

Adalimumab for the Treatment of Japanese Patients With Intestinal Behçet's Disease



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BACKGROUND & AIMS:

Behçet's disease is a chronic, relapsing inflammatory disease that can involve the mouth, skin, eyes, genitals, and intestines. Active intestinal Behçet's disease can be complicated by gastrointestinal (GI) bleeding and perforation. We performed a multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of adalimumab, a fully human monoclonal antibody against tumor necrosis factor α , in patients with intestinal Behçet's disease who were refractory to corticosteroid and/or immunomodulator therapies.

METHODS:

The study was conducted at 12 sites in Japan, from November 2010 through October 2012. Twenty patients were given 160 mg adalimumab at the start of the study and 80 mg 2 weeks later, followed by 40 mg every other week for 52 weeks; for some patients, the dose was increased to 80 mg every other week. A composite efficacy index, combining GI symptom and endoscopic assessments, was used to evaluate efficacy. The primary efficacy end point was the percentage of patients with scores of 1 or lower for GI symptom and endoscopic assessments at week 24. Secondary end points included complete remission and resolution of non-GI Behçet's-related symptoms.

RESULTS:

Nine patients (45%) had GI symptom and endoscopic assessment scores of 1 or lower at week 24 of treatment, and 12 patients (60%) had these scores by week 52. Four patients (20%) achieved complete remission at weeks 24 and 52. Individual global GI symptom and endoscopic scores improved for most patients at weeks 24 and 52. Two thirds of patients with oral aphthous ulcers, skin symptoms, and genital ulcers, and 88% of patients with erythema nodosum had complete resolution of these conditions at week 52. A total of 9 of 13 patients (69%) taking steroids at baseline were able to taper ($n = 1$) or completely discontinue steroids ($n = 8$) during the study. No new safety signals were observed.

CONCLUSIONS:

Adalimumab is a potentially effective treatment for intestinal Behçet's disease in Japanese patients who are refractory to conventional treatments. ClinicalTrials.gov number: NCT01243671.

Keywords: Autoimmunity; Anti-TNF Agent; Endoscopy; Japan.

Abbreviations used in this paper: AAA, anti-adalimumab antibodies; ADA, adalimumab; AE, adverse event; BD, Behçet's disease; CD, Crohn's disease; CRP, C-reactive protein; eow, every other week; GI, gastrointestinal; IBDQ, Intestinal Bowel Disease Questionnaire; LOCF, last observation carried forward; MI, marked improvement; NRI, nonresponder imputation; TNF α , tumor necrosis factor α .

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1542-3565/
<http://dx.doi.org/10.1016/j.cgh.2014.08.042>

Behçet's disease (BD) is a chronic, relapsing inflammatory disease involving multiple organs, including the mouth, skin, eyes, and genitals.¹ Approximately 15% to 20% of patients with BD develop intestinal ulcers,² which are associated with symptoms of abdominal pain and diarrhea. Deep intestinal ulcerations pose a risk of perforation and bleeding.

BD prevalence is highest in countries along the Silk Road, a belt-like region running from the Mediterranean through the Middle East into China and Japan.¹ In Japan, the estimated prevalence is 13 to 20 per 100,000, whereas in the United States and the United Kingdom it is 10-fold lower.³ The average age of onset is 18 to 40 years of age,¹ and intestinal BD affects more males than females.⁴ BD is treated conventionally with corticosteroids and/or nonbiologic immunomodulators, including thiopurines; however, many patients fail to respond to these treatments or become steroid-dependent.^{5,6} For refractory patients, surgical resection of the intestine to address bleeding or bowel perforation often is required.⁷ The postoperative recurrence rate for intestinal ulcers remains high,⁸ however, highlighting a need for treatments that can maintain long-term disease remission.

Intestinal BD is associated with excess production of inflammatory cytokines, including tumor necrosis factor α (TNF α).⁹ Infliximab, a chimeric TNF α inhibitor, is approved in Japan for the treatment of uveitis in patients with BD.¹⁰ Clinical studies have reported the efficacy of adalimumab (ADA),¹¹ a fully human anti-TNF α monoclonal antibody, and infliximab for intestinal BD.^{5,12-19} However, no larger-scale, long-term clinical trials have examined the efficacy of anti-TNF α therapies for the treatment of intestinal BD.²⁰ Adalimumab is widely approved for adult Crohn's disease (CD), adult ulcerative colitis, pediatric CD (Europe), and other immune-mediated inflammatory disorders.^{21,22} Here, we present the 52-week results of a clinical study of ADA in Japanese patients with intestinal BD. Because there was no widely used end point for assessment of signs and symptoms of BD at the time this study was conceived, a novel composite efficacy index was developed that combines evaluations of both gastrointestinal (GI) symptoms and endoscopic appearance.

Methods

Study Design

This 52-week, phase 3, multicenter, open-label, uncontrolled study evaluated the efficacy, safety, and pharmacokinetics of ADA in Japanese patients with active intestinal BD who were refractory to conventional therapies. A novel composite disease activity index was developed (Figure 1A) that consisted of 2 separate scoring components: (1) patient evaluation of the global activity of GI symptoms in the 2 weeks before each study visit on a 4-point scale, and (2) change in ulcer size since baseline endoscopic assessment. For the endoscopic

efficacy assessment, the size of the largest ileocecal ulcer was compared with its size at screening. Ulcer size was evaluated via photography with a comparative object (eg, biopsy forceps) and scored on the basis of change in the longest ulcer diameter using a 4-point scale. If a new ulcer larger than the index ulcer developed, the diameter of the new ulcer was compared with that of the index ulcer during screening.

The study was conducted at 12 sites in Japan. The institutional review board of each center approved the protocol, and each patient provided written informed consent. For patients aged 19 and younger, written consent also was provided by the patient's guardian.

Inclusion criteria. Disease activity for study inclusion was based on the global GI symptom score. Patients aged 15 years and older with BD, an ileocecal ulcer 1 cm or larger in diameter, and a baseline global GI symptom score of 3 or higher were eligible. Patients were refractory to stable treatment with corticosteroids or immunomodulators, or had failed to taper corticosteroids during the 12 months before screening. Patients with intolerance or loss of response to prior infliximab were eligible. Additional inclusion criteria are described in the [Supplementary Methods](#) section.

Exclusion criteria. Exclusion criteria included Crohn's disease, current or prior active tuberculosis, previous ADA treatment, or history of ileocecal resection. Patients with evidence of latent tuberculosis were to complete a 21-day or longer course of tuberculosis prophylaxis before receiving ADA. Evidence of dysplasia or malignancy at screening colonoscopy or a history of cancer, other than a successfully treated nonmetastatic cutaneous squamous or basal cell carcinoma and/or localized carcinoma in situ of the cervix, was exclusionary. Additional exclusion criteria are described in the [Supplementary Methods](#) section.

Treatment administration. All patients received induction treatment with ADA 160 mg at week 0 (baseline) and 80 mg at week 2, and maintenance treatment with 40 mg every other week (eow) from weeks 4 to 50 (Figure 1B). Study drug was administered by a physician or nurse through week 8. After week 8, patients who were willing could self-administer the study drug (or have a family member administer the injection). Doses of BD medications except corticosteroids, colchicine, and enteral nutrition (which could be tapered at the investigator's discretion from week 8 in patients responding to ADA treatment) were maintained stably through week 24 unless treatment-related, moderate-to-severe toxicities arose. Initiation, discontinuation, or change in dosage of concomitant treatments was permitted after week 24.

From week 8, patients with inadequate response or disease flare (both definitions are outlined in the [Supplementary Methods](#) section and were based on global symptom or endoscopic appearance scores) could dose-escalate to ADA 80 mg eow. Patients with inadequate response or disease flare after dose escalation were withdrawn from the study.

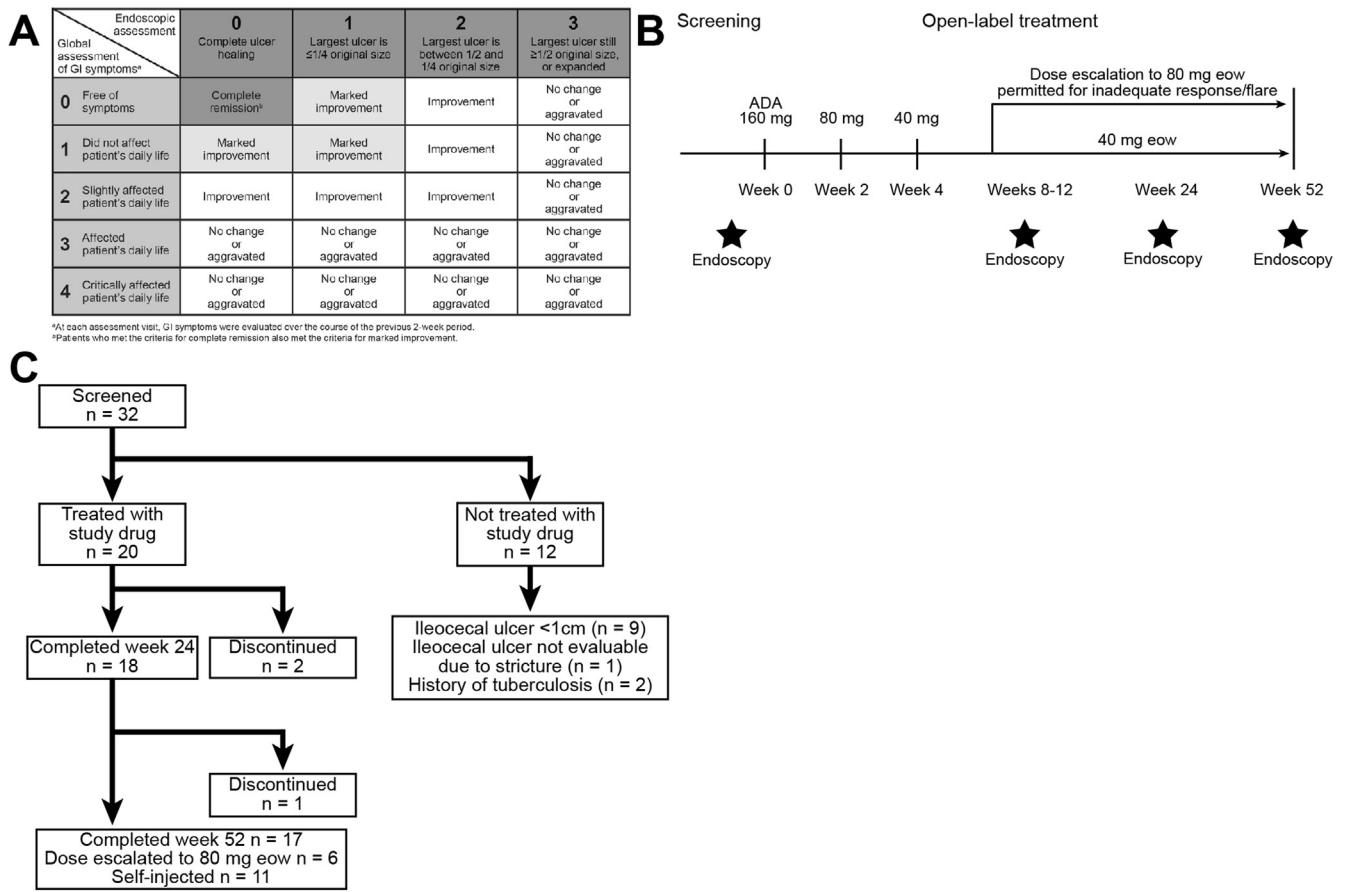


Figure 1. (A) Evaluation criteria for global GI symptom and endoscopic assessment scores. A combination of scores is used to characterize disease state after treatment (complete remission, marked improvement, improvement, and no change/aggravated). (B) Study design. (C) Patient disposition. IC, informed consent.

Efficacy Assessments

Global GI symptom scores were assessed every 4 weeks and endoscopic assessments were conducted at weeks 8/12, 24, and 52/early termination (Figure 1B). At each study visit, patients also assessed the degree that 3 individual GI symptoms (diarrhea, pain, and abdominal discomfort/bloating) affected daily life using the same 4-point scale as the global GI symptom score. In addition, the degree to which 4 other BD-related symptoms affected daily life (oral aphthous ulcers, erythema nodosum, uveitis, and genital ulcers) over the previous 4 weeks was recorded using a 4-point scale. Details of these assessments are located in the Supplementary Methods section. Fecal calprotectin level was not assessed.

The primary efficacy evaluations of the study were based on categorization of patients as having no change/aggravated, improvement, marked improvement (MI), and complete remission using the composite index (Figure 1A). The primary end point was the proportion of patients with MI (values ≤ 1 for both the global GI symptom and endoscopic assessment scores) at week 24. This end point included patients with complete remission, defined as global GI symptom and endoscopic scores of 0. Major secondary end points included MI at

week 52, complete remission at weeks 24/52, and global GI symptom score and endoscopic appearance score of 0 or 1 or less at weeks 24/52. Additional secondary end points at weeks 24 and 52 included individual GI symptom scores of 1 or less or improvement by 1 or more points; improvement by 1 or more points in global GI symptom score; complete disappearance of non-GI BD symptoms; and change from baseline in serum C-reactive protein (CRP) levels. Secondary quality-of-life end points included changes from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) (used under license from McMaster University)²³ and the Short-Form 36 Health Survey.²⁴

Safety Evaluations

Patients were monitored for treatment-emergent adverse events (AEs) every 2 weeks. Physical examinations and clinical laboratory tests (hematology, clinical chemistry, and urinalysis) were conducted at screening and every 4 weeks. All AEs from time of study drug administration until 70 days after discontinuation (regardless of investigator-assigned causality) were reported.

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	FAS (n = 20)
Male sex, n (%)	10 (50.0)
Mean age ± SD, y	42.4 ± 13.3
Weight, kg	
Mean ± SD	55.8 ± 8.4
Range	40.0–78.0
Tobacco, nonsmoker, n (%)	8 (40.0)
Alcohol, nondrinker, n (%)	8 (40.0)
Duration of intestinal BD, y	
Mean ± SD	4.6 ± 7.2
Range	0.1–31.1
Non-GI BD symptoms, n (%)	20 (100)
Oral aphthous ulcer	15 (75)
Erythema nodosum	8 (40)
Uveitis	0
Genital ulcer	3 (15)
Global assessment of GI symptom score	
3	15 (75)
4	5 (25)
Number of ileocecal ulcers	
1	10 (50.0)
2	4 (20.0)
3	2 (10.0)
4	0
≥5	4 (20.0)
Longest diameter of ileocecal open ulcer	
≥1 to <2 cm	8 (40.0)
≥2 to <3 cm	5 (25.0)
≥3 cm	7 (35.0)
IBDQ score, mean ± SD	140.5 ± 36.2
SF-36	
Physical component summary	41.8 ± 5.7
Mental component summary	34.6 ± 12.4
Prior infliximab use, n (%)	3 (15.0)
Mean CRP level, ^a mg/dL	0.8
Concomitant BD medication, ^b n (%)	
Corticosteroids ^c	13 (65.0)
5-Aminosalicylic acid	13 (65.0)
Immunomodulators ^d	3 (15.0)

FAS, full analysis set; SF-36, Short-Form 36 Health Survey.
^aNormal range was ≤0.3 mg/dL.
^bMedications ongoing after the first study drug dose.
^cPrednisolone (mean daily dose, 7.1 mg/d; range, 2.5–20 mg) was the only reported concomitant corticosteroid used.
^dImmunomodulators were defined as methotrexate, azathioprine, or mercaptopurine. All 3 patients were taking azathioprine.

Pharmacokinetic and Immunogenicity Assessments

Blood samples for serum ADA concentration determination were obtained at baseline and before ADA injection at weeks 2, 4, 8, 16, 24, 36, and 52. Serum concentration of anti-ADA antibodies (AAAs) was determined at baseline and weeks 8, 16, 24, 36, and 52. Adalimumab and AAA concentrations were determined using the sponsor’s validated enzyme-linked immunosorbent assays at each time point and summarized using descriptive statistics as described previously.²⁵ Samples were considered to be AAA+ if the AAA concentration was greater than 20 ng/mL in undiluted serum. Patients

were considered AAA+ if they had at least 1 AAA+ sample.

Statistical Analyses

Discrete variables were summarized by counts and percentages with 95% confidence intervals, and continuous variables were summarized by descriptive statistics. Missing data were imputed using nonresponder imputation (NRI) for categorical variables and last observation carried forward (LOCF) or observed case for continuous variables. On the basis of previously observed remission rates after ADA induction treatment in Japanese patients with CD²⁵ and a sample size of 20 patients, a threshold for determining the efficacy of ADA was set at 25% of patients achieving MI. Patients who dose-escalated to 80 mg eow were included in the analysis.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Disposition and Demographics

Patient demographics and baseline characteristics are described in **Table 1** and **Figure 1C**. Twenty patients were enrolled and treated (**Figure 1C**) and represent the full analysis set for efficacy and safety analyses. Seventeen patients completed the study; 2 patients discontinued because of AEs, and 1 patient voluntarily discontinued for personal reasons that were not drug-related.

Efficacy

Nine patients (45%) achieved MI at week 24, and 12 patients (60%) achieved MI at week 52 (NRI) (**Figure 2**). Complete remission was achieved in 4 patients (20%) at week 24 and week 52 (NRI) (**Figure 2**). Improvement of global GI symptoms was observed as early as week 4,

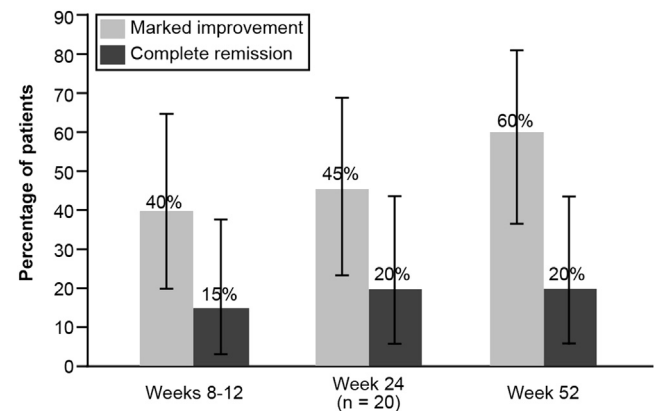


Figure 2. Percentage of patients (95% CI) with marked improvement or complete remission at weeks 8/12, week 24 (primary end point), and week 52. CI, confidence interval.

with 5 patients (25%) reporting scores of 0, and 11 patients (55%) reporting scores of 1 or less (NRI) (Figure 3A and Supplementary Table 1). Improvement in the endoscopic appearance of ulcers was observed early. Eight patients (40%) had an endoscopic assessment score of 1 or less at week 8/12; this end point was achieved by 65% of patients at week 52 (NRI) (Figure 3B and C). No patient reported worsening of the global GI symptom score at week 52 (LOCF) (Supplementary Figure 1A), and the endoscopic score at week 8/12

remained stable or improved by week 52 for all but 1 patient (LOCF) (Supplementary Figure 1B). There was good concordance between the observed symptomatic and endoscopic improvement at weeks 24 and 52 (Figure 3D); the concordance of values of 0 for both scores was lower (Figure 3E).

Treatment with ADA also was associated with rapid resolution of non-GI BD symptoms. Two-thirds of patients with oral aphthous ulcers and genital ulcers and 88% of patients with erythema nodosum had complete

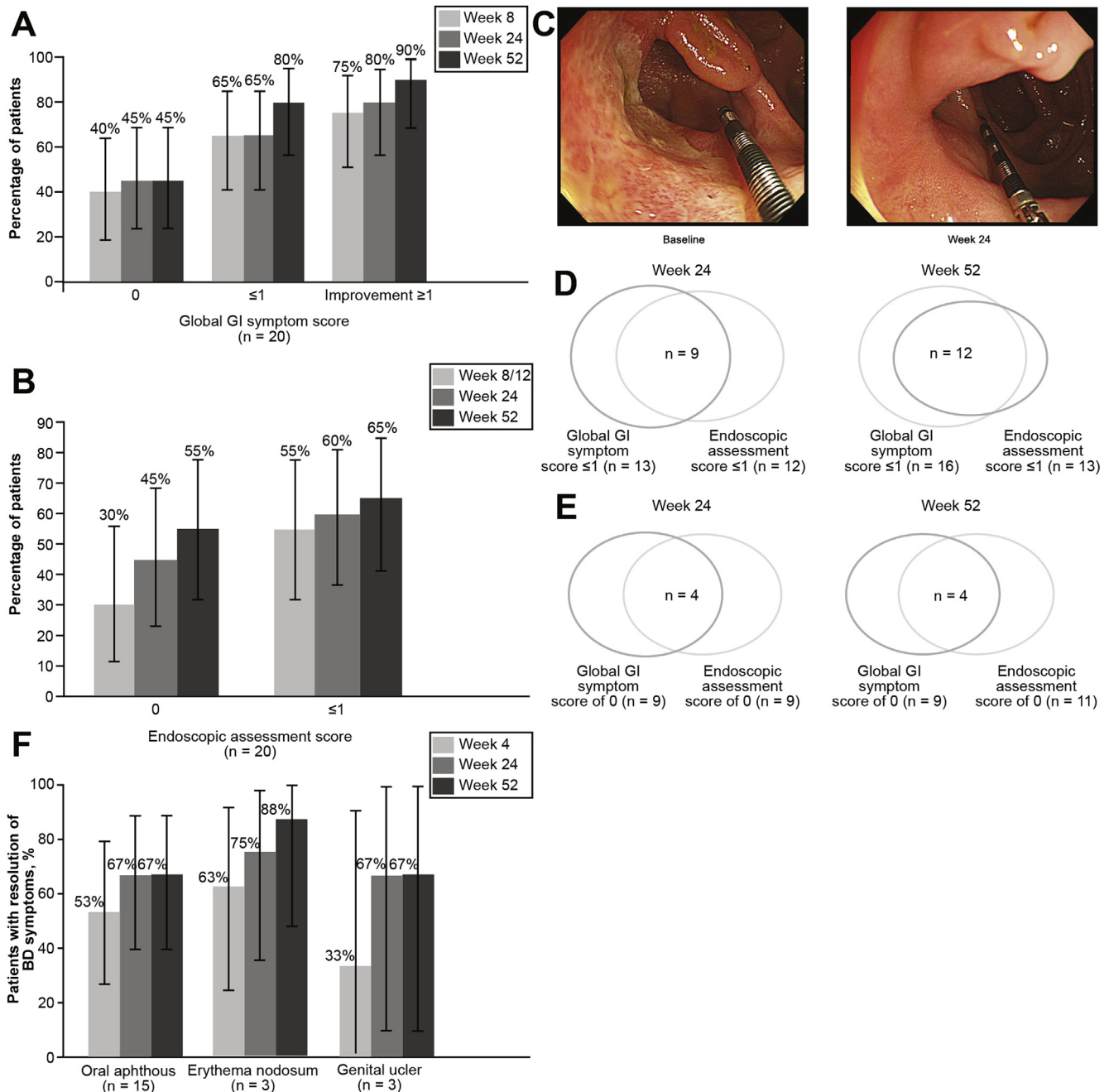


Figure 3. Percentage of patients (95% CI) achieving secondary efficacy end points, including improvement in (A) global GI symptom score (NRI) and (B) endoscopic assessment score; (C) representative patient's intestinal ulcers at baseline (left) and at week 24 (right); (D) concordance of global assessment of GI symptoms and endoscopic assessment scores of 1 or less (as observed); (E) concordance of values of 0 for global assessment of GI symptoms and endoscopic assessment scores; and (F) resolution of non-GI BD symptoms (NRI). CI, confidence interval.

resolution of these conditions at week 52 (NRI) (Figure 3F). Mean serum CRP levels decreased after ADA treatment; the mean decrease from baseline (LOCF) ranged from -0.1 mg/dL (at week 12) to -0.7 mg/dL (at week 48). At week 24, the mean observed serum CRP level was lower in patients with MI (n = 9; 0.3 mg/dL) than in patients without MI (n = 9; 0.7 mg/dL). The corresponding CRP levels at week 52 were 0.1 mg/dL (n = 12) and 1.8 mg/dL (n = 8) for patients with and without MI, respectively.

Six patients escalated to ADA 80 mg eow because of an inadequate response (n = 4) or disease flare (n = 2) during the study. At week 52, 1 patient achieved MI, 1 patient had a global GI symptom score of 1 or less, and a third patient had an endoscopic score of 1 or less.

Adalimumab treatment resulted in mean improvements exceeding the thresholds that were deemed clinically meaningful for both the IBDQ²³ (>16 points) and Short-Form 36 Health Survey²⁴ (≥3 points) quality-of-life measures (Table 2).

Concomitant medication tapering and discontinuation. Nine of the 13 patients receiving concomitant steroids at baseline tapered their dose, and 8 patients discontinued steroids altogether by week 52. Of these 8 patients, 5 achieved MI, including 3 patients with complete remission. The patient who tapered but did not discontinue steroid use went from prednisolone 10 mg at baseline to 6 mg at week 52 and achieved MI. No patient required steroid dose escalation or initiated new steroid treatment during the study.

Pharmacokinetics

Observed mean serum ADA concentrations remained stable during the maintenance period (weeks 16–52) (Supplementary Table 2). Dose escalation to 80 mg eow resulted in approximately twice the serum ADA concentration. The mean serum ADA concentrations for patients at week 52/early termination were as follows: patients with complete remission, 8.5 µg/mL (n = 4, all receiving 40 mg eow dosing); MI but not complete remission, 14.6 µg/mL (n = 8, 1 receiving 80 mg eow dosing); and non-responders, 17.0 µg/mL (n = 6, 4 receiving 80 mg eow dosing; 1 patient who discontinued the study before week 52 and had a serum ADA concentration collected at study

Table 2. Quality-of-Life Variables at Weeks 24 and 52: FAS and LOCF

Efficacy variables, mean change from baseline ± SD	Week 8 (n = 20)	Week 24 (n = 20)	Week 52 (n = 20)
IBDQ	34.0 ± 37.8	37.1 ± 40.0	41.2 ± 41.9
SF-36 summary score			
Physical	6.2 ± 7.4	7.5 ± 7.2	9.0 ± 8.4
Mental	7.0 ± 11.1	8.9 ± 12.9	9.0 ± 13.3

FAS, full analysis set; SF-36, Short-Form 36 Health Survey.

day 351 is included in this group, and week 52 ADA concentrations were not available for the remaining 2 patients who prematurely terminated study participation). One patient was AAA+ (with a serum ADA concentration of 0) at weeks 36 and 52; this patient achieved MI at both weeks 24 and 52. The AAA+ patient did not dose-escalate and was receiving a concomitant immunomodulator (azathioprine) at week 24, which was discontinued on study day 230 (approximately week 33).

Safety

No new safety signals were observed, and no deaths occurred. There were no cases of malignancy, congestive heart failure, demyelination, or lupus-like syndrome. Through week 52, 25% of patients experienced an AE that was assessed as possibly or probably related to study drug (Table 3). The most frequent treatment-emergent AEs were nasopharyngitis (n = 9; 45%) and diarrhea, arthropod sting (not considered to be related to study drug), and cough (n = 3; 15% each). Four of the 6 patients who dose-escalated experienced an infection after dose escalation; none of these patients experienced an infection before dose escalation.

Two patients withdrew from the study because of AEs. One patient experienced a stenotic terminal ileal obstruction on day 7, which was assessed as probably not related to ADA. The patient received endoscopic balloon dilation and improved. The other patient withdrew because of worsening Behçet's syndrome symptoms after ADA dose escalation; this AE was assessed as not related to study drug.

Discussion

The results of this clinical trial show that ADA reduced GI symptoms and led to intestinal ulcer healing

Table 3. Overview of Treatment-Emergent Adverse Events: Full Efficacy Analysis Set

AE, n (%)	Week 24 (n = 20)	Week 52 (n = 20)
Any AE	17 (85)	20 (100)
At least possibly drug related	5 (25)	5 (25)
Serious	1 (5)	1 (5)
Leading to early discontinuation	2 (10)	2 (10)
AE of interest		
Infection	9 (45)	14 (70)
Injection site reaction	2 (10)	2 (10)
Noncutaneous vasculitis	2 (10)	3 (15)
Tuberculosis	0	1 (5)
Hepatic event	2 (10)	3 (15)
Allergic reaction	1 (5)	2 (10)
Intestinal stricture related	1 (5)	1 (5)
Increased ALT levels	1 (5)	1 (5)

ALT, alanine aminotransferase.

in patients with intestinal BD who were refractory to conventional treatment. Forty-five percent of patients achieved the study's primary end point (MI at week 24), exceeding the prespecified threshold for study success. Complete ulcer healing was observed in the majority of patients at week 52. Adalimumab treatment also induced complete remission in 20% of patients at week 24, which was maintained through week 52. Treatment with ADA led to rapid improvement in non-GI BD symptoms at week 4. The mean serum levels of CRP decreased with ADA treatment, indicating biologic anti-inflammatory activity. Pharmacokinetic data showed similar serum ADA concentrations to those observed previously for a similar dosing schedule in Japanese patients,²⁵ and the rate of immunogenicity was low. An exposure-response relationship was not evident; however, the relevance of this finding was limited by the small number of patients in each response category.

Adalimumab treatment also resulted in improvement of quality of life. The majority of patients receiving corticosteroids at baseline were able to taper or discontinue use over the course of the study, with 8 of 9 patients (89%) completely discontinuing steroids at the end of the study. Adalimumab treatment was well tolerated. All reported AEs were similar to those observed in other ADA clinical trials.^{26–29}

There is no consensus for intestinal BD management. Surgical resection is often a short-term solution because many patients experience recurrence of intestinal ulcerations.⁸ On the basis of case reports,^{5,11,12,14–18,20} a Japanese expert panel recently recommended anti-TNF α therapies for intestinal BD.²⁰ Our study provides further support for this recommendation.

Currently, there is no widely accepted clinical index for the assessment of intestinal BD activity, which is complicated by the relatively rare nature of the disease. A new intestinal BD activity index (the disease activity index for intestinal Behçet's disease) based on patient-reported GI symptoms and other factors (fever, extra-intestinal manifestations, abdominal mass, and intestinal complications) recently was proposed; however, this method does not include endoscopic assessment.³⁰ Endoscopic assessment is nonetheless an important objective measure for evaluation of intestinal BD, especially in an unblinded trial in which patient-reported symptoms may be influenced by the knowledge of treatment allocation. In addition, the correlation between endoscopic severity and the disease activity index for intestinal Behçet's disease was found to be weak in 1 series.³¹ Our report describes a novel index that combines separate scores for global symptom severity and intestinal ulcer evaluation. The majority of patients in the study with a global GI symptom score of 1 or less also had an endoscopic assessment score of 1 or less, although the concordance for values of 0 for both scores was lower (Figure 3E). This index can be used to track disease activity and therapeutic efficacy in future studies of intestinal BD; however, because the endoscopic

assessment only assesses changes in ulcer size, it can be used only to measure changes in disease activity.⁸

Limitations of this study included its relatively small sample size and lack of placebo control, which have the potential to bias the findings. However, given the small number of patients with intestinal BD who have failed conventional therapy, it was not feasible to conduct a large placebo-controlled study. A further limitation was the use of an unvalidated composite disease activity index, and the lack of validation of the study's end point. For simplicity of evaluation and because changes in ulcer size were believed to be similar for all ulcers when more than 1 ulcer was present, the endoscopic change index was limited to the assessment of the largest ileocecal ulcer present during screening. This approach neglected evaluation of changes in other ulcers, which could limit the detection of increased inflammation occurring outside of the index ulcer. In addition, the endoscopic index did not include evaluation or weightings for ulcer depth or shape, a count of the number of ulcers, or assessment of absolute ulcer size, all of which may be related to intestinal BD clinical activity, as suggested by a recent analysis.³¹ Additional evaluation of this and other available intestinal BD activity indices, including consideration of incorporation of objective biomarkers, is warranted. Finally, the IBDQ results may not be directly applicable to patients with intestinal BD and should be interpreted with caution.

Together, these data show that a novel composite index, composed of an assessment of GI symptoms and changes in intestinal ulceration, is useful for tracking intestinal BD progression or improvement. This study showed that ADA is safe and effective for the treatment of intestinal BD in patients who are refractory to conventional therapies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2014.08.042>.

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Reprint requests

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Acknowledgments

The authors thank Michael Hast, PhD, and Jennifer Rossi, of MedThink Sci-Com, for medical writing and editorial assistance. The financial support for these services was provided by AbbVie.

Conflicts of interest

These authors disclose the following: Kenji Watanabe has received or is pending receipt of grant support from AbbVie Japan Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Eisai Co, Ltd, JIMRO Co, Ltd, Asahi Kasei Medical Co, Ltd, Ajinomoto Pharmaceuticals Co, Ltd, Kyowa Hakko Kirin Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Astellas Pharma, Inc, UCB Japan Co, Ltd, Takeda Pharmaceutical Co, Ltd, Dainippon Sumitomo Pharma Co, Ltd, and Horii Pharmaceutical, Inc, Ltd, and has received fees for lectures from AbbVie Japan Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Eisai Co, Ltd, JIMRO Co, Ltd, Asahi Kasei Medical Co, Ltd, Ajinomoto Pharmaceuticals Co, Ltd, Kyowa Hakko Kirin Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Astellas Pharma, Inc, UCB Japan Co, Ltd, and Takeda Pharmaceutical Co, Ltd; Keiichi Mitsuyama has received or is pending receipt of grant support from Eisai Co, Ltd, Asahi Kasei Kuraray Medical Co, Ltd, Kyowa Hakko Kirin Co, Ltd, and Kyorin Pharmaceutical Co, Ltd, and has received fees for lectures from AbbVie GK, Eisai Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, and Astellas Pharma, Inc; Yoshiaki Ishigatsubo has received or is pending receipt of grant support from AbbVie GK, Kyowa Hakko Kirin Co, Ltd, MSD Co, Ltd, GlaxoSmithKline Co, Ltd, Teijin Pharma Co, Ltd, Eisai Co, Ltd, Shionogi and Company, Ltd, Chugai Pharmaceutical Co, Ltd, Astellas Pharma, Inc, Taisho Toyama Pharmaceutical Co, Ltd, Dainippon Sumitomo Pharma Co, Ltd, DAIICHI SANKYO Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Meiji Seika Pharma Co, Ltd, Pfizer Japan, Inc, Sanofi KK, Asahi Kasei Pharma Corporation, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company Ltd, Bristol-Myers Squibb, Nippon Boehringer Ingelheim Co, Ltd, Taiho Pharmaceutical Co, Ltd, Actelion Pharmaceuticals Japan Ltd, and Japan Blood Products Organization, and has received fees for lectures from AbbVie GK, Eli Lilly Japan KK, Bristol-Myers Squibb, DAIICHI SANKYO Co, Ltd, Santen Pharmaceutical Co, Ltd, Astellas Pharma, Inc, Eisai Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Pfizer Japan, Inc, Mitsubishi Tanabe Pharma Corporation, ViiV Healthcare KK, Chugai Pharmaceutical Co, Ltd, Taisho Toyama Pharmaceutical Co, Ltd, Torii Pharmaceutical Co, Ltd, Meiji Seika Pharma Co, Ltd, and Ono Pharmaceutical Co, Ltd; Yasuo Suzuki has received fees for lectures from AbbVie GK, Eisai Co, Ltd, Kyorin Pharmaceutical Co, Ltd, and Mitsubishi Tanabe Pharma Corporation; Masakazu Nagahori has received fees for lectures from AbbVie GK and Mitsubishi Tanabe Pharma; Satoshi Motoya has received or is pending receipt of grant support from Janssen Pharmaceutical KK and Ajinomoto Pharmaceuticals Co, Ltd, and has received fees for lectures from Mitsubishi Tanabe Pharma Corporation; Shiro Nakamura received or is

pending receipt of grant support from AbbVie GK, Astellas Pharma Inc, Kyorin Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Ajinomoto Pharma Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Factory, Inc, JIMRO Co, Ltd, ZERIA Pharmaceutical Co, Ltd, and UCB Japan Co, Ltd, and has received fees for lectures from AbbVie GK, Eisai Co, Ltd, Kyorin Pharmaceutical Co, Ltd, and Mitsubishi Tanabe Pharma Corporation; Anne Robinson and Roopal Thakkar are 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 performed and may hold AbbVie stock or options; and Toshifumi Hibi has received or is pending receipt of grants from AbbVie, Ajinomoto Pharmaceuticals Co, Ltd, Asahi Kasei Kuraray Medical Co, Ltd,

AstraZeneca Pharmaceuticals, Janssen Pharmaceutical KK, JIMRO Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Tanabe Mitsubishi Seiyaku, UCB Japan Co, Ltd, UMN Pharma, Inc, and Zeria Pharmaceutical Co, Ltd, and has received fees for lectures from AbbVie, Asahi Kasei Kuraray Medical Co, Ltd, JIMRO Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Tanabe Mitsubishi Seiyaku, and Zeria Pharmaceutical Co, Ltd. The remaining authors disclose no conflicts.

Funding

This study was funded by AbbVie Inc and Eisai Co, Ltd.

Supplementary Methods

Inclusion Criteria

Patients were included if they received (or had failure or intolerance to) at least 1 of the following treatments: prednisolone ≥ 20 mg/d or equivalent for 14 days, prednisolone ≥ 5 but < 20 mg/d for 40 days, azathioprine ≥ 50 mg/d, or 6-mercaptopurine ≥ 30 mg/d; or a dose of an immunomodulator that is the highest tolerated by the patient (eg, as a result of leukopenia, increased liver enzyme levels, or nausea) for 90 days. Stable dosing of corticosteroids or immunomodulators for 14 and 28 days, respectively, before baseline was required for patient inclusion. For patients receiving both oral corticosteroids and immunomodulators, only 1 of the drugs needed to meet the earlier-described criteria.

Exclusion Criteria

Patients were excluded if they had a history of chronic or active hepatitis B or C infection, human immunodeficiency virus, listeriosis, immunodeficiency syndrome, histoplasmosis, or chronic recurring infections. Patients with a history of cyclosporine, tacrolimus, or mycophenolate mofetil use within 28 days of baseline were excluded, as were those who discontinued 5-aminosalicylic acid, colchicine, or enteral nutrition within 28 days of baseline. Patients receiving more than 1200 kcal/d of enteral nutrition were excluded. Patients taking 5-aminosalicylic acid, colchicine, or enteral

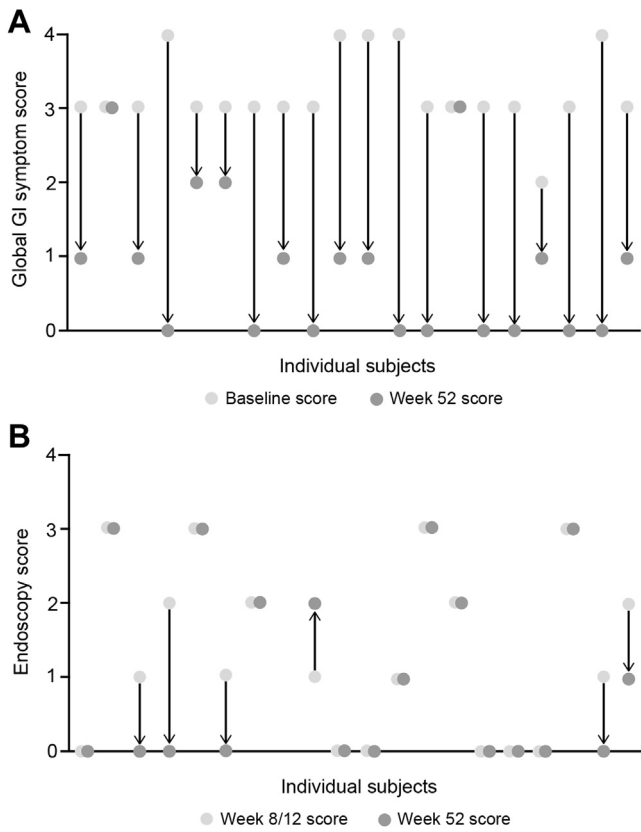
nutrition (≤ 1200 kcal/d) were eligible if their dose had been stable for at least 28 days before baseline.

Efficacy Assessments

Physician assessment of non-GI BD symptoms was conducted using the following criteria: for assessment of uveitis, grades 0 to 3 indicated the number of inflammatory eye events occurring during the previous 4 weeks; and for oral aphthous ulcers, genital ulcers, and erythema nodosum, scores of 0 to 3 were used to describe the degree of symptoms over the previous 4 weeks, with 0 indicating no symptoms, 1 describing symptoms occurring for fewer than 2 weeks, 2 describing symptoms occurring for 2 weeks or longer, and 3 describing symptoms occurring during most of the 4-week interval.

Dose-Escalation Criteria

For the purposes of dose escalation, inadequate response and disease flare were defined as follows: inadequate response was defined as a global GI symptom score of 3 or higher on 2 consecutive visits 14 days apart, or lack of reduction or expansion of a patient's evaluated ileocecal ulcer compared with the size observed during the screening endoscopy; disease flare was defined as a global GI symptom score of 2 or higher on 2 consecutive visits at least 14 days apart, after achievement of global GI symptom score of 1 or less during the study. Disease flare also was defined as the expansion of the largest ileocecal ulcer to more than half of the longest dimension at baseline after the ulcer previously had decreased to one quarter or less of the longest dimension at baseline.



Supplementary Figure 1. Individual changes in (A) global assessment of GI symptom score and (B) endoscopic assessment score by patient. Arrows indicate direction of change during the study. Circles are superimposed for patients for whom there was no score change. One patient did not have a week 8/12 endoscopy and was not included in the second graph.

Supplementary Table 1. Global GI Symptom Score By Visit

Global assessment of GI symptoms, n (%)	0	≤1	Improvement ≥1
Week 4	5 (25.0)	11 (55.0)	18 (90.0)
Week 8	8 (40.0)	13 (65.0)	15 (75.0)
Week 12	8 (20.0)	12 (60.0)	16 (80.0)
Week 24	9 (45.0)	13 (65.0)	16 (80.0)
Week 52	9 (45.0)	16 (80.0)	18 (90.0)

NOTE. FAS (N = 20), NRI.
FAS, full analysis set.

Supplementary Table 2. Mean Serum Adalimumab Trough Concentrations

	Week 2	Week 4	Week 8	Week 16	Week 24	Week 36	Week 52
All patients	13.7 ± 3.7 (20)	13.1 ± 4.6 (19)	10.4 ± 4.3 (19)	9.7 ± 4.3 (18)	10.5 ± 5.2 (18)	13.1 ± 6.4 (18)	13.8 ± 7.4 (17)
Remained on 40 mg eow	14.1 ± 3.8 (15)	13.6 ± 4.0 (14)	11.0 ± 4.0 (14)	8.7 ± 3.8 (14)	9.1 ± 4.5 (14)	10.4 ± 4.8 (13)	11.6 ± 6.3 (13)
Dose escalated to 80 mg eow	12.2 ± 3.1 (5)	11.7 ± 6.3 (5)	8.8 ± 5.2 (5)	13.2 ± 5.0 (4)	15.6 ± 4.7 (4)	20.0 ± 4.6 (5)	20.7 ± 7.0 (4)

NOTE. Values are shown as $\mu\text{g}/\text{mL} \pm \text{SD}$ (N_{nmis}).

N_{nmis} , number of nonmissing observations.