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Efficacy and Safety of Dose Escalation to Adalimumab 80 mg Every Other Week in Japanese Patients with Crohn Disease Who Lost Response to Maintenance Therapy

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Clinical response · Clinical trials · Crohn disease · Dose escalation · Tumor necrosis factor

Abstract
Background: Dose escalation is often recommended for loss of response in anti-TNFα-treated patients with Crohn disease (CD). This 52-week phase 3, multicenter study investigated the efficacy and safety of escalation to adalimumab 80 mg every other week (EOW) in Japanese patients with CD who lost response to maintenance adalimumab 40 mg EOW. ***Methods:*** Twenty-eight patients aged ≥15 years with moderately to severely active CD who had previously attained and subsequently lost clinical response to maintenance adalimumab received open-label adalimumab 80 mg EOW during weeks 0–50. Loss of response was defined as CD activity index (CDAI) ≥200, increases in CDAI ≥50 from minimum observed value, and C-reactive protein (CRP) ≥1 mg/dL at screening. The primary endpoint was the proportion of patients achieving a CDAI decrease ≥50 (CR-50) from baseline at week 8. ***Results:*** At weeks 8 and 52, 75.0 and 57.1% of patients achieved CR-50 and 25.0 and 35.7% achieved clinical remission (CDAI <150), respectively; median CRP changes from baseline were −0.39 and −0.77 mg/dL, respectively. Most treatment-emergent adverse events were mild to moderate. ***Conclusions:*** Adalimumab dose escalation to 80 mg EOW improved CD activity in patients who had lost response to maintenance adalimumab, with no new safety signals.

Introduction

Crohn disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by discretely distributed transmural granulomatous inflammation and fistulas [1]. Based on the results of multiple trials con-

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ducted in patients with moderately to severely active disease [2–6], the antitumor necrosis factor-alpha (anti-TNFα) agent adalimumab was approved globally for induction and maintenance treatment of CD.

In patients with moderately to severely active CD who experience loss of response to a particular anti-TNFα agent, international consensus guidelines recommend reducing the interval between doses or escalating the dose before switching to another anti-TNFα agent [7, 8]. In Western patients with CD who had an inadequate response to adalimumab 40 mg every other week (EOW), escalation to 40 mg every week was shown to recapture responses with no new safety risks [9]. Adalimumab is approved for CD in 88 countries and dose escalation to 40 mg weekly is approved in more than 82 countries.

In Japan, adalimumab is approved for the treatment of moderately to severely active CD at doses of 160 mg at week 0, 80 mg at week 2, and 40 mg EOW thereafter [10]. Dose escalation to adalimumab 80 mg EOW is approved in Japan for rheumatoid arthritis, plaque psoriasis, arthritic psoriasis, and ankylosing spondylitis when adalimumab 40 mg EOW is insufficient [11]. Since adalimumab is frequently administered in Japan by a healthcare provider rather than by self-injection, dose escalation to 80 mg EOW was thought to be preferred to 40 mg weekly, and 80 mg EOW was used in the rescue arm in cases of flare or nonresponse in the Japanese phase 3 study for CD maintenance of remission [6].

The objective of this study was to investigate the efficacy, safety, and pharmacokinetics of adalimumab after dose escalation to 80 mg EOW in Japanese patients with moderately to severely active CD who had lost response to adalimumab 40 mg EOW maintenance therapy.

Methods

Patients

This phase 3, multicenter, open-label, single-arm 52-week study (M13-687; ClinicalTrials.gov identifier: NCT01958827) was conducted from September 18, 2013 to October 01, 2015 (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000486786) at 12 sites in Japan. Patients were invited to participate in the study by the investigators and provided informed consent prior to any study-related screening procedures. If the patient was aged <20 years, his or her parent or legal guardian provided informed consent.

Eligible patients were Japanese individuals ≥15 years of age with moderately to severely active CD who received induction treatment with commercially available adalimumab (Humira®; 160/80 mg at weeks 0/2), achieved a decrease in CD activity index (CDAI) of ≥70 (CR-70) at 4 weeks after initial dose, and then lost response (defined as increased CDAI ≥50 points from the lowest CDAI after initiation of Humira® treatment, an absolute CDAI of ≥200) during maintenance treatment with Humira® 40 mg EOW. CDAI was evaluated at screening and at week 0 (baseline); patients had to meet the definition of loss of response at both time points. The time from screening to first dose was ≤21 days. The investigators evaluated whether the patients met all eligibility criteria from screening to week 0. Eligible patients also had C-reactive protein (CRP) ≥1 mg/dL at screening. Previous use of biologic therapy other than adalimumab was permitted if the patient had discontinued its use >56 days prior to week 0. Female patients with a positive pregnancy test at screening or week 0 were not included.

Study Design

Patients received subcutaneous injections of open-label adalimumab 80 mg EOW from week 0 to week 50. The adalimumab dose could not be reduced to 40 mg EOW during the study. Self-injection of the study drug was permitted with agreement from the investigator for patients who were willing to perform self-injection. Patients were allowed to continue stable doses of aminosalicylates, oral corticosteroids, immunosuppressants (i.e., azathioprine, 6-mercaptopurine, or methotrexate), and CD-related antibiotics from week 0 (baseline) until week 8 (or early termination). At week 8, patients receiving oral corticosteroids were allowed to begin taper if, in the judgment of the investigator, the patient responded to treatment. The schedule for tapering consisted of reducing the daily prednisolone or equivalent dosage by 5 mg/week for doses >10 mg and by 2.5 mg/week for doses <10 mg. Changes to doses of immunosuppressants, aminosalicylates, or antibiotics were allowed after week 8.

Efficacy Evaluations

Disease activity was evaluated by CDAI at screening, week 0 (baseline), and every 4 weeks until week 52. Follow-up was performed 70 days after the last dose of study drug, except for patients who switched to commercial adalimumab (Humira®) at week 52. Patients who did not achieve CR-50 (CDAI decrease ≥50 from week 0) at week 8 or who did not achieve CR-50 at 2 consecutive CDAI evaluations after week 8 were to be withdrawn from the study.

Patients who received at least 1 dose of study medication and had at least 1 posttreatment efficacy assessment were included in the primary efficacy analysis population (i.e., the full analysis set). The safety analysis population consisted of all patients who received at least 1 dose of study medication.

The primary endpoint of the study was the proportion of patients achieving CR-50 at week 8. Secondary endpoints included change in CRP from week 0 at each visit, the proportion of patients achieving CR-50, CR-70, and CR-100 (CDAI decrease ≥100 from week 0) at each visit, and the proportion of patients in clinical remission (CDAI <150) at each visit.

Safety Evaluations

Adverse events (AEs) were monitored on a routine basis throughout the study and were assessed at each study visit, or every 4 weeks for patients who performed self-injection. Treatment-emergent AEs (TEAEs) were logged from the first dose of study drug up to 70 days after the last dose. Serious AEs were logged from the time informed consent was obtained up to 70 days after the last dose. All TEAEs were summarized using the Medical Dictionary for Regulatory Activities (MedDRA version 17.1) by primary sys-

tem organ class and preferred term. The severity of each AE was assessed using the Common Terminology Criteria for Adverse Events, version 4.0 – Japanese translation of the Japan Clinical Oncology Group (JCOG).

All patients underwent radiological evaluations during screening to rule out the presence of tuberculosis or other clinically relevant findings; they also had a purified protein derivative skin test or interferon-γ release assay (QuantiFERON-TB Gold In-Tube test; Quest Diagnostic, Madison, NJ, USA; or T-SPOT.*TB* test; Oxford Immunotec, Ltd., Oxford, UK). Patients with evidence of latent tuberculosis infection were required to complete ≥21 days of tuberculosis prophylaxis or have completed a full course of prophylaxis prior to week 0. During screening, patients also underwent a 12-lead electrocardiogram, physical examination and medical history, general laboratory testing, and testing for hepatitis B and C virus and human immunodeficiency virus.

Pharmacokinetic Evaluations

Blood samples for adalimumab levels were collected before study drug administration at baseline (week 0) and weeks 2, 4, 8, 12, 24, 36, and 52 or at the premature discontinuation visit. Serum concentrations were measured within a 3-day window from week 2 to week 8 and within a 7-day window at or after week 10. Samples were taken for anti-adalimumab antibodies (AAAs) at baseline, weeks 8, 24, 36, and 52, or at the premature discontinuation visit. In patients with prior exposure to infliximab, blood samples for infliximab and human anti-chimeric antibody (HACA) were measured at baseline. Adalimumab serum concentrations were determined using a validated heterogeneous electrochemiluminescence immunoassay. AAAs were determined using a validated double-antigen immunoassay [12]. Subjects with at least one AAA concentration >20 ng/mL in samples collected between baseline and within 30 days after the last adalimumab dose were considered to be AAA+.

Analyses and Statistical Methods

Efficacy data and continuous variables were summarized descriptively. Point estimation and 95% confidence intervals (CIs) of the proportion of patients who achieved CR-50 at week 8 were used for the primary endpoint. The success criterion of the study was considered to have been met if the lower limit of the 95% CI of the primary endpoint (CR-50 at week 8) was >30%. Nonresponder imputation (NRI) was used for patients missing categorical endpoint data for any reason (including patients who terminated study participation for protocol-defined nonresponse). Last observation carried forward (LOCF) was used for the analysis of median change from baseline in CRP levels.

Factors affecting achievement of remission at 24 weeks after dose escalation were analyzed using logistic regression analysis as a preliminary analysis to evaluate the impact of baseline conditions. Factors included in univariate analysis were sex, body weight, disease duration, smoking status, duration of adalimumab treatment, concomitant medication, prior infliximab use, perianal disease, surgery, CDAI, CRP, hemoglobin level, albumin level, and adalimumab trough concentration. To evaluate the robustness of the result, multivariate analysis was performed including significant factors by univariate analysis ($p < 0.05$) and factors that were not significant but considered clinically important. For the continuous variables, the odds ratio (OR) was calculated for every 1-point increase in the levels. Associations between achieving remission 24 weeks after dose escalation and CDAI at week 4 were analyzed using the Wilcoxon rank-sum test. A subgroup analysis of prior infliximab use was also performed.

Serum adalimumab concentrations were summarized at each time point using descriptive statistics. For summary statistics and plots, concentrations below the lower limit of quantitation were set to zero. A comparison of mean adalimumab concentrations stratified by week 52 remission status and by AAA status was performed.

Table 1. Patient demographics and baseline characteristics

	Adalimumab 80 mg EOW (n = 28)
Males	16 (57.1)
Age, years	33.6±10.1
Weight, kg	55.35±11.6
BMI	20.27±4.3
Tobacco	
Current user	2 (7.1)
Never used	25 (89.3)
Alcohol (nondrinker)	13 (46.4)
Duration of CD, years	8.61±6.3
CDAI	308.4±93.4
CRP, mg/dL	2.35 (0.25–6.78)
Prior infliximab use	19 (67.9)
Concomitant medication use at baseline	
Aminosalicylates	23 (82.1)
Immunosuppressants[a]	13 (46.4)
Antibiotics[b]	7 (25.0)
Corticosteroids	2 (7.1)

Values are n (%), mean ± SD, or median (range), as appropriate. BMI, body mass index; CD, Crohn disease; CDAI, Crohn disease activity index; CRP, C-reactive protein; EOW, every other week. [a] Azathioprine, mercaptopurine, tacrolimus. [b] Ciprofloxacin, metronidazole.

Results

Patient Disposition and Demographics

A total of 28 patients were enrolled in the study and received open-label adalimumab. Of these, 25 (89.3%) completed week 8 and 18 (64.3%) completed week 52. Four patients who did not achieve CR-50 at week 8 withdrew from the study. Overall, the main reasons for discontinuation were lack of efficacy (n = 6) and AEs (n = 3) (see online suppl. Fig. 2). Most patients were male (57.1%); the mean age was 33.6 years (range: 17–51 years), the mean body weight was 55.4 kg, and the mean duration of CD was 8.6 years. At baseline (week 0), the mean CDAI

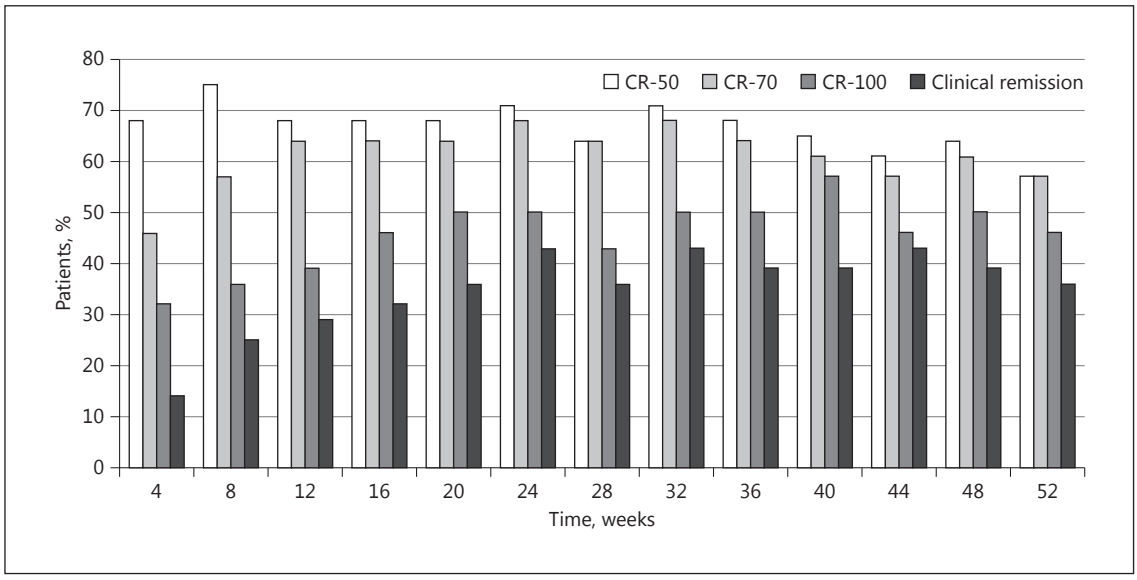

Fig. 1. Proportion of patients with CR-50, CR-70, CR-100, and clinical remission from weeks 4 to 52 (NRI; n = 28). CR-50, decrease in CDAI ≥50; CR-70, decrease in CDAI ≥70; CR-100, decrease in CDAI ≥100. CDAI, Crohn disease activity index; NRI, nonresponder imputation.

was 308.4 and the median CRP was 2.35 mg/dL (range: 0.25–6.78). Additional baseline characteristics are shown in Table 1.

All patients in the primary efficacy population received at least 1 concomitant medication during the study, with 46.4% (13/28) reporting immunosuppressant use, 7.1% (2/28) reporting corticosteroid use, and 82.1% (23/28) reporting aminosalicylate use at baseline. Approximately 68% (19/28) of the patients reported prior infliximab use (Table 1).

Clinical Endpoints

At week 8, the proportion of patients who achieved CR-50 was 75.0% (95% CI: 55.1–89.3, NRI). CR-50, CR-70, CR-100, and clinical remission over time are shown in Figure 1. The proportion of patients achieving CR-50 was maintained from 67.9% at week 4 through 57.1% at week 52 (Fig. 1). The proportion of patients achieving CR-70, CR-100, and clinical remission increased over time from week 4 through week 52 (Fig. 1).

Biological Response

CRP levels decreased throughout the study period. The median change from baseline in CRP levels at week 8 was −0.390 mg/dL (range: −5.56 to 2.99) in LOCF analyses (Fig. 2a). The median change from baseline in CRP levels at week 52 was −0.770 mg/dL (range: −5.56 to 9.18) in LOCF analyses (Fig. 2a). The proportion of patients with ≥50% drop in CRP from baseline increased from 21.4% at week 4 to 46.4% at week 16 and remained steady through week 52 (Fig. 2b).

Pharmacokinetics

All 28 patients were included in the pharmacokinetics analysis. The mean ± standard deviation (SD) concentration of adalimumab was 3.06 ± 2.19 μg/mL at baseline (n = 28), 7.71 ± 4.66 μg/mL at week 24 (n = 20), and 9.47 ± 5.34 μg/mL at week 52 (n = 18) (see online suppl. Fig. 3a) following dose escalation to 80 mg EOW.

The mean ± SD concentration of adalimumab at week 52 by observed remission status was 11.7 ± 5.31 μg/mL (n = 10) and 6.68 ± 4.11 μg/mL (n = 8) for patients with and without remission, respectively (see online suppl. Fig. 3b).

Overall, 4 of 28 patients had a positive AAA result during the study, of whom 3 were AAA+ at week 0 (baseline). One patient became AAA+ during the study (at week 52). Serum adalimumab concentrations tended to be lower in patients who were AAA+ (see online suppl. Fig. 3c). Two of the 3 AAA+ patients at baseline discontinued treatment at week 8 due to lack of response. One AAA+ patient at baseline continued to achieve CR-50 through week 52. Another patient was found to be AAA+ at week 52 and achieved CR-50 at week 8 but not at week 52.

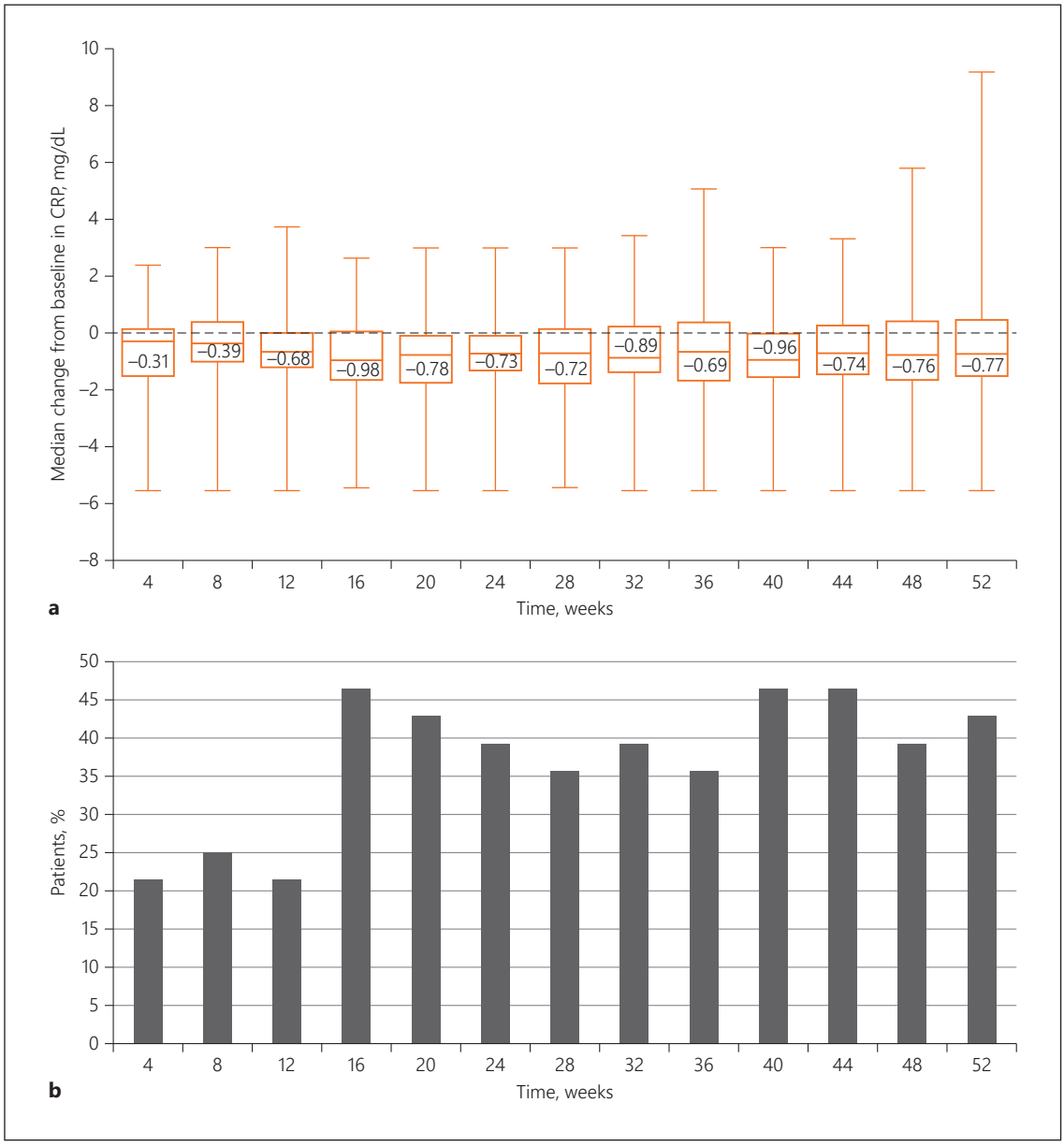

Fig. 2. Median change from baseline (**a**) and proportion of patients with ≥50% drop in CRP over time (**b**) (LOCF; $n = 28$). CRP, C-reactive protein; LOCF, last observation carried forward.

Factors Affecting Efficacy after Dose Escalation

Factors affecting achievement of clinical remission 24 weeks after dose escalation were analyzed using logistic regression analysis. Week 24 was analyzed as clinical remission was the highest at this time point. In both the univariate and multivariate analyses, baseline CDAI was significantly lower in patients who achieved clinical remission at week 24 (257.5 vs. 346.5, OR: 0.978, 95% CI: 0.9603–0.9950 and OR: 0.961, 95% CI: 0.9307–0.9920, respectively) (see online suppl. Table 1). Also, CDAI at 4 weeks after dose escalation was lower for patients with clinical remission at week 24 compared to those without clinical remission (183.4 vs. 270.9, $p = 0.006$). Other background factors such as disease duration, concomitant medication, perianal disease, surgery, and biomarkers were not affected. In the subgroup analysis by prior infliximab use, the rates of clinical remission and CR-100 in infliximab-naïve patients were numerically higher

Table 2. Treatment-emergent adverse events

Adverse events	Adalimumab 80 mg EOW (*n* = 28)
All adverse events	24 (85.7)
Serious adverse events	8 (28.6)
Adverse events leading to discontinuation of therapy	4 (14.3)
Any infection	19 (67.9)
Serious infection	2 (7.1)
Malignant adverse event	0
Injection site reaction	1 (3.6)
Opportunistic infections (excluding tuberculosis)	0
Demyelinating disease	0
Tuberculosis	0
Allergic reactions including angioedema/anaphylaxis	2 (7.1)
Lupus-like syndrome	0

Values are *n* (%). EOW, every other week.

compared to infliximab-experienced patients (see online suppl. Table 2), although prior use of infliximab was not significant in the logistic regression analysis of clinical remission at week 24 (see online suppl. Table 1). Baseline adalimumab trough concentration was numerically higher in patients who achieved clinical remission at week 24, but this was not statistically significant.

Safety

Throughout the study, the mean duration of exposure to adalimumab was 274.5 days (median: 363.5 days, range: 27–384). A total of 24 (85.7%) patients reported at least 1 TEAE (Table 2). Most TEAEs were considered by the investigator to be mild or moderate in severity. The most frequently reported (≥10% of patients) TEAEs were nasopharyngitis (46.4%), CD (14.3%), rash (14.3%), and headache (10.7%). Five patients reported at least 1 TEAE that was considered as having a reasonable possibility of being related to the study drug: 2 patients reported nasopharyngitis, while injection-site reaction, abdominal distension, urticaria, bronchitis, upper respiratory tract infection, and bacterial pneumonia were reported by 1 patient each. Four patients discontinued the study drug due to AEs: 2 reported worsening of CD, 1 reported an ileus event, and 1 reported a subileus event. Worsening of CD and a subileus event were the primary reasons for drug discontinuation for 3 patients. Eight patients experienced serious TEAEs (SAEs). The most frequently reported SAE was worsening of CD (*n* = 4; 14.3%). All other SAEs were reported by 1 patient each (ileus, intestinal obstruction, small intestinal ulcer hemorrhage, subileus, anal abscess, pneumonia bacterial, and allergic transfusion reaction following blood transfusion). In SAEs, pneumonia bacterial was considered as drug-related by the investigator. Two patients (7.1%) reported serious infectious AEs (1 patient with bacterial pneumonia and 1 patient with anal abscess). No opportunistic infections, malignancies, demyelinating diseases, or deaths were reported through week 52.

Discussion

TNFα plays an important role in the pathogenesis of CD [13], and anti-TNF therapy demonstrates marked clinical improvement and mucosal healing of the disease. However, some patients who initially respond to anti-TNF treatment subsequently lose response and experience flare of symptoms. Shortening the interval and/or dose escalation in patients with loss of response is recommended by international guidelines [7, 8]. The efficacy and safety of adalimumab dose escalation to 40 mg weekly has been proven and approved in many countries; however, the efficacy and safety of 80 mg EOW has not been investigated.

This study demonstrated that dose escalation of adalimumab to 80 mg EOW was able to restore and maintain response through week 52 in Japanese patients with moderately to severely active CD who had lost response to 40 mg EOW maintenance therapy as evidenced by elevated CDAI and CRP. The primary endpoint of the trial (CR-50 at week 8) was achieved by 75% of patients. In addition, improvements in secondary endpoints CR-50, CR-70, CR-100, clinical remission, and median change from

baseline in CRP were observed as early as week 4 and sustained through week 52. The efficacy is similar to a Western study in which 37% of patients achieved remission, 58% achieved CR-100, and 63% achieved CR-70 after dose escalation from 40 mg EOW to 40 mg every week [9]. No new safety concerns were identified during this study and the safety results of adalimumab 80 mg EOW that were observed in these Japanese patients are consistent with the known safety profile of adalimumab in Western patients with CD and across other adalimumab indications [9, 14].

The clinical symptoms of CD may be caused by inflammation, as well as by other etiologies such as irritable bowel syndrome, infection, and fibrostenotic strictures. Therefore, when considering dose escalation for control of clinical symptoms, it is important to assess objective markers of inflammation (e.g., imaging outcomes and/or biomarkers) to ensure that the clinical symptoms observed are related to active CD [15]. This study utilized elevated CRP, an objective marker of inflammation, to identify patients for inclusion. CRP has been shown to correlate with disease activity in CD [16]. The combination of CRP and CDAI, which is a score primarily composed of subjective symptoms, for eligibility assessment adds an objective measurement of disease activity. This may be helpful in guiding physicians in deciding which patients can possibly benefit from dose escalation to 80 mg EOW; physicians can be assured that a patient's symptoms are related to CD and not some other etiology.

In logistic regression analysis, only baseline CDAI was identified as a patient factor affecting achievement of clinical remission at week 24. This result suggests that early dose escalation after flare may be more effective. Baseline CRP was numerically but not statistically significantly higher for patients who achieved clinical remission. CRP ≥1 mg/dL at screening was an inclusion criterion, which may explain why a significant difference was not observed. Other factors were not identified: this may have been affected by the small number of patients, so these results should be interpreted with caution.

Serum concentrations of adalimumab observed with 40 mg EOW dosing (i.e., at baseline) in patients who had lost response to therapy were on average lower than those observed in the previous pivotal study of adalimumab in Japanese patients in which serum adalimumab concentrations between 5 and 8 μg/mL were observed in the overall population of patients receiving 40 mg EOW [6]. Mean serum concentrations of adalimumab when dosed at 80 mg EOW were numerically higher in patients achieving remission at week 52 compared to the concentrations in patients who did not achieve remission, although the range of concentrations overlapped. These results suggest that adalimumab concentration may be associated with response.

The small number of AAA+ patients in this study precluded any definitive assessment of the impact of immunogenicity on efficacy and safety. However, serum concentrations were higher in AAA– patients than in AAA+ patients.

There are limitations to this study. First, it was an open-label trial without a comparator arm. Second, a small number of patients were enrolled, which makes factorial analyses difficult to interpret. Third, remission and response were determined only by CDAI, which is primarily composed of subjective symptoms and may not fully reflect mucosal disease activity.

In summary, this study showed that dose escalation to adalimumab 80 mg EOW was efficacious in Japanese CD patients who lost response to adalimumab maintenance treatment with 40 mg EOW. The effects were seen in all patients despite various background factors, such as prior anti-TNFα use, concomitant immunosuppressant use, and disease duration, except disease activity. The safety profile of adalimumab 80 mg EOW was consistent with previous studies. No new safety signals were observed with this increased adalimumab dose.

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Statement of Ethics

This study was conducted in accordance with the protocol, International Conference on Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. Institutional review board approval of the protocol, informed consent forms, and patient information and/or advertising, where relevant, were obtained from each site. Patients were invited to participate in the study by the investigators and provid-

ed informed consent prior to any study-related screening procedures. If the patient was aged <20 years, his or her parent or legal guardian provided informed consent.

Disclosure Statement

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Author Contributions

All authors have made substantial contributions to all of the following: (1) conception and design of the study, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

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