Journal of Crohn's and Colitis (2014) **8**, 1407–1416

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Long-term safety and efficacy of adalimumab in Japanese patients with moderate to severe Crohn's disease☆

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Received 22 November 2013; received in revised form 23 April 2014; accepted 28 April 2014

KEYWORDS
Crohn's disease;
Adalimumab;
Japan;
Long-term;
Maintenance

Abstract

Background and aims: Adalimumab has been shown to be effective and well tolerated in patients with Crohn's disease. This analysis reports the results of a cohort of Japanese patients with moderate to severe Crohn's disease who were evaluated for up to 3 years to assess the long-term use of adalimumab.
Methods: The study consisted of a double-blind part and an open-label part. Patients were included either in the 52-week double-blind, placebo-controlled part of the study followed by a 96-week open-label extension or in the open-label part from the beginning or in the event of a flare. Patients were treated with adalimumab and evaluated for up to 148 weeks as 3 data cohorts: the all-adalimumab cohort (patients receiving $\geq$1 injection of adalimumab), the 148-week follow-up subcohort (patients who completed 148 weeks of follow-up after the first adalimumab dose), and the dose-escalation subcohort (patients receiving adalimumab doses that increased to 80 mg every other week).

Abbreviations: 6-MP, 6-mercaptopurine; AAA, antibodies against adalimumab; ADA, adalimumab; AE, adverse event; AZA, azathioprine; CD, Crohn's disease; CDAI, CD activity index; CR, clinical response; CR-70, CR, decrease in CDAI score of $\geq$70; CR-100, CR, decrease in CDAI score of $\geq$100; eow, every other week; IOIBD, International Organization of Inflammatory Bowel Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; LOCF, last observation carried forward; PY, patient years; QOL, quality of life; SD, standard deviation; SF-36, Short Form 36 Health Survey; TNF-α, tumor necrosis factor-alpha.

☆ This study was presented at the 98th General Meeting of the Japanese Society of Gastroenterology; April 19–21, 2012; Tokyo, Japan.

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http://dx.doi.org/10.1016/j.crohns.2014.04.012

Results: In the all-adalimumab cohort (n = 79), clinical remission rates were approximately 30% after 36 weeks of exposure to adalimumab and for the remainder of the study (35%, 33%, and 28% for weeks 48, 108, and 144, respectively). An improvement in quality of life was also maintained over the same period. In the dose-escalation subcohort (n = 40), the clinical remission rate was 75% (6/8) 48 weeks after dose escalation. Adalimumab was tolerated, and no deaths were reported.
Conclusions: Adalimumab is effective for maintaining long-term clinical remission in Japanese patients with moderate to severe Crohn's disease (NCT00445432).

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract associated with transmural inflammation, which may lead to bowel damage and progressive disability.[1] Overexpression of the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) is a hallmark of CD pathogenesis, with elevated levels of TNF-α present in the colonic mucosa,[2] blood,[3] and stool.[4] Therefore, recent advances in the treatment of CD have focused on the development of biologic agents targeted at neutralizing TNF-α function.[5] Monoclonal antibodies targeting TNF-α, such as infliximab and adalimumab, have demonstrated efficacy in the induction and maintenance of remission in patients with moderate to severe CD.[6,7] Infliximab was the first TNF-α chimerical monoclonal antibody introduced for the treatment of CD. Although infliximab is highly effective in many patients with CD, some patients are unable to continue on long-term infliximab maintenance therapy because of hypersensitivity reactions or loss of response.[8–10]

Adalimumab (Humira®, AbbVie Inc., North Chicago, IL) is a fully human, recombinant, subcutaneously administered immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to TNF-α. Adalimumab is effective for inducing and maintaining remission in patients with moderate to severe CD at an induction dose of 160/80 mg (Week 0/Week 2) and at a maintenance dose of 40 mg every other week (eow).[7,11,12] In addition, adalimumab is effective at inducing clinical remission in patients who have lost response to or are intolerant to infliximab therapy.[13] An open-label extension trial of adalimumab in Western patients has shown maintenance of remission through 4 years.[14]

Recently, the efficacy of adalimumab was demonstrated in the treatment of CD in Japanese patients during a 4-week induction trial followed by a 52-week maintenance trial,[15] and adalimumab was approved for the treatment of CD in Japan on this basis. In the present maintenance trial, the long-term safety and efficacy of adalimumab treatment for maintaining clinical remission as well as its effect on quality of life (QOL) in Japanese patients with moderate to severe CD were assessed.

2. Materials and methods

2.1. Study design

The reported cohort is from a maintenance trial (NCT00445432) that followed a preceding induction trial (NCT00445939) and evaluated the efficacy and safety of adalimumab in Japanese patients with moderate to severe CD in a randomized, double-blind, placebo-controlled design.[15] The study methods and entry criteria have been previously described.[15] Briefly, patients who were older than 15 years but younger than 75 had been diagnosed with CD for longer than 4 months (diagnosis was confirmed by endoscopic or radiologic evaluation), and patients who had a CD activity index (CDAI) of 220 to 450 were included in the induction trial and rolled over into the maintenance trial. Patients who achieved a clinical response (CR), defined as a decrease in CDAI of $\geq$70 points versus baseline (CR-70), at the end of the 4-week induction trial entered the randomized portion of the maintenance trial (for a total of 52 weeks; 40 mg adalimumab or placebo eow). All the patients who did not achieve CR-70 (nonresponders) at the end of the 4-week induction trial entered the open-label arm of the maintenance trial later on. In addition, patients from the randomized, double-blind portion of the maintenance trial who experienced a flare were also moved to the open-label arm of the maintenance trial. Flare was defined as a recurrence of active disease, i.e., an increase of $\geq$70 points in CDAI compared with baseline in the maintenance trial and a CDAI $>$220.[15] Patients in the open-label arm of the maintenance study were given 40 mg adalimumab eow and could increase their dose to 80 mg eow in the event of nonresponse or a flare. After 1 year in the maintenance study, all patients could continue in the extension portion of the maintenance trial and receive open-label adalimumab at a dose of 40 mg eow or 80 mg eow for patients in the open-label arm who had previously been dose escalated to 80 mg eow (Fig. 1).

This study was approved by the institutional review boards of each study site and was conducted according to the principles of the Helsinki Declaration of 1975. Patients, or a parent or legal guardian if the patient was younger than 20 years old, provided written informed consent prior to study participation.

2.2. Clinical assessments

The CDAI and the International Organization of Inflammatory Bowel Disease (IOIBD) scores were assessed every 4 weeks until Week 52x and every 12 weeks afterwards. The Inflammatory Bowel Disease Questionnaire (IBDQ) score and the Short Form 36 Health Survey (SF-36) summary score were assessed at Weeks 8x, 24x, 52x, and every 24 weeks afterwards.

Samples for measurements of adalimumab plasma levels and antibodies against adalimumab (AAAs) were collected every 4 weeks until Week 24x, at Weeks 36x and 52x, and

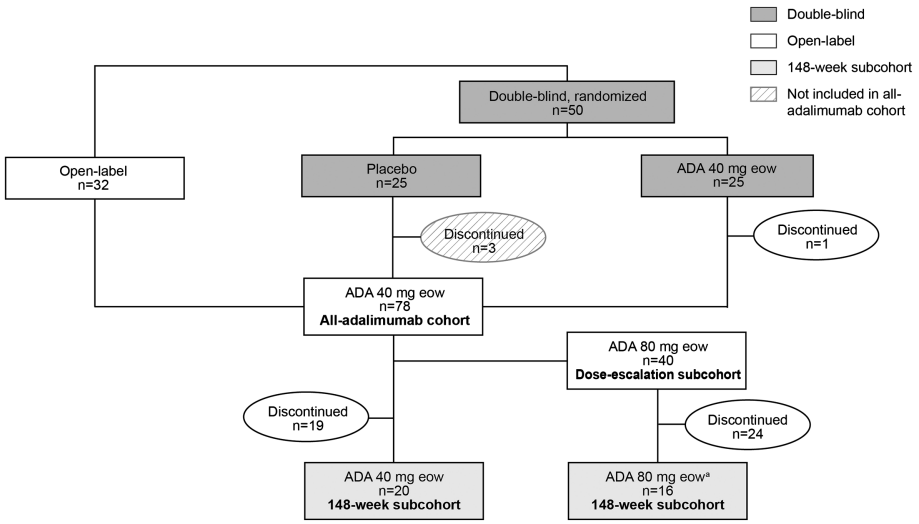

Figure 1 Study design. In this maintenance trial consisting of a 52-week double-blind portion[15] and an open-label extension portion, patients were treated with adalimumab for up to 3 years. ADA, adalimumab; eow, every other week. [a]One patient was dose-escalated to 80 mg but was in the 40-mg group at week 148.

every 12 weeks afterwards. The observation period for reporting pharmacokinetic data was from Week 52x to 148x. The methodologies for analyzing the samples for adalimumab and AAA measurement have been previously published.[15] Safety was assessed by evaluating reported and observed adverse events (AEs), vital sign measurements, and clinical laboratory tests (i.e., chemistry, hematology, urinalysis).

2.3. Patient cohorts

Three cohorts of patients were assessed in this study: the all-adalimumab cohort, which included all patients who received at least 1 injection of adalimumab in the maintenance trial, the dose-escalation subcohort, which included patients whose adalimumab doses were increased to 80 mg eow, and the 148-week follow-up subcohort, a group of patients who completed 148 weeks of follow-up after the first dose of adalimumab, some of whom continued treatment beyond this follow-up time point (Fig. 1). Adalimumab treatment in this study was designed to be continuous.

2.4. Endpoints

For the all-adalimumab cohort and 148-week follow-up subcohort, the proportion of patients achieving clinical remission (CDAI $<$150) was assessed as well as the proportion of patients achieving CR-70 and CR-100 (defined as a decrease in CDAI score of at least 100 points compared with baseline). Other endpoints included mean change from baseline in CDAI and mean change from baseline in IOIBD, IBDQ, and SF-36 summary scores. The primary observation period for the reporting of efficacy, safety, and pharmacokinetic data was 148 weeks after initiation of first dose of adalimumab in this maintenance study. For the dose-escalation subcohort, the proportion of patients achieving clinical remission (CDAI $<$150) was evaluated for 48 weeks after dose escalation.

2.5. Statistical analyses

Baseline and demographic characteristics, efficacy analyses, safety data, and pharmacokinetics were summarized using descriptive statistics. The baseline values for demographic characteristics and safety and efficacy analyses were designated as the values immediately before or during the last evaluation before the first dose of the study drug in the preceding induction trial. Efficacy, safety, and pharmacokinetic measurements were obtained throughout the study. Efficacy was assessed from the initiation of the first dose of adalimumab in the maintenance part of the trial. Some efficacy endpoints were also evaluated using Kaplan–Meier survival time analysis. Missing data on clinical remission rates endpoints were imputed by last observation carried forward (LOCF; missing values were replaced by the last observed value and reported at Week 144 for the primary observation), nonresponder imputation, or as-observed method (reported at Week 148 for the primary observation). All other efficacy and QOL endpoints were assessed by as-observed analysis. Serum adalimumab and AAA concentrations were summarized by patient cohorts at each time point using descriptive statistics. The differing lengths of the induction trial among patients entering the maintenance trial were accommodated by designating the week of entering into the maintenance trial Week "0x," and including an "x" in the numbering on the following weeks. The week "x" designation further differentiates between time on the maintenance trial versus time on adalimumab treatment in the maintenance trial, which is used for several of the analyses.

3. Results

3.1. Patient disposition

Of the 50 patients who were considered to be responders in the 4-week induction trial and entered the double-blind, randomized maintenance trial, 25 patients each were

randomized to adalimumab and placebo treatment (Fig. 2). Of the 25 patients randomized to placebo, 3 (12%) patients discontinued the study and are not considered in the present analysis, 20 (80%) patients moved to the open-label arm of adalimumab treatment, and 2 (8%) patients completed the blinded portion of the study until Week 52x. These 2 patients were then moved to the open-label extension portion of the maintenance trial. Of the 25 patients randomized to adalimumab, 1 patient discontinued the study, 14 patients moved to the open-label arm of adalimumab treatment, and 10 patients completed the blinded portion of the study until Week 52x. Thirty-two of the 33 patients who were nonresponders at Week 4 of the induction trial subsequently entered the open-label arm of the maintenance trial at Week 0x.

In total, 79 patients received at least 1 injection of adalimumab in this study and constitute the all-adalimumab cohort. Of these, efficacy analyses are available for 37 patients who completed 148 weeks of follow-up. These 37 patients compose the 148-week subcohort and have been included in the LOCF analysis; however, 1 patient discontinued before the final efficacy visit, and therefore 36 patients have been included in the as-observed analysis at Week 148 (Fig. 1). Eight of these 37 patients were randomized to placebo and 16 to adalimumab 40 mg eow, and 13 entered the open-label adalimumab arm at Week 0x of the maintenance trial. Forty patients in the all-adalimumab cohort entered the dose-escalation subcohort, and 16 of these patients completed the study. Fig. 2 summarizes the disposition of patients through 148 weeks of follow-up, and patient discontinuations are summarized in Supplemental Table 1.

3.2. Demographics and baseline characteristics

The mean age of patients in the all-adalimumab cohort was 30.9 years, and 59.5% of the patients were male (Table 1). The mean baseline CDAI total score was 301; 57% of the patients had a CDAI score of less than 300 and 43% of the patients had a CDAI score of 300 or greater. The mean IBDQ score, which was an indicator for QOL, was 146.7, and the mean SF-36 scores were 43.8 and 39.3 on the physical and mental components, respectively. For IBDQ, a score above 170 is generally considered to be in IBDQ remission. For SF-36, a score of 50 is considered as a mean for the general population. Corticosteroids were used as a previous medication for CD by 11.4% of the patients in the all-adalimumab cohort, while 19% of patients in this cohort previously used infliximab for the treatment of CD. Immunomodulators and corticosteroids were concomitantly used in 25.3% and 20.3% of the patients in the all-adalimumab cohort, respectively. The demographic and baseline patient characteristics of the dose-escalation and the 148-week follow-up subcohorts were similar to those in the all-adalimumab cohort (Table 1).

3.3. Efficacy

In the all-adalimumab cohort, clinical remission rates (LOCF analysis) were approximately 30% after Week 36 and through Week 144 of adalimumab treatment (Fig. 3), and the clinical remission rate at Week 144 was 28.2% (22/78). Remission rates were slightly lower when analyzed using a nonresponder imputation (i.e., 25.3% of the patients at Week 36 and 26.6% at Week 148). Clinical remission rates were higher (Fig. 4) and median time to remission was shorter in patients treated with concomitant azathioprine or 6-mercaptopurine compared with patients not treated with azathioprine or 6-mercaptopurine at baseline (median, 99 vs 252 days, respectively; hazard ratio, 0.65; 95% confidence interval, 0.35–1.89; $P = 0.16$). Clinical remission rates for patients treated with or without concomitant azathioprine or 6-mercaptopurine throughout the study followed a similar trend and are summarized in Supplemental Table 2.

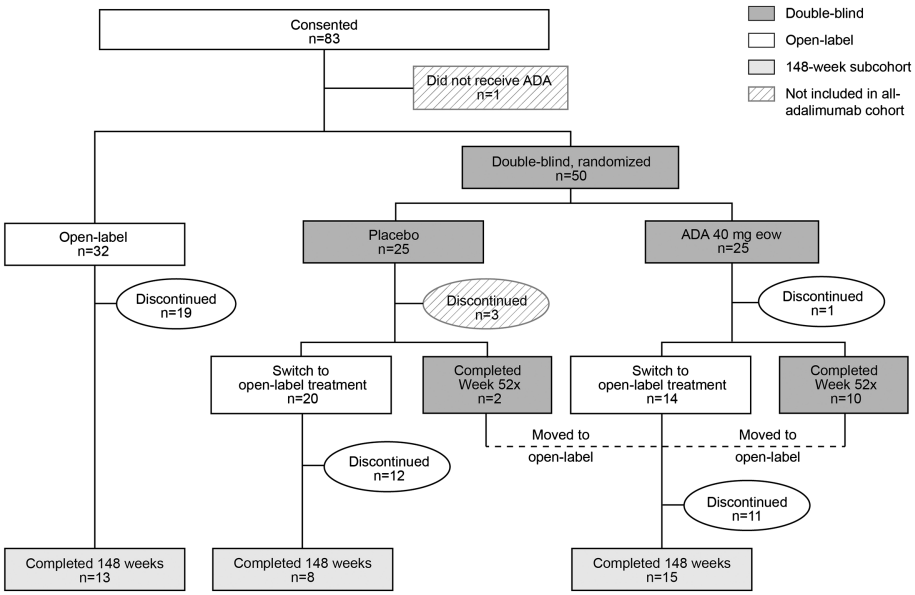

Figure 2 Patient disposition through up to 3 years. ADA, adalimumab; eow, every other week.

Table 1 Patient demographics and baseline characteristics. [a]

Characteristic	All-adalimumab cohort (n = 79)	148-week follow-up subcohort (n = 37)	Dose-escalation subcohort (n = 40)
Sex, n (%)			
Male	47 (59.5)	25 (67.6)	24 (60.0)
Female	32 (40.5)	12 (32.4)	16 (40.0)
Age, mean ± SD, y	30.9 ± 8.0	30.4 ± 8.5	30.2 ± 8.2
Age, n (%)			
<30 y	35 (44.3)	21 (56.8)	18 (45.0)
30–39 y	30 (38.0)	9 (24.3)	14 (35.0)
40–64 y	14 (17.7)	7 (18.9)	8 (20.0)
Weight, kg			
Mean ± SD	56.4 ± 9.7	57.2 ± 10.8	57.5 ± 10.4
Range	37.0–81.4	38.7–81.4	41.3–81.4
Tobacco, nonsmoker, n (%)	49 (62.0)	18 (48.6)	24 (60.0)
Alcohol, nondrinker, n (%)	51 (64.6)	22 (59.5)	21 (52.5)
Duration of CD, y			
Mean ± SD	9.5 ± 6.3	7.9 ± 4.7	9.6 ± 7.2
Range	0.3–27.4	1.1–21.3	0.3–27.4
CDAI score			
Mean ± SD	300.9 ± 62.8	298.6 ± 61.8	297.9 ± 58.4
Range	221–448	221–448	222–448
CDAI score, n (%)			
<300	45 (57.0)	21 (56.8)	23 (57.5)
≥300	34 (43.0)	16 (43.2)	17 (42.5)
IOIBD score			
Mean ± SD	3.3 ± 1.4	3.2 ± 1.1	3.5 ± 1.3
Range	1–7	1–6	1–7
IBDQ score, mean ± SD	146.7 ± 25.4	147.1 ± 25.6	150.3 ± 24.8
SF-36 summary score, mean ± SD			
Physical component	43.8 ± 6.6	44.2 ± 7.0	43.5 ± 5.5
Mental component	39.3 ± 10.6	38.4 ± 10.8	39.9 ± 8.8
C-reactive protein, n (%)			
≥1 mg/dL	53 (67.1)	24 (64.9)	28 (70.0)
<1 mg/dL	26 (32.9)	13 (35.1)	12 (30.0)
Median, mg/dL	1.58	1.24	1.74
Prior CD medication, n (%)			
Infliximab	15 (19.0)	9 (24.3)	25 (62.5)
Prednisolone	9 (11.4)	6 (16.2)	6 (15.0)
Concomitant CD medication, n (%)			
Azathioprine	20 (25.3)	9 (24.3)	6 (15.0)
Prednisolone	16 (20.3)	9 (24.3)	9 (22.5)

CD, Crohn's disease; CDAI, Crohn's disease activity index; IBDQ, Inflammatory Bowel Disease Questionnaire; IOIBD, International Organization of Inflammatory Bowel Disease; ND, not determined; SF-36, Short Form 36 Health Survey; SD, standard deviation.

[a] Baseline is the last measurement time point before the first dose of study medication in the induction trial.

However, clinical remission rates were not affected by baseline corticosteroid use. Using an as-observed analysis, the clinical remission rate after the first administration of adalimumab was 41.7% (20/48 patients) at Week 52, 59.1% (26/44) at Week 100, and 58.3% (21/36) at Week 148. Similar results were observed for the 37 patients who completed 148 weeks of adalimumab therapy. The clinical remission rates in this subcohort (as-observed analysis) were 62.2% (23/37 patients) at Week 100 and 58.3% (21/36) at Week 148. Based on as-observed analysis, clinical remission rates in patients in the all-adalimumab cohort who were responders at Week 4 of the induction period and were randomized to double-blind adalimumab treatment were 80.0% (8/10), 77.8% (7/9), and 71.4% (5/7) for Weeks 48, 100, and 148, respectively. Similar to the clinical remission rates, CR-70 and CR-100 remained at greater than 60% and 55%, respectively, after Week 36 through Week 148 of adalimumab treatment in patients in the all-adalimumab cohort and in the 148-week follow-up subcohort. The median survival time for CR-70 in the all-adalimumab cohort was 45 weeks (95% confidence interval, 13–158; Fig. 5). The analysis of the mean changes from baseline in CDAI in the all-adalimumab cohort indicated a sustained reduction in CDAI (≥100) throughout the 148 weeks of adalimumab

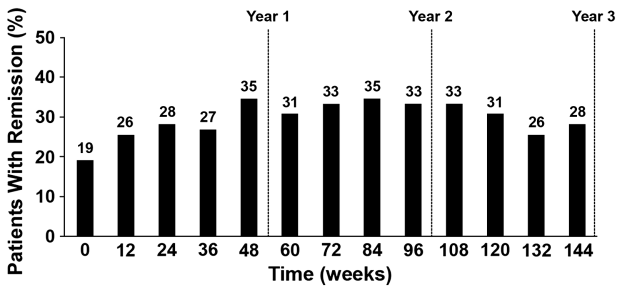

Figure 3 Clinical remission rate in the all-adalimumab cohort: LOCF analysis. The clinical remission rate remained around 30% after Week 36 throughout 148 weeks of adalimumab treatment. Week 0 is the time of the first dose of adalimumab. LOCF, last observation carried forward.

treatment (Table 2). Similarly, the mean changes in IOIBD score from baseline in the all-adalimumab cohort (Fig. 6) and 148-week follow-up subcohort remained reduced by 1 or more at all time points.

In patients in the dose-escalation subcohort (n = 40), the clinical remission rate was 0 at the dose-escalation visit, which subsequently increased after the adalimumab dose increase from 40 mg eow to 80 mg eow and was 75% (6 of 8 patients remaining in the subcohort) at 48 weeks after dose escalation (about 1 year; as-observed analysis). CR-70 and CR-100 were 7.5% (3/40) and 2.5% (1/40), respectively, at the dose-escalation visit and, similar to the CR rate, remained high 48 weeks after dose escalation (100% [8/8] and 87.5% [7/8] for CR-70 and CR-100, respectively). Clinical remission rates and CR-70 and CR-100 values for the dose-escalation cohort (as-observed analysis) for all visits from dose-escalation through the primary observation at Week 48 after dose-escalation are summarized in Supplemental Table 3. Additionally, the mean change from baseline in observed CDAI scores was −191.6 in the dose-escalation subcohort at 48 weeks after dose escalation (n = 8).

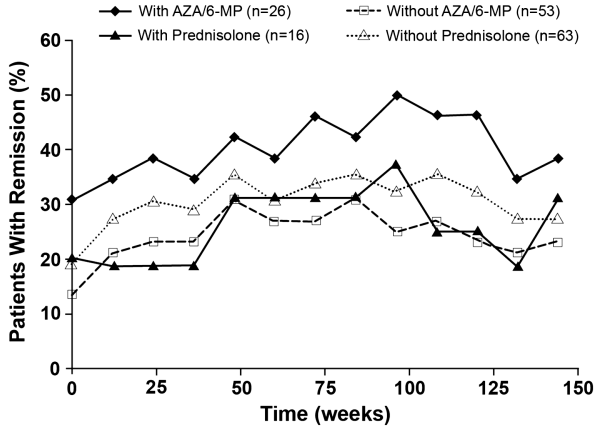

Figure 4 Clinical remission rate with and without concomitant use of AZA/6-MP or prednisolone in the all-adalimumab cohort: LOCF analysis. Clinical remission rates were greater in patients treated with concomitant AZA/6-MP compared with patients not treated with AZA/6-MP at baseline. However, clinical remission rates were not affected by baseline corticosteroid use. AZA/6-MP, azathioprine/6-mercaptopurine; LOCF, last observation carried forward.

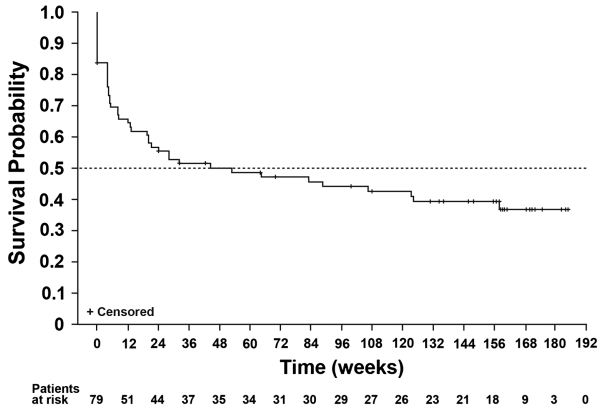

Figure 5 Kaplan–Meier curves for maintenance of long-term clinical response (CR-70). Long-term clinical response was maintained in some patients for approximately 3 years in the all-adalimumab cohort. The median survival time was 45 weeks (95% confidence interval, 13–158). CR-70, clinical response, decrease in Crohn's disease activity index score of ≥70.

3.4. Health-related QOL

The mean changes from baseline in IBDQ score in the all-adalimumab cohort increased and remained at 16 or greater after the first administration of adalimumab (Table 3). A change of 16 points is considered clinically meaningful. At most visits, the change scores were well above the minimal clinically important difference of 16 points. The mean IBDQ score at Week 148 was 174.4, which is above the cut for remission. The percentage of patients with IBDQ scores ≥170 at Week 148 was 56.8% (21/37). Similarly,

Table 2 Mean CDAI and change from baseline in CDAI after first administration of adalimumab in the all-adalimumab cohort. [a]

Week	Patients, n	CDAI, mean	Change from baseline, mean ± SD
0	78	222.8	−76.6 ± 87.9
12	73	197.4	−99.4 ± 90.0
24	63	179.0	−121.9 ± 89.9
36	56	187.6	−110.6 ± 81.3
48	47	159.2	−136.5 ± 85.5
64	51	175.5	−124.8 ± 96.1
76	50	160.8	−139.8 ± 99.4
88	46	150.6	−146.1 ± 100.1
100	44	153.9	−141.9 ± 109.7
112	41	135.7	−158.3 ± 94.7
124	38	142.6	−153.8 ± 97.5
136	39	153.5	−143.2 ± 104.4
148	36	156.9	−143.0 ± 102.5

CDAI, Crohn's disease activity index; SD, standard deviation.

[a] Baseline is the last measurement time point before the first dose of study medication in the induction trial.

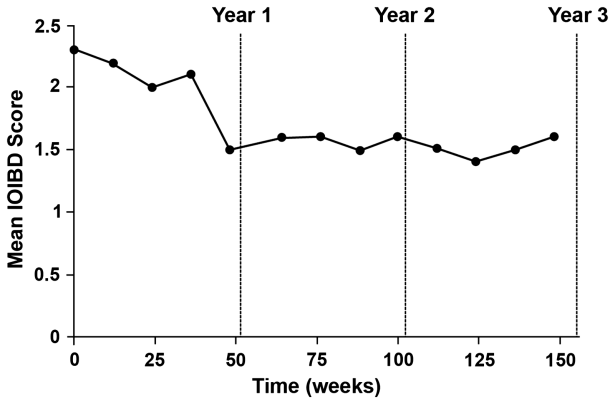

Figure 6 Mean changes in IOIBD score from baseline in the all-adalimumab cohort: as-observed analysis. Mean changes in IOIBD score from baseline remained reduced by at least 1 after the first administration of adalimumab. IOIBD, International Organization of Inflammatory Bowel Disease.

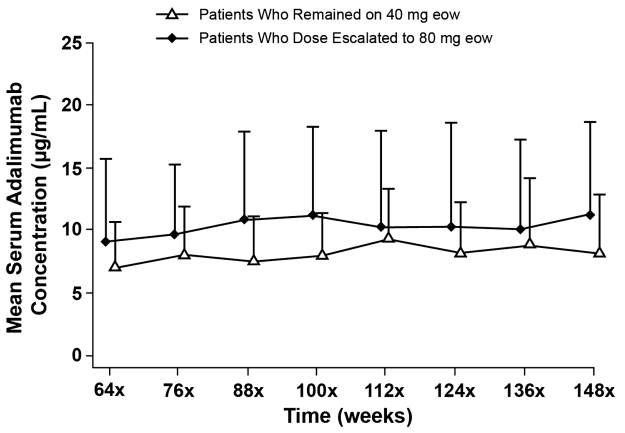

Figure 7 Mean serum adalimumab concentrations versus time after week 52x. Serum adalimumab concentrations remained constant after Week 52x in both patients who remained on 40 mg eow adalimumab treatment and those who dose escalated to 80 mg eow. The error bars denote standard deviation. eow, every other week.

the mean change from baseline in SF-36 scores (the physical and mental components) increased and remained at 3 or greater during most of the period after the first administration of adalimumab. A change of 3 points in SF-36 is considered clinically meaningful. At Week 148, the change in mental component summary score was 2 times that of clinically meaningful difference of 3 points. Similar results were observed for the 148-week follow-up subcohort. In summary, the increases in mean IBDQ and SF-36 scores observed in this study are considered clinically meaningful.

3.5. Pharmacokinetics

After Week 52x, the mean adalimumab trough concentrations in those who continued the open-label period were comparable between the patients receiving 40 mg eow and those who were dose escalated to 80 mg eow (Fig. 7). The mean adalimumab trough concentrations remained relatively constant from Week 64x to 148x (7–9 μg/mL) for the 27 patients who remained on 40 mg eow. The mean adalimumab trough concentrations for the 27 patients who dose escalated to 80 mg eow remained between 9 to 11 μg/mL from Week 64x to 148x. Five patients developed AAAs before Week 52x, and only 2 of these continued the study after Week 52x. No patients developed AAAs after Week 52x.

3.6. Safety

A total of 79 patients received at least 1 injection of adalimumab (constituting the all-adalimumab cohort), representing 155.3 patient-years (PY) of adalimumab exposure (Table 4). Adverse events occurred in all patients within this cohort (n = 79), and the number of AEs per 100 PY was 743.1. The incidence of AEs that were possibly drug related was 59.5% of the total number of AEs. The incidence of serious AEs was 62.0% (56.7 serious AEs/100 PY); the serious AEs were predominantly related to underlying CD. A total of 35.4% of patients discontinued because of an AE. Adverse

Table 3 Mean change from baseline in IBDQ and SF-36 scores after first administration of adalimumab in the all-adalimumab cohort. [a]

Week	Patients, n	IBDQ score		SF-36 physical component		SF-36 mental component	
		Mean	Change from baseline, mean ± SD	Mean	Change from baseline, mean ± SD	Mean	Change from baseline, mean ± SD
0	64	166.3	20.6 ± 23.8	48.1	4.2 ± 5.1	42.5	3.9 ± 9.6
8	74	162.5	16.1 ± 32.1	46.2	2.9 ± 8.3	41.8	2.6 ± 11.2
24	68	165.5	17.0 ± 33.2	47.4	3.4 ± 8.8	44.1	4.4 ± 11.1
52	55	167.3	21.2 ± 29.8	48.6	4.3 ± 7.6	42.9	4.7 ± 12.0
76	52	172.8	25.9 ± 26.7	49.0	4.5 ± 9.2	45.0	6.8 ± 11.1
100	45	174.0	27.9 ± 31.4	50.5	6.4 ± 7.4	43.7	5.4 ± 10.5
124	40	172.5	24.3 ± 33.8	49.9	5.6 ± 8.2	43.6	5.1 ± 10.5
148	37	174.4	27.2 ± 31.2	49.6	5.4 ± 7.2	44.8	6.4 ± 11.2

IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, Short Form 36 Health Survey; SD, standard deviation.

[a] Baseline is the last measurement time point before the first dose of study medication in the induction trial.

Table 4 Summary of AEs After First Administration of Adalimumab to 148 Weeks of Adalimumab Exposure in the All-Adalimumab Cohort.

Type of AE	Patients, n (%) (N = 79)	Number of AEs (AEs/100 PY) [a] PY = 155.3
Any AE	79 (100)	1154 (743.1)
Possibly drug related	47 (59.5)	127 (81.8)
Serious AE	49 (62.0)	88 (56.7)
Leading to early discontinuation	28 (35.4)	29 (18.7)
AE of interest		
Infection	68 (86.1)	337 (217.0)
Serious infection	9 (11.4)	11 (7.1)
Malignancy	0	0
Injection-site reaction	6 (7.6)	6 (3.9)
Opportunistic infection [b]	1 (1.3)	1 (0.6)
Tuberculosis	0	0
Congestive heart failure	0	0
Demyelinating disease	0	0
Hepatic event	21 (26.6)	36 (23.2)
Allergic reaction	1 (1.3)	1 (0.6)
Lupus-like syndrome	0	0
Blood disorder	2 (2.5)	2 (1.3)

AE, adverse event; PY, patient-years.

[a] PY = 155.3.
[b] Excluding tuberculosis.

events of interest with anti-TNF agents include serious infections, malignancies, opportunistic infections (excluding tuberculosis), and demyelinating disease. In the all-adalimumab cohort, 9 (11.4%) patients developed serious infections during the study, 3 of which were possibly related to the study drug. These infections included abdominal abscess in 2 patients and pneumonia in 1 patient. No deaths, lupus-like syndromes, demyelinating disease, congestive heart failure, tuberculosis, or malignancy cases were reported in this patient cohort. The incidence of injection-site reaction was low (7.6%) and mild in severity. The incidence of hepatic events, which were not study related, was 26.6%. The hepatic events that developed in more than 5% of patients were an increase in gamma-glutamyltransferase (7.6%) and abnormal hepatic function (5.1%) (measured as an increase in aspartate aminotransferase < alanine aminotransferase and gamma-glutamyltransferase). Of the 37 patients in the 148-week follow-up subcohort, a serious AE occurred in 18 (48.6%) patients, 3 (8.1%) patients developed a serious infectious AE, and 3 (8.1%) patients discontinued study drug due to an AE. The incidence of AEs was 77.5% (31/40) before the dose escalation and 95.0% (38/40) after the dose escalation. The frequency of AEs was 901.1 AEs/100 PY before dose escalation and 764.8 AEs/100 PY after dose escalation (summarized in Supplemental Table 4). However, the frequency of serious AEs was higher after the dose escalation (34.2 and 63.2 serious AEs/100 PY, respectively, before and after dose escalation). At the time of dose escalation, the symptoms of CD in these patients may have been worse than before dose escalation, as some of the serious AEs observed after dose escalation included aggravation of CD (15 serious AEs in 11 patients), ileus (3 serious AEs in 3 patients), and peritonitis (2 serious AEs in 2 patients), most of which were associated with underlying diseases.

4. Discussion

The purpose of this study was to evaluate the efficacy and safety of adalimumab as a means of maintaining clinical remission in patients with moderate or severe CD who responded to induction therapy with adalimumab during the preceding study[15] and the long-term continued adalimumab treatment in patients with CD who did not respond to induction therapy. In addition, the value of the escalated dose of adalimumab to 80 mg eow in patients who had a relapse of CD was also evaluated.

Because of the low prevalence of CD in Japan,[16] these trials were designed with a small sample size. However, the long-term efficacy and safety of adalimumab in Japanese patients with CD were expected to follow a similar trend as previously shown in Western patients.[14,17] This study enrolled 83 of the 84 patients who completed the preceding induction study[15]; of these, 79 patients received at least 1 injection of adalimumab and constitute the all-adalimumab cohort. The results of this trial demonstrate that the long-term administration of adalimumab as maintenance therapy in Japanese patients with moderate to severe CD was well tolerated and effective. The clinical remission rate and change in CDAI from baseline after open-label adalimumab treatment remained high at each visit, indicating that the disease activity remained reduced over a long period with this therapy. Furthermore, the reduction in IOIBD score from

baseline was also maintained during this period. Despite the limited number of patients enrolled in this study, the results of this long-term study are consistent with the long-term adalimumab data from the ADHERE trial with Western patients.[14,17]

Of the 79 patients included in the all-adalimumab cohort, the dose was increased from 40 mg to 80 mg due to CD relapse or lack of efficacy for 40 patients. About 75% (6/8) of these patients were in clinical remission at 48 weeks after the dose escalation, which is consistent with data from a Western study.[18] These results demonstrate that adequate responses can be obtained by increasing the dosage of adalimumab from 40 mg eow to 80 mg eow in patients who experience a relapse of CD or lack of drug efficacy. The results from the all-adalimumab cohort and subcohort who completed 148 weeks of follow-up also suggest that these responses can be maintained for a long period in some patients. These results are consistent with what was observed in the CHARM trial with Western patients.[7]

Adalimumab therapy resulted in QOL improvement, and long-term treatment with adalimumab maintained this improvement based on IBDQ and SF-36 scores. These results are consistent with QOL improvements observed in the CHARM trial in Western patients with CD.[7] Quality of life is particularly important because patients with active CD are known to show reduced QOL scores over time.[19] Therefore, it is clinically important to reduce the activity level of the disease as well as to maintain improved QOL scores when managing CD.

Serum adalimumab levels remained relatively constant after Week 52x, as was observed in the 1-year study[15] and other studies of adalimumab in Western patients with CD.[11,12] Although the rate of immunogenicity through 1 year of adalimumab treatment was slightly higher than the CLASSIC II trial (6.1% vs 2.6%), there were no new cases in the 2-year period after Week 52x in this study.[12,15]

The adverse event profiles for adalimumab therapy in this study were similar to those reported in other clinical trials of adalimumab in Western patients with CD,[14,17] and no deaths were reported. Adverse events occurred in all patients in the all-adalimumab cohort; the number of AEs per 100 PY was 743.1, which is similar to the 713.0 AEs per 100 PY observed in Western patients with CD in a 2-year long-term study.[12] In addition, patients with CD experience a substantial rate of AEs as evidenced by the AE rates observed for placebo recipients in controlled trials of adalimumab.[11,13] The incidence of serious AEs was 62.0% in this study; however, most of the events were associated with underlying CD. In the patients in the dose-escalation subcohort, the incidence of AEs was higher after dose escalation than before dose escalation. Because CD symptoms tended to be aggravated (relapse of the disease or lack of efficacy) at the time of the dose escalation, it is likely that the incidence of AEs associated with the underlying CD increased after the dose escalation.

Overall, this long-term study demonstrates that adalimumab therapy can sustain remission and improvements in QOL scores for at least 3 years in Japanese patients with moderate to severe CD. The results also demonstrated the usefulness of increasing the adalimumab dosage to 80 mg eow when treating disease relapse in patients who received adalimumab 40 mg eow.

Conflicts of interest

Mamoru Watanabe: Grants: AbbVie GK, Astellas Pharma Inc., Asahi Kasei Kuraray Medical Co., Ltd., Ajinomoto Pharma Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Kyorin Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Mitsubishi Tanabe Pharma Corporation, MSD KK, Otsuka Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., UCB Japan Co., Ltd., and Zeria Pharmaceutical Co., Ltd. Lecture fees/Speakers Bureau: AbbVie GK, Eisai Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation.

Toshifumi Hibi: Grants: AbbVie GK, Ajinomoto Pharmaceuticals Co., Ltd., Asahi Kasei Kuraray Medical Co., Ltd., AstraZeneca KK, Janssen Pharmaceutical KK, JIMRO Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Otsuka Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, UCB Japan Co., Ltd., UMN Pharma Inc., Zeria Pharmaceutical Co., Ltd. Lecture fees/Speakers Bureau: AbbVie GK, Asahi Kasei Kuraray Medical Co., Ltd., JIMRO Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, and Zeria Pharmaceutical Co., Ltd.

Nael Mostafa, Jingdong Chao, Anne Camez, Joel Petersson, Roopal Thakkar: Employees of AbbVie Inc. and may hold AbbVie stock or options. Vipin Arora was an employee of AbbVie Inc at the time this work was done and may hold AbbVie stock or options.

Acknowledgments

This study was supported by AbbVie Inc. and Eisai Co., Ltd. (Tokyo, Japan). The authors and AbbVie scientists designed the study and participated in the interpretation of data, review, and approval of the manuscript. All authors had access to the data, contributed to the development of the content, reviewed each draft of the manuscript, and approved the final content. Medical writing and editorial assistance were provided under the direction of the authors by Pratibha Hebbar, PhD, Jillian Gee, PhD, Rebecca Slager, PhD, MS, and Gina Uhlenbrauck at MedThink SciCom. The financial support for these services was provided by AbbVie. The authors would like to thank the investigators who participated in these trials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2014.04.012.

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