Safety and Efficacy of Adalimumab for Moderate to Severe Crohn's Disease in Children

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BACKGROUND & AIMS: The IMAgINE 1 study (NCT00409682) evaluated the safety and efficacy of adalimumab double-blind maintenance dosing regimens following open-label induction for pediatric patients with moderate to severe Crohn's disease (CD). **METHODS:** We studied 192 patients with Pediatric Crohn's Disease Activity Index (PCDAI) scores >30 for whom conventional treatment was unsuccessful. Patients received open-label induction therapy with subcutaneous adalimumab at weeks 0 and 2 (160 mg and 80 mg, or 80 mg and 40 mg, for body weight ≥40 kg or <40 kg). At week 4, 188 patients were assigned to groups based on achievement of clinical response (defined as decrease in PCDAI ≥15 points from baseline; 155/188 [82.4%]) and prior exposure to infliximab (82/188 [43.6%]). Groups were given double-blind maintenance therapy with adalimumab at high (40 mg or 20 mg for body weight ≥40 kg or <40 kg; n = 93) or low doses (20 mg or 10 mg for body weight ≥40 kg or <40 kg; n = 95) every other week for 48 weeks. Clinical remission (PCDAI ≤10) at week 26 (the primary end point) was compared between groups using the Cochran–Mantel–Haenszel test, adjusting for strata, with nonresponder imputation. Adverse events were monitored to evaluate safety. **RESULTS:** A total of 152 of 188 patients (80.9%) completed all 26 weeks of the study. At week 26, 63 patients (33.5%) were in clinical remission, with no significant difference between high- and low-dose groups (36/93 [38.7%] vs 27/95 [28.4%]; $P = .075$). No new safety signals were detected. **CONCLUSIONS: Adalimumab induced and maintained clinical remission of children with CD, with a safety profile comparable to that of adult patients with CD. More children who received high compared with low dose were in remission at week 26, but the difference between dose groups was not statistically significant.**

Keywords: Clinical Trial; Inflammatory Bowel Disease; Tumor Necrosis Factor; Anti-TNF Agent.

Crohn's disease (CD) is a chronic, debilitating inflammatory disease. Approximately 25% to 30% of patients with CD are diagnosed before the age of 20 years.[1] The reported incidence rates of pediatric CD range from 0.1 to 13.9 per 100,000 persons internationally,[2] and its incidence has increased in recent decades.[2–4] Growth retardation and delayed puberty are common in childhood CD.[5–8] The goal of treatment of CD for children is to induce and maintain clinical remission. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals in children with CD.[1,4]

CD in children may be treated using corticosteroids, which are frequently associated with adverse effects, including growth suppression and development of corticosteroid dependence.[9–11] Other conventional treatment options for pediatric CD include immunomodulators and nutritional therapy.[4,12]

Although the available treatment options for pediatric CD were significantly improved with the introduction of tumor necrosis factor (TNF) antagonists,[13] there are few large clinical trials of anti-TNF therapy in children with CD. The chimeric monoclonal antibody infliximab was evaluated in the REACH study, a phase 3 trial in 112 patients, as an induction and maintenance therapy for pediatric CD.[14] Infliximab is approved for use in children with moderate to severe CD (United States) or severe CD (Europe). However, some patients, once responsive to infliximab, develop intolerance or loss of response.[15]

The fully human monoclonal anti-TNF antibody adalimumab is approved for use in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, and adults with moderate to severe CD (United States) or severe CD (Europe). Adalimumab has been evaluated in pediatric patients with CD in retrospective analyses, case series, and small open-label prospective studies.[16–20] In the Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT)

Abbreviations used in this paper: AAA, anti-adalimumab antibodies; CRP, C-reactive protein; eow, every other week; LOCF, last observation carried forward; NRI, nonresponder imputation; PCDAI, Pediatric Crohn's Disease Activity Index; TNF, tumor necrosis factor.

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analysis of 115 pediatric patients with CD, adalimumab was safe and effective and showed a corticosteroid-sparing effect.[17]

We report the results from IMAgINE 1, a phase 3 randomized trial evaluating the safety and efficacy of 2 adalimumab double-blind maintenance dosing regimens following open-label induction in pediatric patients with moderate to severe CD. This trial represents the largest double-blind study conducted to date with an anti-TNF agent in children with CD.

Patients and Methods

Patients

This phase 3, multicenter, randomized, open-label induction followed by double-blind maintenance trial (IMAgINE 1, ClinicalTrials.gov identifier NCT00409682) was conducted at 45 sites in Canada, Europe, and the United States between April 2007 and May 2010.

Eligible patients were 6 to 17 years old and had a diagnosis of CD that was made at least 12 weeks before screening and confirmed by endoscopy or radiologic evaluation. Eligible patients had moderate to severe CD, defined by a Pediatric Crohn's Disease Activity Index (PCDAI)[21] >30 at baseline, despite concurrent treatment with an oral corticosteroid (prednisone ≥10 mg/day and ≤40 mg/day, or equivalent, including budesonide) at a stable dose for at least 2 weeks before baseline and/or an immunomodulator (ie, azathioprine, 6-mercaptopurine, or methotrexate), initiated at least 8 weeks before baseline, with a stable dose for at least 4 weeks. Concurrent therapy was not required for patients who within the past 2 years had not responded to or could not tolerate corticosteroid or immunomodulator therapy.

Other permitted concomitant treatments included aminosalicylates (if the dose was stable for at least 4 weeks before baseline), CD-related antibiotics (if the dose was stable for at least 4 weeks before baseline), and growth hormone (if the dose was stable for at least 12 weeks before baseline). Patients who had previously received infliximab were eligible to participate in the study if they had experienced an initial response to infliximab (≥5 mg/kg), received at least 2 subsequent doses (≥5 mg/kg), and then discontinued use because of loss of response or adverse reactions. Infliximab had to have been discontinued more than 8 weeks before baseline. Patients were ineligible if they had received previous treatment with any anti-TNF agent other than infliximab or any investigational biologic agent within the past 16 weeks or 5 half-lives before baseline. Prior exposure to natalizumab was not allowed.

The study protocol was approved by an independent ethics committee or institutional review board for each study site. Written informed consent was obtained from parents/legal guardians, and verbal or written assent was obtained from patients. An independent data monitoring committee assessed unblinded data from the study on a regular basis.

Study Design

Patients received open-label induction therapy with adalimumab at baseline (week 0) and week 2 (Figure 1*A*). Patients who weighed ≥40 kg at baseline received subcutaneous adalimumab 160 mg at week 0 and 80 mg at week 2, and patients who weighed <40 kg at baseline received subcutaneous adalimumab 80 mg at week 0 and 40 mg at week 2.

At week 4, patients were randomly assigned (1:1) to high-dose or low-dose adalimumab double-blind maintenance therapy for 48 weeks, stratified according to their week 4 responder status and prior exposure to infliximab. Clinical response was defined as a decrease in PCDAI ≥15 points from baseline. Randomization was performed centrally, according to a schedule generated by the study sponsor. The patients, study site personnel, investigators, and the sponsor were blinded to the treatment assigned. Patients assigned to the high-dose group received adalimumab 40 mg every other week (eow) if their week 4 body weight was ≥40 kg and adalimumab 20 mg eow if their week 4 body weight was <40 kg. Patients assigned to the low-dose group received adalimumab 20 mg eow if their week 4 body weight was ≥40 kg and adalimumab 10 mg eow if their week 4 body weight was <40 kg. At week 26, maintenance dosing was adjusted for patients whose body weight increased from <40 kg to ≥40 kg.

Starting at the week 12 study visit, patients who experienced disease flare or nonresponse to treatment were switched from blinded eow dosing to blinded weekly dosing, continuing with the same dose. Disease flare was defined as an increase in the PCDAI of ≥15 points when compared with week 4 and an absolute PCDAI >30. Nonresponse was defined as 2 consecutive visits at least 2 weeks apart in which a decrease in PCDAI ≥15 points from baseline was not achieved. After 8 weeks of blinded weekly dosing, patients who continued to experience disease flare or nonresponse could switch to open-label weekly rescue therapy at high dose (adalimumab 20 mg weekly for patients weighing <40 kg and adalimumab 40 mg weekly for patients weighing ≥40 kg). If patients continued to have a disease flare or experienced another flare while receiving open-label weekly therapy, or if they were consistent nonresponders, they were discontinued from the study at the investigator's discretion.

Concomitant Medications

Patients receiving corticosteroid therapy maintained a stable dose until week 4, at or after which a defined tapering schedule was initiated if the patient experienced clinical response. The corticosteroid dose could be increased back to the baseline dose if the patients experienced a flare or nonresponse. Immunosuppressant therapy could be discontinued at or after week 26 for patients meeting the clinical response criterion and could not be reinstated. Other CD-specific concomitant medications were to be maintained at a constant dose throughout the study. Initiation of corticosteroids, immunosuppressants, or other therapies was not permitted during the study. If in the judgment of the physician a patient required rescue therapy not allowed in the protocol, the patient was discontinued from the study.

Efficacy Assessments

Patients were assessed at baseline and weeks 2, 4, 8, 12, 16, 20, 26, 32, 40, 48, and 52. Physical examination and PCDAI score calculations were included in each visit. For patients aged ≥13 years at baseline, scores for both PCDAI and the adult-derived Crohn's Disease Activity Index (CDAI) were calculated. A count of the number of cutaneous fistulae was performed as part of the physical examination. Observed height velocity was calculated at baseline, week 26, and week 52, based on height measurements from the 6 to 12 months preceding the study (from screening to week 26) or those obtained at baseline (after week 26) according to the following formula: (Present Height [cm] − Previous Height [cm])/Interval (months) Between Mea-

Figure 1. (*A*) Study design schematic and (*B*) patient flow. All patients were randomized at week 4, whether they responded to open-label induction or not.

surements × 12. Age-specific z-scores for height velocity were calculated for each patient with reference to standard height velocity tables,[22] according to the following formula: (Observed Height Velocity [cm/y] − Mean Height Velocity for Age and Sex [cm/y])/(SD of the Mean). Serum C-reactive protein (CRP) levels were measured at baseline, week 4, week 26, and week 52.

Pharmacokinetic and Immunogenicity Assessments

Serum samples were obtained at baseline and at weeks 2, 4, 16, 26, and 52 (or early termination) for measurement of adalimumab concentrations and at baseline and weeks 16, 26, and 52 (or early termination) for measurement of antibodies to adalimumab. Serum adalimumab concentration and anti-adalimumab antibodies (AAA) were measured at a test facility (Celerion Switzerland AG, Fehraltorf, Switzerland). Adalimumab concentrations in serum were determined using a validated enzyme-linked immunosorbent assay method. The lower limit of quantitation for adalimumab was established at 31.25 ng/mL in undiluted human serum. AAA were measured using a validated double-antigen immunoassay that detects antibodies directed against epitopes on the entire adalimumab molecule. The lower limit of quantitation for AAA was established at 10 ng/mL in human serum. For both serum adalimumab and AAA assays,

samples were diluted appropriately to allow accurate measurement within the analytical range of the assay, and the results were multiplied by the dilution factor to convert to values for undiluted serum.

Safety Assessments

Adverse events, laboratory data, vital signs, and the results of physical examination were assessed throughout the study. Treatment-emergent adverse events were defined as new events that began either at or after the first dose of adalimumab and within 70 days after the last dose.

Efficacy

The primary efficacy end point was the percentage of patients in clinical remission (defined as PCDAI score ≤10) at week 26.

The secondary efficacy end points comparing the high-dose and low-dose treatment groups included the proportion of patients in clinical remission at week 52 and with clinical response at week 26 and week 52. In addition, a sensitivity analysis assessed the proportion of patients aged ≥13 years at baseline who achieved clinical remission according to the CDAI score (CDAI <150) at week 26 and week 52. Additional secondary end points based on PCDAI included the proportion of patients receiving corticosteroids at baseline who discontinued corticosteroids and were in clinical remission at week 26; the proportion of patients receiving immunomodulators at baseline who discontinued immunomodulators and were in clinical remission at week 52; the change from baseline to week 26 and week 52 in height velocity z-scores; the median percentage change from baseline in CRP level at weeks 4, 26, and 52; and remission and improvement of abdominal and perianal fistulae at week 52 in patients with fistula(e) at baseline. Clinical remission and clinical response at week 26 and week 52 were assessed by week 4 responder status (no, yes) and prior infliximab use (no, yes), and clinical remission at week 26 was assessed for the following subgroups: sex, age (<13 years, ≥13 years), baseline weight (<40 kg, ≥40 kg), disease duration (≤3 years, >3 years), disease location (small bowel, large bowel, small and large bowel), and baseline CRP level (<1.0 mg/dL, ≥1.0 mg/dL).

Sample Size Determination and Statistical Analyses

The sample size was determined using a 2-sided χ^2 test with a significance level of .05. Assuming an expected clinical remission rate of 20% in the low-dose adalimumab group and 40% in the high-dose adalimumab group, and a dropout rate of 10%, a total sample size of 164 patients (82 per group) was planned to provide 80% statistical power to detect the difference between the 2 treatment groups. There was no correction for stratification, because no data were available about the effect size within the strata.

The efficacy analyses were performed on the intention-to-treat population, defined as all randomized patients who received at least one dose of double-blind study medication. Safety data were collected for all patients who received at least one dose of study medication. For the primary efficacy analyses, the extended Cochran–Mantel–Haenszel test, adjusting for strata (week 4 response status [yes or no] and prior infliximab therapy [yes or no]), was used to compare the percentage of patients in the high-dose versus low-dose treatment groups achieving clinical remission at week 26. The *P* value was determined for the difference between treatment groups. Patients who prematurely discontinued the study, switched to double-blind weekly dosing, or did not have the relevant PCDAI score were considered to have not achieved clinical remission or clinical response (nonresponder imputation [NRI]). For continuous variables, last observation carried forward (LOCF) analysis was performed based on the patient's most recent, nonmissing postbaseline visit value. All statistical methods and imputations to handle missing data were prespecified unless otherwise indicated. All statistical comparisons used 2-sided tests with an α level of .05.

All prespecified major secondary efficacy end points were ranked in hierarchical order and tested by a stepdown procedure to account for multiplicity. Binary secondary efficacy end points were analyzed using the Cochran–Mantel–Haenszel test as described previously. The proportion of patients in clinical remission at week 26 by subgroups was compared using odds ratios, with 95% confidence intervals, and *P* values from the χ^2 test. Percent change in CRP level from baseline to weeks 4, 26, and 52 (LOCF) was compared post hoc within each treatment group using the signed rank sum test. All primary and secondary comparisons between the 2 dose groups were prespecified in the protocol.

Post hoc analyses for changes from baseline to week 26 and week 52 in continuous secondary efficacy variables within each treatment group were compared using the paired *t* test. Post hoc comparisons within each treatment group for prior anti-TNF use (yes vs no) were performed using the χ^2 test. Comparisons of clinical remission and clinical response in patients with and without prior infliximab use within each dose group were not prespecified and are exploratory in nature.

Treatment-emergent adverse events were summarized by dose group for the double-blind eow dosing period (week 4 to the end of the study or the last date before switching to double-blind weekly dosing). Adverse events experienced in the open-label induction period or at any time during the study were summarized for patients who received at least one dose of adalimumab.

Results

The demographics and baseline characteristics of the study population are shown in Table 1. Of 192 patients who received induction dosing, 4 were not randomized to receive maintenance treatment because of early termination (Figure 1*B*). Thus, 188 patients initiated randomized, double-blind treatment in the maintenance period. In all, 152 patients (80.9%) completed 26 weeks of treatment. In the low-dose group, 77 patients completed 26 weeks of treatment (49 on double-blind eow, 19 on double-blind weekly, and 9 on open-label rescue dosing). In the high-dose group, 75 patients completed 26 weeks of treatment (55 on double-blind eow, 17 on double-blind weekly, and 3 on open-label rescue dosing). A total of 124 patients (66.0%) completed the study (Figure 1*B*). Lack of efficacy and adverse events were the most common reasons for discontinuation.

Efficacy

Of the 188 patients who completed open-label induction and were randomized at week 4, 155 (82.4%) had responded to induction (clinical response defined as decrease in PCDAI ≥15 points from baseline) and 52 (27.7%) were in clinical remission. At week 26, 33.5% of

Table 1. Baseline Characteristics

Characteristic	Low-dose adalimumab (n = 95)	High-dose adalimumab (n = 93)
Age (*y*), mean (SD)	13.5 ± 2.47	13.7 ± 2.52
≥13 y, n (%)	60 (63.2)	62 (66.7)
Male, n (%)	54 (56.8)	51 (54.8)
White, n (%)	85 (89.5)	81 (87.1)
Weight (*kg*), mean (SD)	44.4 (13.96)	46.3 (16.79)
Height (*cm*), mean (SD)	154.4 (15.29)	154.6 (14.20)
Disease duration[a] (*y*), mean (SD)	2.9 (2.20)	3.1 (2.25)
Involved intestinal area,[b] n (%)		
Colon	77 (81.1)	77 (82.8)
Ileum	75 (78.9)	70 (75.3)
Gastroduodenum	35 (36.8)	32 (34.4)
Rectum	32 (33.7)	29 (31.2)
Anal/perianal	30 (31.6)	24 (25.8)
Jejunum	11 (11.6)	3 (3.2)
Other[c]	10 (10.5)	12 (12.9)
Draining fistula(s), n (%)	21 (22.1)	15 (16.1)
PCDAI score, mean (SD)	40.76 (6.77)	41.34 (7.21)
CDAI, mean (SD)	243.0 (73.1)[d]	279.3 (99.4)[e]
CRP (*mg/dL*), median (range)	1.31 (0–12.4)	1.16 (0–16.8)
≥1.0 mg/dL, n (%)	53 (56.4)[f]	50 (54.3)[f]
Erythrocyte sedimentation rate (*mm/h*), median (range)	27.5 (1.0–86.0)	30.0 (1.0–135.0)
Prior infliximab use, n (%)	41 (43.2)	42 (45.2)
Duration of prior infliximab use (*mo*), mean (SD)	14.9 (19.5)[g]	17.6 (16.9)[h]
Concomitant medications at baseline, n (%)		
Corticosteroids[i]	38 (40.0)	33 (35.5)
Immunosuppressants	57 (60.0)	60 (64.5)
Aminosalicylates	33 (34.7)	35 (37.6)
Antibiotics	11 (11.6)	4 (4.3)

[a]Defined as the duration of onset of CD until the first dose of study drug.
[b]Patient could have multiple CD locations.
[c]Includes locations as described by the investigator: antrum, cecum, esophagus, gastric ulcers, mouth and throat ulcers, oral, sigmoid, small bowel, stomach.
[d]n = 60.
[e]n = 62.
[f]One missing value.
[g]n = 40.
[h]n = 42.
[i]Includes budesonide.

patients were in clinical remission. A numerically higher proportion of patients in the high-dose adalimumab group were in clinical remission and clinical response (Figure 2*A*) compared with the low-dose group, but the differences did not achieve statistical significance. For infliximab-naïve patients, treatment with high-dose adalimumab resulted in a statistically significantly higher clinical remission rate at week 26 than treatment with low-dose adalimumab ($P = .026$; Figure 2*B*), although clinical response rates were similar ($P = .541$; Figure 2*C*). In comparisons within the high-dose group, the remission and response rates were significantly higher in the infliximab-naïve patients compared with the infliximab-experienced patients ($P < .001$ for remission, $P = .040$ for response). In the low-dose group, infliximab-naïve patients had significantly higher response rates than infliximab-experienced patients ($P < .001$) but the remission rates were not significantly different ($P = .093$). Remission and response rates at week 26 for patients who responded to induction therapy at week 4 were generally higher than those in the intention-to-treat population presented previously and are shown in Supplementary Table 1.

Results of subgroup analyses for clinical remission at week 26 are shown in Figure 3. For patients younger than 13 years of age, and for patients with disease duration of less than 3 years, treatment with high-dose adalimumab resulted in a statistically significantly greater rate of clinical remission versus treatment with low-dose adalimumab.

As was observed at week 26, the proportion of patients in clinical remission at week 52 was numerically greater but not statistically different in the high-dose group compared with the low-dose group (Figure 2*D*; $P = .100$). The proportion of patients in clinical response at week 52 was statistically significantly greater in the high-dose group than the low-dose group (Figure 2*D*; $P = .038$). Among patients who were naïve to infliximab, the proportion of patients in clinical remission was numerically but not statistically significantly greater in the high-dose versus the low-dose group ($P = .065$; Figure 2*E*); the proportion in clinical response was significantly greater in the high-dose versus the low-dose group ($P = .026$; Figure 2*F*). In the comparisons according to prior infliximab use, patients in the high-dose group who were naïve to inflix-

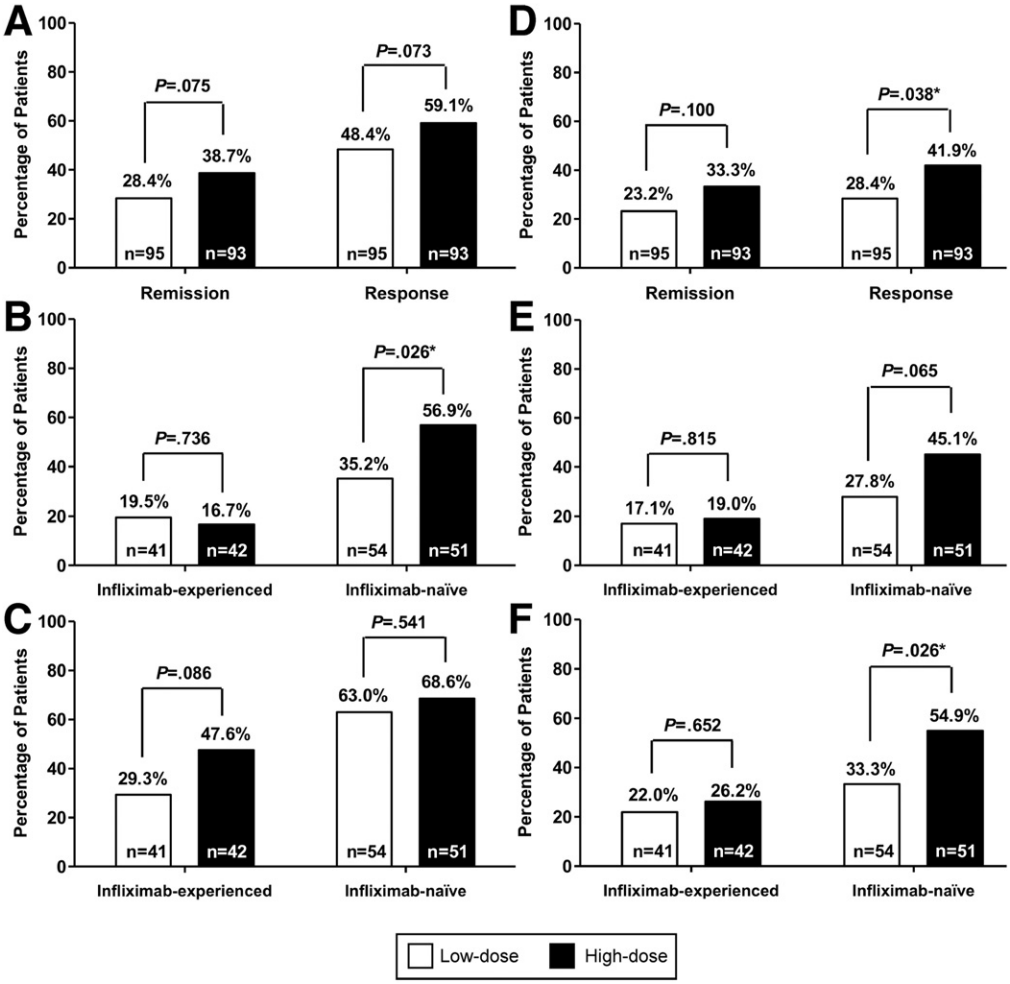


Figure 2. Results at (*A–C*) week 26 and (*D–F*) week 52. (*A*) Clinical remission and clinical response in the low- and high-dose groups at week 26. (*B*) Clinical remission and (*C*) clinical response in the dose groups by prior infliximab use at week 26. (*D*) Clinical remission and clinical response in the low- and high-dose groups at week 52. (*E*) Clinical remission and (*F*) clinical response in the dose groups by prior infliximab use at week 52.

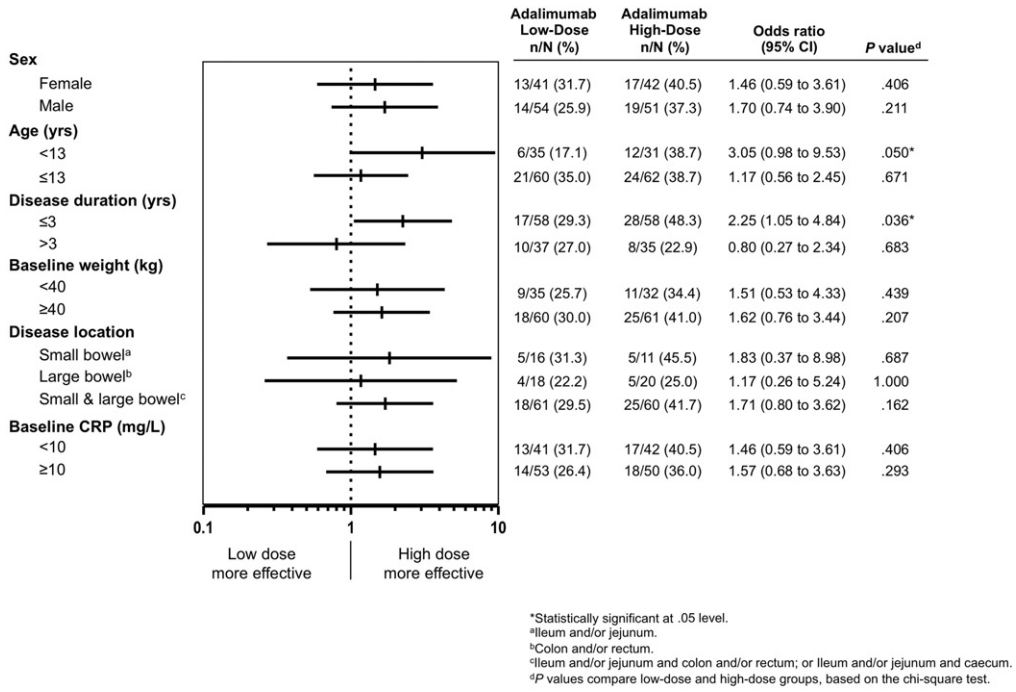
imab had significantly higher remission and response rates at week 52 compared with the infliximab-experienced patients ($P = .008$ for remission, $P = .005$ for response). There were no significant differences in remission ($P = .221$) or response ($P = .223$) at week 52 in the low-dose group between the infliximab-naïve and the infliximab-experienced patients. Remission and response rates at week 52 for patients who responded to induction therapy at week 4 are shown in Supplementary Table 1.

Clinical remission based on the CDAI (CDAI <150) at week 26 and week 52 was determined for the 122 patients who were at least 13 years of age at baseline (low dose, n = 60; high-dose, n = 62). The overall rate of CDAI clinical remission in these patients was 50.8% at week 26 (55.0% in the low-dose group and 46.8% in the high-dose group) and 36.1% at week 52 (35.0% in the low-dose group and 37.1% in the high-dose group).

At baseline, 38 patients (40.0%) in the low-dose group and 33 patients (35.5%) in the high-dose group were receiving corticosteroids. Of these patients, 65.8% (25/38) and 84.8% (28/33), respectively, had discontinued corticosteroid use by week 26, and 26.3% (10/38) and 33.3% (11/33), respectively, were in corticosteroid-free clinical remission at week 26 ($P = .519$). At baseline, 57 patients (60.0%) in the low-dose group and 60 patients (63.2%) in the high-dose group were receiving immunomodulators, which could be discontinued starting at week 26. Of these patients, 29.8% (17/57) and 30.0% (18/60), respectively, discontinued immunomodulator use by week 52, and 7.0% (4/57) and 16.7% (10/60), respectively, were in clinical remission free of immunomodulator use at week 52 ($P = .118$).

Significant improvements from baseline to week 26 and week 52 in z-scores for height velocity were observed for both treatment groups using LOCF (Table 2). Statistically significant reductions from baseline in CRP levels (mg/dL) using LOCF at weeks 4, 26, and 52 are shown in Supplementary Table 2.

The number of draining fistulae was determined at each study visit. At baseline, 21 patients in the low-dose group and 15 patients in the high-dose group had one or more draining fistulae. By week 52, 23.8% of patients (5/21) in the low-dose group had achieved fistula remission (closure for at least 2 consecutive visits of all fistulae that were draining at baseline) and 28.6% (6/21) showed improvement (decrease of ≥50% in the number of draining fistulae for at least 2 consecutive visits). In the high-dose group, 40% of patients (6/15) achieved fistula



*Statistically significant at .05 level.
[a]Ileum and/or jejunum.
[b]Colon and/or rectum.
[c]Ileum and/or jejunum and colon and/or rectum; or Ileum and/or jejunum and caecum.
[d]*P* values compare low-dose and high-dose groups, based on the chi-square test.

Figure 3. Odds ratios for the proportion of patients achieving clinical remission at week 26 for high- vs low-dose adalimumab by subgroup (NRI).

remission and the same percentage showed improvement at week 52.

Pharmacokinetics and Immunogenicity

Adalimumab trough levels were consistent between week 26 and week 52 in patients who continued on their randomized adalimumab treatment. Mean (SD) adalimumab concentrations were 10.4 (4.26) and 9.48 (5.61) μg/mL at weeks 26 and 52, respectively, in the high-dose group and 3.63 (2.50) and 3.51 (2.21) μg/mL at weeks 26 and 52, respectively, in the low-dose group.

Immunogenicity was low, with 6 of 182 patients (3.3%) who developed AAA at any time during the study: 2 (of 87; 2.3%) in the high-dose group and 4 (of 91; 4.4%) in the low-dose group. The latter 4 patients had prior infliximab experience. Two of the 6 AAA-positive patients were on concomitant immunosuppressants. Two AAA-positive patients achieved remission at week 26, both in the low-dose group.

Table 2. Z-scores for Height Velocity for Sex and Age at Baseline, Week 26, and Week 52 (LOCF)

	n	Mean	Mean change (SD)	*P* value[a]
Baseline				
Low-dose adalimumab	61	−0.98		
High-dose adalimumab	68	−0.37		
Week 26				
Low-dose adalimumab	61	1.66	2.64 (4.14)	<.001
High-dose adalimumab	68	1.38	1.75 (5.29)	.008
Week 52				
Low-dose adalimumab	61	1.80	2.77 (4.36)	<.001
High-dose adalimumab	68	2.07	2.44 (6.03)	.001

NOTE. Z-scores were set to zero for female patients older than 14.5 years and male patients older than 17.5 years unless they had significant growth delay and delayed bone age. The equation for z-score calculation was as follows: Observed Height Velocity (cm/y) − Mean Height Velocity for Age and Sex (cm/y)/SD of the Mean.
[a]*P* values from paired *t* test for change from baseline within each treatment group.

Safety

In the open-label induction period, 101 of 192 patients (52.6%) reported treatment-emergent adverse events, including 2 serious infections (1 *Yersinia* infection and 1 viral infection; both events resolved and the patients completed the study). Adverse events and serious adverse events during the double-blind eow period by treatment group are shown in Table 3. Vital signs and laboratory results did not indicate any safety signals, and no statistically significant differences were observed between the low- and high-dose treatment groups. Eight serious infections were observed in the double-blind period. Two patients reported opportunistic infections: nonserious *Aeromonas* infection (low-dose group) and histoplasmosis disseminated (high-dose group). The patient with histoplasmosis disseminated discontinued the study due to the infection, which resolved during follow-up. Adverse events for patients receiving at least one dose of adalimumab at any time during the study are reported in Supplementary Table 3.

Discussion

The pediatric patients included in the IMAgINE 1 study had moderate to severe CD that was resistant to conventional therapy. In many cases, prior infliximab therapy had been given as well with loss of response or development of drug intolerance. In this clinically challenging population, 33.5% of patients treated with adali-

Table 3. Proportion of Patients With Treatment-Emergent Adverse Events and Events Per 100 Patient Years by Dose Group During the Double-Blind eow Maintenance Period (Intention to Treat)

	Double-blind maintenance			
	Low-dose adalimumab 20 mg or 10 mg eow		High-dose adalimumab 40 mg or 20 mg eow	
	n = 95 n (%)	PYs = 47.5 Events (E/100PY)	n = 93 n (%)	PYs = 54.1 Events (E/100PY)
Any adverse event	81 (85.3)	464 (976.8)	86 (92.5)	507 (937.2)
At least possibly drug related[a]	37 (38.9)	110 (231.6)	39 (41.9)	111 (205.2)
Severe adverse event	11 (11.6)	14 (29.5)	19 (20.4)	27 (49.9)
Serious adverse event	19 (20.0)	20 (42.1)	22 (23.7)	24 (44.4)
Leading to discontinuation of study drug	12 (12.6)	13 (27.4)	15 (16.1)	20 (37.0)
At least possibly drug-related serious adverse event[a]	2 (2.1)	2 (4.2)	1 (1.1)	1 (1.8)
Infectious adverse event	47 (49.5)	101 (212.6)	56 (60.2)	98 (181.1)
Serious infections	3 (3.2)[b]	3 (6.3)	5 (5.4)[c]	5 (9.2)
Any malignancies	0	0	0	0
Lymphomas	0	0	0	0
Injection site reactions	10 (10.5)	24 (50.5)	9 (9.7)	25 (46.2)
Opportunistic infections, excluding tuberculosis	1 (1.1)	1 (2.1)	1 (1.1)	1 (1.8)
Congestive heart failure	0	0	0	0
Demyelinating disease	0	0	0	0
Hepatic-related adverse event	5 (5.3)	6 (12.6)	4 (4.3)	5 (9.2)
Allergic reactions	2 (2.1)	3 (6.3)	6 (6.5)	8 (14.8)
Lupus-like syndrome	0	0	0	0
Hematologic-related adverse event	4 (4.2)	5 (10.5)	9 (9.7)	11 (20.3)
Deaths	0	0	0	0

NOTE. Treatment-emergent adverse events were any adverse events with an onset date on or after the first double-blind dose and up to 70 days after the last dose of study drug or up to the first dose of weekly blinded adalimumab.
PY, patient-years.
[a]As assessed by the investigator.
[b]Tooth abscess (1), scarlet fever (1), Bartholin's abscess (1).
[c]Abdominal abscess (1), histoplasmosis disseminated (1), gastroenteritis (1), anal abscess (1), H1N1 influenza (1).

mumab achieved clinical remission at week 26, with 28.4% in clinical remission at week 52. Specifically, adalimumab in the low-dose and high-dose regimens induced and maintained clinical remission in 28% to 39% of patients at week 26 and 23% to 33% at week 52. Adalimumab was generally safe and well tolerated. The safety profiles for the 2 dose groups were similar, and adverse events of special interest occurred infrequently. The safety results in this study are comparable to those reported for adalimumab in other clinical trials in a variety of indications. There were no cases of malignancy, congestive heart failure, demyelinating disease, lupus-like syndrome, or tuberculosis and no deaths. No new safety signals were identified in this study.

In subgroup analyses, remission rates were somewhat higher in male subjects than in female subjects, as has been observed by others.[23] Treatment with high-dose adalimumab resulted in a statistically significantly higher rate of remission for patients with disease duration of ≤3 years or who were younger than 13 years of age compared with low-dose adalimumab treatment. Patients with lower CRP levels at baseline had higher rates of remission overall and in both dose groups, which is at odds with the literature describing results in adults with CD. Previous data identified adult patients with high CRP levels to be more responsive to anti-TNF therapy than those with low CRP levels.[24] It is possible that, in comparison with the pediatric patients, the cohort of adult patients with low CRP levels is enriched in those with fibrostenotic disease, which is more refractory to effective therapy.

Reducing corticosteroid dosing is an important goal in treating patients with CD because of the known adverse effects of prolonged corticosteroid use. In children, the growth-suppressive effects of corticosteroids are of particular concern. In patients receiving corticosteroids at baseline in this trial, more than 65% discontinued corticosteroids before week 26 and more than 20% achieved corticosteroid-free remission at week 26. Of note, treatment with adalimumab was associated with significant improvements in height velocity.

Approximately one-third of the patients with fistulae at baseline achieved fistula remission at week 52, with a higher proportion of patients treated with high-dose adalimumab achieving fistula remission compared with patients in the low-dose group. The number of patients with fistulae at baseline, however, was small.

Comparisons between the results of different trials must be interpreted with caution because of differences in study design. However, among infliximab-naïve children, the results observed in the present study are similar to the results reported in the open-label randomized trial of infliximab in children with moderate to severe CD,

REACH,[14] which included only anti-TNF–naïve patients. The percentage of patients who responded to induction was similar in both trials, as was the percentage of anti-TNF–naïve patients who maintained clinical remission and clinical response among those who responded to induction.

Although not typically used by pediatric gastroenterologists, the CDAI correlates well to the PCDAI[25] and was included as a sensitivity analysis for the PCDAI results of the IMAgINE 1 trial, as well as to allow for a more feasible comparison to data obtained from adult trials. The overall rates of CDAI clinical remission for the 122 patients who were at least 13 years old at baseline were approximately 51% and 36% at week 26 and week 52, respectively, which are comparable to data from CHARM,[26] the placebo-controlled clinical trial of adalimumab in adults with moderately to severely active CD. In CHARM, patients who responded to induction therapy were randomly assigned to treatment with adalimumab 40 mg eow, adalimumab 40 mg weekly, or placebo. At week 26, 40% of patients in the eow adalimumab group achieved clinical remission. The corresponding result at week 56 was 36%. Of note, the CHARM results were reported for patients who responded at week 4, whereas the CDAI results in the pediatric trial include all patients who were 13 years of age or older, regardless of response at week 4.

In IMAgINE 1, patients who were naïve to previous infliximab use were more likely to achieve clinical remission or response than patients who had used infliximab in the past. The differences between the infliximab-naïve and infliximab-experienced patients in the high-dose group were statistically significant for both remission and response at week 26 and week 52. However, it must be pointed out that the protocol-specified stratification at randomization by prior infliximab use ensured approximately equal numbers of infliximab-experienced patients between the high- and low-dose groups, but the study was not designed or powered to assess differences between the infliximab-naive and infliximab-experienced patients within each adalimumab treatment group. Although these results must be considered exploratory, they are consistent with observations in adults with CD in several trials. In the CLASSIC I[27] trial in patients naïve to prior anti-TNF agents, rates of clinical remission and clinical response after adalimumab induction were higher than those reported in the GAIN trial,[28] in which all patients had prior exposure to infliximab. Likewise, in the CHARM trial,[26] patients with no prior anti-TNF exposure had numerically greater rates of clinical remission at week 26 and at week 56 than those who had previously used and lost response to or became intolerant to anti-TNF agents.

The lack of placebo control in the IMAgINE 1 trial is a limitation of the study. The design was considered appropriate for a pediatric trial because of ethical considerations after the principal evidence of efficacy had been established in adult patients with moderate to severe CD and was consistent with that of trials of anti-TNF agents in children with CD[14] and ulcerative colitis,[29] which were not placebo controlled.

In summary, the majority (>80%) of pediatric patients with moderate to severe CD responded to adalimumab induction therapy within 4 weeks. Adalimumab was effective in maintaining remission at 26 weeks in 38.7% of all patients and 56.9% of infliximab-naïve patients receiving the higher dose and in 28.4% of all patients and 35.2% of infliximab-naïve patients in the low-dose group. Both doses were well tolerated, and no new safety concerns were raised. In children with moderately to severely active CD despite conventional treatment, adalimumab therapy in infliximab-naïve patients resulted in rates of response and remission similar to those observed with infliximab treatment. The finding that patients previously treated with infliximab had a lower response to adalimumab therapy in this population deserves further study.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.04.046.

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Conflicts of interest

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Supplementary Table 1. Clinical Remission and Clinical Response Rates at Week 26 and Week 52 by Prior Infliximab Use in Patients Who Responded at Week 4 to Adalimumab Induction (NRI)

	Week 4 responders		
	Low-dose adalimumab 20 mg or 10 mg eow (n = 80) n/N (%)	High-dose adalimumab 40 mg or 20 mg eow (n = 75) n/N (%)	*P* value
Week 26 remission			
Infliximab naïve	18/48 (37.5)	27/43 (62.8)	.016[a]
Infliximab experienced	7/32 (21.9)	6/32 (18.8)	.756
Week 26 response			
Infliximab naïve	32/48 (66.7)	32/43 (74.4)	.419
Infliximab experienced	10/31 (31.3)	18/32 (56.3)	.044[a]
Week 52 remission			
Infliximab naïve	13/48 (27.1)	20/43 (46.5)	.054
Infliximab experienced	5/32 (15.6)	8/32 (25.0)	.351
Week 52 response			
Infliximab naïve	16/48 (33.3)	25/43 (58.1)	.018[a]
Infliximab experienced	7/32 (21.9)	10/32 (31.3)	.396

NOTE. *P* values based on the χ^2 test.
[a]Statistically significant at $P = .05$ level.

Supplementary Table 2. Median Percent Change From Baseline in CRP Level at Weeks 4, 26, and 52 (LOCF)

	n	Median percent change, *mg/dL* (interquartile range)	*P* value[a]
Week 4			
Low-dose adalimumab	94	−85.02 (−93.39, −60.36)	<.001
High-dose adalimumab	92	−74.59 (−89.43, −38.55)	<.001
Week 26			
Low-dose adalimumab	94	−60.91 (−88.52, 0)	<.001
High-dose adalimumab	92	−57.67 (−92.98, −1.92)	.002
Week 52			
Low-dose adalimumab	94	−54.28 (−85.10, 33.18)	.004
High-dose adalimumab	92	−62.63 (−93.07, 1.44)	.010

NOTE. *P* values based on the signed-rank sum test for change from baseline.

Supplementary Table 3. Proportion of Patients With Treatment-Emergent Adverse Events and Events per 100 PYs, All Patients Who Received at Least One Dose of Adalimumab

	Any adalimumab	
	N = 192 n (%)	PYs = 151.8 Events (E/100PY)
Any adverse event	184 (95.8)	1493 (983.5)
At least possibly drug related	96 (49.5)	357 (235.2)
Severe adverse event	52 (27.1)	86 (56.7)
Serious adverse event	63 (32.8)	82 (54.0)
Leading to discontinuation of study drug	42 (21.9)	53 (34.9)
At least possibly drug-related serious adverse event	4 (2.1)	4 (2.6)
Infectious adverse event	129 (67.2)	285 (187.7)
Serious infections	12 (6.3)[a]	13 (8.6)
Any malignancies	0	0
Lymphomas	0	0
Injection site reactions	37 (19.3)	93 (61.3)
Opportunistic infections, excluding tuberculosis	2 (1.0)	2 (1.3)
Congestive heart failure	0	0
Demyelinating disease	0	0
Hepatic-related adverse event	10 (5.2)	12 (7.9)
Allergic reactions	10 (5.2)	14 (9.2)
Lupus-like syndrome	0	0
Hematologic-related adverse event	20 (10.4)	24 (15.8)
Deaths	0	0

NOTE. Treatment-emergent adverse events were any adverse events with an onset date on or after the first dose and up to 70 days after the last dose of study drug.

PY, patient-years.

[a]Abdominal abscess (2), tooth abscess (1), anal abscess (1), Bartholin's abscess (1), scarlet fever (1), histoplasmosis disseminated (1), gastroenteritis (1), H1N1 influenza (1), viral infection (1), *Yersinia* spp (1), device-related sepsis (1).