FD was established only after the publication of Rome II,[5] whereas the concept of IBS has been used for a longer time. Another reason is that other terms such as "chronic gastritis" have also been used in Japan for a clinical condition corresponding to FD. Similarly, sub-grouping categorization was more popular in IBS than FD, and this is because newly defined entities of PDS and EPS were only recently established in Rome III.[3]

It was interesting that 25% of GI specialists used criteria other than Rome II or III for diagnosis of IBS, including Manning diagnostic criteria or BMW (bowel motility workshop) criteria, the

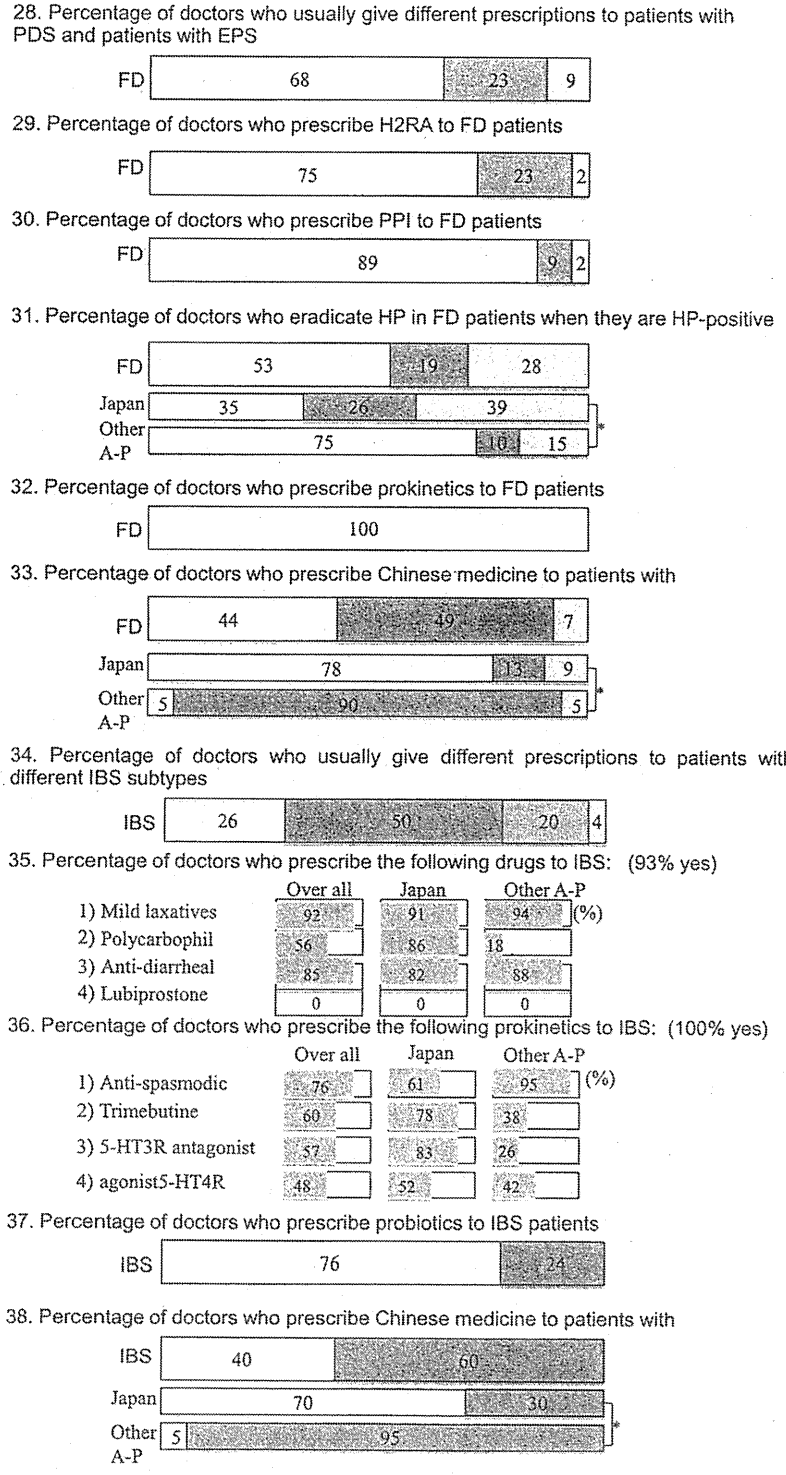

Figure 5 Preferences of panelist doctors in the Asia-Pacific region in management (treatment) of FD and IBS (about medication of GI drugs). Results in answer to items No.28–38 are shown as percentages of doctors. The overall answers from 43 panelist doctors are shown, except for Japan with answers from 23 doctors, and Other A-P, with answers from 20 doctors. An open bar indicates the percentage of "yes" answers, a dark-shaded bar indicates the percentage of "no" answers, and a light-shaded bar indicates the percentage of "equivocal" answers, except No.34-36. No. 34: ▭ yes, ▨ no: partially common, ▭ no: mostly common, ▭ equivocal. In item No.35 and No.36, percentage of prescription of indicated drugs is shown. PDS, postpradial distress syndrome; EPS, epigastric pain syndrome; H2RA, histamine H2-receptor antagonists; PPI, proton pump inhibitors. *$P < 0.05$.

latter especially in Japan.[6] However, there were many common features in approaches for treatment of FD and IBS. The use of prokinetics was very popular, and prokinetics were almost always used for FD as well as for IBS. Prescription of anxiolytic drugs and anti-depressants was also popular for both disorders.

In this survey, only a few differences were found between Japanese and other A-P panelist doctors in diagnosis and treatment of FD and IBS. Most of the doctors (86%) in Japan mandatorily performed upper GI endoscopy for diagnosis of FD and frequently performed blood examination to rule out organic diseases, but only half of other A-P doctors did these examinations. This may be due to the difference in public insurance systems, but another reason may be the greater general concern about gastric cancer in Japan than in other A-P countries. However, it is also interesting that abdominal ultrasound sonography was not usually performed to exclude organic diseases in the diagnosis of FD and IBS even in Japan.

The overall percentage of examination for HP infection status was 58% with no significant difference between Japanese and other A-P doctors. However, surprisingly, for the frequency of HP-eradicative therapy in HP-positive FD patients was significantly lower (35%) in Japan than other A-P regions (75%). This may be because public insurance in Japan does not cover eradication of HP in patients with FD or gastritis. However, this situation may change because the Japanese Society for Helicobacter Research has recently published guidelines recommending eradication for all HP-infected patients.[7] Taking into account that the incidence of gastric cancer is higher in Japan and Korea than in other population area,[8] HP eradication should be more widely considered for HP-positive patients with investigated dyspepsia as recently recommended by the Asia Pacific Consensus on HP infection.[9]

Although not statistically significant, other A-P doctors more frequently checked the dietary conditions or diet-related diseases than did Japanese doctors, especially for IBS patients, to rule out, for example, food allergy, or celiac disease.[10] For the diagnosis of FGID, serological tests for celiac disease were rarely performed. Although celiac disease appears to be extremely rare in Japan,[11] the incidence may increase in the future due to globalization. In other countries, particularly India, Australia and New Zealand, the prevalence of celiac disease is high. For IBS, most of the doctors asked about a history of recent infection in consideration of post-infectious IBS, but they did not usually (only 30%) check concomitant GI infection or bacterial overgrowth. For FD, although almost none of the doctors checked for infections other than HP, the potential relationship between dys-

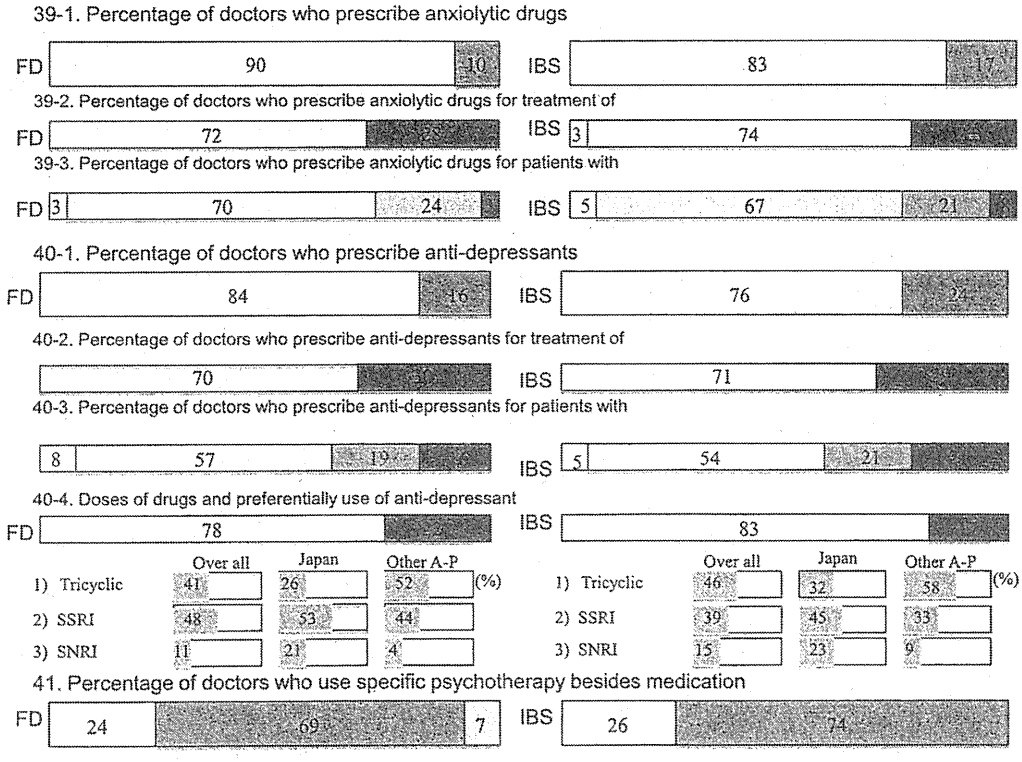

Figure 6 Preferences of panelist doctors in the Asia-Pacific region in management (treatment) of FD and IBS (about medication with psychological drugs and psychological therapy). Results in answer to items No.39–41 are shown as percentages of doctors. The overall answers from 43 panelist doctors are shown. An open bar indicates the percentage of "yes" answers, and a dark-shaded bar indicates the percentage of "no" answers, except some items. No. 39-2, and 40-2: ▭ first line, ▭ second line, ▭ others (third line). No. 39-3, and 40-3: ▭ all, ▭ with anxiety or depressive signs, ▭ positive test, ▭ others. No. 40-4: ▭ low dose, ▭ regular dose. In the lower part of item No.40-4, percentage of prescription of indicated drugs is shown. Tricyclic, tricyclic anti-depressant; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin & norepinephrine reuptake inhibitors. $^*P < 0.05$.

peptic symptoms and acute gastroenteritis should be investigated further because the pathophysiological mechanism of post-infectious FD is now postulated in a subset of patients.[12] More than half of the panelist doctors excluded patients with reflux symptoms when they diagnosed FD in clinical practice, although some overlap has been reported.[13] In contrast, the majority of doctors usually included patients suggesting IBS with lower GI symptoms in FD because there is actually a significant overlap between the two disorders.[14]

Psychological tests for FD or IBS patients were not common (about 26–29%), and many doctors judged the patient's psychological condition through a routine interview. GI motility or visceral hypersensitivity was also not routinely examined even in the institutes of panelist doctors, although the importance of these examinations is recognized in consideration of the pathophysiologic mechanism.[15,16]

For medical treatment of FD, anti-secretory drugs such as H2RA and PPI were widely used by panelist doctors. PPI were prescribed to about 90% of FD patients. A meta-analysis demonstrated that PPI were more effective than a placebo for management of patients with ulcer-like and reflux-like FD,[17] and a recent study has been shown that the prevalence of pathologic acid reflux is approximately 50% in FD with epigastric burning.[18] However, the use of PPI may be limited, because there was a report that lansoprazole treatment was not superior to a placebo for management of FD in Chinese patients.[19] Prokinetics may be effective for symptom relief in some FD patients. A meta-analysis indicates that prokinetic agents were significantly more effective than a placebo in the treatment of FD, and it was also suggested that mosapride citrate may be more effective than cisapride for the treatment of FD.[20] It was also shown that mosapride citrate and famotidine (H2RA) had beneficial effects regardless of FD subtype, age and gender.[21] The effectiveness of PPI therapy and that of prokinetic therapy by mosapride citrate for FD were also reported to be not different, and cannot be predicted by Rome III subgroups.[22] In this study, all of the panelist doctors were using some prokinetics including mosapride citrate, especially for PDS subgroups, in accordance with those reported observations.

For medical treatment of IBS, about 62% of the panelist doctors usually give prescriptions to patients with IBS at the first visit. Although treatment options for IBS-C, IBS-D, and abdominal pain appear to be different,[23] polycarbophil calcium, trimebutine maleate and probiotics were commonly used, especially in Japan. Ramosetoron hydrochloride is a serotonin H3 receptor antagonist that was developed in Japan and is currently used widely for IBS-D treatment, especially in Japan.[24] As complementary alterative therapies, Chinese herbal therapy is very popular in Japan, Rikkunshito for FD and Daikenchuto for IBS, mainly because standardized forms of herbal medicine with regards to quality and quantities of ingredients are commercially available in Japan.[25]

Although results of some studies have suggested the effectiveness of anxiolytic or anti-depressive agents for treatment of FD and IBS,[26,27] these results are not sufficient to prove their benefit.[28] A recent meta-analysis has shown that the relative risk (RR) of IBS symptoms persisting with anti-depressants versus placebo was 0.66, with similar treatment effects for both tricyclic antidepressants and SSRI.[29] Although this survey showed that treatment of FGIDs with psychological drugs appears to be very popular, high-quality, larger studies in the A-P region are needed to determine whether anxiolytic or antidepressant drugs can relieve FD or IBS symptoms. On the other hand, psychotherapy was not so popular among physicians, mainly due to the difficulty in performing psychotherapy in outpatient clinics. However, since psychotherapy can sometimes be effective for chronic patients who do not respond to medical treatments,[30,31] it should be further considered in refractory cases.

From our survey, we were able to obtain valuable information about current clinical practice for diagnosis and management of FD and IBS in the A-P region. The data will be useful for the establishment of consensus guidelines for these disorders.

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Chronic nonspecific multiple ulcer of the small intestine segregates in offspring from consanguinity

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Chronic enteropathy;
Anemia;
Hypoproteinemia;
Family history

Abstract

Background and aims: Chronic nonspecific multiple ulcer of the small intestine is a recently proposed enteropathy characterized by persistent blood and protein loss from the small-bowel. We examined possible segregation of the disease in family pedigrees.
Methods: All cases of the disease diagnosed at our institution were reviewed with respect to particular focuses on the presence of close consanguinity in the families, the enteroscopic findings and the long-term clinical course. The diagnosis was based on persistent occult gastrointestinal bleeding and hypoproteinemia for more than 5 years, and irregularly shaped shallow ulcers in the ileum.
Results: During a 45-year-period, 13 patients were diagnosed as having the disease. There were 11 females and 2 males, with ages ranging from 8 to 37 years at the time of the initial presentation and with those from 13 to 38 years at the diagnosis. Enteroscopy performed in 11 patients with a time duration ranging from 0.5 to 44 years after the diagnosis revealed active ileal ulcers in 10 patients. Parents' consanguineous marriage was verified in 6 patients, two of whom also had siblings with the enteropathy. Another patient without consanguinity had a sibling with protein-losing enteropathy.
Conclusion: Chronic nonspecific multiple ulcer of the small intestine seems to segregate in offspring from consanguineous marriage.

1. Introduction

The use of capsule endoscopy and balloon endoscopy has led to an increase in the chance of encountering small-bowel ulcers, especially in patients with obscure gastrointestinal bleeding.[1,2] While Crohn's disease, intestinal tuberculosis,

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radiation enteropathy, and nonsteroidal anti-inflammatory drug (NSAID) enteropathy are entities predisposing to chronic or recurrent small-bowel ulcers, there are cases of ulcers with obscure origin.

We recently reported on a peculiar form of enteropathy characterized by chronic blood and protein loss through persistent small-bowel ulcers.[3] Because the ulcers of the disease had nonspecific histology, we referred to the condition as "chronic nonspecific multiple ulcer of the small intestine (CNSU)".[3,4] CNSU does not seem to be a rare entity, because cases of exactly the same clinicopathologic features have subsequently been reported in the literature.[5–7] Furthermore, a similar enteropathy with different nomenclatures has been described in Caucasians and referred to as "diaphragm disease of the small bowel without apparent NSAID use"[8] or as "cryptogenic multifocal ulcerous stenosing enteritis".[9] More recently, Adler et al.[10] reported a novel enteropathy in a middle aged American male characterized by blood loss from recurrent small-bowel ulcers. Surprisingly, Adler's case had compound heterozygous mutations in the encoding regions of *cytosolic phospholipase A2α (cPLA2α)* gene. Based on the description, we hypothesized CNSU to be a hereditary condition with genetic alterations. We thus retrospectively investigated family histories of CNSU in patients with the disease identified at our institution.

2. Patients and methods

2.1. Survey for CNSU

We reviewed the diagnosis, the prevalence, and the management of inflammatory bowel diseases diagnosed during a period 1964–2009 at Kyushu University Hospital, Fukuoka University Chikushi Hospital, and their satellite hospitals, and collected data for clinicopathologic features of patients with CNSU. The two referral centers have been treating approximately 600 patients with Crohn's disease and 800 patients with ulcerative colitis.

2.2. Diagnosis of CNSU

The diagnosis of CNSU was made on the basis of clinical manifestations and small-bowel lesions.[4] As for clinical manifestations, patients with CNSU should have iron deficiency anemia and hypoproteinemia in their adolescence.[4] Small-bowel lesions should be multiple shallow ulcers in the ileum, with sharply demarcated margin and linear or oblique configuration (Fig. 1).[11] Furthermore, the repeated ascertainment of those clinical manifestations with time intervals for more than 5 years was inevitable for the diagnosis of CNSU.

2.3. Data collection

We focused on the demographic data regarding the initial clinical manifestation, which led to the identification of small-bowel ulcers, the age at the onset, and the laboratory values of serum protein, serum albumin, C-reactive protein (CRP), hemoglobin, and white blood cell count at the time of the initial diagnosis. We also reviewed histories and laboratory data presumably associated with other enteropathy. They included history of NSAID use, purified protein derivative (PPD) skin test, interferon-γ assays (IGRA) for *Mycobacterium* infection, anti-tissue transglutaminase (tTGA) antibodies, findings obtained by esophagogastroduodenoscopy with forceps biopsy, and histologic findings of the resected small bowel. In addition, medical and surgical treatments, response to the medication as determined by changes in serum protein value, and prognosis were retrospectively investigated. We also collected data of the final enteroscopic findings. The procedures for enteroscopy included retrograde ileoscopy (RI), double balloon endoscopy (DBE) and intraoperative endoscopy (IOE). The enteroscopic findings were evaluated with regard to the stage (open or scarred), the depth (deep or shallow), and the configuration (circular, linear, or their combination) of the representative lesion.[11]

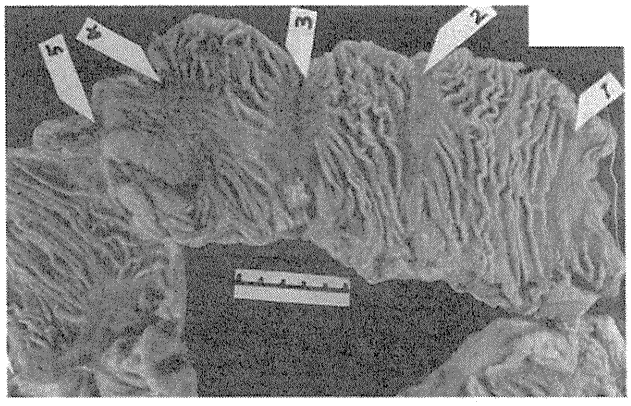

Figure 1 Typical macroscopic findings of the resected ileum in a case of CNSU (Case 9). There are shallow and clear ulcers in circular or linear configuration in the ileum. The intervening mucosa is not affected.

We directly contacted the patients and/or their relatives to obtain family histories. The items of special interest were consanguinity, anemia, malnutrition, abdominal surgery, and clinical diagnosis of enteropathy, if any, in the family pedigrees. Family history of enteropathy was regarded as positive in the case of surgical interventions for the small bowel, the established diagnosis of small-bowel ulcers or both. We examined the medical records of the relatives with enteropathy in the case that the records were available.

This retrospective study was approved by the ethical committee at Kyushu University Hospital, and it was undertaken in accordance with Helsinki Declaration.

3. Results

3.1. Clinical features and laboratory data

During a period from 1964 to 2009, 13 patients were diagnosed with CNSU. Table 1 summarizes the clinical features of the patients. There were 11 females and two males. All patients had anemia of obscure origin as the presenting symptom. In addition, three patients had edema and other two patients complained of abdominal pain. The age at the time of the onset ranged from 8 to 37 years. Eleven patients complained of the symptoms at the age of less than 20 years. The time interval

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Table 1 Cases of CNSU diagnosed at our institution during 1964–2009.

Case no.	Age (yrs)/gender		Presenting symptoms	Laboratory data		
	Onset	Diagnosis of CNSU		Hemoglobin (g/dl)	Serum protein (g/dl)	CRP (mg/dl)
1.	20/F	27	Anemia, edema	8.2	4.9	–*
2.	15/F	24	Anemia, edema	3.5	5.0	–*
3.	10/M	26	Anemia, growth retardation	4.4	4.5	–*
4.	15/F	28	Anemia, edema	4.7	5.3	–*
5.	12/F	27	Anemia, abdominal pain	9.7	5.8	0.3
6.	17/F	34	Anemia	9.6	4.6	0.5
7.	10/F	13	Anemia, abdominal pain	7.4	5.4	0.1
8.	37/F	38	Anemia	9.5	6.7	0.5
9.	15/M	30	Anemia, edema	7.4	8.2	0.1
10.	13/F	29	Anemia	5.9	4.6	0.2
11.	16/F	52	Anemia	5.3	6.3	0.1
12.	13/F	40	Anemia	9.4	4.1	1.1
13.	8/F	33	Anemia, edema	8.6	4.5	0.6

* CRP was determined to be negative under semi-quantitative measurement.

from the onset until diagnosis of CNSU ranged from 1 to 27 years (median; 15 years). NSAID use was not verified in any patient at the time of the initial diagnosis. We further confirmed possible use of NSAID in seven patients who had been under observation. Those patients again clearly denied any continuous use of NSAID or other medications at the time of their first diagnosis of CNSU.

Laboratory data at the initial diagnosis showed hypochromic anemia and hypoproteinemia. The hemoglobin value ranged from 3.5 to 9.7 g/dl and serum protein value from 4.1 to 8.2 g/dl. In four patients (Cases 1–4) with the diagnosis of CNSU in 1970s, CRP value was not quantified. In the remaining nine patients, there were slight increases in CRP with values from 0.1 to 1.1 mg/dl.

Eleven patients were treated by surgery. The remaining two patients (Cases 11 and 13) were diagnosed with CNSU on the basis of the clinical and enteroscopic findings. Results of the diagnostic work-up are summarized in Table 2. PPD skin test and IGRA showed none of the patients to be positive for *Mycobacterium* infection. Anti-tTGA antibodies were measured

Table 2 Results of diagnostic work up for patients with CNSU.

Case no.	PPD skin test	IGRA test	Anti-tTGA antobody	Gastroduodenal lesions			Surgically removed ileal lesions			Final enteroscopic findings			
										Concentric stenosis		Non-stricturing ulcers	
				Endoscopy	Granuloma	Villous atrophy	Maximal depth of ulcer	Granuloma	Villous atrophy	Number	Open ulcer at stenosis	Circular	Linear
1.	–	NE	NE	NS	–	–	Submucosa	–	–	NE	NE	NE	NE
2.	–	NE	NE	Gastric ulcer	–	–	Submucosa	–	–	Multiple	+	+	+
3.	–	NE	NE	NS	–	–	Submucosa	–	–	NE	NE	NE	NE
4.	–	NE	NE	NS	–	–	Submucosa	–	–	Single	+	–	–
5.	+	–	NE	Duodenal ulcer	–	–	Submucosa	–	–	NE	NE	NE	NE
6.	+	–	NE	NS	–	–	Submucosa	–	–	Multiple	+	+	+
7.	–	–	NE	NS	–	–	Submucosa	–	–	Single	+	+	–
8.	±	–	NE	Stomal ulcer	–	–	Submucosa	–	–	-		+	+
9.	–	NE	NE	Stomal ulcer	–	–	Submucosa	–	–	Single	+	+	–
10.	–	NE	NE	NS	–	–	Submucosa	–	–	Multiple	+	+	+
11.	–	NE	NE	NS	–	–	NE	NE	NE	Single	+	–	–
12.	–	NE	NE	NS	–	–	Submucosa	–	–	Multiple	+	–	+
13.	–	–	–	NS	–	–	NE	NE	NE	Single	+	–	+

PPD; purified protein derivative. IGRA; interferon-γ release assays for tuberculosis. tTGA; tissue transglutaminase.
NS; no significant finding. NE; not examined.

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in only one patient, who showed a negative result. Two patients had a prior history of gastrectomy for gastroduodenal ulcers. Both patients had stomal ulcers. Two patients had gastric or duodenal ulcer. However, duodenal biopsies performed in all the patients were negative for villous atrophy. Also, villous atrophy of the ileum was not evident in any patient treated by ileal resection. The depth of the ileal ulcer was restricted to the submucosa in those patients. There was not any patient who had caseating or non-caseating granuloma in the biopsy or surgical specimens.

Table 3 summarizes the treatments applied for the patients. During the follow-up periods, prednisolone, aminosalicylates, combined anti-*Mycobacterium* agents, azathioprine and infliximab were used for nine patients, seven patients, six patients, two patients and a patient, respectively. The serum protein did not respond to any of those medications. In nine patients, the malnutrition transiently improved after total parenteral nutrition. Eleven patients were treated by ileal resection because of small-bowel stricture. Ten of those 11 patients, however, required repeated surgery after the recurrence of strictures. As indicated in Table 3, two patients were lost to follow up, while other four patients died. The remaining seven patients have been under observation. They still have hypoproteinemia and anemia, which require iron supplementation and total parenteral or enteral nutrition.

3.2. Final enteroscopic findings

We attempted enteroscopy in 11 patients during the clinical course. The time interval from the initial diagnosis until the final enteroscopy ranged from 0.5 to 44 years. In a patient (Case 5), however, enteroscopy was unavailable because of a duodenal stenosis.

The enteroscopic findings are indicated in Table 2. Nine patients had single or multiple concentric stenoses. In those patients, shallow and clearly demarcated ulcers were seen at the most severe stenosis (Figs. 2A and 3A). In addition, shallow ulcers accompanied by faint mucous exudates were seen in eight patients (Figs. 2B and 3B). A patient had a single stenosis without any accompanying mucosal defects.

3.3. Family history

Family histories of the patients are indicated in Table 4. The interviews to the patients and their relatives revealed that four patients were offspring of consanguineous marriage of 3 degrees, which means that their parents were cousins. In addition, other two patients were those of 5 degrees, indicating that their maternal and paternal grandparents were cousins. Four patients denied any such consanguinity in their family pedigrees. In the remaining three patients, we were not able to confirm their family pedigrees.

Information with regard to family histories of enteropathy was available in 11 patients. None of the patients commented on enteropathy in their parents or in their offspring. However, three patients commented on enteropathy in their siblings. The enteropathy included small intestinal stenoses of obscure origin (an elder sister of Case 4), CNSU (a younger sister of Case 10) verified in her medical record, and protein-losing enteropathy of obscure origin (an elder sister in Case 13). Two of the three family pedigrees were siblings of consanguineous marriage, while consanguinity was not evident in the remaining pedigree.

4. Discussion

We could confirm in this report that 1) CNSU is an enteropathy characterized by persistent anemia and hypoproteinemia occurring in childhood or in adolescence, 2) patients with CNSU had life-long illness, and 3) more than half of the patients had consanguinity and/or family history of enteropathy in their siblings even though vertical heredity was not obvious. These clinical observations suggest that CNSU is possibly a chronic enteropathy, which segregates in offspring from consanguinity. Even though most autosomal recessive disorders of the human bowel occur in infancy,[12] there have been recently reported two gastrointestinal disorders with such a hereditary trait, one being adenomatous polyposis with homozygous mutations of *MUTYH*[13–15] and the other chronic colitis with homozygous mutations of *IL10R*.[16]

Table 3 Treatment and prognosis of patients with CNSU.

Case no.	Medication		Efficacy of total parenteral nutrition	Number of ileal resection	Prognosis
	Species	Efficacy			
1.	PSL, cAMA	Not effective	Effective	2	Lost to follow-up
2.	PSL, cAMA, SASP	Not effective	Effective	3	Died of liver cirrhosis at age of 49 years
3.	PSL, cAMA	Not effective	(Not performed)	6	Lost to follow-up
4.	PSL, cAMA, SASP	Not effective	Effective	3	Died of pancreas cancer at age of 73 years
5.	PSL	Not effective	Effective	2	Alive at age of 59 years
6.	PSL, 5ASA, AZA	Not effective	Effective	1	Alive at age of 58 years
7.	PSL, cAMA	Not effective	Effective	6	Died of thyroid cancer at age of 58 years
8.	PSL, 5ASA	Not effective	Effective	2	Alive at age of 75 years
9.	PSL, cAMA, SASP	Not effective	(Not performed)	2	Alive at age of 67 years
10.	5ASA	Not effective	Effective	2	Died of stroke at age of 46 years
11.	IFX	Not effective	(Not performed)	0	Alive at the age of 60 years
12.	(None)		Effective	3	Alive at the age of 50 years
13.	5ASA, AZA	Not effective	(Not performed)	0	Alive at the age of 35 years

PSL; prednisolone, cAMA; combined anti-*Mycobacterium* agents, SASP; sulfasalazine, 5ASA; 5-aminosalicylate, AZA; azathioprine, IFX; infliximab.

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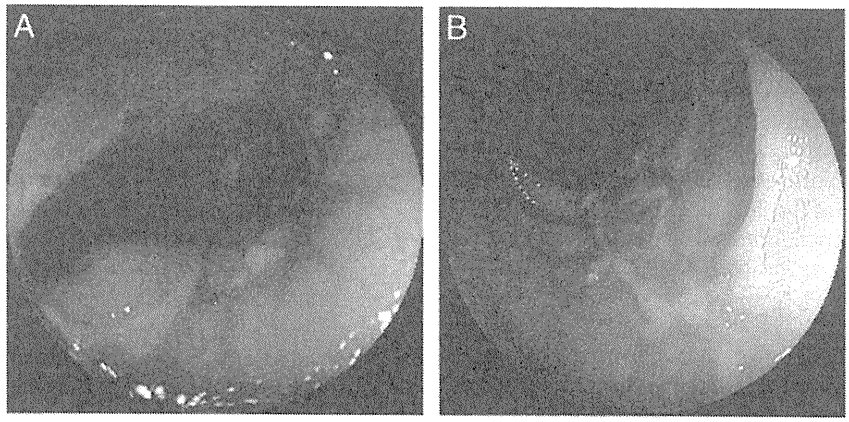

Figure 2 Enteroscopic findings of Case 13. This case is a daughter of a consanguineous marriage of 3 degrees, who has an elderly sister with protein-losing enteropathy. A; DBE reveals a severe concentric stenosis in the middle ileum. The stenostic area is accompanied by circular and sharply demarcated ulcer. B; DBE also shows a shallow, linear mucosal effect with clear margin in the distal ileum.

Small-bowel ulcers are known to occur in various types of chronic enteropathy of obscure etiology. These include Crohn's disease, chronic ulcerative duodenojejunoileitis,[17 19] cryptogenic multifocal ulcerous stenosing enteritis (CMUSE),[9] and diaphragm disease of the small bowel without apparent NSAID use.[8] CNSU shares common clinical manifestations with CMUSE and diaphragms unrelated to NSAID with respect to less severe inflammatory infiltrates and stenosing lesions of the ileum. We thus cannot conclusively distinguish CNSU from those two conditions. There also seems to be an argument that CNSU, together with CMUSE and diaphragms, belongs to a peculiar phenotype of Crohn's disease with less severe inflammation. The occurrence in adolescents with predominant involvement of the ileum in CNSU apparently mimics Crohn's disease, although the ileal phenotype is different between the two diseases.

In 1990s, data on the familial acquisition of Crohn's disease were accumulated. Analyses of those data from all over the world showed that the occurrence of Crohn's disease in the first-degree relatives of a proband ranged from 2.2% to 13.6%.[20 26] A common trend in those analyses was that the siblings of a proband were at the highest risk for the occurrence of the disease while parents have the lowest risk. Although a similar trend was also found in our patients with CNSU, the occurrence of enteropathy in the siblings was much higher, with a value of 23%. In contrast, the consanguinity has rarely been described in Crohn's disease. It thus seems likely that CNSU is genetically different from Crohn's disease.

So far as we reviewed the literature, two types of enteropathy are described in association of consanguinity. The first one is an intractable ulcerating enterocolitis of infancy characterized by diarrhea in the first year of life with large and deep ulcers in the colon.[27] The other enteropathy, referred to as intestinal epithelial dysphasia, has also been characterized by severe diarrhea in infants with disorganization of entrecotes in the epithelium and basement membrane abnormalities of the small-bowel.[28,29] The clinicopathologic features of the infantile enteropathy are obviously different from those of CNSU with respect to the age of onset and the clinical course.

Glocker et al.[16] recently analyzed two unrelated consanguineous families with an early onset of colitis, and they identified homozygous mutations in *IL10RA* and *IL-10RB* genes in the families. Even though the predominant site of involvement and other phenotypes are different between the cases reported by Glocker et al.[16] and those of CNSU, *IL-10R* may be one of the candidate genes associated with CNSU. Adler et al.[10] reported on another peculiar form of enteropathy with a life-long history of occult gastrointestinal

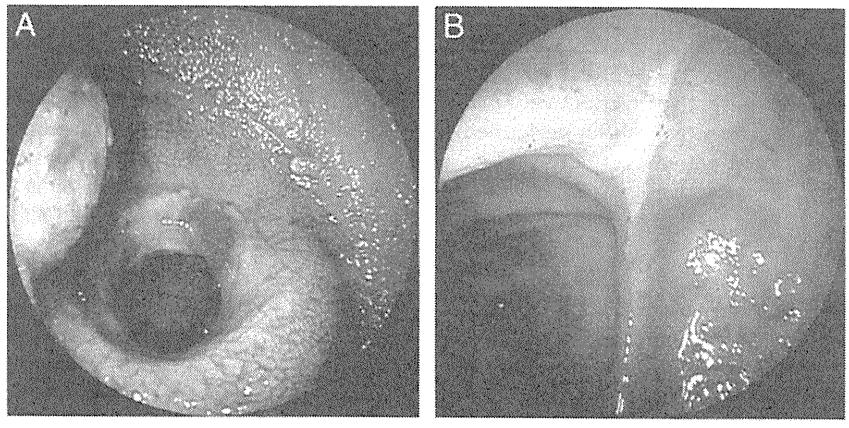

Figure 3 Enteroscopic findings of Case 6. This case is a daughter of a consanguineous marriage of 5 degrees. A; DBE shows a concentric stenosis with a clear ulcer in the ileum. B; in the distal ileum, sharply demarcated and linear mucosal defects are also seen.

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Table 4 Consanguinity and family history of patients with CNSU.

Case no.	Consanguinity (degrees)	Family history of enteropathy
1.	Present (3)	None
2.	Absent	None
3.	Unknown	Unknown
4.	Absent	None
5.	Absent	A sibling
6.	Present (5)	None
7.	Present (5)	None
8.	Present (3)	None
9.	Unknown	Unknown
10.	Present (3)	A sibling
11.	Unknown	None
12.	Absent	None
13.	Present (3)	A sibling

blood loss, iron deficiency anemia and relapsing abdominal pain. The male patient had multiple, sharply demarcated ulcers and stenoses in the jejunum and in the ileum during his middle-aged period. Histological examination of the resected small-bowel disclosed nonspecific ulcers with minimal inflammatory infiltrates. Furthermore, Adler et al.[10] confirmed that the patient had inherited compound heterozygosity in *cPLA2α* gene, which resulted in a reduction in eicosanoid biosynthesis in platelets and leukocytes. Based on these observations, it was suggested that homozygous or compound heterozygous mutations of *cPLA2α* gene and a consequent reduction in substrates for arachidonic acids result in an enteropathy with recurrent small-bowel ulcers. It thus seems possible that *cPLA2α* is another candidate gene for CNSU. This hypothesis is under investigation.

The present case series has some limitations due to a retrospective analysis of historically accumulated patients. First, we cannot completely deny undisclosed use of NSAID, because we did not measure its metabolites in blood or urine samples.[8,30] However, we believe the enterosopic findings and the extra-ordinary long-term clinical course of CNSU to be completely different from NSAID enteropathy.[3] Second, we could not serologically deny chronic jejunoileitis complicating celiac disease in 12 of 13 patients. However, we consider celiac disease to be unlikely, because the patients did not have any villous atrophy, and furthermore, the disease is extremely rare among Asians.

In conclusion, a retrospective analysis of patients with CNSU revealed that the disease is possibly an enteropathy segregating in offsprings from consanguineous marriage. This concept may explain the rarity of the disease, and suggests that CNSU is a disease distinct from Crohn's disease. Further accumulation of the patients together with genetic analyses will be needed to conclude that CNSU is an autosomal recessive disorder.

Acknowledgment

TaM contributed to the analysis of the data and the writing of the manuscript. NK collected all the demographic and endoscopic data. ToM, MI and TY contributed to the concept of the manuscript and the management of the study subjects.

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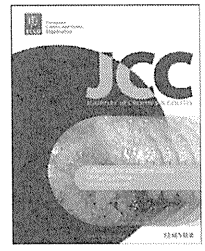

Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease

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KEYWORDS
Crohn's disease;
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Abstract

Background and aims: Adalimumab has been shown to be efficacious and well-tolerated in Western patients with Crohn's disease. These 2 randomized, double-blind clinical trials evaluated adalimumab efficacy and safety in Japanese patients with moderate to severe Crohn's disease. *Methods:* 90 patients enrolled in the induction trial and were randomized to receive adalimumab 160/80 mg, adalimumab 80/40 mg or placebo at Weeks 0/2. At Week 4, patients who achieved a decrease in CDAI ≥ 70 points versus Baseline entered the maintenance trial and were randomized to adalimumab 40 mg every other week or placebo for 52 weeks. All other patients received 4 more weeks of blinded adalimumab before entering the open-label portion of

Abbreviations: CD, Crohn's disease; PPD, purified protein derivative; TPN, total parenteral nutrition; CDAI, CD activity index; CR-70, decrease in CDAI score from Baseline ≥ 70; CR-100, decrease in CDAI score from Baseline ≥ 100; eow, every other week; 6-MP, 6-mercaptopurine; BCG, Bacillus Calmette-Guérin; IOIBD, International Organization of Inflammatory Bowel Disease; PCS, physical component summary; MCS, mental component summary; SF-36, Short Form-36 Health Survey; IBDQ, Inflammatory Bowel Disease Questionnaire; AAA, anti-adalimumab antibody; AAA+, patients positive for anti-adalimumab antibody; FAS, full analysis set; mFAS, modified full analysis set; HRQOL, health-related quality of life; IMM, immunomodulator; 5-ASA, 5-aminosalicyclate.

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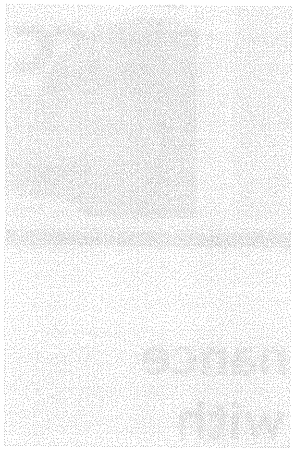

the maintenance trial. At/after Week 4 of the maintenance trial, blinded patients who flared/failed to respond entered the open-label portion. Open-label maintenance patients received adalimumab 40 mg every other week with the option of 80 mg every other week for flare/non-response.

Results: Clinical remission rates at Week 4 in the induction trial were 33.3%, 17.6% and 13.0% in the adalimumab 160/80 mg, adalimumab 80/40 mg and placebo groups, respectively. Maintenance remission rates were 38.1% for adalimumab and 9.1% for placebo at Week 52. Anti-TNF naïve patients achieved greater efficacy than anti-TNF exposed patients. Patients randomized to adalimumab achieved greater quality of life improvement versus placebo. There were no clinically relevant differences in safety between adalimumab and placebo.

Conclusions: Adalimumab is effective and well-tolerated for inducing and maintaining clinical remission in Japanese patients with moderate to severe Crohn's disease. NCT00445939; NCT00445432.

1. Introduction

The incidence and prevalence of Crohn's disease (CD) in Japan are lower than in other regions, although these have been shown to be increasing in Japan,[1] as they are in Western countries. Characteristics of CD in Japanese patients are the same as in Western patients. Though the positioning of nutritional therapy differs, the same drugs are used in Japanese and Western patients, and data supporting the use of anti-tumor necrosis factor (TNF) agents in the treatment of Japanese patients with CD are available.[2]

Adalimumab (HUMIRA, Abbott Laboratories, Abbott Park, Illinois, USA), a fully human monoclonal antibody that targets TNF, is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, CD, psoriasis, and juvenile idiopathic arthritis in the United States, Europe, and elsewhere.[3] In Japan, adalimumab is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis. Adalimumab was also approved for the treatment of CD in Japan on the basis of the present trials. Adalimumab has been shown to be effective for the induction and maintenance of remission in Western patients with moderate to severe CD.[4] Adalimumab is also effective in patients who have had an inadequate response to conventional therapy or who have lost response to or are unable to tolerate infliximab, the chimeric monoclonal antibody to TNF.[5] In addition, adalimumab has been shown to provide rapid and sustained improvements in quality of life, both physical and psychological, in adults with active CD in Western countries.[6–9]

The objectives of these 2 multicenter clinical trials were to determine the efficacy and safety of adalimumab in inducing and maintaining remission, and to determine the effect of adalimumab on quality of life in Japanese patients with moderate to severe CD. In addition, the pharmacokinetics and immunogenicity of adalimumab treatment in Japanese patients were assessed.

2. Methods

2.1. Patients

This report describes results from 2 related clinical trials conducted in Japanese patients: first, a multicenter, randomized, double-blind, placebo-controlled trial (NCT00445939, January 2007 to December 2007) for induction of remission of CD; then a follow-on multicenter, placebo-controlled 52-week trial (NCT00445432, March 2007 to December 2008) for maintenance of remission.

Japanese adults and adolescents ≥15 and ≤75 years of age, with a diagnosis of moderate to severely active CD (CD Activity Index [CDAI] score of 220–450) for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation, were included. Previous exposure to anti-TNF agents other than adalimumab was allowed; primary non-responders to prior anti-TNF therapy were excluded. Women of childbearing potential were not pregnant or breast-feeding and were practicing an acceptable method of birth control throughout the trial and for 150 days after the last study drug administration. Patients provided written informed consent and complied with the requirements of this study protocol. Written informed consent was provided by a parent or legal guardian if the patient was <20 years old.

Patients were excluded for a diagnosis of ulcerative colitis or indeterminate colitis; history of cancer, lymphoma, leukemia or lymphoproliferative disease; active tuberculosis, chest X-ray findings suggestive of previous or current tuberculosis infection, "strongly positive" purified protein derivative (PPD) skin test with induration and erythema ≥ 10 mm with either bulla, necrosis or double redness (concentric surrounding of strong redness by weaker redness)[10]; human immunodeficiency virus infection; persistent chronic infections or recent infections unrelated to CD, requiring hospitalization or treatment with anti-infectives (intravenous within 28 days or oral within 14 days); history of neurologic symptoms suggestive of central nervous system demyelinating disease; presence or suspicion of abscess; surgical bowel resections within the past 6 months; positive *C. difficile* stool assay at Screening; body weight<30 kg; clinically significant abnormalities found during the electrocardiogram evaluation or laboratory assessment at the Screening visit; or a poorly controlled medical condition or any condition which, in the opinion of the investigator, would put the patient at risk by participation in the trial. Patients who received total parenteral nutrition within 14 days before Baseline or enteral nutrition>1200 kcal/day were excluded, as were patients who used infliximab or any biological agent within 8 weeks of Baseline. Previous treatment with adalimumab or participation in an

adalimumab clinical trial, any prior exposure to natalizumab, and receipt of any investigational chemical agent in the past 28 days or 5 half-lives prior to Baseline were not allowed.

2.2. Study design

In the induction trial, patients were randomly assigned (3:3:2) to receive induction therapy with adalimumab 160/80 mg, adalimumab 80/40 mg, or placebo at Baseline and Week 2 (Fig. 1). Patients achieving a clinical response 70 (CR-70, decrease from Baseline in CDAI ≥ 70 points) at Week 4 in the induction trial entered the blinded portion of the 52-week maintenance trial and were randomly assigned (1:1) to receive adalimumab 40 mg every other week (eow) or placebo. CR-70 non-responder patients at Week 4 in the induction trial continued for a further 4 weeks in the induction trial and were given double-blind adalimumab, with the dose of adalimumab depending on the induction regimen to which the patients were initially randomized. Week 4 CR-70 non-responder patients who had been randomized to placebo in the induction trial were given blinded adalimumab 160/80 mg induction therapy at Weeks 4 and 6 in the induction trial, and then entered the open-label portion of the maintenance trial. Week 4 CR-70 non-responder patients who had been randomized to adalimumab at either induction dose in the induction trial were given blinded adalimumab 40 mg at Weeks 4 and 6, and then entered the open-label portion of the maintenance trial. To accommodate the differing lengths of the induction trial for the CR-70 responders (4 weeks) and the CR-70 non-responders (8 weeks), the Baseline week of the maintenance trial is called Week 0x and the numbering of the following weeks includes "x" to describe the follow-on nature of the maintenance trial.

At or after Week 4x, patients in the blinded portion of the maintenance trial who flared could enter the open-label portion. Patients in the open-label portion received adalimumab 40 mg eow with the ability to increase the adalimumab dose to 80 mg eow in case of flare or non-response; the escalation dose of 80 mg eow has been approved in Japan, instead of 40 mg weekly, for other indications including rheumatoid arthritis, psoriasis, and ankylosing spondylitis. Flare was defined as a recurrence of very active disease, specifically an increase of ≥ 70 points in CDAI when compared with Week 0x in the maintenance trial and a CDAI > 220. Lack of response was defined as not attaining a CDAI decrease of ≥ 70 points compared with Week 0 of the induction trial for 2 consecutive visits, at least 2 weeks apart.

Concomitant use of immunomodulators (azathioprine and 6-mercaptopurine), aminosalicylates, and Crohn's-related antibiotics, was permitted in the induction and maintenance trials, provided that the doses remained stable. Stable doses of corticosteroids (≤40 mg/day of prednisolone or equivalent), and stable enteral nutrition ≤1200 kcal/day were permitted. No changes of Crohn's-related concomitant therapies were allowed during the induction trial. At Week 4x of the maintenance trial, patients who had experienced a significant improvement in their Crohn's symptoms (defined as a CDAI decrease of ≥ 70 points compared to Baseline of induction trial) could taper enteral nutritional therapy and corticosteroid doses, with the possibility to increase back to the amount at Week 0x if the disease was aggravated. In the open-label treatment group in the maintenance trial, patients were allowed to reduce or discontinue Crohn's-related concomitant treatments after 12 weeks of exposure to open-label adalimumab, with the possibility to increase back to the initial dose if the patient experienced a loss of clinical response. In both the induction and maintenance trials, patients could receive isoniazide for the prophylaxis of tuberculosis infection in patients with induration ≥ 5 mm on the PPD skin test, irrespective of the Bacillus Calmette–Guérin (BCG) vaccination status.

2.3. Endpoints

2.3.1. Induction trial

The CDAI score and International Organization of Inflammatory Bowel Disease[11] (IOIBD) score were assessed at Baseline and every 2 weeks. The mental component summary (MCS) and physical component summary (PCS) of the Short Form-36 (SF-36) Health Survey and the Inflammatory Bowel Disease Questionnaire (IBDQ) were assessed at Baseline and every 4 weeks.[12–14] The primary endpoint was the proportion of patients in clinical remission (CDAI < 150) at Week 4. Secondary endpoints included the proportion of patients in clinical remission at Week 2 and with clinical response CR-100 or clinical response CR-70 (CDAI decrease of ≥ 100 or ≥ 70 from Baseline, respectively) at Week 2 and Week 4. Additional secondary endpoints included changes from Baseline in CDAI and IOIBD at Week 2 and Week 4 and changes from Baseline in SF-36 MCS and PCS, and IBDQ scores in each treatment group at Week 4. In *post-hoc* analyses, clinical remission, CR-100, and CR-70 at Week 4 were assessed in each treatment group after stratification by patients' previous use of anti-TNF therapies.

2.3.2. Maintenance trial

The CDAI and IOIBD were measured at Baseline (Week 0x) and every 4 weeks to Week 52x in the maintenance trial. The SF-36 MCS and PCS and the IBDQ were assessed at Baseline and Weeks 8x, 24x, and 52x. The primary endpoint was clinical remission (CDAI < 150) at Week 52x in the double-blind portion. Secondary endpoints included the proportion of patients in clinical remission, CR-100, or CR-70 every 4 weeks until Week 52x; changes from Baseline of the induction trial (Week 0) to Week 52x in CDAI, IOIBD, SF-36 MCS and PCS scores and IBDQ in the double-blind portion.

2.3.3. Pharmacokinetics and immunogenicity

Blood samples for serum adalimumab and anti-adalimumab antibody (AAA) assays were collected at Week 1 and prior to dose administration at Weeks 0, 2 and 4 in the induction trial and Weeks 0x, 4x, 8x, 12x, 16x, 20x, 24x, 36x and 52x in the maintenance trial. Adalimumab and AAA samples were analyzed at MDS Pharma Services (Switzerland AG) using validated enzyme-linked immunosorbent assay (ELISA) methods based on a double-antigen technique.[15] The lower limit of quantitation (LLOQ) for adalimumab concentration was established at 3.1 ng/mL in diluted serum or 31.3 ng/mL in undiluted serum. The coefficient of variation (CV) for adalimumab concentration was ≤7.0% and the analytical

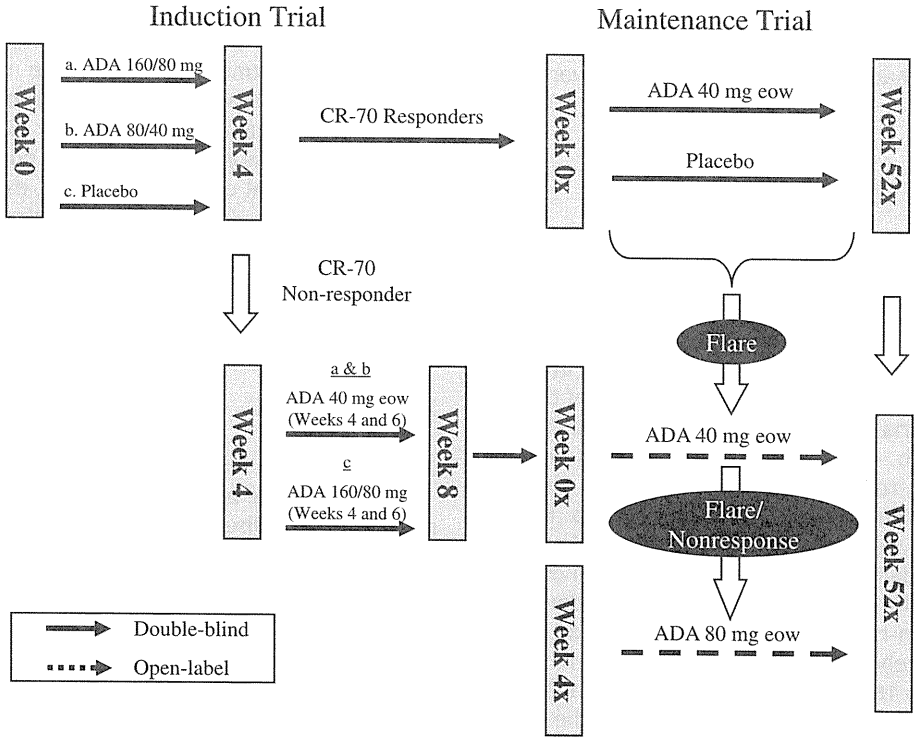

Figure 1 Study design. The primary efficacy analysis for the induction trial is at Week 4 and for the maintenance trial is at Week 52x. The "x" designation beside the week numbers indicates the follow-on nature of maintenance trial. ADA = adalimumab; eow = every other week; CR-70 = decrease in CDAI from Baseline ≥ 70.

recovery ranged from 97.5% to 108.5%. The LLOQ for AAA was established at 1.0 ng/mL in diluted serum or 10.0 ng/mL in undiluted serum. The CV for AAA was ≤ 23.4% and the percent bias ranged from −11.0% to 9.5%.

2.4. Statistics

The purpose of the induction trial was to show that at Week 4 the clinical remission rate in the adalimumab group was numerically higher than in the placebo group. This trial did not have a statistical hypothesis, and sample size was not calculated using statistical techniques. The small sample size of these trials relates to the overall low prevalence of CD in the Japanese population and therefore it was not possible to design the trials with power to reach statistical significance. The purpose of these trials was to show only a numerical difference between adalimumab and placebo. The study protocol stipulated 30 patients per adalimumab group and 20 patients per placebo group. Eighty patients in total were to be enrolled in the induction trial. All patients who completed the induction trial were eligible for the maintenance trial.

All patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug constituted the full analysis set (FAS) of the induction trial and were included in the primary and secondary efficacy analyses, and in the safety analyses for the induction trial. In the maintenance trial, patients who entered the double-blind portion and who received at least 1 dose of study drug comprised the FAS of the maintenance trial, for which the safety analysis was performed. Among the FAS of the maintenance trial, patients who received adalimumab in the induction trial constituted the modified FAS (mFAS), for which the primary and secondary efficacy analyses were performed. Patients who received at least 1 dose of adalimumab either during the induction trial or the maintenance trial comprised the all-adalimumab set. The dose escalation set included patients who received adalimumab 80 mg eow in the open-label portion of the maintenance trial.

In both trials, the primary and secondary efficacy analyses were performed using descriptive statistics. *Post-hoc* statistical analyses of rates of clinical remission and response were performed using Chi-square test or Fisher's exact test. Quality of life scores for adalimumab versus placebo and changes in scores from Baseline of the induction trial were compared using Student's *t*-tests. For all analyses of the proportion of patients in clinical remission, clinical response CR-100 and clinical response CR-70, patients who had missing values for the endpoint in question were not considered to have met the endpoint. Patients in the mFAS of the maintenance trial who switched to the open-label portion were also not considered to have met the endpoint in question after the switch. For the analyses of mean change from Baseline in CDAI, IOIBD, SF-36 MCS, SF-36 PCS and IBDQ, missing data were imputed using the last observation carried forward (LOCF) method. However, the measurements at Week 0x were not used to impute the missing values after Week 0x using the LOCF method.

Adalimumab concentrations were summarized by treatment group at each time point using descriptive statistics. Serum AAA concentrations were listed by treatment group at

each collection time. The proportion of patients positive for AAA (AAA+) was calculated and efficacy and safety for AAA+ patients assessed.

2.4.1. Safety

Adverse events (AE), laboratory values, and vital signs were assessed on a routine basis throughout both the induction and maintenance trials. AEs were analyzed using a descriptive analysis. In the induction and maintenance trials, a treatment-emergent AE (TEAE) was defined as any AE with onset from the first dose of study drug, with differing endpoints depending on whether the patient continued in the adalimumab development program or not. Specifically, for patients who continued in the adalimumab development program, the end-date for reporting TEAEs was at the trial end (Week 4 or 8 for the induction trial; Week 52x for the maintenance trial); for patients who discontinued the trial and did not continue in the adalimumab development program, the end-date for reporting TEAEs was up to 70 days following the last study drug administration. For analysis of the any adalimumab set (combines induction and maintenance trial), a TEAE was defined as any AE with onset from the first dose of adalimumab the patient ever received (which could have been in the induction trial for those randomized to adalimumab, or in the maintenance trial for those randomized to placebo in the induction trial) through

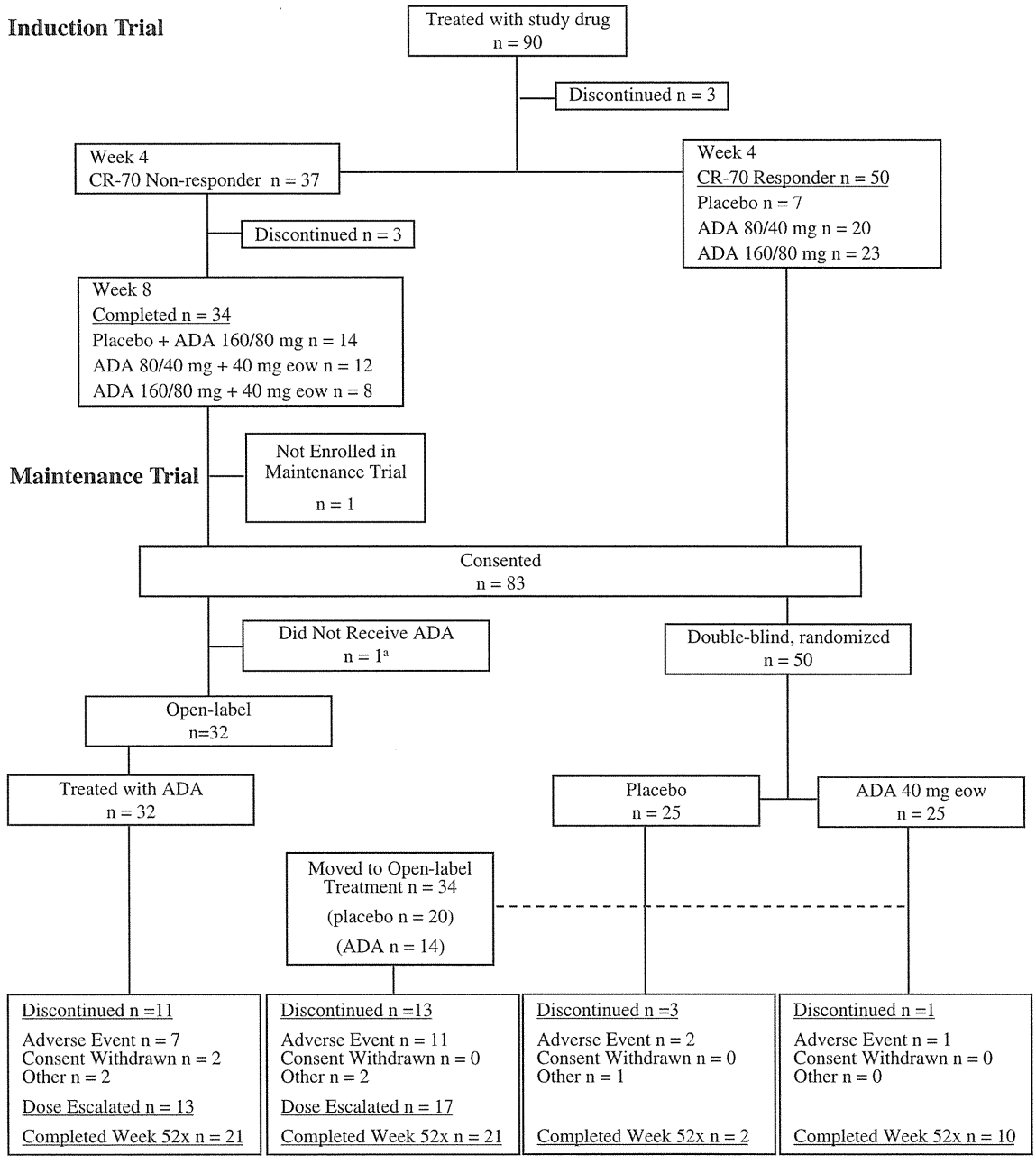

Figure 2 Patient disposition. The "x" designation beside the week numbers indicates the follow-on nature of maintenance trial. [a]One patient in the adalimumab 160/80 mg+40 mg eow group in the induction trial enrolled in the maintenance trial but was not dosed. ADA = adalimumab; CR-70 = decrease in CDAI from Baseline ≥ 70; eow = every other week.

an end-date up to the last dose received in the maintenance trial if the patient continued after Week 52x, or up to 70 days after the last dose of adalimumab if the patient discontinued either trial. Of note, for any adalimumab set, events that occurred during the placebo period prior to receipt of any adalimumab were excluded.

3. Results

3.1. Patient population

3.1.1. Induction trial

Informed consent was obtained from 108 patients, of which 90 were randomly assigned to receive study drug (adalimumab 160/80 mg, n=33; adalimumab 80/40 mg, n=34; placebo, n=23). 18 patients dropped out of the study prior to randomization. The reasons were ineligibility (n=13), serious adverse events (n=3), withdrawal of consent (n=1) and aggravation of CD (n=1).

3.1.2. Maintenance trial

Of 90 patients enrolled in the induction trial, 83 consented to continue in the maintenance trial (for the 7 patients who did not continue, 6 were terminated early from the induction trial due to adverse events and 1 did not continue in the maintenance trial because of the patient's demand); 50 entered the double-blind randomized portion (FAS) and 32 entered the open-label portion (1 patient was not treated). Of the 50 patients who entered the double-blind portion, 43 received adalimumab in the induction trial and were included in the mFAS. Patient disposition for the follow-on maintenance trial is summarized in Fig. 2.

3.2. Baseline characteristics

Baseline demographics, assessments of disease activity, efficacy parameters, health-related quality of life (HRQOL) scales, and concomitant medication use are summarized in Tables 1 and 2. There were no clinically important

Table 1 Baseline characteristics. [a]

	Induction trial				Maintenance trial		
	Full analysis set [b]				Full analysis set [c]		
	Placebo n=23	Adalimumab 80/40 mg n=34	Adalimumab 160/80 mg n=33	Total N=90	Placebo n=25	Adalimumab 40 mg eow n=25	Total N=50
Female, n (%)	7 (30.4)	18 (52.9)	13 (39.4)	38 (42.2)	10 (40.0)	9 (36.0)	19 (38.0)
Age (years)							
Mean±SD	30.4±6.9	30.6±9.3	32.0±9.6	31.1±8.8	30.8±10.9	31.6±7.2	31.2±9.2
<30 years	9 (39.1)	15 (44.1)	16 (48.5)	40 (44.4)	11 (44.0)	12 (48.0)	23 (46.0)
Weight (kg)							
Mean±SD	56.5±8.4	55.3±10.4	54.1±10.5	55.2±9.9	56.5±9.2	58.0±11.0	57.3±10.1
Min–Max	43.9–80.3	37.3–80.0	37.0–81.4	37.0–81.4	38.7–74.8	42.1–81.4	38.7–81.4
Tobacco, never used (n, %)	17 (73.9)	19 (55.9)	22 (66.7)	58 (64.4)	11 (44.0)	16 (64.0)	27 (54.0)
Alcohol, non-drinker (n, %)	14 (60.9)	21 (61.8)	24 (72.7)	59 (65.6)	14 (56.0)	15 (60.0)	29 (58.0)
Duration of CD (years)							
Mean±SD	7.9±4.7	9.2±6.6	11.0±7.1	9.5±6.4	8.2 (7.4)	9.9 (5.3)	9.1 (6.4)
Range	0.7–19.2	0.4–27.4	0.3–24.2	0.3–27.4	0.3–27.4	2.4–21.3	0.3–27.4
CDAI score							
Mean±SD	308.1±63.8	302.7±66.6	300.5±66.5	303.3±65.2	296.7±65.3	325.5±62.3	311.1±64.9
Range	221–444	221–448	221–448	221–448	221–448	223–448	221–448
CDAI score (n, %)							
<300	13 (56.5)	19 (55.9)	18 (54.5)	50 (55.6)	13 (52.0)	11 (44.0)	24 (48.0)
≥300	10 (43.5)	15 (44.1)	15 (45.5)	40 (44.4)	12 (48.0)	14 (56.0)	26 (52.0)
IOIBD score							
Mean±SD	3.7±1.2	3.4±1.6	3.3±1.5	3.4±1.5	3.2±1.8	3.1±1.2	3.2±1.5
Range	2–7	1–6	1–7	1–7	1–7	1–6	1–7
IBDQ score, Mean±SD	139.4±26.8	148.6±27.9	145.9±25.2	145.2±26.6	151.6±26.2	144.2±23.1	147.9±24.7
SF-36 summary score, Mean±SD							
Mental component	39.0±11.7	39.5±10.3	38.7±10.5	39.1±10.6	41.4±10.7	38.2±10.4	39.8±10.6
Physical component	43.8±7.6	42.9±7.8	43.3±6.3	43.3±7.2	45.0±6.5	42.9±7.7	43.9±7.1
C-reactive protein (mg/dL), Mean±SD	2.5±2.0	3.0±2.8	2.2±2.0	2.6±2.3	2.6±2.0	2.2±1.8	2.4±2.0

Eow = every other week; CD = Crohn's disease; CDAI = Crohn's disease activity index; IOIBD = International Organization for the Study of Inflammatory Bowel Disease; IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = Short Form-36.

[a] Baseline is Week 0 of induction trial for both the induction and maintenance trials.

[b] Patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug.

[c] Patients who entered the double-blind portion of the maintenance trial and received at least 1 dose of study drug.

Table 2 Crohn's disease-related medication prior to or at baseline of induction and maintenance trials. [a]

Baseline medication use	Induction trial				Maintenance trial		
	Full analysis set [b]				Full analysis set [c]		
	Placebo n=23	Adalimumab 80/40 mg n=34	Adalimumab 160/80 mg n=33	Total N=90	Placebo n=25	Adalimumab 40 mg eow n=25	Total N=50
Aminosalicylates	23 (100)	27 (79.4)	32 (97.0)	82 (91.1)	19 (76.0)	25 (100.0)	44 (88.0)
Immunosuppressants	8 (34.8)	11 (32.4)	10 (30.3)	29 (32.2)	7 (28.0)	11 (44.0)	18 (36.0)
Corticosteroids	5 (21.7)	6 (17.6)	8 (24.2)	19 (21.1)	5 (20.0)	3 (12.0)	8 (16.0)
CD-related antibiotics	2 (8.7)	1 (2.9)	2 (6.1)	5 (5.6)	1 (4.0)	1 (4.0)	2 (4.0)
Enteral nutrition	16 (69.6)	22 (64.7)	23 (69.7)	61 (67.8)	12 (48.0)	17 (68.0)	29 (58.0)
Anti-TNF [d]	13 (56.5)	20 (58.8)	19 (57.6)	52 (57.8)	14 (56.0)	13 (52.0)	27 (54.0)

Data are n (%).
Eow = every other week; CD = Crohn's disease.
[a] Baseline is Week 0 of induction trial for both the induction and maintenance trials.
[b] Patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug.
[c] Patients who entered the double-blind portion of the maintenance trial and received at least 1 dose of study drug.
[d] Previous use of infliximab or biologic, if any, had to be discontinued at least 8 weeks before Baseline.

differences in Baseline characteristics across treatment groups for either trial.

3.3. Efficacy

3.3.1. Induction trial

Patients who received adalimumab had rapid improvement in disease activity by Week 2, with continued improvement at Week 4 (Fig. 3A). Patients treated with adalimumab 160/80 mg had the highest rate of clinical remission at Week 4, compared with patients treated with adalimumab 80/40 mg or placebo (Fig. 3A). Anti-TNF-naïve patients were more likely to reach remission at Week 4 compared with patients who had prior anti-TNF exposure in all 3 treatment groups (Fig. 3B). Among patients with prior anti-TNF exposure, the clinical remission rate with adalimumab 160/80 mg treatment was more than double than that with adalimumab 80/40 mg treatment (Fig. 3B).

Significantly more patients treated with adalimumab reached CR-100 at Week 4 compared with placebo ($p<0.05$ for adalimumab 160/80 mg versus placebo and adalimumab 80/40 mg versus placebo) (Fig. 4A). Treatment with adalimumab was effective regardless of previous exposure to anti-TNF agents, although patients who had not been previously treated with anti-TNF therapy were more likely to reach CR-100 than those previously exposed to anti-TNF agents (Fig. 4A). The percentage of patients achieving CR-70 at Week 4 was greater in the adalimumab groups compared with placebo. However, results were significant only in the group treated with adalimumab 160/80 mg ($p=0.0062$, Fig. 4B). Adalimumab-treated patients who had not received previous anti-TNF therapy were more likely to reach CR-70 (Fig. 4B).

The mean changes in CDAI from Baseline to Week 2 and Week 4 were, respectively, −75.9 and −101.3 in the adalimumab 160/80 mg group, −74.4 and −81.3 in the adalimumab 80/40 mg group, and −27.2 and −37.5 in the placebo group. The mean changes in IOIBD score from Baseline to Week 2 and Week 4 were, respectively, −1.2 and −1.5 in the adalimumab 160/80 mg group, −0.7 and −0.8 in

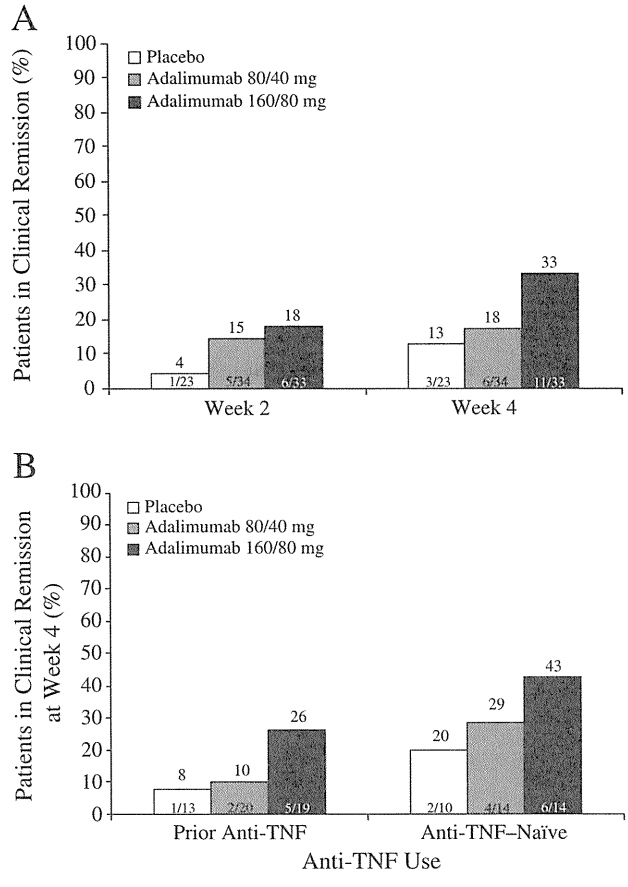

Figure 3 Clinical remission during the induction trial: (A) Remission at Weeks 2 and 4; (B) Remission at Week 4 stratified by prior anti-TNF exposure. Clinical remission is defined as CDAI<150. Analyses were conducted using non-responder imputation in the FAS (patients who enrolled in the induction trial, were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug). CDAI = Crohn's disease activity index; FAS = full analysis set.

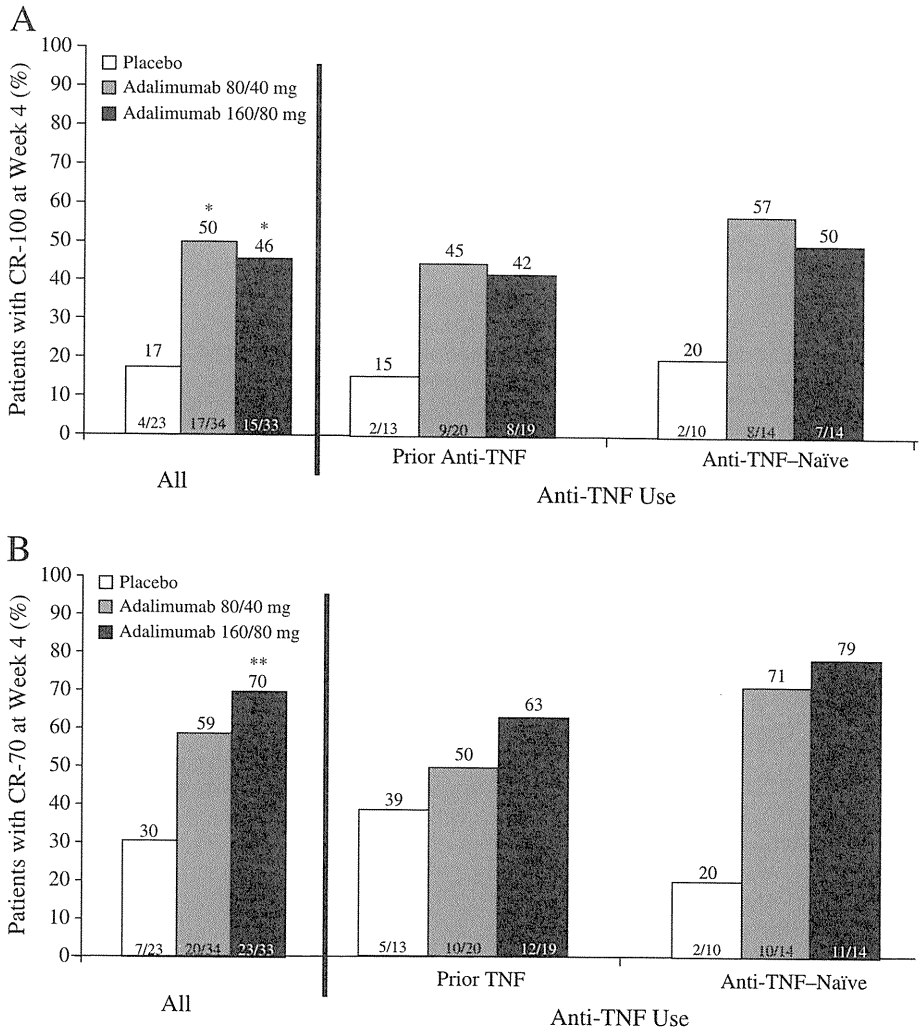

Figure 4 Clinical response during the induction trial: (A) CR-100 at Week 4 [All Patients and Stratified by Prior Anti-TNF Exposure]; (B) CR-70 at Week 4 [All Patients and Stratified by Prior Anti-TNF Exposure]. Analyses were conducted using non-responder imputation in the FAS (patients who enrolled in the induction trial, were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug). *$p<0.05$ versus placebo; **$p=0.0062$ versus placebo; all other p-values>0.05. CR-100 = decrease in CDAI from Baseline $\geq$ 100; CR-70 = decrease in CDAI from Baseline $\geq$ 70; CDAI = Crohn's disease activity index; FAS = full analysis set.

the adalimumab 80/40 mg group and −0.4 and −0.5 in the placebo group.

3.3.2. Maintenance trial

In the mFAS, a significantly greater percentage of adalimumab-treated patients achieved clinical remission at Week 52x compared with placebo ($p<0.05$, Fig. 5A). Adalimumab therapy was more effective than placebo in maintaining clinical remission, CR-100, and CR-70 over the course of the trial (Fig. 5A–C). Eight (16%) randomized patients (5 placebo-treated and 3 adalimumab-treated) were on corticosteroids when entering the maintenance trial (FAS). Of these, 6 patients (4 placebo-treated and 2 adalimumab-treated) were included in the mFAS population. Among these 6 patients, only 1 (adalimumab-treated) was in steroid-free remission at Week 52x (mFAS). Most of the placebo patients in the double-blind portion (20 of 25) relapsed and switched to open-label adalimumab, whereas 14 out of the 25 adalimumab patients moved from the double-blind portion to the open-label portion (Fig. 2).

In the mFAS, the mean changes (using LOCF) in CDAI from Baseline of the induction trial to Week 0x and 52x were −147.7 and −83.7 in the adalimumab-treated patients and −139.0 and −9.1 in the placebo-treated patients, respectively. The mean changes in IOIBD from Baseline of the induction trial to Week 0x and Week 52x were −2.0 and −0.8 in adalimumab-treated patients and −1.2 and −0.2 in placebo-treated patients, respectively.

The dose escalation set consisted of 30 patients receiving open-label treatment in the maintenance trial for whom the adalimumab dose was increased from 40 mg to 80 mg eow after Week 4x. Within this dose escalation set, 13 patients entered the open-label portion of the maintenance trial at Week 0x and 17 patients moved to the open-label portion after switching from the double-blind portion of the maintenance trial. In the dose escalation set, the percentage of patients who achieved clinical remission, CR-100 or CR-70

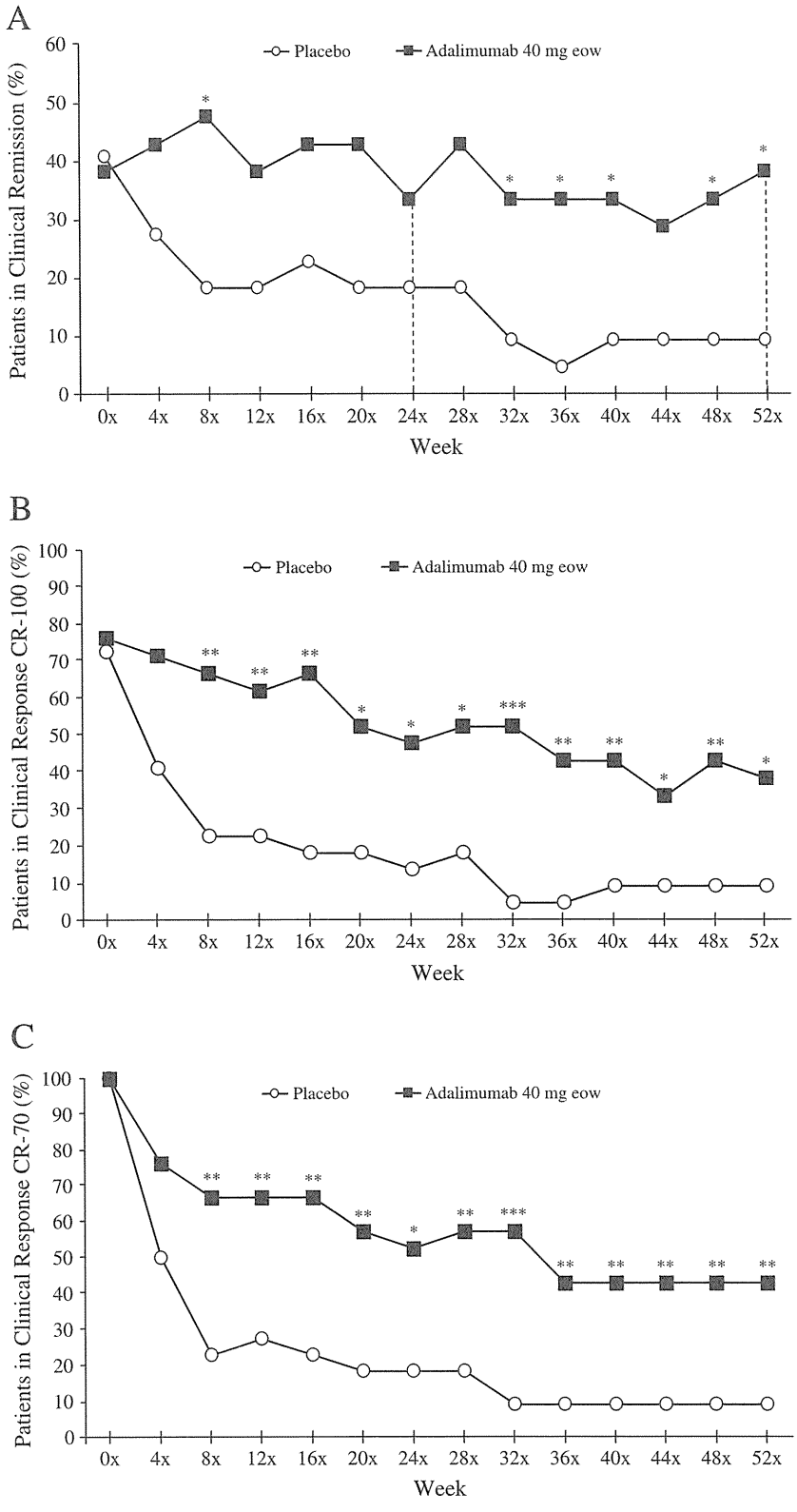

Figure 5 (A) Clinical remission, (B) Clinical response CR-100, and (C) Clinical response CR-70 over time in the maintenance trial. Clinical remission is defined as CDAI<150. Analyses were conducted using non-responder imputation in the mFAS (patients who received adalimumab in the induction trial, entered the double-blind portion of maintenance trial and received at least 1 dose of study drug); n=22 for placebo; n=21 for adalimumab. The "x" beside the week number designates the follow-on nature of the maintenance trial. *$p<0.05$, **$p<0.01$; ***$p<0.001$; all other p-values>0.05. CR-100 = decrease in CDAI from Baseline≥100; CR-70 = decrease in CDAI from Baseline≥70; CDAI = Crohn's disease activity index; mFAS = modified full analysis set; eow = every other week.