, Kim YH, Song GA, Han DS, Kim WH and Kim JS: Disease Phenotype, Activity and Clinical Course Prediction Based on C-Reactive Protein Levels at Diagnosis in Patients with Crohn's Disease: Results from the CONNECT Study. Gut Liver (2016) 10: 595–603.
31. Hashiguchi K, Takeshima F, Akazawa Y, Matsushima K, Minami H, Yamaguchi N, Shiozawa K, Ohnita K, Ichikawa T, Isomoto H and Nakao K: Bamboo joint-like appearance of the stomach: a stable endoscopic landmark for Crohn's disease regardless of anti-tumor necrosis factor alpha treatment. Med Sci Monit (2014) 20: 1918–1924.
32. Fujiya M, Sakatani A, Dokoshi T, Tanaka K, Ando K, Ueno N, Gotoh T, Kashima S, Tominaga M, Inaba Y, Ito T, Moriichi K, Tanabe H, Ikuta K, Ohtake T, Yokota K, Watari J, Saitoh Y and Kohgo Y: A Bamboo Joint-Like Appearance is a Characteristic Finding in the Upper Gastrointestinal Tract of Crohn's Disease Patients: A Case-Control Study. Medicine (2015) 94: e1500.
33. Kuriyama M, Kato J, Morimoto N, Fujimoto T, Okada H and Yamamoto K: Specific gastroduodenoscopic findings in Crohn's disease: comparison with findings in patients with ulcerative colitis and gastroesophageal reflux disease. Dig Liver Dis (2008) 40: 468–475.
34. Korelitz BI, Waye JD, Kreuning J, Sommers SC, Fein HD, Beeber J and Gelberg BJ: Crohn's disease in endoscopic biopsies of the gastric antrum and duodenum. Am J Gastroenterol (1981) 76: 103-109.
35. Alcantara M, Rodriguez R, Potenciano JL, Carrobles JL, Muñoz C and Gomez R: Endoscopic and bioptic findings in the upper gastrointestinal lesions in patients with Crohn's disease. Endoscopy (1993) 25 : 282–286.
36. Sakuraba A, Iwao Y, Matsuoka K, Naganuma M, Ogata H, Kanai T and Hibi T: Endoscopic and pathologic changes of the upper gastrointestinal tract in Crohn's disease. Biomed Res Int (2014) 2014: 610767.
37. Ledder O, Church P, Cytter-Kuint R, Martínez-León M, Sladek M, Coppenrath E, Weiss B, Yerushalmi B, Martin de Carpi J, Duchano L, Towbin A, Assa A, Shaoul R, Mearin ML, Alex G, Griffiths A and Turner D: A Simple Endoscopic Score Modified for the Upper Gastrointestinal tract in Crohn's Disease (UGI-SES-CD): a report from the ImageKids study. J Crohns Colitis (2018) 12: 1073–1078.