demonstrated the therapeutic effect of infliximab in CD.[8–12] Based on the results of the ACCENT I study, 5 mg/kg of infliximab at 8-week intervals is considered the standard therapy for maintenance of remission of CD.[10] In clinical practice, we have often encountered patients in whom the therapeutic effect did not persist for 8 weeks. In these cases the dose should be escalated or the interval shortened.[13] However, no clinical study has yet examined the efficacy of the recommended treatment, and the ACCENT I study only clarified the efficacy of episodic administration with increased dosing at the time of loss of response.

In the current study, 5 mg/kg infliximab was administered as standard therapy to active CD patients at 8-week intervals. Patients showing loss of response continued infliximab by shortening the dosing interval to 4 weeks. We aimed to assess whether this treatment strategy is useful for maintaining remission in CD and investigated the association between the clinical efficacy of infliximab and its serum trough level.

PATIENTS AND METHODS

Patients

This multicenter, open-label, controlled study was conducted at 18 institutions from July 2004 until May 2006. The protocol was approved by each Institutional Review Board and the study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice. Prior to registration, written informed consent was obtained from all patients.

Patients included in the study had CD for more than 6 months, with a score of Crohn's Disease Activity Index (CDAI) between 220 and 400, despite conventional treatments. Exclusion criteria were: 1) age ≤15 years; 2) marked stenosis of the bowel, short bowel syndrome, ostomy, abscess, or marked internal fistula; 3) previous treatment with any biologic targeting TNF-α; 4) use of parenteral nutrition, total enteral nutrition, or cyclosporine/tacrolimus/corticosteroids (intravenous) within 4 weeks before the start of the observation period; 5) leukocytapheresis within 3 months before the start of the observation period; 6) serious/opportunistic infection, tuberculosis, active hepatitis B/C, and human immunodeficiency virus (HIV) infection within 6 months before the start of the observation period, and chronic infectious disease of any kind.

Combination of nutritional and/or drug therapies at a stable dose were allowed as follows: 1) azathioprine/mercaptopurine had to be started at least 16 weeks before and maintained at a stable dose from 8 weeks before the start of the observation period; 2) corticosteroids and 5-aminosalicylates had to be started at least 8 weeks before and maintained at a stable dose from 4 weeks before the start of the observation period; 3) enteral nutrition therapy (elemental diet/nutritional supplement) had to be maintained at a stable dose from 4 weeks before the start of the observation period; and 4) metronidazole and ciprofloxacin had to be maintained at a stable dose from 2 weeks before the start of the observation period. The doses of corticosteroids, metronidazole, and ciprofloxacin could be decreased or discontinued.

Study Design

Patients were screened for eligibility 2 weeks before enrolment. Patients who met the inclusion criteria were enrolled and received 5 mg/kg intravenous infusion of infliximab at weeks 0, 2, and 6. Responders were defined as those who achieved at least a 25% reduction and a decrease of 70 points or more from the baseline CDAI score on at least one occasion, and subsequently not ever meeting the below loss of response criteria during the initial 10 weeks. Responders received 5 mg/kg of infliximab at 8-week intervals until week 46. For those who met the criteria for dosing interval switching at weeks 14, 22, 30, 38, or 46, 5 mg/kg infliximab was administered at 4-week intervals from that point until week 50. Loss of response was defined as follows: 1) patients with a CDAI score of at least 175, a CDAI score increase of 35% or more, and a CDAI score increase of 70 points or more in comparison with the CDAI score that fulfilled the clinical response criteria for the first time, and patients who met these conditions again at least once on the succeeding two evaluation days; 2) those in whom a contraindicated medication was newly used or the dose of medications used for CD was increased; 3) those who underwent surgery for CD; and 4) those who discontinued the study because of insufficient efficacy. In patients who met criterion (1), the point at which they initially met the criterion was regarded as the time to loss of response, and thereafter they were given infliximab at 4-week interval. In those meeting criteria (2–4), the earliest point was regarded as the time to loss of response, infliximab was discontinued, and alternative treatment was chosen. Patients with no response by week 10 were regarded as dropouts and subjected to alternative treatments.

Outcome Measures

CDAI was assessed at weeks 0, 2, and 6, and then at 4-week intervals until week 54. The IBD Questionnaire (IBDQ) and the number of draining fistulas were assessed at weeks 0, 10, 30, and 54.

Adverse events were ascertained until week 54 (in those who discontinued: 12 weeks after the final administration). An infusion reaction was defined as any adverse event that occurred during or within 2 hours after the infusion.

To assess the serum levels of infliximab, blood samples were obtained before each infusion at weeks 0, 2, and 6, and then every 4 weeks until week 54. The serum infliximab concentration was measured by enzyme-linked immunosorbent assay using anti-infliximab monoclonal antibody (Centocor Ortho Biotech, Horsham, PA) at Mitsubishi Tanabe Pharma (Osaka, Japan). The minimum detectable infliximab concentration was 0.1 μg/mL. The association between clinical efficacy and serum trough level of infliximab was analyzed in patients in whom both results were obtained at week 14.

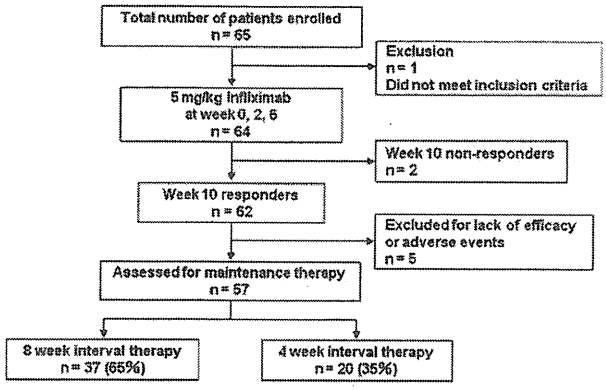

FIGURE 1. Flow chart of patients enrolled in the study.

Statistical Analysis

Efficacy was assessed in the full analysis set by the last observation carried forward approach. Patients who did not receive infliximab after week 14 were excluded from analysis. Analysis was done on an intention-to-treat basis.

The primary endpoints were the proportion of patients showing a clinical response (reduction in CDAI of 25% or more and 70 points or more from baseline) and remission (CDAI: less than 150 points) at week 54 in the week 10 responder group. These data were expressed as values with 95% confidence intervals (CI). The secondary endpoints were the proportion of patients showing a clinical response and remission at each point, the time to loss of response, the median IBDQ score, the doses and withdrawal rates of oral corticosteroids, and the number of draining fistulas. Fisher's exact test was used for the analysis between the proportion of patients showing clinical response and remission in the 8- and 4-week interval therapy group.

The duration of efficacy was expressed as the cumulative sustained efficacy rate and the median time to loss of response, which was calculated by the life table analysis system using the week in which a clinical response was initially observed as the starting point. When the cumulative sustained efficacy rate exceeded 0.5 after week 52, it was impossible to estimate the median time to loss of response; therefore, it was considered 52 weeks or more.

Regarding oral corticosteroids, the mean dose for 7 days prior to the date of evaluation was measured, and the point at which it reached 0 mg was regarded as the discontinuation point. The dosages of corticosteroids are expressed as mean ± standard error of the mean (SEM) and were compared with that at baseline using the Wilcoxon signed rank test. The proportions of patients with a closure of 50% or more or a closure of 100% of draining fistulas observed during the observation period were defined as the fistula response or complete fistula closure rates.

Correlation between clinical responses and serum trough level of infliximab was analyzed by Spearman's rank correlation coefficient using the data collected at week 14, so that it could be assessed 8 weeks after the previous dosing in all subjects. In patients who were switched to a 4-week interval, the median serum trough level at each point was calculated, considering the time of interval switching as baseline.

Patients who received at least one dose of infliximab were assessed in the safety analysis. Incidences of adverse events between the 8- and 4-week interval group were compared. The former group included one patient who met the criteria for interval switching, but did not undergo any subsequent treatment.

RESULTS

Patients

Of the 65 patients enrolled, 64 received 5 mg/kg of infliximab at weeks 0, 2, and 6 (Fig. 1). One patient did not meet the inclusion criteria and was excluded. The characteristics of the patients are shown in Table 1.

Of the 62 that met the response criteria during the initial 10 weeks, 57 received infliximab after week 14 as maintenance therapy and five withdrew from the study because of insufficient efficacy or adverse events. Thirty-seven patients completed the study at 8-week intervals. In 20, the interval was switched to 4 weeks, thus demonstrating an annual switching rate of ≈35%. Treatment was switched at weeks 14, 22, 30, and 38, in 10 (50%), 5 (25%), 4 (20%), and 1 (5%) patient, respectively, indicating that shortening the interval occurred at an early stage.

Efficacy

The overall clinical response and remission rates of both groups (95% CI) at week 14 were 84.2% (72.1–92.5)

TABLE 1. Baseline Patient Characteristics (n = 64)

Gender (male: female)	49: 15
Age (years), median (IQR)	29.0 (24.5–36.0)
Disease duration (years), median (range)	5.8 (0.5–27.0)
Disease location (ileum: colon: ileocolonic)	14: 15: 35
Patients with previous surgery for Crohn's disease, n (%)	31 (48.4)
Resection: stricturoplasty	23: 8
Smoker, n (%)	21 (32.8)
Patients with concomitant medication, n (%)	
Corticosteroids	21 (32.8)
5-Aminosalicylates	62 (96.9)
Immunomodulators	10 (15.6)
Metronidazole/ciprofloxacin	12 (18.8)
Enteral nutrition	40 (62.5)
Crohn's Disease Activity Index, median (IQR)	285.0 (249.0–337.0)
Inflammatory Bowel Disease Questionnaire, median (IQR)	146.5 (129.5–163.5)
Draining fistulas (none: 1: 2: 3 or more)	56: 4: 3: 1
C-reactive protein (mg/dLl), median (IQR)	1.7 (0.7–4.3)

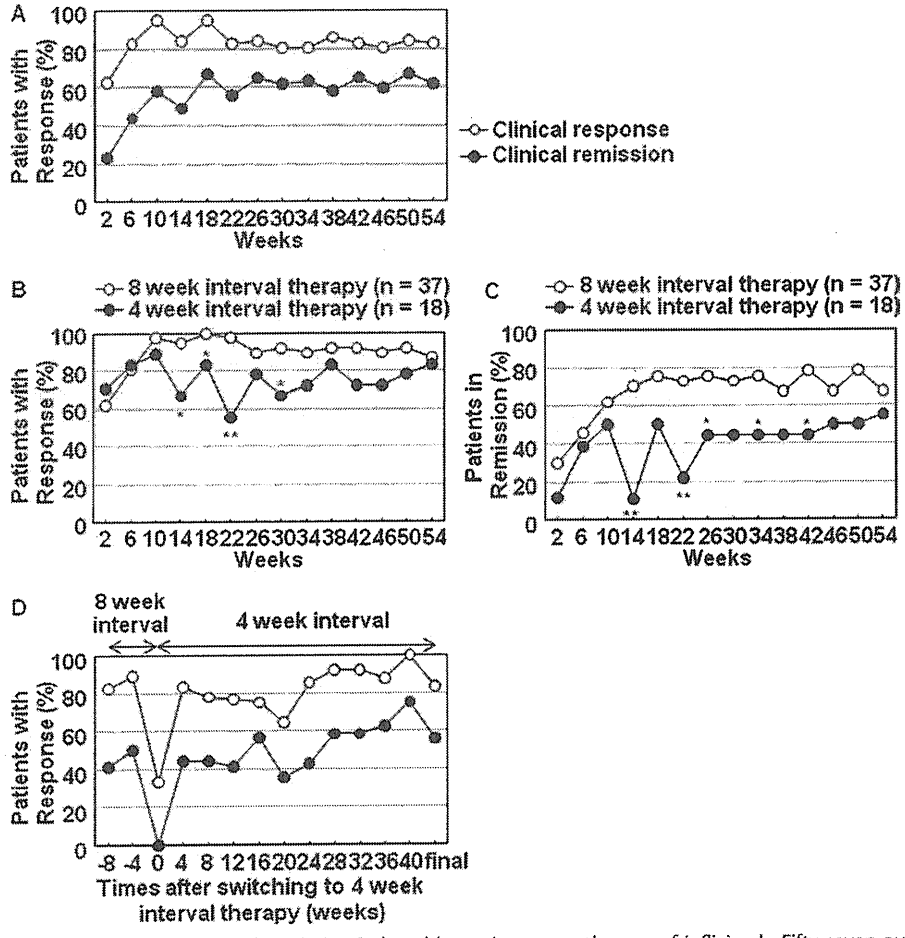

FIGURE 2. Time courses of clinical response and remission induced by maintenance therapy of infliximab. Fifty-seven out of 62 week-10 responders completed the study, at either 8- or 4-week intervals. (A) Time courses of clinical response and remission in the overall group. The overall clinical response and remission rates of both groups (95% CI) at week 14 were 84.2% (72.1–92.5) and 49.1% (35.6–62.7), respectively. At week 54 they were 82.5% (70.1–91.3) and 61.4% (47.6–74.0), respectively, similar to those at week 14. (B,C) Time courses of clinical response (B) and remission (C) for 8- and 4-week interval therapy group. Thirty-seven patients completed the study with infusions at 8-week intervals and 18 patients required switching to a 4-week interval. *$P < 0.05$, **$P < 0.01$ (8-week vs. 4-week interval therapy, calculated by Fisher exact test). (D) Clinical efficacy of infliximab in patients switched to 4-week interval therapy. Of the 18 patients, clinical response was achieved in 15 (83.3%) and clinical remission in 10 (55.6%) at 54 weeks.

and 49.1% (35.6–62.7), respectively. At week 54 they were 82.5% (70.1–91.3) and 61.4% (47.6–74.0), respectively, similar to those at week 14 (Fig. 2A). This suggests that the clinical responses and remissions obtained by week 14 could be sustained over 1 year, confirming the usefulness of the standard regimen and, furthermore, the option of shortening the dosing interval to 4 weeks in patients who have lost response.

When comparing the clinical response and remission rates in the 8- and 4-week interval therapy groups, the efficacy was also sustained after week 14 in the former and clinical response and remission rates were 86.5% (32/37) and 67.6% (25/37), respectively (Fig. 2B). On the other hand, in the latter these rates decreased transiently between 14 to 30 weeks, but recovered to almost similar levels to the former at week 54 (Fig. 2C).

Figure 2D shows the clinical response and remission rates of patients in the 4-week interval therapy group, considering the switching point to 4-week interval as the starting point. Of the 20 patients who were switched to 4-week interval, two were excluded due to lack of sufficient data at some timepoint during the study. At the switching point, the clinical response and remission rates were 33.3% (6/18) and 0% (0/18), respectively. Treatment at the 4-week interval resulted in clinical response and remission rates of 83.3% (15/18) and 55.6% (10/18), respectively, at week 54. This suggests that shortening the dosing interval to 4 weeks could retrieve clinical response and remission.

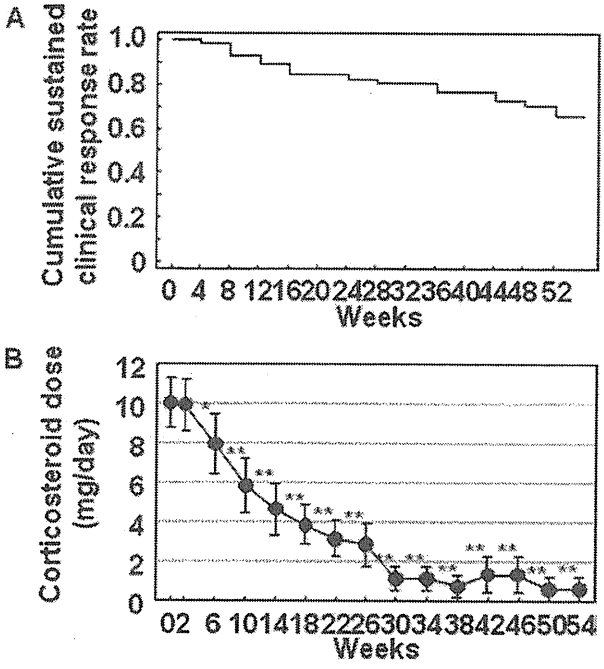

FIGURE 3. (A) Effect of infliximab on sustained clinical response. The median duration of efficacy in the overall 57 patients using life table analysis was 52 weeks or more. (B) Changes in the mean daily oral corticosteroid dose. Data are shown as the means ± SEM of prednisolone of the 18 patients who were taking oral corticosteroids at baseline. Statistical differences as compared with dosage at baseline were calculated by the Wilcoxon signed rank test (*P < 0.05, **P < 0.01).

The median duration of efficacy was 52 weeks or more (Fig. 3A), suggesting that the efficacy of infliximab could be sustained over a year.

The median IBDQ score at week 0 was 152, and this increased to 180 at week 10, showing early improvement in the quality of life (QOL) (data not shown). At weeks 30 and 54 the median IBDQ scores were 185 and 180, respectively. This suggests that maintenance treatment with infliximab sustains improvement in QOL over a period of 1 year.

Corticosteroids were administered to 18 patients (31.6%) at baseline. Changes in the doses of corticosteroids, which were converted to prednisolone, in these patients are shown in Figure 3B. The mean values of doses at weeks 0, 10, 30, and 50 were 10.0, 5.8, 1.1, and 0.6 mg, respectively. Maintenance infliximab sequentially increased the number of patients achieving withdrawal from corticosteroids to 72.2% (13/18) at week 54.

The numbers of draining fistulas before the study were as follows: 1 in 4 patients, 2 in 3, and 4 in 1. The fistula response rates at weeks 10 and 54 were 62.5% (5/8) and 75.0% (6/8), respectively, and complete closure of fistulas were obtained in 50.0% (4/8) and 62.5% (5/8), respectively (data not shown).

Relationship Between Efficacy and Serum Infliximab Concentration

The median serum trough levels of infliximab at week 14 were 0.80 μg/mL in 9 patients with no response, 1.10 μg/mL in 19 patients with a clinical response (not in remission), and 3.40 μg/mL in 29 patients in remission, respectively, thus showing a significant correlation (P < 0.01, overall; Fig. 4A). Of the patients whose serum trough level of infliximab was below its detection limit (0.1 μg/mL), 33% were nonresponders and no patient achieved clinical remission (Fig. 4B). On the other hand, the number of patients showing a clinical response/remission increased depending on the serum trough level. Of the patients with a serum trough level of 5 μg/mL or more, clinical response/remission was observed in 89%, thus showing a significant correlation between the clinical efficacy and serum trough level (P < 0.05, overall).

Figure 4C shows the serum trough level of infliximab in those patients in whom the dosing interval was switched to 4 weeks, considering the time of switching as the starting point. The clinical response and remission rates at the time of switching were 33.3% (6/18) and 0% (0/18), respectively, and the median serum trough level was 0.8 μg/mL. Administration at 4-week intervals increased both the clinical response and remission rates, and the serum trough levels to the range of 4.9–8.9 μg/mL. In patients receiving maintenance therapy at 8-week intervals, the efficacy also persisted after week 14, and the median serum trough levels 8 weeks after each dosing until week 54 ranged between 2.0–3.1 μg/mL.

Safety

All 64 patients treated with infliximab were included in the safety evaluation. The rate of patients experiencing at least one adverse event, including any minor ones, during the 54-week study period was 63/64 (98.4%) (Table 2). The incidence of serious adverse events was 18.8%. The most frequent serious adverse event was exacerbation of CD, occurring in 12.5%. No patient showed any fatal adverse reaction.

The incidences of adverse events and infections were similar between the patients receiving 8- and 4-week interval therapy. The incidence of serious adverse reactions in the latter was slightly higher than that in the former. In the latter, infection developed in two patients (tonsillitis: one, venereal wart: one). Tonsillitis resolved with antibiotic treatment without the discontinuation of infliximab. Venereal wart appeared after 14 weeks of the study. Administration of infliximab was continued but resection was selected and, after all, infliximab therapy was discontinued.

DISCUSSION

The current study assessed the efficacy and safety of the standard maintenance therapy of infliximab at 5 mg/kg every 8 weeks, and the option of shortening the interval to

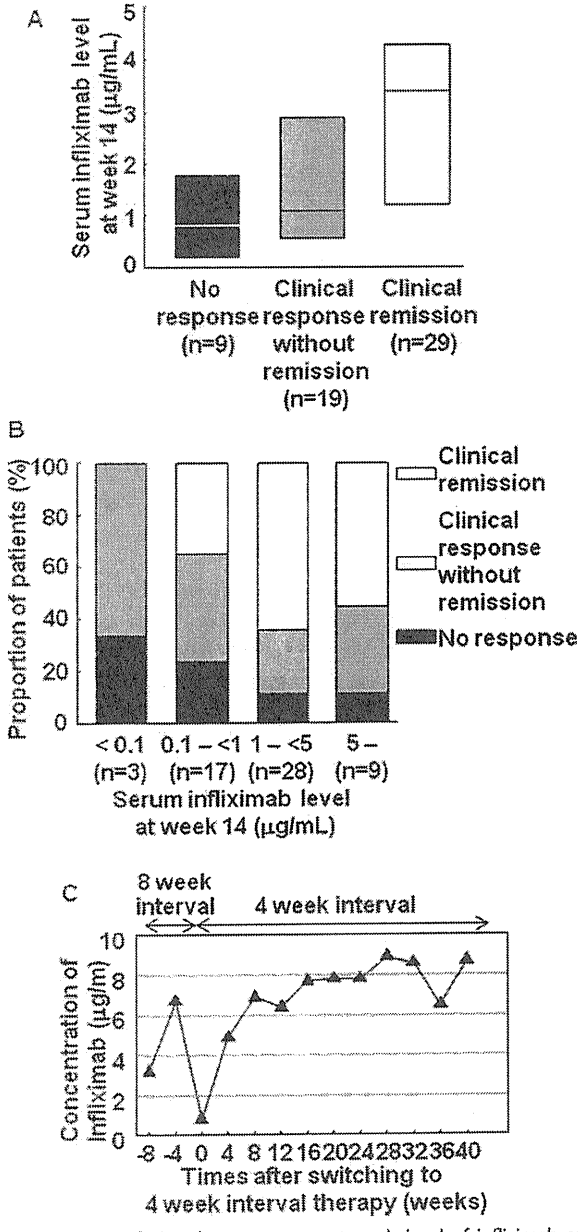

FIGURE 4. Correlation between serum trough level of infliximab and clinical efficacy. (A) Serum trough level of infliximab according to the clinical efficacy at week 14. Results are shown as median (IQR). Significant correlation between serum trough level and efficacy was seen ($P < 0.01$, overall). (B) Proportion of patients in clinical remission, clinical response without remission, and no response at different trough levels. In patients with a serum trough level below its detection limit (0.1 μg/mL), 33% were nonresponders and no patient achieved clinical remission. In those with a serum trough level of 5 μg/mL or more, no response was observed in 11%, whereas clinical response without remission was observed in 33% and clinical remission was achieved in 56%. There was a significant correlation between the clinical efficacy and serum trough level ($P < 0.05$, overall). (C) Changes in the median serum trough level of infliximab in patients switched to a 4-week interval. The serum trough level of infliximab increased compared to the timepoint of switching (week 0 on graph) after switching to a 4-week interval.

4 weeks in patients who have lost response in CD. We have shown that patients who have lost response to the standard regimen will recover response when their infusion interval was shortened to 4 weeks. This was accompanied by an increase in the serum trough level of infliximab and the threshold of its clinical efficacy was ≈1 μg/mL.

The clinical response and remission rates after 54 weeks were 82.5% and 61.4%, respectively, in the whole treatment group. In ACCENT I, they were 43% and 28%, respectively, for patients treated with 5 mg/kg infliximab.[10] The duration of efficacy was >52 weeks in our study and 38 weeks in ACCENT I. The two studies cannot be compared directly; however, our results suggest that the treatment strategy including administration at a 4-week interval will result in reachieving response.

Few studies have investigated the association between the efficacies of infliximab in CD with its serum trough level. Maser et al[14] reported that remission and endoscopic improvement were achieved in CD patients in whom the serum trough level was maintained at a higher level. Afif et al[15] assessed the usefulness of measuring infliximab and human antichimeric antibody concentrations in patients with inflammatory bowel disease, in a retrospective fashion, and showed that in those with subtherapeutic infliximab concentrations, dose escalation was associated with complete or partial clinical response in more than 80% of patients. They also demonstrated that concurrent immunosuppressive therapy was significantly associated with therapeutic infliximab concentrations. In the current study we showed that the efficacy of infliximab correlated with its serum trough level. The median serum trough levels in patients with a clinical response and in nonresponders were 1.10 and 0.80 μg/mL, respectively. In addition, the trough level at the time of switching was 0.80 μg/mL in patients in whom the interval was shortened. These findings suggest that the threshold of trough levels of infliximab to obtain clinical efficacy is ≈1 μg/mL. Loss of response was possibly due to insufficient serum trough levels, and shortening the interval increased the serum trough levels leading to sustained effect. Studies in rheumatoid arthritis indicated that more potent effects were achieved at a higher serum trough levels and that the threshold of the clinical responses was 1 μg/mL,[16,17] similar to our study. In our study the concurrent use of immunomodulators showed trends toward increased time until loss of response, higher trough levels at week 14, and more likelihood to maintain clinical response with 8-week interval treatment (data not shown). None of these were significantly different when compared to patients not on immunomodulators, which may have been due to the relatively small number of patients included in our study, eight on concurrent and 49 on no immunomodulators. The concurrent use of steroids also showed a trend toward higher trough levels at

TABLE 2. Summary of Safety Data

Patients Involved in Maintenance Treatment	All Patients	Total Patients	8 Week Interval	4 Week Interval
Patients, *n*	64	57	38	19
Adverse events, *n* (%)	63 (98.4)	56 (98.2)	37 (97.4)	19 (100.0)
Infections, *n* (%)	49 (76.6)	43 (75.4)	29 (76.3)	14 (73.7)
Infusion reactions, *n* (%)	9 (14.1)	8 (14.0)	6 (15.8)	2 (10.5)
Serious adverse events, *n* (%)	12 (18.8)	7 (12.3)	4 (10.5)	3 (15.8)
Worsening of Crohn's disease	8 (12.5)	4 (7.0)	3 (7.9)	1 (5.3)
Nausea	1 (1.6)	1 (1.8)	1 (2.6)	
Ileus	1 (1.6)	1 (1.8)	1 (2.6)	
Peritonitis	1 (1.6)			
Tonsillitis	1 (1.6)	1 (1.8)		1 (5.3)
Venereal wart	1 (1.6)	1 (1.8)		1 (5.3)
Pneumonia	1 (1.6)			
Serious infection, *n* (%)	6 (9.4)	4 (7.0)	2 (5.3)	2 (10.5)
Serious infusion reaction, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

week 14 (data not shown) at levels that were comparable to immunomodulators.

We chose to shorten the infusion interval of infliximab from 8 weeks to 4 weeks to achieve sufficient trough levels; however, we assume that similar levels may be achieved by infusion intervals of around 6 weeks in some patients. Other reasonable options that may also achieve sufficient trough levels include dose escalation or another induction therapy (0, 2, 6 weeks). We suggest that, depending on the patient condition and available options, the interval may be tailored according to the measured trough level, or the infusion interval may be gradually reduced until sufficient trough level and/or clinical efficacy is achieved. We are also aware that our study lacks a control group, which ideally should be a placebo-treated population or a group that was continuously treated at an 8-week interval.

In summary, we performed a standard maintenance therapy with 5 mg/kg of infliximab for CD at 8-week intervals and in patients showing loss of response the dosing interval was shortened to 4 weeks. This strategy led to high serum trough level of infliximab, which was accompanied by retrieval of clinical response, and, in some, clinical remission. Shortening the infusion interval of infliximab and monitoring its trough level may be useful and safe for maintaining long-term efficacy of infliximab in patients who have lost response to it.

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Magnetic Resonance Enterocolonography Is Useful for Simultaneous Evaluation of Small and Large Intestinal Lesions in Crohn's Disease

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Background: We developed novel magnetic resonance enterocolonography (MREC) for simultaneously evaluating both small and large bowel lesions in patients with Crohn's disease (CD). The aim of this study was to evaluate the diagnostic performance of MREC by comparing results of this procedure to those of endoscopies for evaluating the small and large bowel lesions of patients with CD.

Methods: Thirty patients with established CD were prospectively examined by newly developed MREC. Patients underwent ileocolonoscopy (ICS) (24 procedures) or double-balloon endoscopy (DBE) (10 procedures) after MREC on the same day. Two gastroenterologists and two radiologists who were blinded to the results of another study evaluated endoscopy and MREC findings, respectively.

Results: In colonic lesions the sensitivities of the MREC for deep mucosal lesions (DML), all CD lesions, and stenosis were 88.2, 61.8, and 71.4%, respectively, while the specificities were 98.1, 95.3, and 97.7%, respectively. In small intestinal lesions, MREC sensitivities for DML, all CD lesions, and stenosis were 100, 85.7, and 100%, respectively, while specificities were 100, 90.5, and 93.1%, respectively. Endoscopic scores were significantly correlated with MREC scores. Eleven (46%) of the 24 patients who were clinically not suspected to show stricture were observed to demonstrate stricture by radiologists.

Conclusions: Our results demonstrated that MREC can simultaneously detect the CD lesions of the small and large intestine. MREC can be performed without radiation exposure, the use of enema, or the placement of a naso-jejunal catheter. MREC and endoscopy have comparable abilities for evaluating mucosal lesions of patients with CD.

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Key Words: magnetic resonance enterocolonography, Crohn's disease

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBDs) associated with abdominal symptoms such as diarrhea, abdominal pain, and bloody stools. The inflammation of CD involves the entire gastrointestinal tract, particularly the small intestine. Assessing the extension and severity of the disease is critical in order to determine appropriate therapeutic strategies.[1,2] To assess whether CD lesions are present is important for patients with CD because mucosal healing has been reported to be associated with better long-term prognosis of CD.[2,3] Conventionally, evaluation of CD mainly has relied on ileocolonoscopy (ICS) and barium-based procedures, such as conventional enteroclysis (CE) and small bowel follow-through (SBFT). ICS is useful to detect inflammation in the colon and the distal end of the ileum, but the mid-small intestine is impossible to reach with this method. Because small bowel lesions are present in 4%–65% of CD patients,[4–7] conventional ICS has diagnostic limitations in detecting lesions present in CD.[4,5,7,8] SBFT is helpful for confirming the presence of fistulae or the extent of inflammation in CD. However, the detection of small erosions or aphthae by SBFT is beyond its capabilities.

Over the past few years the spectrum of diagnostic and therapeutic investigations of small bowel CD has widened considerably with recent technical advances such as wireless capsule endoscopy (WCE),[9–11] double-balloon

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endoscopy (DBE),[12,13] high-resolution computed tomography (CT),[14] and magnetic resonance enteroclysis or enterography (MRE).[15–18] Although SBFT is widely used in CD, it carries a high radiation burden. A recent study has highlighted the high cumulative radiation dosages imparted to patients with CD.[19] In this study, CT accounted for up to 84.7% of the cumulative dose imparted to patients, and 15.5% of patients received cumulative dosage in excess of 75 mSv, which has been reported to increase cancer mortality by 7.3%. Brenner et al[20] reported that the typical mean dose imparted in adult CT use (stomach dose from abdominal scan) was 10 mSv. The carcinogenic effect of radiation can be particularly significant in patients with CD who are already at increased risk of developing gastrointestinal and hepatobiliary cancer[21] as well as small bowel lymphoma.[22]

Magnetic resonance imaging (MRI) has the potential to overcome these limitations without radiation exposure. It is characterized by a very high soft-tissue contrast, a lack of ionizing radiation, and a lower incidence of adverse events related to intravenous contrast as compared to CT.

MRE is particularly useful in providing tissue-specific information on CD at its various stages from the acute inflammatory, regenerative, fistulizing, and perforating stages to the fibrostenotic stage due to its excellent soft-tissue contrast.[15,23–27] Because conventional ICS and VCE are problematic due to CD complications, such as stenosis and fistula, the use of MRE has been expected to allow us to detect more CD lesions. However, few studies have investigated the usefulness of MRE to detect CD lesions or to distinguish CD from UC or indeterminate colitis. Furthermore, there is only one report known to us comparing the findings of magnetic resonance enterocolonography (MREC) and DBE; however, in that study the DBE procedure did not allow for the observation of ileal mucosa, in which CD lesions were frequent.[28]

The aim of this study was to evaluate the efficacy of MREC for CD lesions in the small bowel and the colon by comparing its findings to those of DBE or ICS. This is the first prospective study to evaluate both small and large bowel lesions simultaneously with the use of MREC and without enema. In the present study the severity of CD lesions on MRE were assessed and compared to endoscopic activity using a simplified endoscopic activity score for Crohn's disease (SES-CD) and a Rutgeert's score. The strictures visible on MREC were also compared to clinical symptoms or endoscopic findings.

PATIENTS AND METHODS

Patients

From July 2009 to June 2010, a total of 30 patients (20 male, 10 female; mean age 29.5 years, range 24.0–37.5) from the inpatient and outpatient departments of Tokyo Medical and Dental University Hospital were enrolled in this study. Written informed consent concerning both diagnostic procedures and participation in this prospective trial was obtained from all patients. The study was approved by the Ethics Committee of Tokyo Medical and Dental University. All patients had been diagnosed with CD using the criteria of the Research Committee on Inflammatory Bowel Disease in Japan.[29] To compare the mucosal lesions in the colon and the small intestine, DBE or ICS procedures were performed after MREC. Patients agreed to receive both MREC and DBE/ICS at entry into this study. Because hospitalization was required for DBE,[30] patients were first asked if hospitalization (3 days) was acceptable. If patients agreed to be hospitalized for DBE, they received MREC and DBE. A total of 24 patients did not consent to hospitalization; therefore, in these cases MREC and ICS were done on an outpatient basis. Thus, the small intestinal lesions proximal to the terminal ileum using MREC were compared to those obtained using 10 DBE procedures (six were done from an anal approach, four were done from an oral approach), whereas terminal ileum and colonic lesions could be assessed in all patients. Clinical disease severity was also assessed using the Crohn's Disease Activity Index (CDAI) and C-reactive protein (CRP) levels.

Reference Standards

Ten DBE and 24 ICS procedures were performed. Endoscopy was performed using video colonoscopy (ileocolonoscopy, EC-590MP, Fjinon Optical, Tokyo, Japan; double-balloon endoscopy, EN-450, Fjinon Optical). If necessary, patients were given pethidine hydrochloride (Tanabemitsubishi, Tokyo, Japan) during ICS. All patients were given midazolam (Sando, Tokyo, Japan) sedation during DBE. DBE was performed with minimum radiation for fluoroscopy.[30]

MREC

MRI was performed with a 1.5T scanner (EXCELART Vantage powered by Atlas, Toshiba Medical Systems, Japan). All MR images were acquired in a supine position with the 32 elements Atlas SPEEDER Body Coil, which covers the anterior and lateral sides of a patient's body, and the Atlas SPEEDER Spine Coil, which is embedded in the table of the MR unit. Magnesium citrate and polyethylene glycol were used for oral contrast media. Patients were given 50 g of magnesium citrate (Horii, Tokyo, Japan), which comes packaged in a powder form that the patient can reconstitute with 200 mL of water for ingestion. A typical bowel-cleansing protocol consists of ingesting the substance the day before MREC is conducted at ≈7 PM. It is then followed by ingestion of an additional

TABLE 1. Acquisition parameters of MR enterocolonography

Parameter	MR sequence			
	FASE	True SSFP	Quick 3Ds	
section orientation	coronal	coronal	axial	coronal
TR/TE (msec)	13500/78	5/2.5	5/1.9	5/1.9
flip angle (degrees)	90/140	75	13	13
fat saturation	No	No	Enhanced FatSAT	Enhanced FatSAT
SPEEDER Factor	2.0	2.0	2.2	1.8
matrix size (interpolated)	256 × 320 (320 × 320)	256 × 256 (512 × 512)	128 × 288 (528 × 576)	128 × 288 (528 × 576)
field of view (cm)	40–42	40–42	32–33 × 36–37	40–42
section thickness (interpolated) (mm)	6	4(2)	5(2.5)	5 (2.5)
section gap (mm)	0	0	0	0

Note. FASE=Fast Advanced Spin Echo, True SSFP=True Steady State Free Precession, Quick3Ds=Quick Dimensional Dynamic Diagnostic Scan, or three-dimensional gradient echo sequence, TR=repetition time, TE=echo time, FatSAT=fat saturation, SPEEDER Factor= acceleration factor of parallel imaging technique in the phase-encoding direction

200 mL of water. To further achieve an adequate distension of the distal ileum, all patients were required to drink 1000 mL-1500 mL of polyethylene glycol (PEG) (Ajinomotofarma, Tokyo, Japan) within 60 minutes before the MR, based on the patients tolerance to the PEG. Patients ingested 1000 mL of contrast medium over the initial 30 minutes, and 500 mL over the next 30 minutes. We first confirmed the liquid amount that was ingested to ensure the optimal timing of the mixture in the terminal ileum with MRI of the True SSFP (true steady state free precession). Next, FASE (fast advanced spine echo) was acquired in a coronal orientation. After 20 mg of scopolamine butylbromide (Boehringer, Tokyo, Japan) was injected intravenously to reduce bowel peristalsis, True SSFP and Quick 3Ds (quick dimensional dynamic diagnostic scan) or 3D T1-weighted gradient echo sequence were acquired in a coronal orientation. After 60 seconds of intravenous administration of gadolinium chelate (gadodiamide 0.5 mmol/L Omniscan; Daiichi Pharmaceutical, Tokyo, Japan) at a dose of 0.2 mL/kg body weight and a rate of 2 mL/s, Quick 3Ds was acquired in axial and coronal orientations. All imaging covered the entire small and large bowels and anal area. FASE, True SSFP, and Quick 3Ds in the axial orientation were acquired during a single breath-hold. However, Quick 3Ds in the axial required individuals to hold their breath twice. Acquisition parameters are listed in Table 1.

Segmentation for MREC and Endoscopy of CD

The small bowel was divided into three distinct anatomic sections for the purposes of analysis.[11] In MREC analyses, these sections were determined relative to the position of the small bowel in the abdominal cavity: the jejunum section, located in the left upper quadrant (LUQ) of the abdomen; the ileum segment, located in the left lower quadrant (LLQ), the segment corresponding to bowel loops located in the right upper and lower quadrant (RULQ); and the terminal ileum segment extending 10 cm from the ileocecal valve. The colon and terminal ileum were divided into five distinct anatomic sections based on SES-CD.[31] The lesions in the terminal ileum, right colon segment, transverse colon, left colon segment, and rectum segment were separately scored and evaluated. To assess the severity of CD lesions in each segment, the most severe lesion in each segment was selected to be scored by MREC, ICS, and DBE.

Classification and Evaluation of CD Lesions for MREC and Endoscopies

Endoscopic and MREC findings in each segment for the individual patient were classified as in Table 2. The morphologic severities in CD lesions were classified in the following manner: no pathologic changes (NPC: 0), superficial mucosal lesions (SML: 1), and deep mucosal lesions (DML: 2). In the present study, scars were defined as NPC. In the endoscopic findings, edema, erythema, and aphthoid lesions were classified as SML, whereas ulcers, fissures, and lesions with a cobblestone appearance were classified as DML (Table 2).[11] The presence of at least two indicative criteria for each category was needed to diagnose as SML or DML. The per-segment comparisons between MREC and endoscopies only included those segments that were evaluated by both modalities.

Next, endoscopic severity of CD lesions in the colon and terminal ileum was scored by SES-CD for each

TABLE 2. Criteria at endoscopy and MREC for classification of small and large bowel lesion of CD

	endoscopic findings	imaging findings at MREC
A. morphologic changes	0) NPC: no pathologic changes (no mucosal or mural pathology)	
	1) SML: superficial mucosal lesion	
		• subtly increased contrast enhancement
	• edema	• subtle irregularity of the fold pattern
	• erythema	• no wall thickening
	• aphtous without ulcerous lesions	• no submucosal edema
		• no extra-mural hypervascularity
	2) DML: deep mucosal lesion	
		• markedly increased contrast uptake
		•wall thickening>4mm
	• ulcers	• disrupted the fold pattern
	• fissures	• cobble stone
	• cobble stone pattern	• deep mucosal fissures
		• submucosal edema
		• extra-mural hypervascularity
	absent = no obstruction present = obstruction	
B. obstruction		
	incomplete through the stenotic lesion	luminal narrowing(<11 mm) and consensus of radiologist about presence of radiologic stenoses

patient.[31] To be compared with SES-CD, MRCE score was also defined in this study by modifying SES-CD as shown in Table 3.

For the evaluation of endoscopic findings, exclusively in the small intestine, each segment severity was also scored using a modified Rutgeert's score[32]: grade 0a indicates the absence of small bowel lesions; grade 0b indicates stricture without inflammation; grade 1 indicates five or fewer aphthoid lesions; grade 2 indicates more than five aphthoid lesions; grade 3 indicates diffuse aphthous ileitis with diffusely inflamed mucosa; grade 4 indicates diffuse inflammation with larger ulcers; and grade 5 indicates ulcerated stricture. Grades 0a and 0b were considered inactive disease, whereas grades 1+ reflected active disease. For the comparison, severity of each small intestine segment was assessed in MREC as well, as shown in Table 2.

Stricture was also assessed in accordance with "B. Obstruction" in Table 2. The severity of stricture was scored (1 = very unlikely, 2 = unlikely, 3 = not sure, 4 = likely, 5 = very likely) both by clinicians in charge of each patient and radiologists who interpreted the MREC.[33] Correlation coefficients and kappa scores were then calculated to determine the agreement between clinical and radiologic assessments of stricture.

Image Interpretation

Two independent physicians performed endoscopies, and two board-certified radiologists assessed the MRCE findings. Both the physicians and radiologists were blinded to the patient clinical presentation and the results of the other studies (endoscopic or MRI findings) as well.

TABLE 3. Criteria at MREC score based on SES-CD

Variable	0	1	2	3
size of ulcers, wall thickness, highly enhancement, and deep depressions	none	aphthousulcers (ϕ 0.1 to 0.5 cm)	largeulcers (ϕ 0.5 to 2 cm)	very large ulcers (ϕ > 2cm)
ulcerated surface	none	<10%	10–30%	>30%
affected surface when present hyperintensity on T2 relative to the signal of psoas muscle, and slightly enhancement on T1	none	<50%	50–75%	>75%
presence of narrowing	>11mm	11–6mm	6mm>	6–0mm

TABLE 4. Clinical characteristics of 30 patients at inclusion into the study

female, n (%)	10 (33)
mean age at examination (IQR)	29.5 (24.0–37.5)
mean disease duration (month) (IQR)	48.5 (14.3–150.3)
mean BMI (IQR)	198 (181–217)
disease location	
ileal, n (%)	8 (26)
ileocolonic, n (%)	20 (67)
colonic, n (%)	2 (7)
perianal involvement,n (%)	4 (13)
symptomatic, n (%)	20 (67)
mean CDAI score (IQR)	82 (42–138)
CDAI>150, n (%)	7 (23)
mean CRP(mg/dL) (IQR)	0.31 (0.05–0.83)
CRP>0.3mg/dL	16 (53)
previous surgery, n (%)	11 (37)
concomitant treatments	
5-ASA, n (%)	11 (37)
steroids, n (%)	3 (10)
immunosuppressants, n (%)	10 (33)
anti-TNF antibodies, n (%)	6 (20)
no medication, n (%)	7 (23)

Statistical Methods

All statistical analyses were performed with standard statistical software. JMP8 (SAS Institute, Cary, NC) was used for statistical analysis. Spearman correlation coefficients (two-sided) were determined to examine associations between endoscopic score, MRI score, CDAI, CRP, and stricture likelihood scores. Kappa scores were also calculated to examine the agreement between clinicians and radiologists on the likelihood of stricture. *P*-values less than 0.05 were considered significant.

RESULTS

MREC Is Comparable to Conventional ICS in the Detection of CD Lesions in the Terminal Ileum and Colon of CD Patients

The patients clinical characteristics are shown in Table 4. MREC and ICS/DBE were performed on the same day in all patients. Ten patients did not have abdominal symptoms and MREC/endoscopies were performed for screening. Another 20 patients received MREC/endoscopies to assess the severities and extension of disease due to abdominal symptoms (Table 4). Supporting Table 1 details the endoscopic and MREC findings in the small and large intestines of all patients. DML was observed in 35 (23%) of the 150 segments by MREC, while in 34 (24%) of the 140 segments by ICS/DBE. SML could be detected in the terminal ileum and colonic segments less frequently in MRCE (3 [2%] of 150 segments) than in endoscopy (20 [14%] of 140 segments). Eighteen patients (60%) exhibited either SML or DML in the terminal ileum or colon by MREC. Stenosis was observed in nine patients (30%) by MREC. MREC sensitivities for DML, any CD lesion (both SML and DML), and stenosis were 88.2, 61.8, and 71.4%, respectively, while specificities were 98.1, 95.3, and 97.7%, respectively (Fig. 1a). An example of the classification and scoring is shown

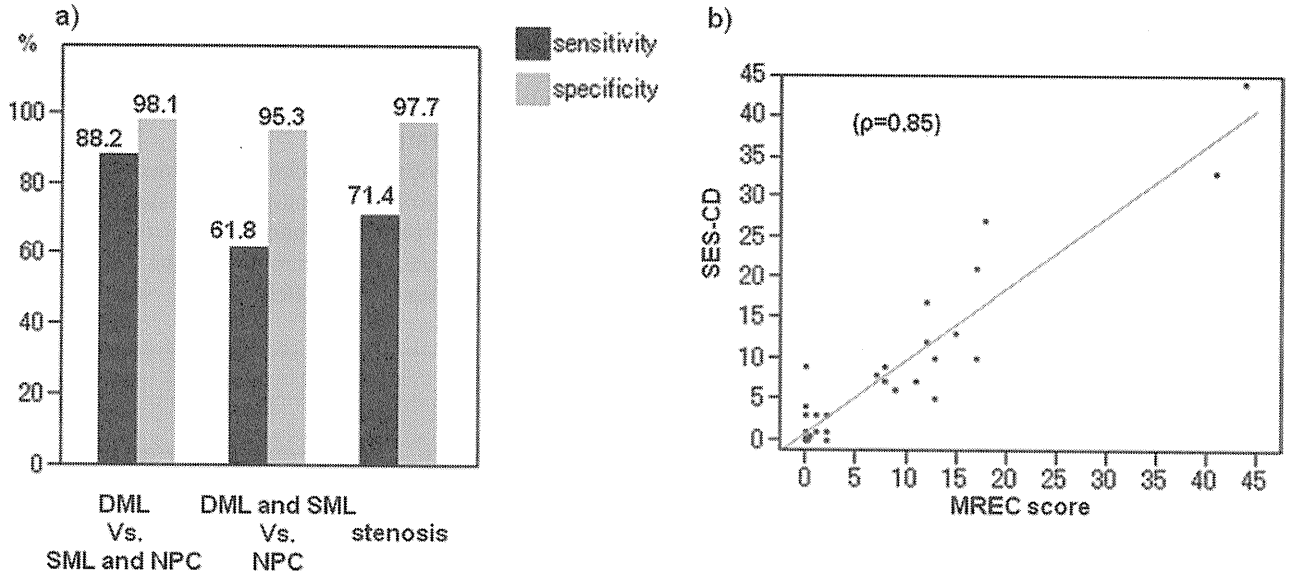

FIGURE 1. Diagnostic capabilities of MRCE in the assessment of terminal ileum and colonic lesions. (a) The sensitivity and specificity of MREC for DML, any CD lesions (DML + SML), and stenosis. (b) Correlation between MREC scores and SES-CD scores.

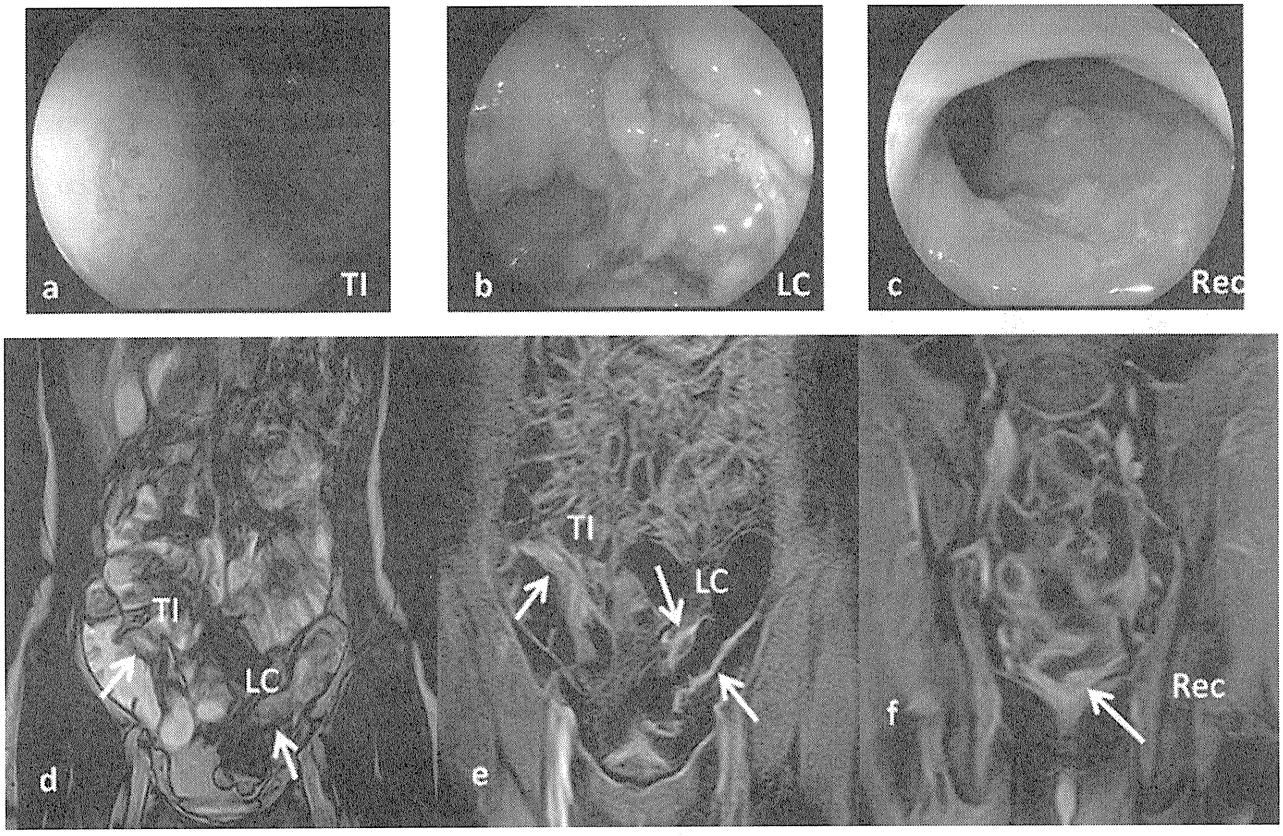

FIGURE 2. An example of comparison between endoscopy and MREC in terminal ileum and colonic lesions. Conventional colonoscopy detected DMLs in the terminal ileum (a), sigmoid colon (b), and rectum (c). MREC with True SSFP sequence in coronal view (d) and 3D T1-weighted contrast-enhanced GRE sequence (e,f; coronal view) in a patient with multifocal CD. TI: terminal ileum, LC: left sided colon, Rec: rectum.

in Figure 2. Wall thickening, mucosal irregularities, markedly increased contrast enhancement by MREC were indicative of DML. Figure 1b indicates that a strong correlation ($\rho = 0.85$, $P < 0.0001$) was found between SES-CD (median 5.5, interquartile range [IQR] 1.0–10.5) and MREC score (median 4.5, IQR 0–13.3) in terminal ileum and colonic lesions. Both CDAI and CRP moderately correlated with endoscopic and MREC scores (CDAI versus SES-CD; $\rho = 0.56$, $P = 0.001$, CDAI versus MREC score; $\rho = 0.41$, $P = 0.024$, CRP:SES-CD; $\rho = 0.40$, $P = 0.025$, CRP versus MREC score; $\rho = 0.36$, $P = 0.049$). These results indicate that MREC was comparable to colonoscopy in the detection of terminal ileum and colonic lesions.

MREC Is Useful in the Detection of CD Lesions in the Small Intestine

Because the usefulness of MREC for the detection of CD lesions in the small intestine has not been well investigated, we assessed the detection rate of CD lesions in the jejunum, ileum, and terminal ileum by MREC. Twenty-seven DML lesions (30%) and 3 (3%) SML lesions were observed in 90 segments by MRE. Surprisingly, any small intestine lesions were found in 23 (77%) of 30 patients.

Next we compared CD lesions detected by MREC with those obtained by DBE. Most intestinal lesions observed by MREC were consistent with those by DBE. For the small intestinal lesions, the sensitivities of MREC in detecting DML, any CD lesions (12 DML and 2 SML), and stenosis were 100 (12/12), 85.7 (12/14), and 100% (6/6), respectively, while the specificities were 100 (25/25), 90.5 (19/21), and 93.1% (130/133), respectively (Fig. 3a). Figure 4 indicates an example where stenosis could be detected by MREC, which could not be reached by DBE because of another distal stricture.

There was also a strong correlation ($\rho = 0.88$, $P < 0.0001$) between Rutgeert's scores (median 0, IQR 0–4) and MREC scores (median 0, IQR 0–2) for small bowel lesions (Fig. 3b). CDAI moderately correlated with Rutgeert's scores ($\rho = 0.44$, $P = 0.03$), and weakly correlated with MREC scores ($\rho = 0.25$, $P = 0.24$). CRP did not

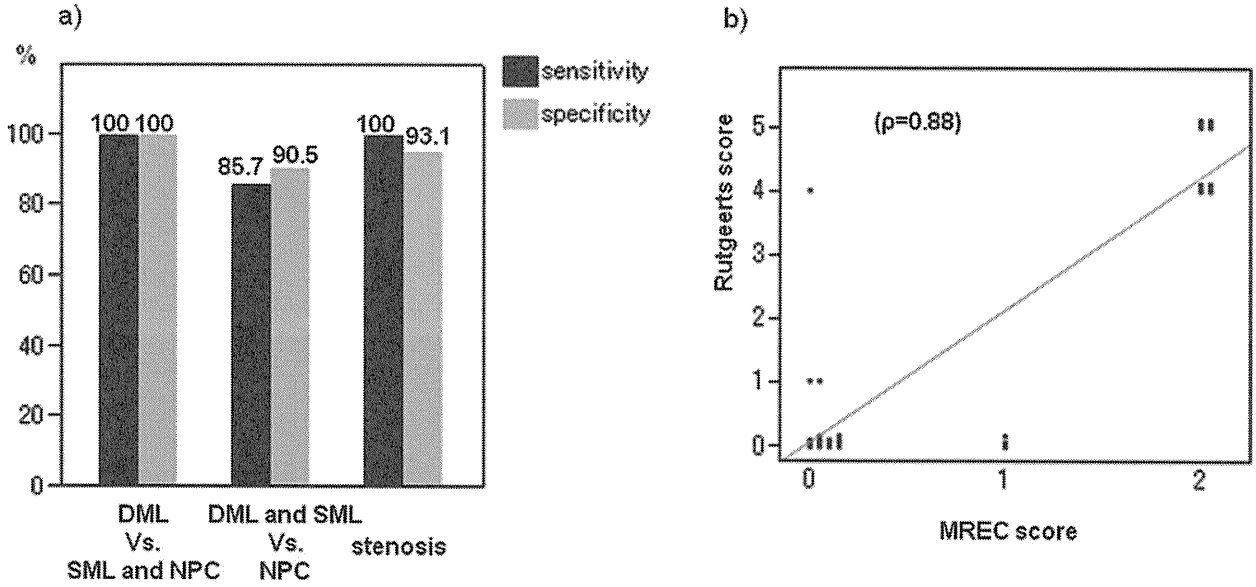

FIGURE 3. Diagnostic capabilities of MRCE in the assessment of the small intestinal lesions. (a) The sensitivity and specificity of MREC for DML, any CD lesions (DML + SML), and stenosis. (b) Correlation between MREC scores and Rutgeert's scores for CD lesions in the small intestine.

correlate with Rutgeert's scores ($\rho = 0.11$, $P = 0.61$) or MREC scores ($\rho = 0.10$, $P = 0.65$). These results suggest that MREC is comparable to DBE in detecting active lesions in the small intestine.

Physicians' Assessment for Strictures May Be Consistent with Findings from MREC

A moderate correlation ($\rho = 0.57$, $P = 0.001$) and kappa score (0.32, $P < 0.001$) were calculated, demonstrating

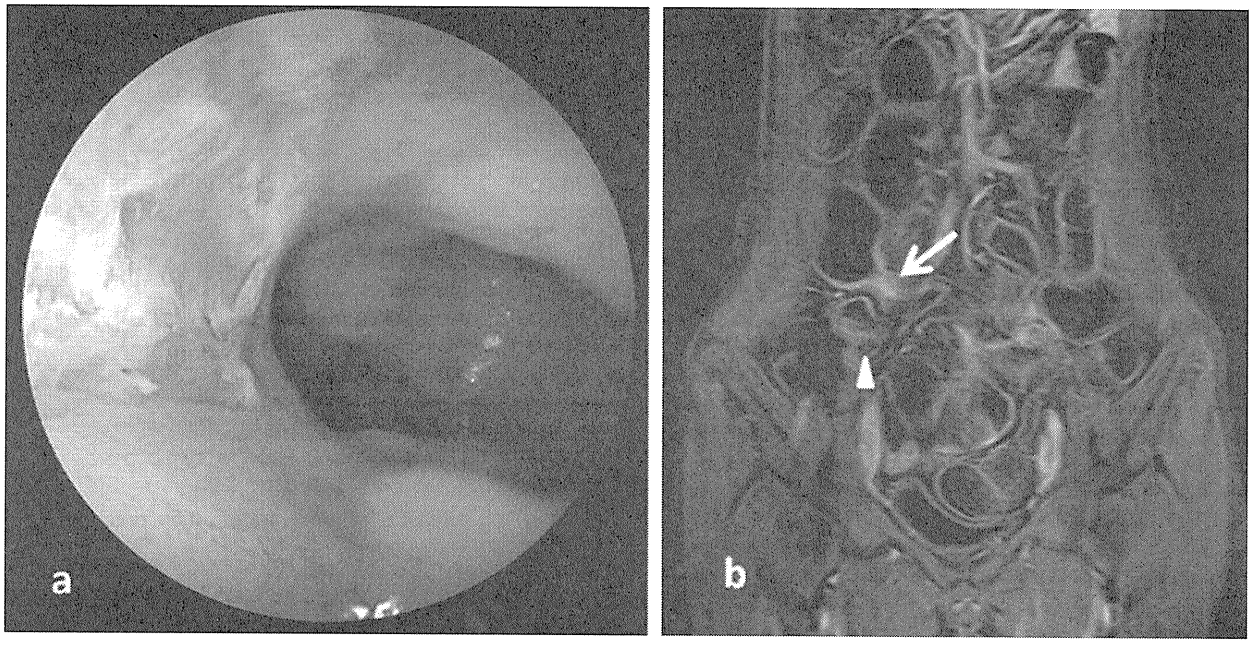

FIGURE 4. An example of cases where ileal stenosis was detected by DBE (a) and MREC (b). (a) DBE revealed severe stenosis with deep longitudinal ulceration in the terminal segment of the ileum. DBE instrument could not be passed through the stenosis. (b) MREC detected the ileal lesion (white arrow). Furthermore, multifocal DML (arrowhead) above the distal stenosis was also detected.

TABLE 5. Agreement between clinical and radiologic stenosis

clinical likelihood of stenosis	radiologic stenosis	
	present	absent
very unlikely or unlikely	11	13
not sure, likely, or very likely	6	0

Kappa = 0.32 (95% CI: 0.12–0.58).

the fair level of agreement between clinical and radiologic assessments. Interestingly, radiologists pointed out stenosis in 11 (46%) patients who did not have obstructive symptoms (Table 5).

DISCUSSION

Previously, Rimola et al[34] demonstrated that MRE is useful for detecting disease activity and assessing severity of CD lesions in the colon and terminal ileum. However, they did not evaluate CD lesions in the jejunum and proximal to terminal ileum. Furthermore, rectal balloon catheter was retrogradely instilled when MRE was done. Seiderer et al[28] also showed the usefulness of MR enteroclysis to evaluate the CD lesions in the small intestine; however, a nasojejunal catheter was used in that study. Our study is the first prospective report to evaluate jejunal, ileal, and colonic CD lesions simultaneously using MREC. It should be emphasized that gastroduodenal intubation and enema were not needed to perform MREC in the present study. We also confirmed that MREC demonstrated high sensitivity and specificity for CD lesions such as DML and stenosis. MREC was able to detect lesions in the small intestines of 23 (77%) of 30 patients. Our study also indicated that the sensitivity of MREC for stenosis in the large bowel was 71.4% and that in the small bowel was 100%. Interestingly, jejunal and ileal CD lesions (inflammation, stenosis) beyond the first stenosis were detectable with MREC, although endoscopies could not pass through the first one. Furthermore, the severity detected with MREC was closely correlated with that obtained with endoscopies. These results suggest that MREC can be a useful tool in the detection of CD lesions without excessive pain/radiological exposure.

Our study also indicated that MREC was less sensitive than endoscopy for the detection of superficial lesions. Another study showed that MRE was inferior to VCE for the detection of mucosal lesions consistent with CD. However, the long-term prognosis of CD patients with superficial small-bowel lesions is unknown. Thus, MREC is thought to be a useful modality despite its potential for misdiagnosis of the small lesions of CD patients.

DBE is the only method that allows for tissue sampling and pathological examination in the jejunum and ileum. Histological examination can provide valuable information to aid in assessing the severity of inflammatory changes. Therefore, DBE can be used to diagnose CD in inconclusive cases in which histological diagnosis would alter treatment strategy.[35] However, the disadvantages of DBE for CD patients should be emphasized as well. First, adhesions and fistulas are frequently observed in CD patients and can result in technical difficulties of observing the entire small intestine. Second, it is impossible to observe the mucosa along the entire length of the small intestine using either the oral or anal approach in one session of DBE. It was difficult to observe the entire small intestine in some cases, even though both oral and anal approaches to DBE were conducted. Finally, DBE is accompanied by severe complications in $\approx$1% of cases. With the use of MREC, observation of both the entire small intestine and colon were possible and were less complicated than with DBE.

Most patients would likely prefer MRE to MR enteroclysis because of reduced abdominal discomfort and nausea.[36,37] When MR enteroclysis is performed, patients are still exposed to radiation during the placement of the nasojejunal catheter. Moreover, the complicated logistics of using two diagnostic rooms in tandem needs to be considered. A prospective randomized study showed similar diagnostic sensitivities for MRE and MR enteroclysis (88 versus 88%).[36] Therefore, we performed MRE to detect CD lesions.

In the present study, patients ingested a total of 1500 mL contrast medium, as previously described,[38] with 1000 mL ingested over the initial 30 minutes and 500 mL ingested 30 minutes later. It should be emphasized that patients were administrated magnesium citrate oral contrast media 1 day prior to the administration of MREC in this study. This method could potentially enable radiologists to evaluate colonic lesions more easily.

Our prospective evaluation indicated that clinical and radiologic assessments of stricture were significantly correlated. This correlation was greater in the colonic lesion and in small intestinal lesion. A kappa score (kappa = 0.32) was also calculated and confirmed the significant agreement. Our results are consistent with the results (kappa = 0.34) of Higgins et al,[33] which showed that assessment using CT enterography was comparable to clinical assessment for strictures. Radiological findings were significantly correlated, but discrepancies between radiological and clinical assessments were observed in 11 patients. This result suggests that MREC has the possibility to detect the obstructive lesions before patients have abdominal symptoms.

There are some limitations to our study. Our patient group was very small and was possibly preselected

considering the relatively high prevalence of multifocal small bowel disease, which may not be representative of a general CD population. Despite the small number of patients, we believe that our study has value as a preliminary or exploratory study. Future studies should include the enrollment of a larger number of patients to obtain more conclusive results.

In conclusion, MREC demonstrated comparative ability to endoscopy for the simultaneous assessment of both small and large intestinal lesions in a follow-up of CD patients. Additionally, the technique was accompanied by minimal risks and no radiation exposure. Moreover, our results suggest that MREC can enable clinicians to detect strictures or severe lesions early in the course of the disease. Because of the minimal risk involved in MREC, this diagnostic tool can be repeated. Recently, mucosal healing has been reported to be critical for the long-term prognosis of CD. MREC may be useful in confirming improvement of the CD lesions in both large and small bowel as a result of intensive treatments, such as infliximab.

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Ⅷ.　研究成果の刊行物

潰瘍性大腸炎・クローン病
診断基準・治療指針

厚生労働科学研究費補助金 難治性疾患克服研究事業
「難治性炎症性腸管障害に関する調査研究」班（渡辺班）
平成22年度分担研究報告書 別冊

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