


Predicting a rapid response to adalimumab treatment and favorable short-term outcomes through the high platelet count in patients with ulcerative colitis

A multicenter retrospective cohort study

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Abstract

This study aimed to investigate the short-term effectiveness of adalimumab therapy in patients with ulcerative colitis (UC), especially its rapid response.

This retrospective, multicenter, cohort study involved 7 institutes in Japan, compiling data from patients with UC who had received at least 1 induction dose of 160mg of adalimumab between June 2013 and May 2017. Patients should have a Lichtiger clinical activity index score of ≥ 5 at the initial adalimumab administration. Remission was defined as clinical activity index score of ≤ 4 , whereas response was defined as a reduction of $\geq 50\%$ from the baseline value. Rapid responders are defined as patients who achieved response at 2 weeks.

A total of 91 patients were included in this study: 37.4% and 45.1% achieved clinical response at 2 and 8 weeks, respectively, whereas clinical remission rates 12 weeks were 45.1%. Among the rapid responders, 82.4% achieved clinical remission at 12 weeks. Multivariate logistic regression analysis identified a higher platelet count as an independent prognostic factor for a higher rate of rapid response. Receiver operating characteristic curve showed that a platelet counts cutoff value of $\geq 312 \times 10^9/L$ was associated with a rapid response.

Approximately 40% of patients with UC showed a rapid response to adalimumab therapy after 2 weeks. Up to 80% of the rapid responders also achieved remission at 12 weeks. A higher platelet count was identified as an independent prognostic factor for a higher rapid response rate.

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Abbreviations: AUC = area under the ROC curve, CAI = clinical activity index, CI = confidence interval, CRP = C-reactive protein, IBD = inflammatory bowel disease, IQR = interquartile ranges, RCT = randomized controlled trial, ROC = receiver operating characteristic, TNF = tumor necrosis factor, UC = ulcerative colitis, ULTRA = ulcerative colitis long-term remission and maintenance with adalimumab.

Keywords: adalimumab, anti-tumor necrosis factor agent, biologic therapy, inflammatory bowel disease, platelet count, rapid response, ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory bowel disease (IBD), characterized by continuous mucosal inflammation of the large intestine. Its common clinical symptoms are bloody diarrhea, fecal incontinence, urgency, tenesmus, and/or abdominal pain.^[1,2] Patients experience relapse and remission periods, lower health-related quality of life than the general population, reduced work productivity, and high direct medical costs.^[3–5] The therapy primarily aimed to induce and maintain clinical remission in order to avoid colectomy and reduce the risk of disease progression.^[6] Tumor necrosis factor (TNF) is considered to be an important cytokine involved in the pathogenesis and therapeutic targeting cytokine of UC.^[7] To date, randomized, double-blind clinical trials of 3 anti-TNF agents, i.e., infliximab, adalimumab, and golimumab, for patients with moderate to severe UC have been reported in several countries worldwide.^[8–14]

Adalimumab is a subcutaneously administered, fully human immunoglobulin G1 monoclonal antibody against TNF. Two phase III trials entitled UC long-term remission and maintenance with adalimumab (ULTRA 1 and ULTRA 2 conducted in Western countries showed that adalimumab was more effective than placebo for induction and maintenance of remission in moderate to severe UC.^[9,10] ULTRA 1 and ULTRA 2 trials showed that clinical remission at 8 weeks in patients who received adalimumab was achieved in 18.5% and 16.5%, respectively.^[9,10] In a double-blind randomized controlled trial (RCT) for patients with UC conducted in Japan, the remission rate of adalimumab treatment at 8 weeks as a primary end-point showed only 10%, which was lower than those of studies in Western countries, and no statistically significant difference could be obtained for the placebo group (11%). In contrast, response rates at 8 (50%), 32 (36%), and 52 weeks (31%); rates of mucosal healing at 8 (44%) and 52 weeks (29%); and remission rates at 32 (18%) and 52 weeks (23%) were significantly improved in patients treated with adalimumab than in those treated with placebo.^[13] As a result, adalimumab was approved for the treatment of UC in Japan in June 2013 and is widely used in clinical practice as a self-injectable anti-TNF agent.

Few reports have examined the short-term effectiveness of adalimumab treatment within 8 weeks for patients with UC in the real world. In Western countries, Afif et al reported a retrospective cohort study with only 5% clinical remission rate of adalimumab treatment at 8 weeks in patients with UC.^[15] In contrast, several cohort studies in Western countries reported clinical remission rates of 42% to 49%.^[16–18] In Japan, Nishio et al have reported a small cohort study, showing a clinical remission rate of 27% at 8 weeks,^[19] which is approximately 15% lower than those of Western countries mentioned above. However, their cohort study had some limitations including small sample size, single-center study, and adalimumab evaluated as a

rescue therapy for tacrolimus treatment. Almarino et al reported that “short-term improvement” was reported by patients with UC as the one of the top 4 most important factors including long-term remission rates, mode of administration, and lymphoma risk.^[20] Therefore, larger-scale studies should be conducted to clarify the short-term effectiveness of adalimumab treatment for patients with UC.

In this report, we describe the Adalimumab Multicenter Cohort Study on Effectiveness in Patients with Ulcerative Colitis (ADVENTURE) that primarily aimed to investigate short-term outcomes and prognostic factors associated with adalimumab treatment in patients with UC. In addition, characteristics of rapid responders who responded very quickly to adalimumab treatment were examined.

2. Methods

2.1. Study patients

This retrospective, multicenter cohort study included all patients with UC who had received at least 1 induction dose of 160 mg of adalimumab in Japanese medical institutions between June 2013 and May 2017. The diagnosis of UC was based on the criteria determined by the Japanese Ministry of Health, Labor, and Welfare. Patients should have a Lichtiger clinical activity index (CAI) score of ≥ 5 at the initial adalimumab administration.^[21,22] Patients who underwent colectomy, received biologic agents except for infliximab before the initiation of adalimumab, and with unmeasured Lichtiger CAI from a medical record at the time of adalimumab administration were excluded.

2.2. Data collection

All data were obtained from medical records from the included institutions. Demographic data collected at the initiation of adalimumab were sex, age, body weight; duration of disease prior to adalimumab therapy; extent of disease; C-reactive protein (CRP) and albumin levels; platelet count; previous use of infliximab, cytapheresis therapy, prednisolone, and calcineurin inhibitors including cyclosporine and tacrolimus; and smoking status. The extent of disease was categorized according to the Montreal classification as follows: proctitis (E1), left-sided colitis (E2), and pancolitis (E3).^[23] Concomitant medications at the initiation of adalimumab, including oral and topical 5-aminosalicylic acid, azathioprine or 6-mercaptopurine, prednisolone, and cytapheresis therapy, were also documented. The Lichtiger CAI scores; laboratory data including CRP, and albumin levels; and platelet counts at baseline and at 2, 4, 8, and 12 weeks after the initial adalimumab administration were obtained. The reasons for adalimumab discontinuation were classified into 4 categories: lack of effectiveness, adverse event occurrence, patient's decision, and lost to follow-up. All adverse events during the study period were also recorded.

2.3. Assessment of the effectiveness of adalimumab treatment

Clinical remission was defined as Lichtiger CAI score of ≤ 4 , whereas clinical response was defined as a decrease by $\geq 50\%$ relative to the baseline score or Lichtiger CAI score of ≤ 4 . The clinical response and remission rates were assessed at 2, 4, 8, and 12 weeks. The primary end-point of this study was to evaluate the clinical response rate of adalimumab treatment at 8 weeks. The secondary end-points were to assess the clinical response rates at 2, 4, and 12 weeks and clinical remission rates at 2, 4, 8, and 12 weeks. Independent prognostic factors related to clinical response and remission rates at 8 weeks and those related to clinical remission rates at 12 weeks were assessed using univariate and multivariate logistic regression analyses. Additionally, rapid responders were defined as patients who achieved response at 2 weeks. The clinical remission rate at 12 weeks in rapid responders was compared to that at 12 weeks in non-rapid responders. The related prognostic factors in rapid responders were also evaluated using univariate and multivariate analyses. For several prognostic factors of continuous values in rapid responders identified by multivariate analysis, receiver operating characteristic (ROC) curves were also determined, and the area under the ROC curve (AUC) was calculated to determine the cutoff value of prognostic factors of rapid response. Further, rapid response and clinical remission rates at 12 weeks stratified by the independent prognostic factors identified above were also investigated.

2.4. Statistical analysis

Categorical variables were described as frequencies and percentages, whereas continuous variables were described as medians and interquartile ranges (IQR). Analyses of the Lichtiger CAI score and CRP level at baseline relative to 2, 4, 8, and 12 weeks were performed using the Wilcoxon signed-rank test. The percentage of clinical response and remission at each week was calculated by dividing the number of patients achieving clinical response and remission by the total number of patients in each group, respectively. Continuous variables were divided into 2 groups according to the median to perform univariate and multivariate analyses. Further, ROC curves were constructed, and the AUC was calculated to determine the cutoff value for several continuous values of rapid response identified in the multivariate analysis. Fisher exact test was used to compare categorical variables. A multivariate logistic regression analysis was performed to identify factors that predict the clinical response at 2 and 8 weeks and clinical remission at 8 and 12 weeks. The presumed prognostic factors including age and gender, as well as all variables with a statistical significance of $P < .2$ in the univariate analyses were considered as variables in each multivariate logistic regression analysis. Results are presented as odds ratio with 95% confidence interval (CI). P -values of $< .05$ were considered statistically significant. Missing values were imputed using the last observation carried forward method. The target sample size of the study was 100, which was determined based on the number of patients with UC who were treated with adalimumab during the study period and the feasibility of enrolment in the study. Assuming a response rate of 50% at 8 weeks from the RCT conducted in Japan,^[13] the 90% CI for this sample size was within 8.7%, with a probability of $\geq 99\%$. Statistical analyses were performed using SPSS software,

Table 1

Baseline characteristics of 91 patients at the first administration of adalimumab.

Female/Male, n (%)	37 (40.7%)/54 (59.3%)
Median age, yr (IQR)	37.8 (26.3–51.9)
Body weight, (kg) median (IQR)	56.1 (49.7–64.0)
Median disease duration, yr (IQR)	3.3 (1.40–7.84)
Extent of disease, n (%)	
Pancolitis	61 (67.0%)
Left-sided colitis	29 (31.9%)
Proctitis	1 (1.1%)
Active smoker	4 (4.4%)
C-reactive protein, (mg/dL), median (IQR)	0.4 (0.1–1.5)
Platelet count, ($\times 10^9/L$), median (IQR)	300 (232–387)
Albumin, (g/dL), median (IQR)	3.8 (3.3–4.2)
Concomitant medications, n (%)	
Oral 5-aminosalicylic acid	70 (76.9%)
Topical 5-aminosalicylic acid	23 (25.3%)
Prednisolone	26 (28.6%)
Cytapheresis	6 (6.6%)
Azathioprine or 6-mercaptopurine	49 (53.8%)
Previous use of infliximab, n (%)	32 (35.2%)
Previous medications (excluding biologics), n (%)	
Calcineurin inhibitors	24 (26.4%)
Prednisolone	76 (83.5%)
Cytapheresis	55 (60.4%)
Lichtiger CAI, median (IQR)	9 (8–12)

CAI=clinical activity index, IQR=interquartile range.

version 25.0 (SPSS, Chicago, IL) and EZR (Saitama Medical Center, Jichi Medical University).

2.5. Ethical considerations

This study was approved by the Ethics Committees of each institution and was registered at the University Hospital Medical Information Network in Japan (number 000029030). Written informed consent was not required because of the retrospective nature of the study.

3. Results

3.1. Patient characteristics

A total of 91 patients with UC in 7 medical institutions were included in this study. Thirty-seven (40.7%) patients were female, and the median age and disease duration were 37.8 years (IQR 26.3–51.9) and 3.3 years (IQR 1.40–7.84), respectively. At baseline, the median Lichtiger CAI score was 9 (IQR 8–12). The median CRP and albumin levels were 0.4 mg/dL (IQR 0.1–1.5) and 3.8 g/dL (IQR 3.3–4.2), respectively. Before initiating the adalimumab therapy, 32 (35.2%) patients had previously used infliximab. Patients' baseline characteristics during the first administration of adalimumab are shown in Table 1.

3.2. Effectiveness of adalimumab treatment

A total of 22 patients (24.2%) discontinued adalimumab treatment within 12 weeks due to lack of effectiveness in 20 patients (22.0%), adverse events in 1 (1.1%), and patient's decision in 1 (1.1%). Colectomy was performed in 4.4% of patients (4 of 91) during the study period.

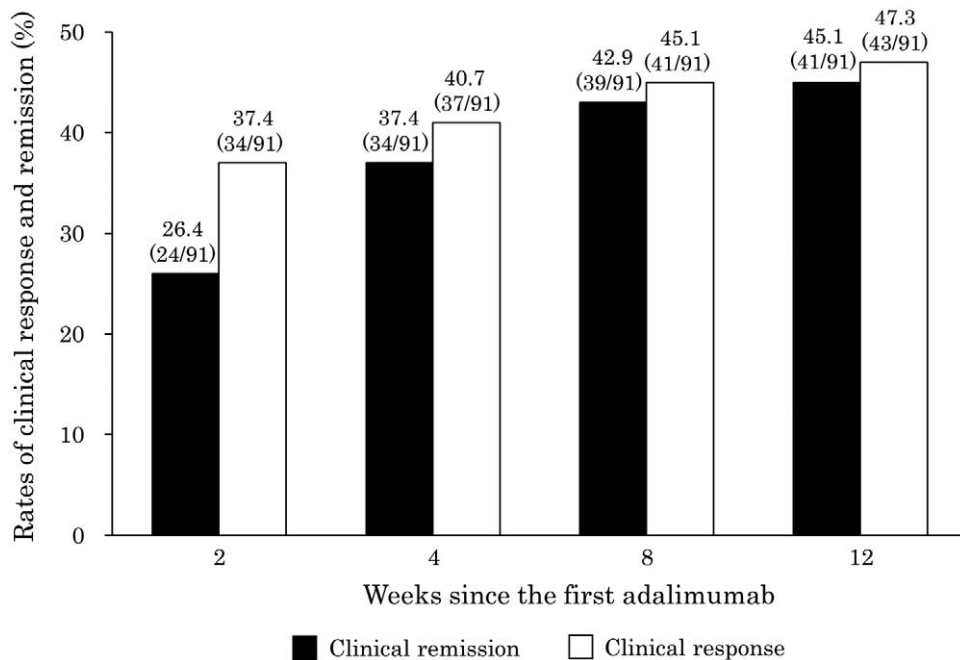


Figure 1. Rates of clinical response and remission at 2, 4, 8, and 12 weeks.

The median Lichtiger CAI scores significantly decreased sequentially from baseline to 2, 4, 8, and 12 weeks as follows: 9 (IQR 8–12), 6 (IQR 4–8), 6 (IQR 3–10), 5 (IQR 3–8), and 5 (IQR 2–8), respectively. Similarly, the median CRP levels also significantly decreased sequentially as follows: 0.44 (IQR 0.10–1.54), 0.13 (IQR 0.05–0.35), 0.11 (IQR 0.04–0.41), 0.08 (IQR 0.04–0.27), and 0.11 (IQR 0.04–0.39) mg/dL, respectively. Changes in Lichtiger CAI scores and CRP levels during the study period are presented in Supplementary Figure 1a and 1b, <http://links.lww.com/MD/F249>, respectively. The clinical response rates at 2, 4, 8, and 12 weeks were 37.4% (34 of 91), 40.7% (37 of 91), 45.1% (41 of 91), and 47.3% (43 of 91), respectively. The clinical remission rates at 2, 4, 8, and 12 weeks were 26.4% (24 of 91), 37.4% (34 of 91), 42.9% (39 of 91), and 45.1% (41 of 91), respectively (Fig. 1). The proportion of patients with Lichtiger CAI score of 0, 1, 2, 3, or 4 at 2, 4, 8, and 12 weeks since the first administration of adalimumab is presented in Supplementary Table 1, <http://links.lww.com/MD/F253>.

At 8 weeks, no prognostic factors were associated with both clinical response and remission in the univariate and multivariate logistic regression analysis (Supplementary Tables 2, <http://links.lww.com/MD/F254> and 3, <http://links.lww.com/MD/F255>). At 12 weeks, previous use of infliximab was a prognostic factor for lower clinical remission rate in the univariate analysis. In the multivariate logistic regression analysis, previous use of infliximab was also identified as an independent prognostic factor for lower clinical remission rate at 12 weeks (Supplementary Table 4, <http://links.lww.com/MD/F256>).

3.3. Rapid response assessments

Among 91 patients, 34 (37.4%) were rapid responders who achieved clinical response at 2 weeks. The clinical remission rate at 12 weeks in 34 rapid responders was significantly higher than that in 57 non-rapid responders (82.4% vs 22.8%; $P < .001$)

(Fig. 2). Table 2 shows the univariate and multivariate logistic regression analyses of rapid responders. Higher platelet counts of $> 300 \times 10^9/L$ was a prognostic factor for higher rapid response rate in the univariate analysis. Higher platelet counts of $> 300 \times 10^9/L$ and lower body weight of < 56.1 kg were identified as independent prognostic factors for higher rapid response rates in the multivariate logistic regression analysis. Figure 3 shows the ROC curves for rapid response in relation to platelet count (Fig. 3a) and body weight (Fig. 3b) at baseline. The AUC of platelet count and body weight to predict rapid response were 0.725 (95% CI, 0.614–0.836) and 0.593 (95% CI, 0.472–0.715), respectively. The best cutoff value of platelet count and body weight to predict rapid response were $\geq 312 \times 10^9/L$ (73.7% specificity, 70.6% sensitivity) and ≤ 53.0 kg (66.7% specificity, 55.9% sensitivity), respectively.

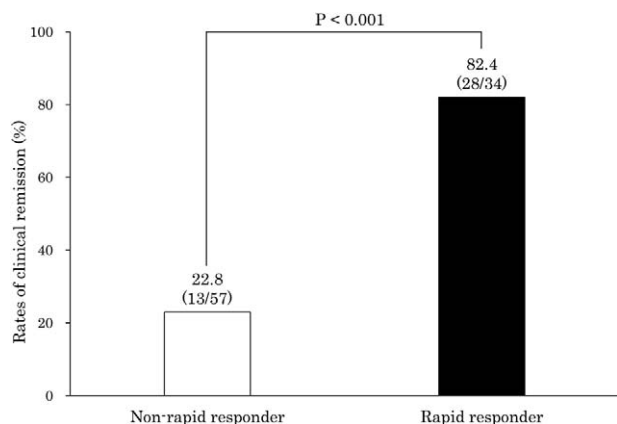


Figure 2. Rates of clinical remission at 12 weeks stratified in the order of rapid response. P -values were determined using Fisher exact test.

Table 2
Factors associated with clinical response at 2 weeks using univariate and multivariate logistic regression analysis.

Variables	Univariate analysis			Multivariate logistic regression analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Gender, female (vs male)	1.035	0.436–2.455	1.000	0.519	0.165–1.626	.260
Age (≥ 37.8 yr)	0.858	0.367–2.009	.829	1.348	0.491–3.704	.562
Duration of disease (≥ 3.4 yr)	0.324	0.133–0.790	.017	0.427	0.157–1.166	.097
Body weight at baseline (≥ 56.1 kg)	0.547	0.231–1.293	.197	0.285	0.089–0.911	.034
Extent of disease (pancolitis)	1.297	0.519–3.244	.649			
Lichtiger CAI at baseline (≥ 9)	1.297	0.519–3.244	.649			
Concomitant therapy						
Prednisolone	0.923	0.355–2.400	1.000			
Azathioprine or 6-mercaptopurine	1.379	0.585–3.253	.519			
Previous use of infliximab	0.532	0.210–1.346	.257	0.591	0.194–1.801	.355
Previous treatment (excluding biologics)						
Calcineurin inhibitors	0.464	0.163–1.318	.219			
Prednisolone	1.793	0.522–6.156	.398			
Cytapheresis	1.093	0.457–2.611	1.000			
Platelet count at baseline ($\geq 300 \times 10^9/L$)	6.013	2.299–15.721	< .001	7.807	2.535–24.039	< .001
CRP at baseline (≥ 0.4 mg/dL)	0.800	0.342–1.873	.668			
Albumin at baseline (≥ 3.8 g/dL)	0.966	0.413–2.258	1.000			

CAI=clinical activity index, CI=confidence interval, CRP=C-reactive protein, OR=odds ratio.

3.4. Stratified analysis according to prognostic factors

The rapid response and clinical remission rates at 12 weeks stratified by prognostic factors identified in the study are shown in Figure 4 and Supplementary Figure 2, <http://links.lww.com/MD/F250>, respectively. The rapid response rate with platelet count of $\geq 312 \times 10^9/L$ and body weight of ≤ 53.0 kg were significantly higher than those with platelet count of $< 312 \times 10^9/L$ (61.5% vs 19.2%; $P < .001$) and body weight of > 53.0 kg (50.0% vs 28.3%; $P = .048$), respectively (Fig. 4a, 4b). At 12 weeks, the clinical remission rate of patients not previously treated with infliximab and platelet count of $\geq 312 \times 10^9/L$ were significantly higher than those with those who previously used infliximab (55.9% vs 25.0%; $P = .008$) and platelet count of $< 312 \times 10^9/L$ (61.5% vs 32.7%; $P = .010$), respectively

(Supplementary Fig. 2a, 2b, <http://links.lww.com/MD/F250>). Furthermore, the rapid response and clinical remission rates at 12 weeks stratified in the order of previous use of infliximab, body weight of ≤ 53.0 kg, and platelet count of $\geq 312 \times 10^9/L$ are shown in Supplementary Figure 3, <http://links.lww.com/MD/F251>. Both rapid response and clinical remission rates at 12 weeks were best in patients not previously treated with infliximab, body weight of ≤ 53.0 kg, and platelet count of $\geq 312 \times 10^9/L$. In patients who previously used infliximab, both rapid response and clinical remission rates at 12 weeks were very poor in patients with platelet count of $< 312 \times 10^9/L$, regardless of their body weight above or below 53.0 kg (Supplementary Fig. 3a, 3b, <http://links.lww.com/MD/F251>).

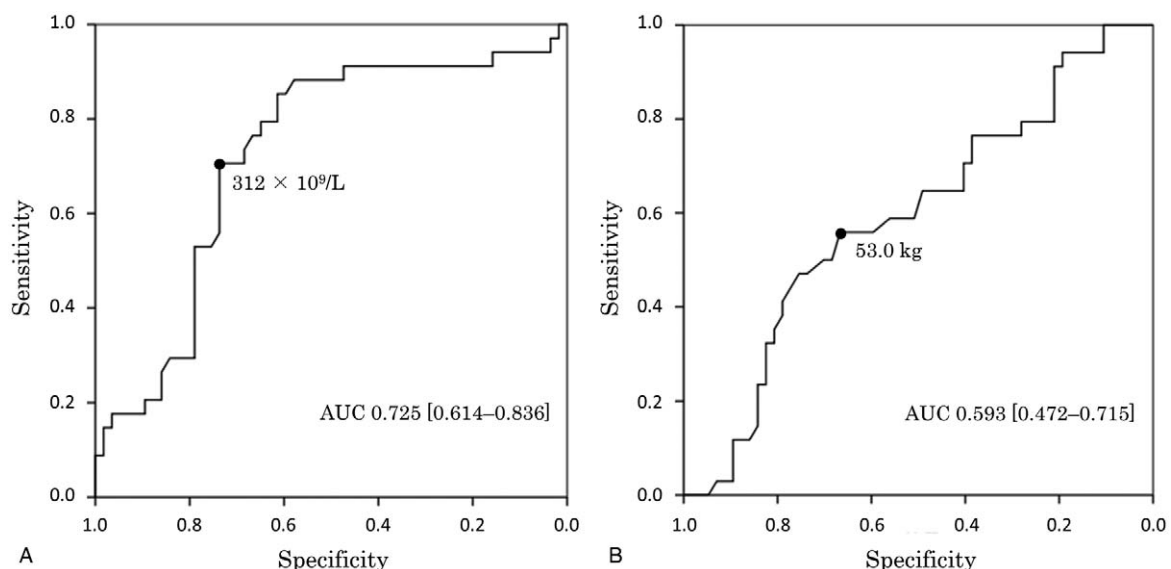


Figure 3. Receiver operating characteristic curves for rapid response in relation to platelet count (a) and body weight (b) at baseline.

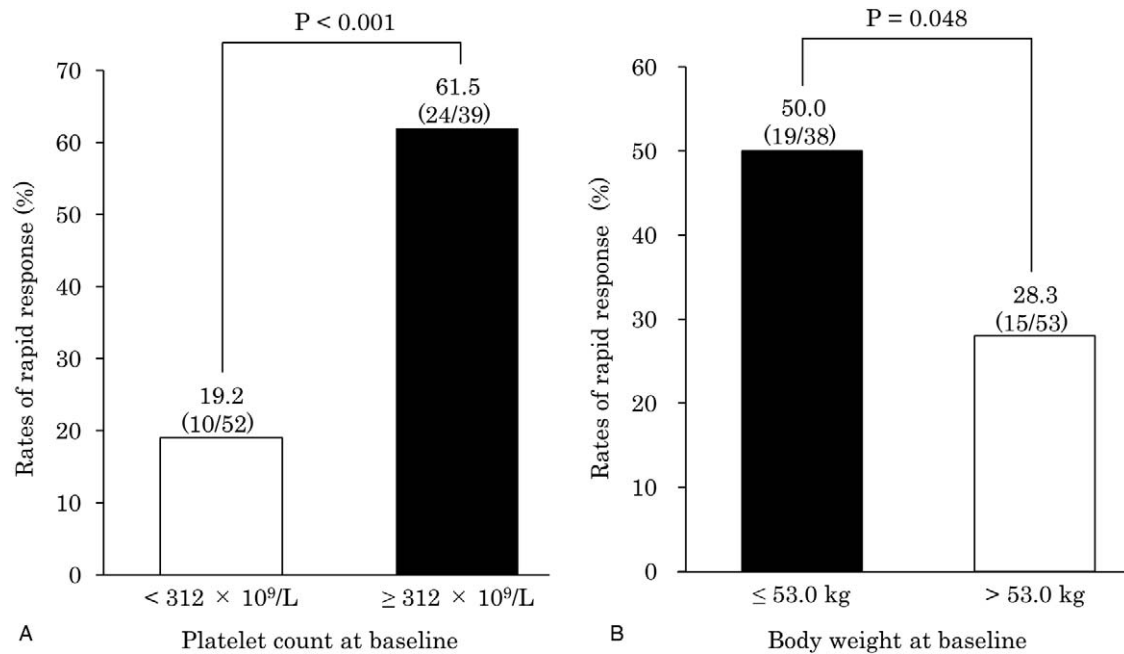


Figure 4. Rates of rapid response stratified in the order of platelet count of $\geq 312 \times 10^9/L$ (a) and body weight of ≤ 53.0 kg (b). *P*-values were determined using Fisher exact test.

3.5. Adverse events

All adverse events occurring during the study period are shown in Table 3. The incidence of adverse events was 21.9% (20 of 91) in this short-term cohort study. The major adverse event was infections in 8 patients (8.8%), followed by injection-site reactions in 4 (4.4%), abdominal discomforts in 3 (3.3%), skin lesions in 2 (2.2%), and pancreatic enzyme elevation, transaminase elevation, headache, leg numbness, paralytic ileus, and fever in 1 patient each (1.1%). Serious infections were reported in 5 patients (5.5%). Adalimumab treatment was discontinued in 1 patient due to paralytic ileus.

4. Discussion

To the best of our knowledge, this is the first and largest retrospective, multicenter cohort study in Asia including Japan

that sought to access short-term outcomes of adalimumab treatment, including rapid response, in patients with UC. Among 91 patients included in this study, the clinical response and remission rates at 8 weeks were 45.1% and 42.9%, respectively. Furthermore, the clinical remission rate at 12 weeks in rapid responders who achieved clinical response at 2 weeks was 82.4%, which was significantly higher than that in non-rapid responders (22.8%). The multivariate logistic regression analysis confirmed the higher platelet count and lower body weight as significant independent prognostic factors for higher rates of rapid response.

The clinical response rate at 8 weeks in this study was similar to the results of the RCT in Japan reported by Suzuki et al^[13] Surprisingly, the remission rate at 8 weeks in this study far exceeded that of RCT results in Japan. Although why the remission rate at 8 weeks in this study was better than that in the RCT conducted in Japan remains unclear, the fact that the RCT and this study were evaluated by different indices might have affected the difference in remission rates at 8 weeks in these 2 studies. The Mayo score, which is calculated based on the worst score in 3 days, used in the RCT in Japan likely resulted in a lower estimate of therapeutic effect.^[13] Additionally, the Mayo score included the endoscopic evaluation.^[24] Nishio et al reported that the higher clinical remission rate in their study seems to be attributed to their use of CAI without endoscopic findings.^[19] In this study, the remission rate at 8 weeks might be better than that in the RCT in Japan, as assessed using the Lichtiger CAI score,^[21,22] calculated based on a 1-day score only and without endoscopic findings.

Further, in a cohort study of adalimumab treatment for patients with UC reported by Arumuzzi et al, the remission rate at 12 and 54 weeks were 28.4% and 43.2%, respectively,^[25] suggesting that 1 reason of better than ULTRA 2 (16.5% and 17.3% at 8 and 52 weeks, respectively) was the concomitant

Table 3

Adverse events of interest and adverse events leading to the discontinuation of adalimumab.

Adverse events of interest	
Infection, n (%)	8 (8.8)
Serious infections, n (%)	5 (5.5)
Injection site of reactions, n (%)	4 (4.4)
Abdominal discomfort, n (%)	3 (3.3)
Skin lesions, n (%)	2 (2.2)
Pancreatic enzyme elevation, n (%)	1 (1.1)
Transaminase elevation, n (%)	1 (1.1)
Headache, n (%)	1 (1.1)
Numbness of legs, n (%)	1 (1.1)
Paralytic ileus, n (%)	1 (1.1)
Fever, n (%)	1 (1.1)
Adverse events leading to discontinuation of adalimumab	
Paralytic ileus, n (%)	1 (1.1)

topical therapy with aminosalicylates. Similarly, the inclusion of 25% of patients with topical therapy of 5-aminosalicylic acid might be one of the reasons for the better remission rate in this study than that in RCT in Japan.

In addition, our result on remission rate at 8 weeks (42.9%) was similar to the results in 3 cohort studies from Western countries reported by Travis et al (49%), Zacharias et al (42%), and Munoz-Villafranca et al (49%).^[16–18] In the first cohort study reported by Afif et al, with 20 patients in 2009, the remission rate at 8 weeks was only 5%.^[15] Although 65% of patients who previously used infliximab were included in the cohort study reported by Afif et al,^[15] in 3 cohort studies with remission rates in 40% range reported since 2017, $\geq 60\%$ patients who had not previously used anti-TNF agents were enrolled.^[16–18] Further, all patients included Munoz-Villafranca et al were patients who had not previously used anti-TNF agents.^[18] The proportion of patients who had not previously used infliximab in this study was 64.8%, similar to the proportions in 3 cohort studies reported since 2017. Although no statistically significant difference was observed in the remission rates at 8 weeks between patients who had previously used infliximab and those who had not previously used infliximab in this study, the remission rate at 12 weeks in this study was significantly better in patients who had not previously used infliximab than in those who had previously used infliximab.

In addition, the remission rate at 8 weeks in the cohort study reported by Nishio et al in Japan was 27%, worse than that in this study.^[19] Although the proportion of patients who had previously used infliximab was as low as 17% in the cohort study reported by Nishio et al, all patients included in their study had previously used calcineurin inhibitors. In this study, the proportion of patients who had previously calcineurin inhibitors was 26%. Patients who had previously used calcineurin inhibitors tended to have lower remission rate at both 8 and 12 weeks than in those who had not previously used calcineurin inhibitors. The reason that the remission rate at 8 weeks was relatively good in this study may be that this study included a small number of patients who had previously used anti-TNF agents or calcineurin inhibitors.

“Short-term improvement” was valued in patients with UC for decision-making to determine each therapeutic from a number of biologic agents^[20]; however, few studies have investigated the rapid response with short-term improvement before 8 weeks, and the clinical course of rapid responders with shorter-term improvement within 2 weeks of adalimumab treatment in patients with UC. Recently, Hanauer et al reported a post hoc analysis of ULTRA 1 and ULTRA 2, which evaluated early changes including Mayo subscores.^[26] Post hoc analysis from ULTRA 1 and ULTRA 2 demonstrated that the mean reduction in Mayo subscores of rectal bleeding and stool frequency from baseline to 2 weeks was significantly larger in patients with UC receiving adalimumab as compared with placebo. In the InspiraDA, a Phase 3b, prospective, multicenter, multinational, open-label, clinical trial to evaluate including clinical outcomes among patients with UC treated with adalimumab reported by Travis et al, percentages of patients achieving Simple Clinical Colitis Activity Index response and remission at 2 weeks were 74% and 27%, respectively.^[16] Further, the VARSITY trial, a Phase 3b, randomized, double-blind, double-dummy, active-controlled superiority trial to detect treatment differences between vedolizumab and adalimumab in patients with UC,

recently reported by Sands et al demonstrated that 45.6% of patients received adalimumab that achieved the clinical response at 2 weeks, assessed by the partial Mayo score.^[27] In this study, the rapid response rate defined as achieving the clinical response at 2 weeks was 37.4%, which was slightly worse than that in the VARSITY trial. Approximately 82.4% of rapid responders achieved clinical remission at 12 weeks. Based on study results and some previous reports described above, at least approximately 40% of patients with UC demonstrated to achieve rapid response by adalimumab treatment within 2 weeks. In addition, we have shown for the first time in this study rapid response after 2 weeks may predict the efficacy of adalimumab after 12 weeks in patients with UC treated with adalimumab.

Few reports on prognostic factors predicted short-term outcomes of adalimumab treatment in patients with UC. Iborra et al reported that patients previously exposed to anti-TNF had lower clinical remission than naïve anti-TNF patients at 12 weeks.^[28] In this study, previous infliximab use was also identified as an independent prognostic factor for lower clinical remission rate at 12 weeks in the multivariate logistic regression analysis.

An interesting finding of this study is that the multivariate logistic regression analysis identified a higher platelet count as a significant independent prognostic factor of higher rapid response rate for adalimumab treatment in patients with UC. The best cutoff value of platelet counts to predict the rapid response was $\geq 312 \times 10^9/L$. The rapid response rate with platelet count of $\geq 312 \times 10^9/L$ was significantly higher than those with platelet count of $< 312 \times 10^9/L$ (61.5% vs 19.2%; $P < .001$). We believe that this study was the first to report an association between the rapid response of adalimumab treatment within 2 weeks and platelet count during the first administration of adalimumab for patients with UC.

Hanauer et al reported that adalimumab treatment in patients with UC led to early improvement in laboratory parameters including platelet count, which significantly decreased from baseline to 4 and 8 weeks.^[26] Our results also showed that platelet count in rapid responders with a higher platelet count of $\geq 312 \times 10^9/L$ significantly reduced at 2 and 12 weeks compared to baseline (Supplementary Fig. 4, <http://links.lww.com/MD/F252>).

Several reports have shown that platelet counts are elevated in patients with IBD and that several biological mechanisms have been presumed to be associated with disease activity in IBD and platelet count.^[29–31] Moreover, platelets in the peripheral blood have also been reported to increase in the inflamed mucosa of patients with UC, especially increasing the number of activated platelets in colonic lesions that was related to the UC severity.^[32] Activated platelets express a cluster of differentiation 40 ligand due to the presence of high levels of several platelet-activating substances in the circulation and the mucosa of patients with IBD, and cluster of differentiation 40 ligand + platelets were present in tissue sections of the inflamed human colonic mucosa. Further, activated platelets in patients with IBD induce IL-8 overexpression when co-cultured with human intestinal microvascular endothelial cells in an experimental colitis model, and the activated platelet also increased the production of inflammatory substances such as IL-1 β , histamine, and serotonin.^[33–35] Mitsuyama et al reported that IL-8 level in the affected tissue of patients with UC increased during the active phase of UC and decreased as patients' disease activity went into remission. In addition, they also reported that tissue IL-1 β and TNF- α

correlated well with IL-8 level.^[36] Neutralization of TNF- α by anti-TNF- α antibody demonstrated to reduce IL-6, IL-8, and IL-1 β production in rheumatoid arthritis synovial cell cultures.^[37] Although the reason for rapid response of adalimumab treatment in patients with high platelet counts in this study is unknown, IL-8 neutralization by anti-TNF agents may be 1 mechanism.

With respect to the higher body weight shown as a poor prognostic factor in this study, the higher baseline weight (≥ 82.0 kg) was also shown in the ULTRA-1 trial to be associated with reduced remission. In the ULTRA-1 trial, the clinical remission rate at 8 weeks for patients weighing < 82 kg was more than twice that for patients weighing ≥ 82 kg.^[9] Higher body weight is associated with increased clearance of anti-TNF agents in patients with IBD.^[38,39] A multicenter, prospective, open-label trial entitled Deep remission of Immunomodulator and Adalimumab Combination Therapy for Crohn Disease study also showed that higher body weight had a trend toward lower adalimumab trough level.^[40] Our study supports these results, showing that patients with higher body weight (> 53.0 kg) had lower effectiveness of adalimumab treatment than in those with lower body weight.

The incidence of adverse events was 21.9% (20/91) in this short-term cohort study. The major adverse event was infection (8.8%). No death, malignancies, and tuberculosis were observed. Discontinuation of adalimumab treatment due to adverse events was performed in only 1 patient with paralytic ileus. Although the incidence rate of adverse events at 8 weeks in this study was lower than that of RCT for patients with UC conducted in Japan, the rate of serious infections in this study (5.5%) was similar to the RCT in Japan (3.3%).^[13] Eight of 9 patients who developed infections during adalimumab treatment in this study were receiving concomitant treatments with azathioprine or prednisolone.

This is a multicenter retrospective cohort study on the effectiveness of adalimumab treatment for patients with UC with the highest number of patients in Asia including Japan. However, this study has several limitations. First, since the endoscopic activity or fecal calprotectin could not be evaluated in all patients, the effectiveness of adalimumab treatment might have been overestimated. Second, due to the retrospective nature of the study, we could not assess serum adalimumab concentration, anti-adalimumab antibody levels, and inflammatory cytokine levels involved in platelet activation including IL-8. Therefore, further studies are needed to identify the association between the effectiveness of adalimumab treatment and platelet counts. Finally, this study cannot examine the effectiveness of escalating the adalimumab dosage because it has not been approved for patients with UC in Japan. Nevertheless, we believe that short-term outcomes of adalimumab treatment for patients with UC obtained in the ADVENTURE study can provide useful information to both patients with UC and clinicians in the biologic selection.

5. Conclusion

This multicenter retrospective cohort study demonstrated that patients with UC treated with adalimumab had clinical response and remission of 45% and 43% at 8 weeks, respectively. In addition, rapid response to adalimumab treatment after 2 weeks was shown to be approximately 40% of patients with UC. Up to an 80% of rapid responders also achieved clinical remission at 12 weeks. This was also the first study to show that the rapid

response rate of adalimumab treatment in patients with UC was significantly higher in patients with higher platelet count.

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