Circulating Interleukin 6 and Albumin, and Infliximab Levels Are Good Predictors of Recovering Efficacy After Dose Escalation Infliximab Therapy in Patients with Loss of Response to Treatment for Crohn's Disease: A Prospective Clinical Trial

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Background: We aimed to clarify the efficacy, safety, and factors associated with remission on dose escalation in patients with Crohn's disease showing loss of response (LOR) to infliximab treatment of 5 mg/kg at 8-week intervals in a clinical trial.

Methods: Thirty-nine patients with LOR to 5 mg/kg infliximab therapy started treatment with 10 mg/kg per 8 weeks. LOR was defined as both a Crohn's Disease Activity Index of ≥175 at 8 weeks after infusion of 5 mg/kg infliximab and a Crohn's Disease Activity Index increase of ≥50 from 4 to 8 weeks after infusion.

Results: At week 8 after the first infusion of 10 mg/kg, median (95% confidence interval) reduction in Crohn's Disease Activity Index of 33 patients evaluated was 95.0 (70.0–134.0), meeting the primary endpoint. Remission rate at week 40 was 41% (16 of 39), with correlation noted between remission achievement and serum infliximab level ($P = 0.036$). Univariate analysis revealed that "infliximab trough level ≥1 μg/mL," "interleukin 6 level ≤2.41 pg/mL," and "albumin level ≥3.8 g/dL" before dose escalation were significantly associated with remission at week 40 ($P = 0.017$, $P = 0.011$, and $P = 0.019$, respectively), and these variables were correlated with each other (all: $P < 0.001$). The cutoff infliximab level for remission was 0.42 μg/mL in receiver operating characteristic curve analysis. No adverse events related to dose escalation were observed.

Conclusions: Doubling the infliximab dose safely led to remission in patients with Crohn's disease with LOR to 5 mg/kg treatment. Remission was associated with pre-escalation levels of infliximab, interleukin 6, and albumin. Our findings suggest that dose escalation while maintaining a certain level of infliximab is important in achieving remission.

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Key Words: Crohn's disease, infliximab, dose escalation, trough serum infliximab level, interleukin 6, albumin

Given the risk of stricturing or perforating complications with repeated relapse and remission,[1] induction of remission and its long-term maintenance are required in Crohn's disease (CD) therapy. Infliximab, an antihuman tumor necrosis factor-α (TNF-α) monoclonal antibody, has been reported effective as both induction and maintenance therapy for luminal and fistulizing CD.[2,3] However, some patients experience loss of response (LOR) on standard therapy (5 mg/kg at weeks 0, 2, 6, and thereafter at 8-week intervals), with an annual risk for LOR of 13% per patient-year.[4]

The LOR to maintenance therapy of infliximab is considered to be related to a decrease in serum trough level[3,5,6]; therefore, a decrease in dose interval or increase in dosage of infliximab is recommended for patients with CD showing LOR to standard therapy.[4,6–8] Shortening the dose interval of infliximab has indeed been found useful for regaining response.[3] However, the efficacy of infliximab dose escalation has been demonstrated only in the ACCENT I study[9] with 10 mg/kg episodic treatment and in several retrospective studies.[10–12] Data regarding the usefulness of infliximab dose escalation are therefore insufficient at present, and no report has demonstrated a relationship between

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the efficacy of dose escalation and trough serum levels of infliximab.

Here, to assess the efficacy, safety, and relationship of trough serum level with clinical efficacy after infliximab dose escalation, an increased dose of 10 mg/kg was administered to patients with CD showing LOR to infliximab treatment of 5 mg/kg at 8-week intervals in a clinical trial. In addition, to identify the factors related to remission, baseline characteristics were compared between patients with and without remission after dose escalation.

METHODS

Patients and Study Design

This multicenter, open-label clinical study (ClinicalTrials.gov number, NCT00805766) was performed at 9 medical institutions in Japan from December 2008 to July 2010. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and the protocol was approved by the institutional review board at each medical institution.

The study schema is shown in Figure 1. Potential subjects were patients with CD aged 16 to 75 years who were judged by the attending gastroenterologist as showing insufficient efficacy of infliximab at 5 mg/kg every 8 weeks in daily medical practice. After obtaining written informed consent, potential subjects received the last infusion of 5 mg/kg infliximab and were assessed for compliance with the LOR criteria at 8 weeks after administration. Subjects who met the LOR criteria were enrolled in this dose escalation study. LOR was defined as follows: (1) Crohn's disease activity index (CDAI) ≥175 at 8 weeks, based on the ACCENT I study[2] and (2) an increase in CDAI of ≥50 points over that at 4 weeks, based on the criteria for exacerbation reported by D'Haens et al.[13] instead of the criteria for CDAI increase from the qualifying score.[2] This was done because CDAI scores at the time of primary response to infliximab were unknown.

Patients were excluded from the study if they had marked stenosis of the bowel, short bowel syndrome, ostomy, abscess, or marked internal fistula; use of parenteral nutrition, total enteral nutrition, leukocytapheresis, or cyclosporin/tacrolimus within 4 weeks before the initial assessment; use of intravenous corticosteroids within 2 weeks before the initial assessment; surgery or fasting therapy within 4 weeks before the initial assessment; serious/opportunistic infection within 6 months before the initial assessment; tuberculosis, active hepatitis B/C, HIV infection, or any chronic infectious disease; or a history of serious infusion reaction to infliximab.

Of the 52 patients who provided written informed consent, 45 entered the screening group and received 5 mg/kg of infliximab (Fig. 2). Five patients were excluded due to exclusion criteria, and 2 patients discontinued due to exacerbation of CD. Of the remaining 45 patients, 2 did not meet the LOR criteria and 4 discontinued due to the exacerbation of CD, lack of efficacy, adverse events, or pregnancy. Consequently, 39 patients were enrolled in this study and started treatment with infliximab at a dose of 10 mg/kg every 8 weeks (week 0). The dose and interval of infliximab infusion were not changed.

Efficacy was evaluated by CDAI every 8 weeks from week 0 until week 40. Safety was evaluated from week 0 until week 40. Safety was additionally evaluated in those who discontinued infliximab administration for 12 weeks after the last administration of 10 mg/kg infliximab.

The primary endpoint was defined as a median reduction in CDAI of ≥50 points between week 0 and week 8. This definition was based on the degree of decrease in CDAI at 8 weeks after treatment with infliximab at 10 mg/kg in patients who showed LOR to scheduled treatment with 5 mg/kg in the ACCENT I study.[14]

The secondary endpoints were the proportion of patients who had achieved ≥50-point, ≥70-point, and ≥100-point improvements in CDAI and remission (CDAI <150 points) on measurement at 8-week intervals after dose escalation. In addition, we also measured trough serum infliximab and serum C-reactive protein (CRP) levels at week 0 and every 8 weeks thereafter; antibodies to infliximab (ATI) before dose escalation and at weeks 24 and 40; and levels of plasma interleukin 6 (IL-6) and serum albumin, prealbumin, transferrin, and retinol-binding protein at week 0. Plasma TNF-α level was not measured, as accurate measurement is not possible in the presence of infliximab. Blood samples were drawn immediately before each infliximab administration.

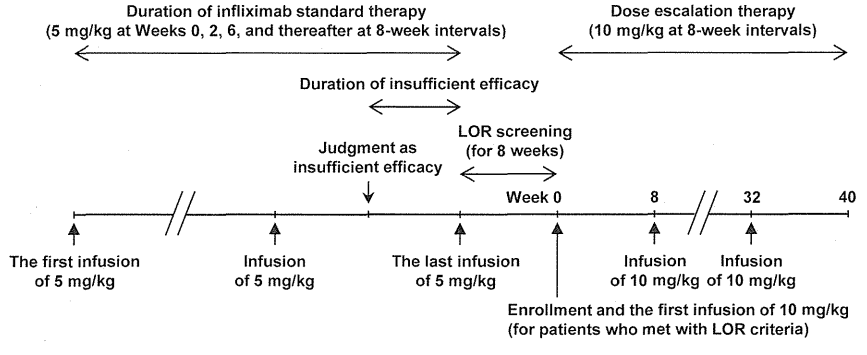

FIGURE 1. Study schema.

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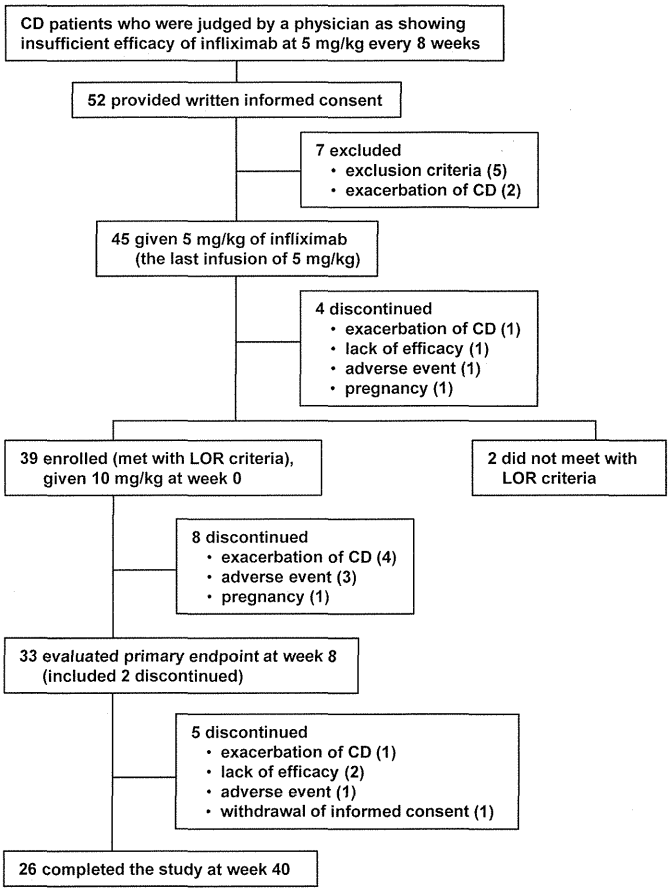

FIGURE 2. Study design and patient disposition.

Combination of either or both nutritional or drug therapies was allowed as follows, with changing dosage not allowed until week 8: immunomodulators (azathioprine, mercaptopurine, and methotrexate) had to be started at least 12 weeks before CDAI evaluation for LOR screening and maintained at a stable dose from at least 4 weeks before CDAI evaluation for LOR screening; corticosteroids, metronidazole, and ciprofloxacin had to be maintained at a stable dose from at least 2 weeks before CDAI evaluation for LOR screening; and 5-aminosalicylates and enteral nutrition therapy had to be maintained at a stable dose from at least 4 weeks before CDAI evaluation for LOR screening.

Measurement Methods

Serum infliximab levels and ATI were measured using an enzyme-linked immunosorbent assay[15] at Mitsubishi Tanabe Pharma Corporation (Osaka, Japan). The minimum detectable infliximab concentration was 0.1 μg/mL. Plasma IL-6 level was determined using a chemiluminescence enzyme immunoassay (reference range in healthy subjects: ≤2.41 pg/mL), CRP level using a latex agglutination immunoassay (reference range: ≤0.5 mg/dL), albumin using the bromocresol green method (reference range: 3.8–5.3 g/dL), prealbumin and retinol-binding protein levels using nephelometry (reference range: 22–40 mg/dL and 2.9–7.9 mg/dL, respectively), and transferrin level using turbidimetric immunoassay (reference range: 190–320 mg/dL). Measurements were performed at Life Science Institute Inc. (Tokyo, Japan).

Analytical Methods

Efficacy was assessed in the full analysis set. Patients for whom data were evaluated at week 8 were subject to investigation of the primary endpoint. Changes in CDAI between weeks 0 and 8 were also calculated even after compensation for data missing due to discontinuation up to week 8 using the last observation carried forward method.

Responses at each measurement time point were calculated in subjects from whom data were obtained at each point. Missing data at week 40 were compensated for using the last observation carried forward method to show overall data at week 40 (week 40 [overall]).

Correlations between remission and trough serum infliximab levels at week 40 and between laboratory parameters at week 0 were analyzed using Spearman's rank correlation coefficient. Differences in baseline patient characteristics between those with and without remission at week 40 (overall) were analyzed using the Wilcoxon rank test or Fisher's exact test. Stratified analyses by age, duration of infliximab standard therapy, and duration of insufficient efficacy used median values as cutoff. The criteria-proposed definition of early CD[16] was adopted as the cutoff value of disease duration. The cutoff value for infliximab level was 1 μg/mL, based on the threshold of trough level for clinical response,[3,5] and cutoff values of other endpoints were their reference values. Receiver operating characteristic curve analysis was performed to determine the cutoff value of the trough serum infliximab level before dose escalation for predicting remission at week 40 (overall).

Mitsubishi Tanabe Pharma Corporation sponsored this clinical trial and was responsible for the collection and analysis of data.

RESULTS

Patients

Infliximab at 10 mg/kg was administered to 39 patients. Thirty-three of these 39 were subject to evaluation at week 8, and 26 of the 33 completed the study at week 40 (Fig. 1). Thirteen patients (33%) discontinued treatment, mainly due to exacerbation of CD (n = 5) and adverse events (n = 4).

Baseline characteristics of the 39 patients are shown in Table 1. Twenty-nine were male (74%) and 10 were female (26%), with a median (interquartile range [IQR]) age of 29.0 years (24.0–34.0 yr). Median (range) duration of infliximab standard therapy was 1.7 years (0.3–6.0 yr), and that of insufficient efficacy was 1.4 months (0.3–32.9 mo). Median (IQR) CDAI at week 0 was 293.0 (247.0–352.0) points.

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TABLE 1. Baseline Characteristics of Patients Administered Infliximab at a Dose of 10 mg/kg

Patients, n	39
Sex (male:female)	29:10
Age, yr	29.0 (24.0–34.0)
Disease duration, median (range), yr	8.2 (0.7–31.1)
Disease location (ileum:colon:ileocolonic)	1:7:31
Previous surgery for CD	
Resection	15 (38%)
Stricturoplasty	3 (8%)
Smoker	12 (31%)
Concomitant medications	
Corticosteroids	1 (3%)
5-Aminosalicylates	34 (87%)
Immunomodulators	13 (33%)
Metronidazole/ciprofloxacin	2 (5%)
Enteral nutrition	13 (33%)
Duration of infliximab standard therapy, median (range), yr	1.7 (0.3–6.0)
Duration of insufficient efficacy, median (range), mo	1.4 (0.3–32.9)
CDAI	293.0 (247.0–352.0)
Serum infliximab level, μg/mL	0.30 (<0.10–1.48)
<0.1	17 (44%)
0.1 to <1	9 (23%)
Plasma IL-6, pg/mL	6.60 (3.29–11.40)
CRP, mg/dL	2.4 (0.8–4.2)
>0.5	30 (77%)
Albumin, g/dL	3.6 (3.3–4.2)
Prealbumin, mg/dL	18.1 (13.8–22.5)
Transferrin, mg/dL	223.0 (194.0–255.0)
Retinol-binding protein, mg/dL	2.2 (1.9–3.1)

Data are shown as the median (IQR) or number of patients (%), except where indicated otherwise.

Efficacy After Dose Escalation

Median CDAI reduction between weeks 0 and 8 in the 33 patients evaluated at week 8 was significantly higher than 50 points, with a value (95% confidence interval [CI]) of 95.0 (70.0–134.0) points; the primary endpoint was therefore attained. Even after compensating for missing data using the last observation carried forward method, the median (95% CI) CDAI change between weeks 0 and 8 in the total of 39 patients was still 79.0 (53.0–112.5) points—a reduction in CDAI of ≥50 points. Twenty-three patients achieved ≥50-point improvement at week 8. Of the 21 patients remaining after 2 dropped out due to adverse events or withdrawal of consent, 13 patients maintained ≥50-point improvement until week 40. The proportion of patients who achieved ≥50-point, ≥70-point, and ≥100-point improvements in CDAI at week 8 was 70% (23 of 33), 61% (20 of 33), and 45% (15 of 33). Respective proportions at week 40 (overall) were 67% (26 of 39), 59% (23 of 39), and 46% (18 of 39) (Fig. 3).

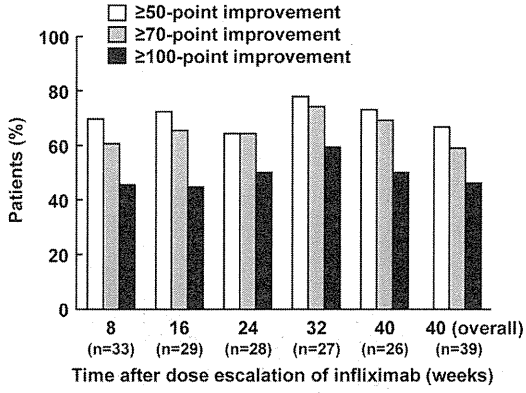

FIGURE 3. Proportion of patients who achieved ≥50-point, ≥70-point, and ≥100-point improvement in CDAI.

Disease activity by CDAI at week 0 was mild in 5 (13%) of the 39 patients and moderate to severe in 34 (87%) (Fig. 4A). The proportion of subjects in remission was 39% (13 of 33) at week 8, ranged from 29% to 50% after week 8, and was 41% (16 of 39) at week 40 (overall).

Median (IQR) CRP levels were 2.4 (0.8–4.2) mg/dL at week 0, 1.2 (0.3–3.3) mg/dL at week 8, and ranged from 0.7 to 1.2 mg/dL between weeks 8 and 40 (Fig. 4B). Median (IQR) trough serum infliximab levels were 0.30 (<0.1–1.48) μg/mL at week 0, 1.29 (0.21–3.71) μg/mL at week 8, and ranged from 1.29 to 2.18 μg/mL between weeks 8 and 40 (Fig. 4C). Five of the 17 patients (29%) whose trough serum infliximab level at week 0 was <0.1 μg/mL achieved remission at week 40 (overall).

Remission rate among 4 patients groups stratified by trough serum infliximab level at week 40 <0.56 μg/mL (25th percentile), ≥0.56 to <2.18 μg/mL (median), ≥2.18 to <5.44 μg/mL (75th percentile), and ≥5.44 μg/mL were 17%, 43%, 67%, and 71%, respectively (Fig. 5). Achievement of remission showed a significant correlation with trough serum level (rho = 0.413, $P = 0.036$).

Two of the 39 patients had detectable ATI before and after dose escalation; one discontinued treatment due to lack of efficacy and the other achieved remission at week 40.

Factors Associated with Remission After Dose Escalation

Patient characteristics before dose escalation were compared between those with and without remission at week 40 (overall) (Table 2). Significant differences were observed in trough serum infliximab level, plasma IL-6 level, and serum albumin level at week 0. Remission rate at week 40 (overall) was higher in patients with a trough serum infliximab level of ≥1 μg/mL than in those with <1 μg/mL at week 0, with similar findings seen in patients with a plasma IL-6 level of ≤2.41 pg/mL versus those with >2.41 pg/mL at week 0 and in patients with a serum albumin level of ≥3.8 g/dL versus those with <3.8 g/dL at week 0.

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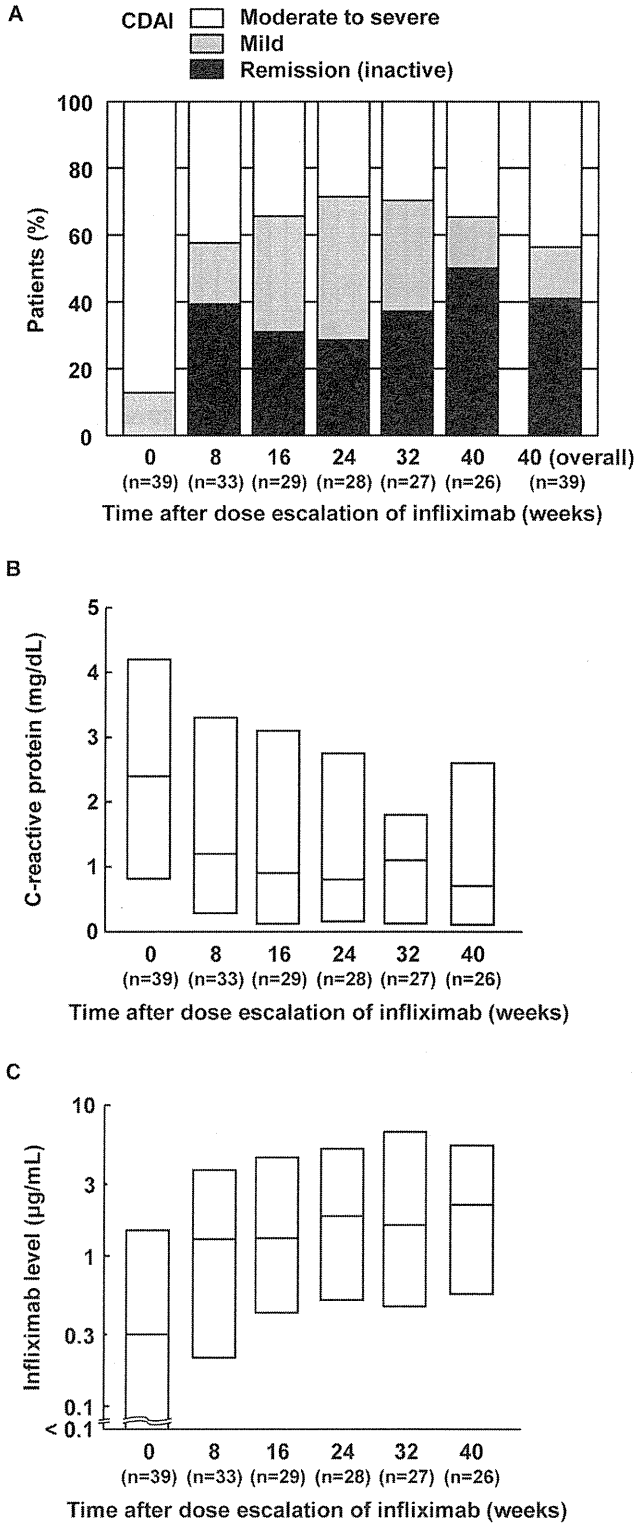

FIGURE 4. Efficacy after dose escalation to 10 mg/kg in patients with LOR to infliximab maintenance therapy. A, Proportion of patients with inactive CD (remission, CDAI: <150 points), mild CD (CDAI: between ≥150 points and <220 points), and moderate or severe CD (CDAI: ≥220 points). B, Serum CRP level (median and IQR). C, Trough serum infliximab level (median and IQR).

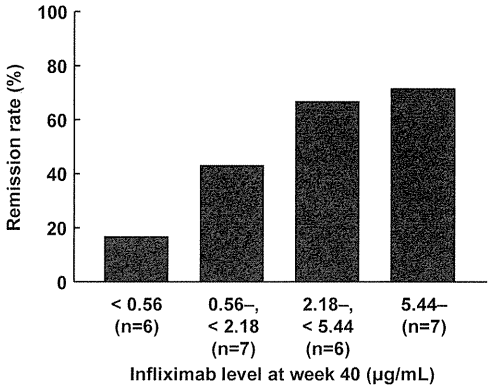

FIGURE 5. Remission rate according to trough serum infliximab level at 40 weeks after dose escalation. Remission rates for <0.56 μg/mL (25th percentile), between ≥0.56 μg/mL and <2.18 μg/mL (median), between ≥2.18 μg/mL and <5.44 μg/mL (75th percentile), and for ≥5.44 μg/mL were calculated. Proportions of patients who achieved remission are shown according to trough serum infliximab level.

The area under the receiver operating characteristic curve for trough serum infliximab level at week 0 to predict remission at week 40 (overall) was 0.70 (95% CI, 0.50–0.84), and the optimal cutoff value of trough serum infliximab level at week 0 was calculated as 0.42 μg/mL. The respective remission rates at week 40 (overall) in patients with a trough serum infliximab level of ≥0.42 μg/mL and those with <0.42 μg/mL at week 0 were 65% (11 of 17) and 23% (5 of 22). Based on this cutoff value, the sensitivity, specificity, positive predictive value, and negative predictive value for detecting remission at week 40 (overall) were 69%, 74%, 65%, and 77%, respectively.

Trough serum infliximab level before dose escalation showed a negative correlation with plasma IL-6 level before dose escalation (rho = −0.552, $P < 0.001$) and a positive correlation with serum albumin level before dose escalation (rho = 0.681, $P < 0.001$). Furthermore, a negative correlation was noted between the plasma IL-6 level and serum albumin level before dose escalation (rho = −0.668, $P < 0.001$).

No significant association was noted between concomitant medication use and remission status. Five patients started new concomitant medications from weeks 8 to 40 (corticosteroids in 2 patients; immunomodulators in 3; metronidazole in 1; ciprofloxacin in 2; enteral nutrition in 1). However, no significant differences were noted in rates of concomitant medication use from week 0 (Table 2) to week 40 (data not shown) between patients with and without remission at week 40 (overall).

Safety

The mean (range) duration of safety evaluation in the 39 patients administered infliximab at a dose of 10 mg/kg was 230.0 (71–323) days, with an average of 3.9 doses (Table 3). The proportion of patients with adverse events and serious adverse events after dose escalation was 79% (31 of 39) and

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TABLE 2. Factors Associated with Remission at 40 Weeks After Dose Escalation of Infliximab

	Remission (n = 16)	No remission (n = 23)	P^a
Sex, Male	13 (81%)	16 (70%)	0.480
Age, yr	31.5 (26.8–34.8)	27.0 (22.5–33.0)	0.137[b]
<29	6 (38%)	12 (52%)	0.516
Disease duration, yr	11.3 (3.0–14.8)	5.3 (2.8–9.5)	0.084[b]
≤2	4 (25%)	2 (9%)	0.205
Disease location, ileum:colon:ileocolonic	0 (0%):3(19%):13(81%)	1 (4%):4 (17%):18 (78%)	1.000
Previous surgery for CD	6 (38%)	9 (39%)	1.000
Smoker	7 (44%)	5 (22%)	0.174
Concomitant medications			
Corticosteroids	0 (0%)	1 (4%)	1.000
5-Aminosalicylates	14 (88%)	20 (87%)	1.000
Immunomodulators	7 (44%)	6 (26%)	0.312
Metronidazole/ciprofloxacin	1 (6%)	1 (4%)	1.000
Enteral nutrition	5 (31%)	8 (35%)	1.000
Duration of infliximab standard therapy, yr	1.6 (0.8–3.4)	1.7 (1.0–3.2)	0.966[b]
<1.7	8 (50%)	13 (57%)	0.752
Duration of insufficient efficacy, mo	1.4 (0.5–2.0)	1.5 (0.9–2.3)	0.597[b]
<1.4	7 (44%)	10 (43%)	1.000
CDAI	266.5 (218.8–327.0)	311.0 (262.0–354.5)	0.116[b]
<220	4 (25%)	1 (4%)	0.139
Serum infliximab level, μg/mL	1.25 (<0.10–2.88)	<0.10 (<0.10–0.43)	0.033[b]
≥1	9 (56%)	4 (17%)	0.017
Plasma IL-6, pg/mL	4.22 (1.24–9.12)	8.26 (4.39–15.90)	0.029[b]
≤2.41	7 (44%)	2 (9%)	0.019
CRP, mg/dL	1.8 (0.1–2.8)	2.6 (1.0–5.1)	0.123[b]
≤0.5	5 (31%)	4 (17%)	0.444
Albumin, g/dL	4.1 (3.6–4.3)	3.5 (3.3–3.9)	0.023[b]
≥3.8	11 (69%)	6 (26%)	0.011
Prealbumin, mg/dL	17.3 (15.3–27.4)	19.3 (13.4–22.0)	0.247[b]
≥22	6 (38%)	6 (26%)	0.498
Transferrin, mg/dL	206.5 (191.0–246.3)	229.0 (210.0–268.0)	0.242[b]
≥190	12 (75%)	19 (83%)	0.694
Retinol binding protein, mg/dL	2.2 (2.0–3.5)	2.3 (1.6–2.7)	0.253[b]
≥2.9	6 (38%)	4 (17%)	0.264

For stratified analyses, medians of age, duration of infliximab maintenance therapy, and duration of treatment after LOR were used as cutoff values. The cutoff value of disease duration was the criteria-proposed definition of early CD.[14] The cutoff value of trough serum infliximab level was the threshold level for clinical response.[3,5] The cutoff values of other endpoints were their reference values. Missing data at week 40 were compensated for using the last observation carried forward method.
Data are shown as the median (IQR) or number of patients (%).
[a]*P*-values were calculated by Fisher's exact test.
[b]*P*-values were calculated by the Wilcoxon rank test.

21% (8 of 39), respectively. The most frequent serious adverse event was exacerbation of CD, which occurred in 13% of participants (5 of 39). The incidence of serious infection was 5% (2 of 39; cytomegalovirus infection in 1 and bronchitis in 1), and no serious infusion reactions to infliximab were reported. The patients who had serious bronchitis, melena, or peritonitis discontinued the study. All serious adverse events were ultimately resolved.

DISCUSSION

In this study, we showed that infliximab at a dose of 10 mg/kg safely induced remission in patients with CD with LOR to infliximab maintenance therapy of 5 mg/kg at 8-week intervals. Remission after dose escalation was associated with circulating infliximab, IL-6, and albumin levels before escalation. These findings suggest that dose escalation to 10 mg/kg is a useful option for achieving remission after LOR at 5 mg/kg and that dose

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TABLE 3. Summary of Safety Findings for All Patients Receiving 10 mg/kg Infliximab Treatment

Patients, n	39
Mean duration of follow-up (range), d	230.0 (71–323)
Mean number of doses	3.9 (1 dose:8 patients; 2:2; 3:1; 4:1; 5:27)
Adverse events	31 (79%)
Infections	22 (56%)
Infusion reactions	3 (8%)
Serious adverse events	8 (21%)
Worsening of CD	5 (13%)
Cytomegalovirus infection	1 (3%)
Bronchitis	1 (3%)
Melena	1 (3%)
Peritonitis	1 (3%)
Upper limb fracture	1 (3%)
Serious infections	2 (5%)
Serious infusion reactions	0 (0%)

Data are shown as the number of patients (%), except where indicated otherwise.

escalation while maintaining a certain level of infliximab maximizes its efficacy.

The median (95% CI) CDAI reduction at week 8 was 95.0 (70.0–134.0) points, indicating that the primary endpoint was attained. Sixty-two percent (13 of 21) maintained a ≥50-point improvement from weeks 8 to 40. The proportions of patients in whom CDAI was reduced by at least 50, 70, and 100 points and who achieved remission were 70%, 61%, 45%, and 39% at week 8, and 67%, 59%, 46%, and 41% at week 40 (overall), respectively. These results are comparable with those after dose escalation to 10 mg/kg in retrospective studies (short/long-term response rate: 77%/50%[11]; short-term remission rate: 28%[12]).

LOR to infliximab maintenance therapy seems attributable to not only low trough serum infliximab levels but also increase in other inflammatory molecules.[17] In this study, trough infliximab level at week 0 was <1 μg/mL (the threshold trough infliximab level to obtain a clinical response[3,5]) in 67%, indicating that the main reason for LOR in these patients was a subtherapeutic trough infliximab level. The proportion of patients showing LOR with a therapeutic trough infliximab level in this study was similar to that in the study of Afif and colleagues.[18] In this study, the median trough serum infliximab level in LOR patients was 0.30 μg/mL at week 0 and ≥1 μg/mL after dose escalation. The remission rate at week 40 improved when week 40 trough serum infliximab level was high, suggesting that the efficacy of infliximab at 10 mg/kg correlates with serum level, similarly to the case at 5 mg/kg.[3,5] In contrast, among 7 patients with serum trough infliximab levels at week 40 exceeding 5.44 μg/mL, 2 failed to obtain remission.

The remission rate at week 40 (overall) was significantly higher in patients with trough serum infliximab levels before dose escalation of ≥1 μg/mL than in those without. Receiver operating characteristic curve analysis showed that patients with before dose escalation trough serum infliximab levels of ≥0.42 μg/mL were more likely to achieve remission after dose escalation to 10 mg/kg than those with levels of <0.42 μg/mL (remission rate: 65% versus 23%). Because trough serum infliximab level before dose escalation was a moderate predictor of remission at week 40 (overall), we regarded an "infliximab level of 0.42 μg/mL" as a rough guide for dose escalation. One study reported that a decrease in trough serum infliximab level to <1 μg/mL predicts LOR during 5 mg/kg maintenance therapy,[19] suggesting that dose escalation therapy probably should be considered when trough serum infliximab levels are <1 μg/mL.

Remission rate was also significantly higher in patients with plasma IL-6 levels within the reference range than in those with levels outside the range. The same trend was also seen in patients with serum albumin levels within or above the reference range compared with those with levels below the reference range. In addition, relationships were noted between the trough serum infliximab level, plasma IL-6 level, and serum albumin level before dose escalation. Circulating IL-6 level is reported to decrease during infliximab treatment[20,21] and like CRP level to predict a decrease in trough infliximab level.[19] Albumin level may serve as a measure of infliximab pharmacokinetic expectations, given that the common rescue pathway for albumin and immunoglobulin G involves the neonatal Fc receptor.[22] Accordingly, low levels of IL-6 and high levels of albumin are thought to imply not only low disease activity but also that trough serum infliximab levels are ≥1 μg/mL. These findings from this study suggest that, similarly to trough serum infliximab level, assessing plasma IL-6 and serum albumin levels may aid in achieving remission after dose escalation.

Trough serum infliximab levels are reported to be sustained in a large proportion of patients with normal CRP levels,[5,19] and normal CRP levels have been found to predict a response to infliximab after dose escalation.[11] However, our present findings showed no significant correlation between normal CRP levels before dose escalation and remission likely because the patient population with a normal CRP level before dose escalation in this study was too small (23%) to detect any marked differences. Antidrug antibody formation has also been reported to significantly affect serum levels of anti–TNF-α monoclonal antibodies.[6] In addition, dose escalation of infliximab in patients with ATI has been suggested to be ineffective.[18] However, we were unfortunately unable to analyze the relationship between ATI and remission after dose escalation in this study because only 2 patients showed ATI.

No significant differences were noted in rates of concomitant medication use between remission and nonremission patients at week 40 (overall). Under our eligibility criterion, patients on combined therapy started to use concomitant medications at least 12 weeks CDAI evaluation for LOR screening. This medication schedule may therefore have hampered identification of any influence of concomitant medication on outcomes.

As mentioned above, having an infliximab trough level ≥1 μg/mL before dose escalation was significantly associated with remission at week 40 (overall). This result was also observed

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even after excluding the 5 patients who started new concomitant medications (data not shown). In patients with trough serum infliximab levels ≥1 μg/mL before dose escalation, the trough serum infliximab levels at week 40 were significantly higher than in patients with <1 μg/mL (median trough level at week 40 [IQR]: 6.75 [3.89, 10.23] versus 0.78 [<0.10, 1.68] μg/mL, $P < 0.001$). We therefore speculate that the threshold trough level for clinical response in patients with LOR exceeds 1 μg/mL and that the proportion of patients who reach the threshold level is higher among patients with levels ≥1 μg/mL than those with levels <1 μg/mL. Two patients with trough levels at week 40 exceeding 5.44 μg/mL failed to obtain remission in this study, an outcome we believe to be due to subtherapeutic trough levels or LOR-related factors other than trough level. Further investigation is necessary to clarify whether these patients' LOR was due to subtherapeutic trough levels or other factors such as TNF-α–unrelated inflammation.

In addition, increases in trough serum infliximab levels (from weeks 0 to 40) in patients with levels ≥1 μg/mL before dose escalation were significantly higher than in those with levels <1 μg/mL (median increase in trough level at week 40 [IQR]: 2.70 [1.58, 4.64] versus 0.43 [<0.10, 1.43], $P = 0.002$). We therefore believe that the lower remission rate after dose escalation in patients with levels <1 μg/mL before dose escalation is due to higher clearance of infliximab and subsequent difficulty in maintaining an adequate serum level for good response. However, further studies in a larger population will be necessary to confirm whether the rate of remission after dose escalation is higher in patients with trough serum infliximab levels ≥1 μg/mL before dose escalation than in those with trough serum infliximab levels <1 μg/mL. Patient tolerance of a dose of 10 mg/kg was comparable with the reported safety profiles of 5 mg/kg,[2,3] and no particular adverse events were observed.

Two limitations to this study warrant mention. First, we were unable to conduct multivariate analysis because the sample size was too small to permit the investigation of factors associated with remission after dose escalation. Second, we were unable to predict which patients would not respond, even among those with high trough serum levels of infliximab after dose escalation. Previous reports have noted that expression of inflammatory cytokines involved in innate immunity (e.g., TNF-α and IL-6) and acquired immunity (e.g., interferon-γ and IL-17) in patients with CD is upregulated.[23] Thus, measuring and analyzing levels of not only IL-6 but also other cytokines associated with CD may enable identification of factors related to LOR other than low trough serum infliximab levels. Such clarification may help to select appropriate therapeutic regimens for patients with CD who lose response to infliximab.

In conclusion, our study suggests that dose escalation of infliximab to 10 mg/kg is a useful option in achieving remission in patients with CD with LOR to therapy at 5 mg/kg at 8-week intervals. Our findings also suggest that the efficacy of infliximab dose escalation depends on the maintenance of a particular level of infliximab.

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Author contributions: T. Hibi *conceptualized and designed the study*. Y. Suzuki, T. Matsui, H. Ito, T. Ashida, S. Nakamura, S. Motoya, T. Matsumoto, M. Watanabe, and T. Hibi *contributed to the acquisition of data*. Y. Suzuki, N. Sato, K. Ozaki, and T. Hibi *analyzed the data*. Y. Suzuki and T. Hibi *interpreted the data*. Y. Suzuki *prepared the manuscript*. T. Hibi *conducted the study and critically reviewed the manuscript*. All authors have read and approved the final version of the manuscript.

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Correlation of the Endoscopic and Magnetic Resonance Scoring Systems in the Deep Small Intestine in Crohn's Disease

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Background: There are no widely accepted endoscopic or magnetic resonance scoring systems to evaluate deep small intestinal lesions in Crohn's disease (CD). This study aimed to determine whether the simplified endoscopic activity score for Crohn's disease (SES-CD) and the Magnetic Resonance Index of Activity (MaRIA) could be adapted for assessing CD lesions in the deep small intestine.

Methods: Magnetic resonance enterocolonography and single-balloon enteroscopy were prospectively performed in 125 patients with CD. SES-CD and MaRIA were applied to the deep small intestine. The correlation between the SES-CD and MaRIA was evaluated.

Results: Endoscopic and magnetic resonance active lesions were detected in the terminal and proximal ileal segments at a similar rate. The total MaRIA scores correlated well with the total SES-CD scores ($R = 0.808$, $P < 0.001$). A MaRIA score of ≥ 11 had a high sensitivity, specificity, and diagnostic accuracy for ulcerative lesions that were defined by enteroscopy (sensitivity: 78.3%; specificity: 98.0%). Similarly, an MaRIA score of ≥ 7 had a high sensitivity, specificity, and diagnostic accuracy for all mucosal lesions defined by enteroscopy (sensitivity: 87.0%; specificity: 86.0%).

Conclusions: The MaRIA closely correlates with the SES-CD in the deep small intestine, indicating these scoring systems can be used to assess deep small intestinal lesions. We also showed the validity of MaRIA to evaluate the active lesions in the deep small intestine.

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Key Words: Crohn's disease, diagnosis, MR, endoscopy

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that is associated with abdominal symptoms such as diarrhea, abdominal pain, and bloody stools. CD lesions can involve the entire gastrointestinal tract, particularly the small intestine. Small intestinal lesions are present in 40% to 65% of patients with CD,[1,2] but clinical symptoms are a poor predictor for the presence and severity of active lesions.[3–5] The objective assessment of active lesions is important because mucosal healing is associated with better prognosis.[6,7] Balloon-assisted enteroscopy (BAE) procedures, such as double-balloon endoscopy[8,9] and single-balloon endoscopy (SBE),[10,11] and the magnetic resonance (MR) enterography test[12–15] are recent technical advances that can examine small intestinal lesions.

BAE can assess areas of the bowel that conventional colonoscopy cannot reach; one advantage of BAE is that it enables the concise assessment of the mucosa and the acquisition of biopsy specimens. In addition, therapeutic procedures such as balloon dilatation of stenoses can be performed with BAE. The simplified endoscopic activity score for Crohn's disease (SES-CD)[16] is a validated endoscopic scoring system for CD. However, the SES-CD does not include the deep small intestine.

The guidelines of the European Crohn's and Colitis Organization recommend MR enterography as the imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement in CD.[17] The Magnetic Resonance Index of Activity (MaRIA)[18,19] is the only validated MR scores for CD, and a recent study has shown that the MaRIA could assess response to therapy and mucosal healing in patients with CD.[20] In developing the MaRIA scoring system, however, colonoscopy was used as the endoscopic reference, raising a question on the ability of the MaRIA to evaluate deep small intestinal lesions.

We developed MR enterocolonography to be able to simultaneously image both small intestinal and colonic CD lesions.[21] In addition, we evaluated these MR findings in comparison with the enteroscopic findings and reported that MR could detect active lesions in the deep small intestine.[22] However, in the

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previous study, we only used positive/negative criteria for the MR evaluation. There is no widely accepted endoscopic or MR scoring system that focuses on the deep small intestine. This study aimed to determine whether the SES-CD and MaRIA scoring systems could be adapted for the assessment of CD lesions in the deep small intestine.

MATERIALS AND METHODS

Patients

From July 2012 to May 2014, a total of 125 patients who had already been diagnosed with CD were prospectively studied at Tokyo Medical and Dental University Hospital. All patients had been diagnosed according to the criteria of the Research Committee on Inflammatory Bowel Disease in Japan.[23] We excluded patients who had colonic CD because we focused solely on the small intestinal lesions. We also excluded patients who had a colostomy/ileostomy, who had an abdominal abscess, or who were intolerant of or contraindicated to the BAE or MR procedure.

Patients' clinical characteristics on the day of the MR procedure are shown in Table 1. Written informed consent was obtained from all the patients. The study was approved by the Ethics Committee of Tokyo Medical and Dental University.

Enteroscopic Procedures and Evaluation

SBE (Olympus Medical Systems, Tokyo, Japan) was performed by experienced endoscopists on an outpatient basis in most of the patients (88 of 125, 70.4%). We used a retrograde approach and advanced SBE as deep as possible. If stenoses inhibited the passage of the scope or overtube, endoscopic balloon dilatation was performed. In our protocol, we limited the total insertion time to 90 minutes. Using the number of strokes of the endoscopic overtube, we calculated the length of the small intestine from the ileocecal valve.

We applied the items and grading system of the SES-CD to the deep intestine (Table 2). Small intestinal segmentation was defined as described in our previous study.[22] The small intestine was divided into 3 sections. First, the terminal ileum was defined as the section ≤10 cm from the ileocecal valve. In addition, in cases of an ileocolonic anastomosis, the terminal ileum included lesions <10 cm from the anastomotic site. Second, the proximal ileum was defined as the part of the bowel that extended between the proximal end of the terminal ileum ≤300 cm from the ileocecal valve. Finally, the jejunum was defined as the proximal part of the small bowel, excluding the section defined as the proximal ileum. All 3 segments were separately scored and evaluated.

The SES-CD system included the 4 endoscopic variables (size of ulcers, proportion of ulcerated surface, proportion of affected surface, and stenosis), and each variable was scored 0 to 3 for each segment. We calculated SES-CD scores using endoscopic findings within the scope's reach in each segment as per our previous study.[22] The total SES-CD score in the small intestine was calculated as the sum of SES-CD in the terminal ileum, proximal ileum, and jejunum. We used score 0 as a dummy variable in the jejunum for the patients on whom we could not insert the scope into that segment; this dummy was used only in global analysis, not in segmental analysis. In addition, we defined the SES-CD active score (SES-CDa),[22] where we excluded the item of stenosis from the SES-CD because it represents bowel damage rather than active inflammation and calculated the sum of the scores of the size of ulcers, ulcerated surface, and affected surface. The active endoscopic lesions were defined as follows: all mucosal lesions (AML; SES-CDa ≥ 1) and ulcerative lesions (UL; SES-CDa ≥ 5).

TABLE 1. Clinical Characteristics of 125 Patients on the Day of Examination

Female, n (%)	42 (34.4)
Median age at examination (range), yr	31 (12–71)
Median disease duration (range), yr	4 (0–32)
Disease type, n (%)	
Ileal	35 (28.7)
Ileocolonic	87 (71.3)
Perianal involvement, n (%)	31 (25.4)
Previous surgery, n (%)	38 (31.1)
Median CDAI score (range)	98 (0–382)
CDAI > 150, n (%)	28 (23.0)
Median CRP, (range), mg/dL	0.17 (0.02–7.23)
CRP > 0.3 mg/dL, n (%)	49 (40.2)
Concomitant treatments, n (%)	
Mesalazine	80 (65.6)
Steroids	3 (2.5)
Thiopurine	38 (31.1)
Anti-TNF antibodies	41 (33.6)
Elementary diet	30 (24.6)

TNF, tumor necrosis factor.

MR Procedure and Evaluation

The MR enterocolonography protocol used in this study has been previously described.[21,22] MRI was performed using a 1.5-T scanner (EXCELART Vantage powered by Atlas; Toshiba Medical Systems, Tokyo, Japan). We first confirmed adequate distention of bowel by MR imaging while using true steady-state free precession. Next, we performed a coronal balanced sequence that comprised true steady-state free precession and a cine coronal single-shot fast spin echo sequence, termed as fast advanced spin echo. After the intravenous injection of scopolamine butylbromide, the patients underwent a coronal true steady-state free precession and a coronal 3-dimensional T1-weighted gradient echo sequence, termed as quick dimensional dynamic diagnostic scan (Quick 3Ds). After intravenous administration of gadolinium chelate, Quick 3Ds were performed in the axial and coronal orientations. Finally, transverse diffusion-weighted imaging was performed. All imaging included the entire small and large intestine.

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TABLE 2. Classification and Evaluation of Small Intestinal Lesions for Enteroscopy and MR Enterocolonography

Definitions of Endoscopic Scores				
Original SES-CD				
Variables	0	1	2	3
A: Size of ulcers (φ), cm	None	0.1–0.5	0.5–2	>2
B: Ulcerated surface, %	None	<10	10–30	>30
C: Affected surface, %	Unaffected segment	<50	50–75	>75
D: Presence of stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed
Definitions of Endoscopic Segmentation				
Original SES-CD				
Ileum	No definition			
Applied SES-CD				
Terminal ileum (TI)	≤10 cm from the ileocecal valve			
Proximal ileum (PI)	10–300 cm from the ileocecal valve			
Jejunum (J)	The proximal part, excluding the section defined as the proximal ileum			
Definitions of MR Scores				
Original MaRIA				
MaRIA score	1.5 × wall thickness (mm) + 0.02 × RCE + 5 × edema + 10 × ulcer			
Definitions of MR Segmentation				
Original MaRIA				
Ileum	No definition			
Applied MaRIA				
Terminal ileum (TI)	≤10 cm from the ileocecal valve			
Proximal ileum (PI)	Left lower quadrant, right upper and lower quadrants			
Jejunum (J)	Left upper quadrant			

Table 2 also shows classification and evaluation for MR enterocolonography. The small intestine was divided into 3 segments using the same manner as that used for the endoscopic segmentation.[22] The terminal ileum extended 10 cm from the ileocecal valve or the anastomotic site, the proximal ileum was located in the left lower quadrant, the segment that corresponded to the bowel loops was located in the right upper and lower quadrants, and the jejunum was located in the left upper quadrant.

To assess the severity of CD lesions, the MaRIA score of each segment was calculated according to the following formula[18,19]:

$$\begin{aligned}\text{MaRIA} = {} & 1.5 \times \text{wall thickness (mm)} \\ & + 0.02 \times \text{relative contrast enhancement (RCE)} \\ & + 5 \times \text{edema} + 10 \times \text{ulcers.}\end{aligned}$$

The total MaRIA score for the small intestine was calculated as the sum of MaRIA in the terminal ileum, proximal ileum, and jejunum. In addition, MR active lesions were defined in the following manner: active disease (MaRIA ≥ 7) and severe disease (MaRIA ≥ 11).[19]

Study Design

The MR procedure was performed initially, with SBE performed subsequently within 3 days. The endoscopist and radiologist were blinded to the results of other examinations. The SES-CD and MaRIA scores were calculated globally and per segment to quantify disease activity. The deep small intestine was defined as the intestine that included the proximal ileum and the jejunum.

Statistical Analysis

The level of statistical significance was set at $P < 0.05$. Sensitivities and specificities are shown with their 95% confidence intervals (CIs). The Pearson's chi-square test was used to analyze categorical data and compare proportions. Correlations between the MR and endoscopic examinations as well as the clinical disease activity and biomarkers were calculated using Spearman's rank correlation test. Contingency tables that took the presence or absence of endoscopic active lesions (SES-CDa ≥ 1 and SES-CDa ≥ 5) into account in relation with MR lesions (MaRIA ≥ 7 and MaRIA ≥ 11) were constructed to determine

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the sensitivity, specificity, positive and negative predictive values, and overall diagnostic accuracy of MR.

RESULTS

The SBE and MR examinations were performed on the same day in the majority of the patients (110 of 125, 88.0%). There were no severe complications with SBE, such as perforation or bleeding that required transfusion. Balloon dilatation was performed in 25 patients (20.0%). The scope reached the proximal ileum in 125 patients (100.0%), the jejunum in 53 (42.4%), and the entire intestine in 13 (10.4%; see Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A901). The median reach for the scope was 210 cm from the ileocecal valve. There were no complications with MR, such as injection allergy, either and our MR protocol was tolerated in all the patients.

We first took at the detection rate of UL and AML with BAE and severe disease and active disease with MR in each segment (see Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A901). UL were observed by SBE in 45 of the 125 terminal ileal segments (36.0%), 48 of the 125 proximal ileal segments (38.4%), and 6 of the 53 jejunal segments (11.3%). AML were observed in 70 of the 125 terminal ileal segments (56.0%), 74 of the 125 proximal ileal segments (59.2%), and 6 of the 53 jejunal segments (11.3%). UL and AML were detected in the terminal ileal segment and the proximal ileal segment at a similar rate ($P = 0.695$ and $P = 0.609$, respectively). Severe disease was observed on MR in the terminal ileum of 44 patients (35.2%), proximal ileum of 41 (32.8%), and jejunum of 5 (4.0%). Active disease was observed in the terminal ileum of 75 patients (60.0%), proximal ileum of 75 patients (60.0%), and jejunum of 12 patients (9.6%). Severe disease and active disease were detected in the terminal ileal segment and the proximal ileal segment at a similar rate ($P = 0.689$ and $P = 1.000$, respectively). An example case with UL defined by SBE and severe disease defined by MR is shown in Figure 1.

We next evaluated the correlation of the SES-CD or MaRIA scores in the small intestine with the Crohn's Disease Activity Index (CDAI) scores or C-reactive protein (CRP) levels (see Fig., Supplemental Digital Content 2, http://links.lww.com/IBD/A902). The Spearman's rank correlation coefficient between total SES-CD and CDAI was 0.177 ($P = 0.052$), and that between total MaRIA and CDAI was 0.221 ($P = 0.015$). Similarly, the Spearman's rank correlation coefficient between total SES-CD and the CRP level was 0.345 ($P < 0.001$), and that between total MaRIA and the CRP level was 0.371 ($P < 0.001$).

In contrast, total MaRIA scores correlated well with total SES-CD scores ($R = 0.808$, $P < 0.001$; Figure 2). When the

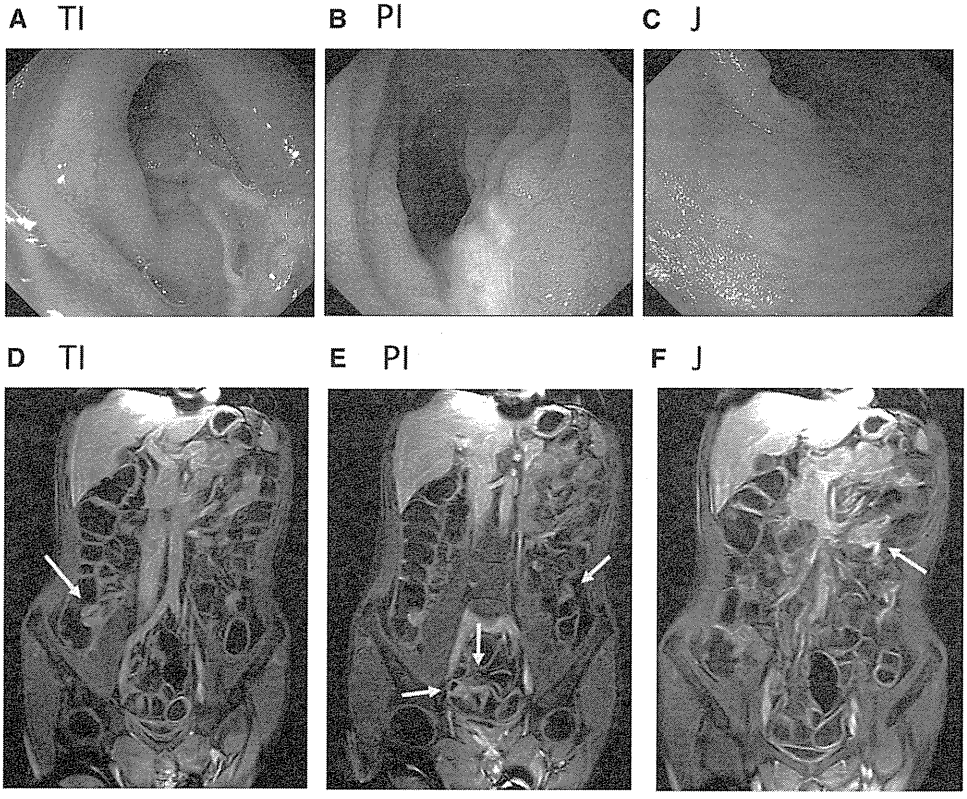

FIGURE 1. An example of small intestinal lesions. Enteroscopy detected a longitudinal ulcer both in the terminal ileum (TI; A) and proximal ileum (PI; B) and detected a small ulcer in the jejunum (J; C). The SES-CD was 7 in TI, 6 in PI, and 5 in J. MR enterocolonography with 3D T1-weighted contrast-enhanced sequence also detected active lesions as wall thickness and contrast enhancement both in TI and PI (D–F; yellow arrows). The MaRIA score was 29.4 in TI, 17.2 in PI, and 10.8 in J.

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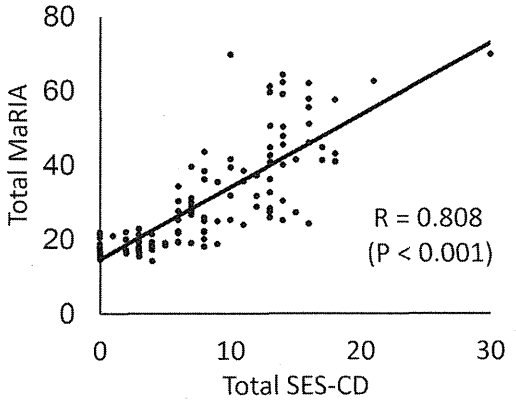

FIGURE 2. The correlation between the SES-CD and MaRIA in the small intestine.

specific segments were analyzed, we found that the correlation between the SES-CD and MaRIA scores were also statistically significant both in the terminal ileum and the deep small intestine (combined proximal ileum and jejunum) (R = 0.725, $P < 0.001$; R = 0.806, $P < 0.001$; Figure 3). The subscore A of SES-CD indicates ulcer size. The MaRIA criteria contain the positive/negative element of "ulcers." Lesions with a subscore A of 3 were observed in 75 of the 303 small intestinal segments. In 38 of 75 segments (50.7%), "ulcers" were positively detected by MR.

Finally, we examined the accuracy of the MaRIA score to assess disease activity quantitatively (Table 3). An MaRIA score of ≥11 had a high sensitivity (78.3%; 95% CI, 73.8–80.5), specificity (98.0%; 95% CI, 95.6–99.2), and diagnostic accuracy (91.1%; 95% CI, 88.0%–92.7%) for UL as defined by the SES-CD. Similarly, an MaRIA score of ≥7 had a high sensitivity (87.0%; 95% CI, 82.9%–90.2%), specificity (86.0%; 95% CI, 81.4%–89.6%), and diagnostic accuracy (86.5%; 95% CI, 82.2%–89.9%) for AML as defined by the SES-CD. Of 303 small intestinal segments, MR-positive (MaRIA ≥7) and endoscopic-negative (SES-CDa = 0) lesions were detected in 24 segments (7.9%). MR findings for these lesions were as follows: the mean MaRIA was 8.46; the mean wall thickness was 3.7 mm; the mean relative contrast enhancement was 126; edema was not observed; and ulcers were detected in 1 segment (4%). Endoscopic-positive (SES-CDa ≥1) and MR-negative (MaRIA <7) lesions were observed in 14 of the 303 segments (4.6%). The SES-CD subscore A (ulcer size) was 1 or 2 in 12 segments (86%) and 3 in 2 segments (14%).

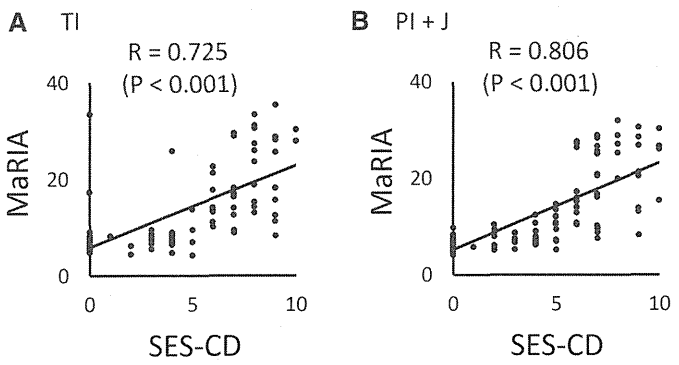

FIGURE 3. The correlation between the SES-CD and MaRIA in the terminal ileum (A) and the proximal ileum and jejunum (B).

DISCUSSION

In the management of CD, a new "treat-to-target" paradigm has emerged with movement beyond clinical symptoms to objective endpoints, specifically mucosal healing.[24] Scoring systems are necessary to assess mucosal healing quantitatively in both clinical practice and clinical trials. In this prospective study, we applied the SES-CD and MaRIA to small intestinal lesions and directly compared them. The results of this study demonstrate the possibility of adapting the SES-CD and MaRIA scoring systems to assessing the deep intestine.

We performed BAE and MR procedures on a large number of patients and showed the importance of imaging the deep small intestine in patients with CD. Recent studies have suggested that mucosal healing is critical for good prognosis of CD.[6,7] Colonoscopy is generally used for the assessment of endoscopic lesions in patients CD; however, it can only be used to assess the colon and the terminal ileum. Our results showed that endoscopic or MR active lesions could be detected in the terminal ileal segment and the proximal ileal segment at a similar or even at a higher rate in the proximal ileal segment than in the terminal ileal segment. In addition, CDAI, based on clinical symptoms, did not correlate with either the SES-CD or MaRIA of the deep small intestine, consistent with several previous studies demonstrating a similar poor correlation between the clinical symptoms and the endoscopic findings.[25,26] These scoring systems of the small intestine did not correlate with CRP, either. Our results suggest that both CDAI and CRP do not reflect the small intestinal CD lesions, and imaging examinations are necessary for optimal management.

The most important finding in this study was that there was a positive correlation between the SES-CD and MaRIA scores in the small intestine (R = 0.808). This suggests that these scoring systems could be adapted for the assessment of the deep small intestine. Patients with CD can have active disease both in the small and large intestine. The SES-CD and MaRIA have been validated as scoring systems for CD, but these scoring systems mainly evaluate large intestinal lesions. Our finding can contribute to the development of an endoscopic or MR scoring system that includes the entire intestine.

Another important finding was that an MaRIA score of ≥11 and ≥7 had a high diagnostic accuracy for UL and AML in the small intestine, respectively. These results were similar to those from the previous research in which the MaRIA system was originally defined,[19,20] and these results support the validity

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TABLE 3. Diagnostic Accuracy of MR for Endoscopic Lesions

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Severe disease (MaRIA ≥11) for UL (SES-CDa ≥5)	78.3	98.0	95.4	89.4	91.1
Active disease (MaRIA ≥7) for AML (SES-CDa ≥1)	87.0	86.0	87.5	85.4	86.5

NPV, negative predictive value; PPV, positive predictive value; RCE, relative contrast enhancement.

of using the cutoff for MaRIA even in the deep intestine. But, it should be noted that some patients had MR-positive and endoscopic-negative lesions (7.9%) or MR-negative and endoscopic-positive lesions (4.6%). These discrepancies can be explained by 2 reasons. First, BAE can detect minute changes in the mucosa, and the limitations of MR in the detection of superficial mucosal lesions have been previously shown.[11,13] Second, CD is a transmural disease that may affect the entire thickness of the bowel wall, and some intramural diseases may not be detected by endoscopy. Our results suggest that MR is effective for examining extramucosal active lesions, whereas endoscopy is more sensitive for examining superficial or small mucosal lesion. Further studies are needed to clarify the clinical significance of these lesions in the deep small intestine and also to determine what degree of endoscopic or MR lesions is associated with favorable long-term prognosis.

Agreement statistics showed "ulcers" were positively detected by MR in 38 of the segments (50.7%) with SES-CD subscore A of 3. This percentage was low because the MaRIA criteria require an "ulcer" to have a definite large depression,[18] and lesions with a subscore A of 3 do not satisfy this definition. Other subscores include ulcerated surface, affected surface, and presence of stenosis. The MaRIA criteria do not include these elements, and thus, we cannot compare the 2 examinations. The agreement regarding detection of strictures is of great importance, and new scoring systems such as the Lemann score have been developed[27,28]; we have reported on strictures in a previous study.[22]

Several new advanced techniques, such as computed tomography enterography, MRE, ultrasonography (US), capsule endoscopy (CE), and BAE, can all be used to examine the small intestine. Although the anatomical resolution with computed tomography enterography is excellent, routine monitoring with computed tomography should be weighed against the potential risks associated with radiation exposure.[29] US examination is inexpensive and safe and has additional benefits because they can characterize bowel function in real time. Additionally, US is an acceptable imaging option both at diagnosis and for monitoring according to the European guidelines[30]; however, reproducibility and interobserver variability have limited the use of US in clinical trials. Although CE can detect mucosal lesions in the small intestine, the impact on the clinical outcomes of detecting small intestinal lesions in CD remains uncertain.[31,32] The retention of CE still remains a critical problem with patients with CD even if the patency CE can be used. We used the BAE and MR procedures in this study. BAE requires expertized technique and is an invasive examination, but it has an advantage in its ability to assess the mucosa directly and in detail. Additionally, pathological examinations and therapeutic balloon dilatation also can be performed with BAE. The advantage of MR is that the entire intestine can be examined in 1 sitting even in patients who have a penetrating disease and who are at risk with endoscopy. Moreover, MR eliminates the concern about radiation exposure, which is a huge benefit to patients with CD who need long-term follow-up.

The study has some limitations. First, most patients enrolled in this study were in clinical remission, and the results might not reflect findings in all types of patients with CD. Our results are, however, of high clinical value to patients with a mild-to-moderate disease because our data clearly showed that there were deep small intestinal lesions in a number of patients even in clinical remission, and MR and BAE are the most suitable for these types of patients. Patients who had severe symptoms required immediate strong medical therapeutics, hospitalization, or surgical procedures. In contrast, objective and detailed assessment of CD lesions is more important when determining treatment of patients with clinical remission than those with severe disease. Secondary, this was a single-center study, with a limited number of endoscopists and radiologists evaluating the diagnostic examinations. This may have reduced the interobserver variability. A multicenter study is warranted to further confirm our findings.

In conclusion, we adapted the SES-CD and MaRIA scoring system to evaluate deep small intestinal lesions of CD and showed a good correlation between them. An MaRIA score of ≥11 and ≥7 in the small intestine had a high diagnostic accuracy for UL and AML detected by BAE, respectively, confirming the validity of the MaRIA to evaluate active CD lesions in the deep small intestine. These results will be valuable for the development of a new scoring system that includes both the small and large intestine in CD.

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K. Takenaka were involved in drafting the manuscript and collecting and interpreting data; K. Ohtsuka and Y. Kitazume were involved in collecting and interpreting data; M. Nagahori, T. Fujii, E. Saito, and T. Fujioka were involved in collecting data;

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K. Matsuoka and M. Naganuma were involved in revision of the manuscript; and M. Watanabe was involved in study supervision. K. Takenaka, K. Ohtsuka, and Y. Kitazume contributed equally to this study.

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Safety and Efficacy of AJM300, an Oral Antagonist of α4 Integrin, in Induction Therapy for Patients With Active Ulcerative Colitis

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See editorial on page 1669.

BACKGROUND & AIMS: AJM300 is an orally active small-molecule antagonist of the α4 integrin subunit. We performed a randomized trial to investigate the efficacy and safety of AJM300 in patients with active ulcerative colitis (UC). **METHODS:** In a double-blind, placebo-controlled, phase 2a study, 102 patients with moderately active UC (Mayo Clinic scores of 6–10, endoscopic subscores ≥2, and rectal bleeding subscores ≥1) who had inadequate response or intolerance to mesalamine or corticosteroids were randomly assigned to receive AJM300 (960 mg) or placebo 3 times daily for 8 weeks. The primary end point was a clinical response at week 8, defined as a decrease in Mayo Clinic score of at least 3 points and a decrease of at least 30% from baseline, with a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. **RESULTS:** Clinical response rates were 62.7% and 25.5% at week 8 in the AJM300 group and placebo group, respectively (odds ratio [OR] = 5.35; 95% confidence interval [CI]: 2.23–12.82; P = .0002). Rates of clinical remission (Mayo Clinic score ≤2 and no subscore >1) were 23.5% and 3.9% in the AJM300 group and placebo groups, respectively (OR = 7.81; 95% CI: 1.64–37.24; P = .0099), and rates of mucosal healing (endoscopic subscores of 0 or 1) were 58.8% and 29.4% (OR = 4.65; 95% CI: 1.81–11.90; P = .0014). No serious adverse event, including progressive multifocal leukoencephalopathy, was observed, although more investigations are needed to confirm the safety profile of this drug. **CONCLUSIONS:** AJM300 was well tolerated and more effective than placebo in inducing clinical response, clinical remission, and mucosal healing in patients with moderately active UC. ClinicalTrials.jp no: JapicCTI-132293.

Keywords: Integrin; IBD; Randomized Clinical Trial; Lymphocyte Trafficking.

Inflammatory bowel disease (IBD)—the main forms of which are Crohn's disease and ulcerative colitis (UC)—is a chronic inflammatory disease of the gastrointestinal tract. Although the cause of the disease remains unknown, the infiltration of lymphocytes into the lamina propria at the sites of inflammation is a well-documented pathogenic mechanism of IBD.[1,2] Infiltration of lymphocytes is accelerated by increased expression of adhesion molecules, such as vascular cell adhesion molecule-1 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the surface of endothelial cells at the site of inflammatory lesions.[3,4] The binding of lymphocytes to vascular cell adhesion molecule-1 or MAdCAM-1 requires the expression of α4β1 or α4β7 integrin on lymphocytes, respectively. Vascular cell adhesion molecule-1 is expressed on the luminal surface of endothelium in numerous types of tissues, and MAdCAM-1 is expressed predominantly in the intestinal lamina propria.[4,5]

Several clinical studies have demonstrated that α4 integrin blockade is clinically effective as a therapeutic approach for IBD, for example, anti-α4 integrin antibody, natalizumab,[6,7] or anti-α4 β7 integrin antibody, vedolizumab.[8,9] Furthermore, anti-β7 integrin antibody, etrolizumab,[10] and anti–MAdCAM-1 antibodies[11] are being developed for the treatment of IBD. However, all the agents are biologics and raise some concerns regarding the long-term administration. Adverse effects specifically related to biologics have been observed in the treatment with anti-tumor necrosis factor–α (TNFα) antibodies,[12] such as immunogenicity, infusion reaction, and the loss of efficacy related to the production of antidrug antibodies. Therefore, the development of orally active chemical medicine is a reasonable and preferable approach. Although several small-molecule α4 integrin antagonists have been studied in clinical trials for the treatment of asthma and multiple sclerosis,[13–15] there are no reports on the efficacy of oral α4 integrin antagonist in patients with IBD.

*Authors share co-first authorship.

Abbreviations used in this paper: CI, confidence interval; IBD, inflammatory bowel disease; JCV, John Cunningham virus; MAdCAM-1, mucosal addressin cell adhesion molecule-1; OR, odds ratio; PML, progressive multifocal leukoencephalopathy; TNF, tumor necrosis factor; UC, ulcerative colitis.

Most current article

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AJM300 is a novel, orally active, small-molecule α4 integrin antagonist that is classified as a phenylalanine derivative[16] and is currently being developed for IBD.[17,18] In animal models, an oral treatment with AJM300 inhibited the lymphocyte from homing to the gut, and prevented the development of experimental colitis in mice.[19] Orally administrated AJM300 can be absorbed through the intestine, distributed to various tissues through systemic blood circulation, and excreted mainly into the feces. The pharmacodynamics of α4 integrin antagonist are well known to increase the peripheral lymphocyte counts, probably due to inhibition of lymphocyte attachment to the vascular endothelium. For AJM300, the increase in peripheral lymphocyte counts was maintained throughout the day at a 960-mg dosage, but not at a 480-mg dosage, 3 times daily in healthy volunteers.

Progressive multifocal leukoencephalopathy (PML) is a side effect of anti-α4 integrin therapy. PML is an opportunistic brain infection that is caused by the John Cunningham virus (JCV), and usually leads to death or severe disability. Natalizumab is currently available through a special restricted distribution program to mitigate the risk of PML in clinical practice. The clinical development of oral α4 integrin antagonists also needs to minimize the potential risk of PML carefully. Therefore, we designed the 8-week, placebo-controlled trial to investigate the efficacy and safety of AJM300 as remission induction therapy in patients with moderately active UC, under the study protocol to mitigate the potential risk of PML.

Methods

Ethics Statement

The study was approved by the Institutional Review Board at each center and conducted in accordance with the Good Clinical Practice, other relevant rules and regulations, and Helsinki declaration. All patients provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Study Design and Patients

This was a randomized, double-blind, placebo-controlled, phase 2a study, conducted at 42 medical centers in Japan between May 2012 and July 2013 (ClinicalTrials.jp number: JapicCTI-132293). This study was conducted to obtain information on the efficacy and safety profile of AJM300 as induction therapy in patients with moderately active UC. The target number was 60 patients per group, 120 in total.

Eligible patients were 20 to 65 years of age with a diagnosis of moderately active UC, with the Mayo Clinic score[20] of 6–10, a rectal bleeding subscore of 1 or higher, and an endoscopic subscore of 2 or higher. Additional inclusion criteria were documentation of inadequate response or intolerance to mesalamine (4.0 g or higher of salazosulfapyridine, 4.0 g Pentasa, or 3.6 g Asacol per day) and/or corticosteroids (30–40 mg of oral prednisolone or the equivalent per day). Patients continued to take mesalamine at a constant dose for at least 4 weeks or prednisolone for at least 2 weeks before enrollment. Although concomitant oral mesalamine was administrated at a constant dose throughout the study, concomitant corticosteroid dose was allowed to taper within 5 mg per 2 weeks, according to a predefined regimen for patients showing any clinical response to the study drug. Patients were ineligible if they had received azathioprine or 6-mercaptopurine within 8 weeks before enrollment, or TNF antagonists, cyclosporine, tacrolimus, or methotrexate within 12 weeks before enrollment. Rectal therapy with mesalamine or corticosteroids, as well as leukocytapheresis, was discontinued 4 weeks before enrollment. Other criteria for exclusion included proctitis, corticosteroid dependence, severe colonic stricture, infectious enteritis, a history of bowel surgery, major organ dysfunction, malignant neoplasm, drug hypersensitivity or dependence, alcoholism, psychiatric symptom, pregnancy or lactation, and a white blood-cell count $\leq 3.0 \times 10^3/\mu L$, concomitant use of immunosuppressants (eg, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, or tacrolimus), and the presence of neurologic symptoms (eg, motor paralysis, impaired vision, alogia, symptoms of dementia, and facial nerve palsy) for an increased potential risk of PML.

Randomization and Blinding

Patients were randomized to the active treatment group or placebo group in a 1:1 ratio by dynamic balancing allocation with minimization method based on the strata of the inadequate response or intolerance to mesalamine and/or corticosteroids and the baseline Mayo Clinic score (6–7 or 8–10). Randomization was performed centrally. Patients, assessing physicians, and the funder were blinded to the assignment of treatment throughout the study.

Study Procedures

Patients were assigned to receive either AJM300 960 mg or placebo 3 times daily for 8 weeks. The dose regimen of AJM300 was determined according to the following data from the phase 1 multiple oral dose study (data not shown). For pharmacokinetics, although the drug exposure (maximum serum concentration and area under the concentration-time curve) was mostly saturated at the $\geq$480 mg 3 times daily dosage, the trough drug concentration in plasma was higher with the 960 mg 3 times daily dosage than the 480 mg 3 times daily dosage. In addition, the pharmacologic activity of AJM300 (surrogated by the increase in peripheral lymphocyte count) was maintained throughout the day at the 960 mg 3 times daily dosage, but not at the 480 mg 3 times daily dosage.

The patients visited at weeks 0, 2, 4, and 8. At each visit, a partial Mayo Clinic score (excluding endoscopic subscore) was calculated, adverse events were noted, and neurologic symptom questionnaires were administrated. Blood samples for hematologic testing were obtained at each visit. The peripheral lymphocyte counts at weeks 0, 2, 4, and 8 was measured as the pharmacodynamics parameter, and neutrophil counts were assessed to investigate the effect on leukocytes lacking α4 integrin. At week 8 only, administration of AJM300 or placebo was terminated in the morning on the day before the last visit, for the purpose of confirmation of the recovery of pharmacodynamics. Pharmacokinetics measurement was not performed in this study.

Colonoscopy or sigmoidscopy was performed at baseline and week 8 with biopsy. Endoscopic subscores were assessed primarily by the on-site investigators. The central evaluation committee for colonoscopy was established to assure the reliability of the assessment by the on-site investigators.

End Points

The primary end point was a clinical response, defined as a decrease in the Mayo Clinic score of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1. The main secondary end points were clinical remission, defined as a Mayo Clinic score of 2 or lower and no subscore higher than 1 and mucosal healing, defined as an endoscopic subscore of 0 or 1, and partial Mayo Clinic score. The endoscopic subscores assessed by the on-site investigators (investigator or subinvestigator) were applied to the Mayo Clinic score. The on-site investigators evaluated and determined the most severely affected site up to the sigmoid colon from the anus at week 0, and evaluated the same site at week 8. In addition, the endoscopic subscores were also evaluated by the central evaluation committee for endoscopic evaluation to assure the reliability of the evaluation by the on-site investigators. The on-site investigators collected 2 biopsy specimens of colonic mucosal tissue in the marginal region of the most severely affected site during colonoscopy at week 0 and in the same region at week 8. Histologic activity was evaluated using the Riley score[21] by the central evaluation committee for histopathologic evaluation.

Safety evaluations, which included all reports of adverse events and clinical laboratory tests, were conducted throughout the study. The investigators and the sponsor were not informed of the patients' differential counts of white blood cells, so that the increase in circulating lymphocyte counts observed in the active treatment group would not lead to unblinding of the treatment assignments.

For all patients, new occurrence of neurologic signs and symptoms potentially consistent with PML were assessed cautiously throughout the study using the standardized questionnaires. If PML-related signs or symptoms were suspected, administration of the study drug was immediately terminated. Neurologic examination using magnetic resonance imaging scans and polymerase chain reaction analyses was available as necessary. An independent safety assessment committee consisting of a panel of PML experts was organized to secure the patient's safety against the onset of PML and to provide a further guidance for the on-site investigators and the sponsor.

Statistical Analysis

The full analysis set, which consisted of all patients who were randomized, received at least 1 dose of study drug, and had at least 1 available efficacy data point, was used for the analysis of efficacy. The safety analysis set, which consisted of all patients who were randomized and received at least 1 dose of study drug, was used for the analysis of safety. The last observation carried forward method was used for statistical analyses on the efficacy variables to handle of the missing data, especially for withdrawal. On the other hand, for the safety variables, the imputation methods were not used. The primary end point was analyzed by the logistic regression model after adjustment for inadequate response or intolerance to mesalamine and/or corticosteroids, and baseline Mayo Clinic score (6–7 or 8–10) to compare the clinical response between the treatment groups. Additionally, the proportion of patients who had good clinical response in each treatment group and its difference between the treatment groups were calculated. The secondary end point, clinical remission, was analyzed by the logistic regression model after adjustment for the baseline Mayo Clinic score (6–7 or 8–10). Mucosal healing was analyzed by logistic regression model, after adjustment for the inadequate response or intolerance to mesalamine and/or corticosteroids and baseline Mayo Clinic score (6–7 or 8–10). The proportions of patients in clinical remission and patients with mucosal healing were calculated by treatment group. Summary statistics of the change from baseline in the partial Mayo Clinic score and the peripheral lymphocyte counts at each evaluation time were calculated by treatment group. A t test was used to compare the change in the partial Mayo Clinic scores and the peripheral lymphocyte counts between the 2 treatment groups. For evaluating safety, the adverse events were tabulated by treatment group. All statistical tests were conducted at the .05 level of significance (2-sided). No adjustment was made for multiple comparisons.

The determination of sample size was based on the following calculations. The clinical response rate was estimated to be 54.8% to 66.0% for the active treatment group, and 33.0% to 35.6% for the placebo group. The number of subjects required to provide power of 80% with 2-sided significance level of 5% was computed.

Results

Randomization and Baseline Characteristics

Of 127 patients that gave informed consent, 3 patients withdrew from the study before randomization. After excluding 22 patients who did not meet inclusion criteria or met exclusion criteria, 102 patients underwent randomization. Those patients were randomly assigned to receive the active treatment (AJM300) or placebo (51 patients for each) (Figure 1). Study treatment was started in all 102 patients. The full analysis set was equivalent to the safety analysis set. Demographics and baseline characteristics were similar between the placebo and active treatment groups (Table 1). In the 102 randomized patients, the therapeutic outcomes of the current relapse were an inadequate response to mesalamine (n = 92 [90.2%]), intolerance to mesalamine (n = 3 [2.9%], inadequate response to corticosteroid (n = 3 [2.9%]), and intolerance to corticosteroids (n = 4 [3.9%]).

Efficacy

A total of 32 of 51 patients receiving the active treatment (62.7%) and 13 of 51 patients receiving placebo (25.5%) had a clinical response at week 8 (OR = 5.35; 95% CI: 2.23–12.82; logistic regression, P = .0002) (Figure 2). A total of 12 patients receiving the active treatment (23.5%) and 2 receiving placebo (3.9%) had clinical remission (OR = 7.81; 95% CI: 1.64–37.24; logistic regression; P = .0099). Proportions of patients with mucosal healing were 58.8% (30 of 51 patients) with the active treatment and 29.4% (15 of 51 patients) with placebo (OR = 4.65; 95% CI: 1.81–11.90; logistic regression, P = .0014) (Figure 2). The efficacy of the active treatment was generally consistent across subgroups (Supplementary Figure 1).

The proportion of patients achieving endoscopic subscore of 0 at week 8 was also higher in the active treatment group than that in the placebo group, although the

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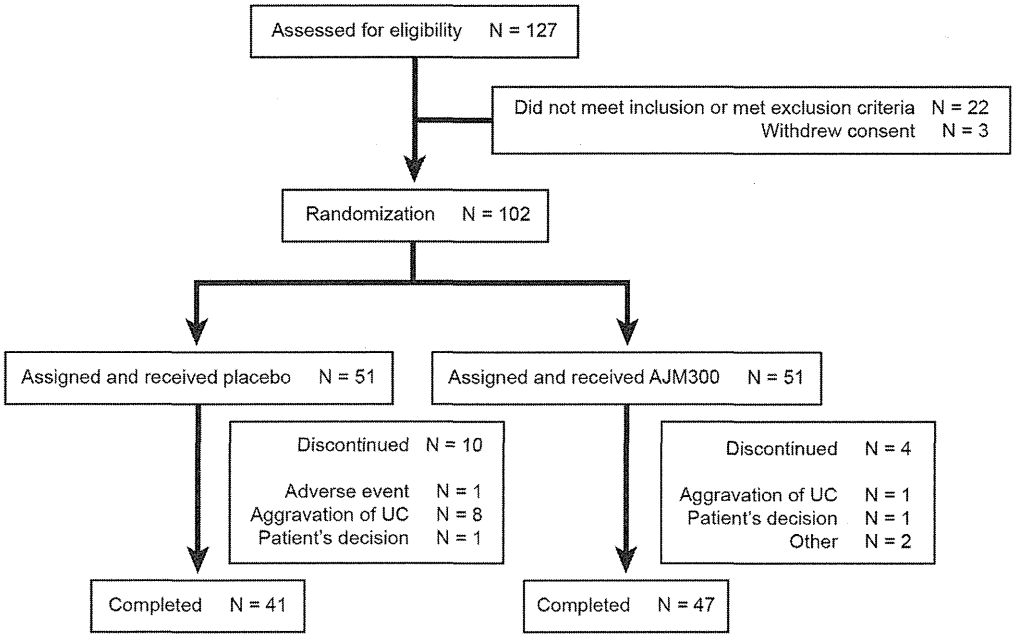

Figure 1. Enrollment and treatment. In the study, a total of 102 patients with ulcerative colitis were randomly assigned to receive placebo (n = 51) or AJM300 (n = 51).

difference was not statistically significant (15.7% vs 5.9% in the active treatment group and placebo group, respectively; difference, 9.8; 95% CI: −2.7 to 22.7). The significant efficacies of the active treatment (clinical response, clinical remission, and mucosal healing) were also confirmed by the assessment of the central evaluation committee for endoscopic evaluation as well (data not shown). Consistency of the endoscopic subscores between the on-site investigators and the central evaluation committee was 64% at baseline and 59% for outcome measures.

Table 1. Demographics and Baseline Characteristics

Characteristic	Placebo (n = 51)	AJM300 (n = 51)	Total (n = 102)
Age, *y*	42.6 ± 13.4	41.7 ± 11.4	42.2 ± 12.4
Male sex, n (%)	26 (51.0)	31 (60.8)	57 (55.9)
Body weight, *kg*	60.7 ± 12.0	62.0 ± 11.3	61.4 ± 11.6
Current smoker, n (%)	3 (5.9)	4 (7.8)	7 (6.9)
Duration of disease, *y*	9.3 ± 8.9	8.6 ± 9.2	9.0 ± 9.0
C-reactive protein, *mg/dL*	0.60 ± 1.16	0.50 ± 0.82	0.55 ± 1.00
Disease extent, n (%)			
Left sided	31 (60.8)	29 (56.9)	60 (58.8)
Pancolitis or extensive	20 (39.2)	22 (43.1)	42 (41.2)
Mayo Clinic score[a]	7.7 ± 1.2	7.8 ± 1.2	7.8 ± 1.2
Score 6–7, n (%)	22 (43.1)	20 (39.2)	42 (41.2)
Score 8–10, n (%)	29 (56.9)	31 (60.8)	60 (58.8)
Components of Mayo Clinic score[a]			
Stool frequency subscore	2.0 ± 0.8	2.1 ± 0.8	2.1 ± 0.8
Rectal bleeding subscore	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.6
Endoscopic subscore	2.2 ± 0.4	2.1 ± 0.3	2.1 ± 0.4
Physician's global assessment subscore	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
Riley score[b]	11.8 ± 3.3	11.8 ± 2.8	11.8 ± 3.0
Response to treatment of current relapse, n (%)			
Inadequate response to mesalamine	46 (90.2)	46 (90.2)	92 (90.2)
Intolerance to mesalamine	1 (2.0)	2 (3.9)	3 (2.9)
Inadequate response to corticosteroids	1 (2.0)	2 (3.9)	3 (2.9)
Intolerance to corticosteroids	3 (5.9)	1 (2.0)	4 (3.9)

NOTE. Values are mean ± SD unless indicated otherwise.
[a]The Mayo Clinic score ranges from 0 to 12, with higher scores indicating more severe disease. Each subscore ranges from 0 to 3.
[b]The Riley score ranges from 0 to 18, with higher scores indicating more severe disease.