Growth Improvement with Adalimumab Treatment in Children with Moderately to Severely Active Crohn's Disease

Thomas D. Walters, MD, William A. Faubion, MD,† Anne M. Griffiths, MD,* Robert N. Baldassano, MD,‡ Johanna Escher, MD, PhD,§ Frank M. Ruemmele, MD, PhD,‖ Jeffrey S. Hyams, MD,¶ Andreas Lazar, MD,** Samantha Eichner, PharmD,†† Bidan Huang, PhD,†† Yao Li, PhD,†† and Roopal B. Thakkar, MD††*

Background: Growth failure is common in children with Crohn's disease. The effect of adalimumab (ADA), a fully human antitumor necrosis factor antagonist, on height velocity in pediatric patients with baseline (BL) linear growth impairment in the IMAgINE 1 trial is presented.

Methods: This analysis included female and male patients with growth potential (bone age ≤13 and ≤14 yr, respectively), with BL Pediatric Crohn's disease Activity Index >30, and who failed or were intolerant to conventional therapy. Patients received open-label induction ADA at weeks 0 and 2 by body weight (≥40 kg, 160 and 80 mg and <40 kg, 80 and 40 mg). At week 4, patients were randomized to double-blind high (40 or 20 mg for ≥40 kg or <40 kg) or low dose (20 or 10 mg for ≥40 kg or <40 kg) every other week ADA to week 52. Height velocity z-score was summarized at BL, week 26, and week 52 by patients with BL growth impairment (z-score ≤−1.0) or normal growth (z-score >−1.0).

Results: ADA therapy significantly improved and normalized growth rate at weeks 26 and 52 in patients with BL growth impairment (median z-score, BL, −3.25; week 26, −0.34; and week 52, 0.21; $P < 0.001$ versus BL for both), but not in patients with normal growth. Growth improvement was significantly greater at week 26 in week 4 responders to induction therapy compared with nonresponders (median z-score 0.09 versus −2.92; $P = 0.02$).

Conclusions: ADA treatment resulted in growth rate normalization as early as week 26 in children with moderately to severely active Crohn's disease and growth impairment.

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Key Words: pediatric Crohn's disease, anti-TNF antibody, adalimumab, linear growth, height velocity z-score

Approximately one-third of children and adolescents with Crohn's disease (CD) suffer from growth failure and delayed puberty.[1,2] Psychological and social dysfunction are often associated with delayed puberty, especially in boys.[3] Pubertal delay in CD may also impact the normal growth spurt and lead to short adult height and sexual immaturity.[3] For instance, up to 85% of patients with pediatric onset CD were reported to have missed their target height at maturity,[4] and approximately 60% of patients with distinct growth retardation at diagnosis did not ultimately achieve a normal height[5] in the preanti-TNF-α era. In addition,

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From the *Department of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada; †Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; ‡Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; §Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; ‖Department of Pediatrics, Pediatric Gastroenterology, Universite Sorbonne Paris-Cite, Hospital Necker-Enfants Malades, Paris, France; ¶Division of Digestive Diseases, Hepatology and Nutrition, Connecticut Children's Medical Center, Hartford, CT; **AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; and ††AbbVie Inc., North Chicago, IL.

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Address correspondence to: Thomas D. Walters, MD, Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada (e-mail: Thomas.Walters@sickkids.ca).

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reduced bone mineral density in children with CD has been reported to be associated with increased risk of fractures later in adulthood.[6] Physicians may encounter these clinical problems more frequently because approximately 25% of patients with CD are children, and the incidence of pediatric CD is increasing worldwide.[7] Restoration of linear growth is a therapeutic goal and a marker of treatment success in pediatric patients with CD.[8]

Growth failure in children with CD has a multifactorial etiology, including chronic inflammation, undernutrition, corticosteroid therapy, and low levels of insulin-like growth factor 1.[1,3,9,10] Data from clinical trials have shown that anti-TNF therapy can improve height velocity in children with CD.[11,12] Furthermore, early treatment with anti-TNF therapy (≤3 mo after diagnosis) starting before or in early puberty leads to greater improvement in height and height velocity.[13,14]

The ADA pediatric CD clinical trial, IMAgINE 1 (ClinicalTrials.gov identifier NCT00409682), demonstrated that ADA, a fully human monoclonal antibody against TNF-α, is effective and safe in inducing and maintaining remission in children with moderately to severely active CD.[12] In this trial, treatment with ADA also led to an improvement in height velocity z-scores in patients at weeks 26 and 52. In this analysis, we assessed the effect of ADA on linear growth specifically in children with CD from the IMAgINE 1 trial who had linear growth impairment at baseline (BL). In addition, bone-specific alkaline phosphatase (BSAP), which has been shown to correlate with osteoblast activity and height velocity in previous studies, was evaluated as a biomarker of bone formation.[15]

Materials and Methods

Study Design and Patients

IMAgINE 1 (ClinicalTrials.gov identifier, NCT00409682) was a 52-week, phase 3, multicenter, randomized, double-blind trial that assessed the efficacy and safety of 2 induction doses and 2 maintenance dose regimens of ADA in 6- to 17-year-old patients with moderately to severely active CD. The details have been published previously.[12] Briefly, pediatric patients with a diagnosis of CD for ≥12 weeks before study screening and Pediatric CD Activity Index (PCDAI) >30, despite concurrent treatment with oral corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate, received open-label induction of ADA at weeks 0 and 2 according to body weight (patients weighing ≥40 kg received 160 and 80 mg, whereas patients weighing <40 kg received 80 and 40 mg). At week 4, patients were randomized according to body weight to double-blind high-dose (≥40 kg received 40 mg every other week [eow] and <40 kg received 20 mg eow) or low-dose (≥40 kg received 20 mg eow and <40 kg received 10 mg eow) ADA. Patients with previous exposure and response to infliximab were permitted to enroll in IMAgINE 1. All doses of CD-related therapy were to remain stable throughout the study, except for immunomodulators that could be discontinued at or after week 26, at the discretion of the investigator, and corticosteroids that could be tapered beginning after week 4 for patients experiencing clinical response (PCDAI decrease ≥15 points compared with BL score).

Beginning at week 12, patients who met the protocol-defined criteria for flare or nonresponse could escalate from blinded eow to weekly dosing, continuing with the same blinded dose, either high dose or low dose. After 8 weeks of blinded weekly dosing, patients with continued flare or nonresponse could move to open-label weekly high-dose ADA (≥40 kg received 40 mg weekly and <40 kg received 20 mg weekly). Flare was defined as increase in PCDAI ≥15 points compared with week 4 and PCDAI >30. Nonresponse was defined as 2 consecutive visits at least 2 weeks apart without PCDAI decrease ≥15 points compared with the BL score.

Patients assessed in this analysis were a subset of patients from the IMAgINE 1 clinical trial because the analysis was limited to patients with growth potential, i.e., those who most likely had not finished growing physiologically (females with a bone age ≤13 years and males with a bone age ≤14 years; Fig. 1).[16]

Bone Age

Because bone age is a more reliable reflection of skeletal maturation status than chronological age, especially in children with growth impairment, all patients underwent a bone x-ray of the left wrist at screening and at week 52. Bone age was determined using the Greulich and Pyle method for reading x-rays.[17] Because x-rays were not obtained at week 26, per IMAgINE 1 study design to limit exposure to x-ray, week 26 bone age was imputed by calculating the midpoint between bone age at BL and at week 52. There were fewer patients with bone age information available (N = 52) than patients with calendar age information available (N = 59) at week 26.

Height Velocity Z-Scores

Linear growth impairment was defined as a height velocity z-score ≤−1.0, and analyses were performed on patients with or without linear growth impairment at BL. The z-score metric is an SD classification system that is generally accepted as the most appropriate system for the analysis of anthropometric data.[18] A z-score expresses a value as a number of SDs below or above the mean of the reference population, i.e., a z-score of 1 corresponds to a value that is 1 SD above the mean of the distribution of the reference values, whereas a z-score of 0 represents the mean of the reference values.

Observed height velocity was calculated according to the following: (present height [cm] − height 6–12 mo previously [cm]/interval [mo] between heights) × 12. Bone age–specific z-scores for height velocity were calculated for each patient with reference to standard height velocity tables[19] according to the equation: (observed height velocity [cm/y] − median height velocity for age and sex [cm/y])/SD of the median. A patient's bone age was used to identify the median height velocity in the reference table.

Height Z-Scores

Height z-scores (in patients with a height velocity z-score ≤−1.0 versus >−1.0) were calculated using calendar age to

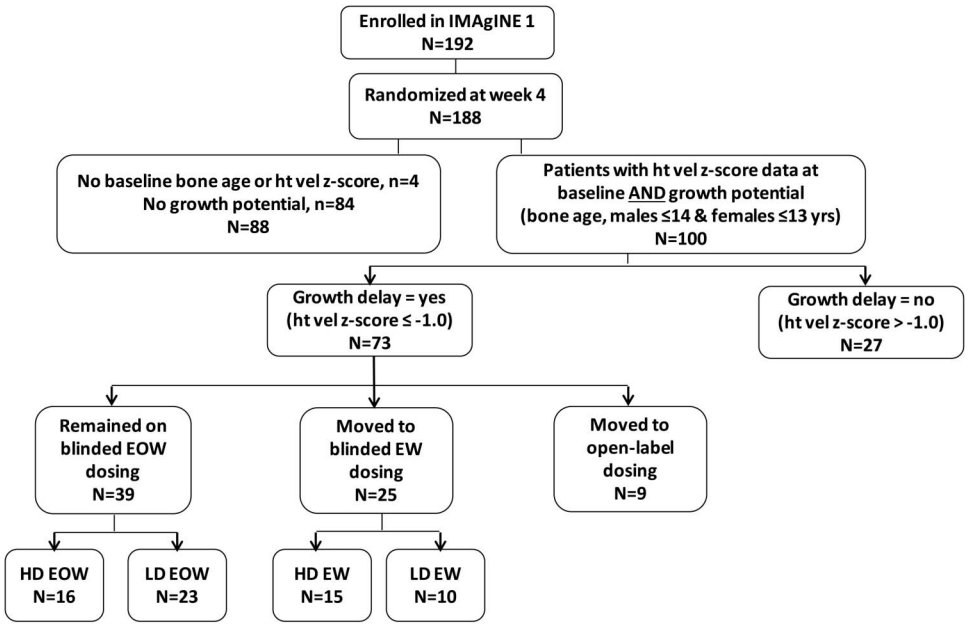


FIGURE 1. Study design and patient flow. EOW, every other week; EW, every week; HD, high dose; ht vel, height velocity; LD, low dose.

identify the median height and SD of an age- and sex-matched pediatric population as a reference standard.[19] The following equation was used: (observed height [cm] − median height for age and sex [cm])/SD of the median.

BSAP

BSAP was assessed at weeks 0, 26, and 52. Serum levels of BSAP were measured using an enzyme immunoassay. BSAP is produced by osteoblasts in the bone and then secreted into the blood stream. Studies have shown that it is a marker of bone formation that correlates with osteoblast activity and height velocity.[15]

Statistical Analysis

Combined data from all patients receiving ADA treatment (both low- and high-dose groups) are presented. Median height velocity z-scores and changes in BSAP from BL were assessed at weeks 26 and 52 in patients with and without linear growth impairment at BL and reported as observed. Observed data from the double-blind and open-label phases are reported. A Wilcoxon signed rank test was used to determine the within group median change from BL in height velocity z-scores and BSAP in all patients treated with ADA. Wilcoxon rank sum test was used to compare median height velocity z-scores and median changes in BSAP in patients with BL linear growth impairment with those with normal linear growth, and to compare the median height velocity z-scores, median height z-scores, and median changes in BSAP between the strata of each subgroup in patients with BL linear growth impairment. Demographics were compared between patients with and without linear growth impairment at BL using 1-way analysis of variance for continuous variables and the Fisher's exact test for categorical variables. Multivariate logistic regression was used to determine prognostic factors for growth normalization, as defined by achieving a height velocity z-score of ≥0. BL variables assessed were bone age, sex, weight, disease duration, disease severity (based on the median PCDAI in IMAgINE 1; moderate [PCDAI <40] versus severe [PCDAI ≥40]),[12,20] C-reactive protein, corticosteroid use, immunomodulator use, and previous infliximab use. Week 4 serum ADA trough levels and week 4 response status were also assessed in the logistic regression analysis. Receiver-operating characteristic (ROC) curve analysis was used to determine the cut point for ADA trough levels that are predictive of normalization of linear growth velocity at week 52. The association between normalization in growth rate at week 52 and both durable remission (PCDAI ≤10 at ≥80% of visits after week 4) and durable response (decrease in PCDAI ≥15 from BL with or without remission at ≥80% of visits after week 4) were tested using the Fisher's exact test. The definition of durability (≥80% of visits after week 4 [i.e., 4/5 and 7/9 visits at weeks 26 and 52, respectively]) was adapted from published literature.[21] In addition, the correlation between PCDAI and height velocity z-scores at weeks 26 and 52 was calculated using Pearson's correlation coefficient. A linear logistic regression model was used to evaluate the association between week 4 ADA trough levels and change from BL in height velocity z-score at weeks 26 and 52.

Ethical Considerations

The study was conducted with the approval of an independent ethics committee or an institutional review board for each site, and in accordance with the guidelines of the International Conference on Harmonization and ethical principles originating in the Declaration of Helsinki. All participating patients provided their written informed consent.

RESULTS

Patients

Demographics and BL characteristics for patients with and without linear growth impairment at BL are shown in Table 1. Notably, the majority of patients (73/100, 73%) with growth potential presented with linear growth impairment (height velocity z-score ≤ -1.0) at BL. However, beyond a significantly lower median height velocity z-score (-3.25 versus 0.88, $P < 0.001$), there were no statistically significant differences between both groups for most variables (Table 1).

Improvement in Growth

As anticipated, in patients who did not demonstrate linear growth impairment at BL, linear growth remained stable over time (Fig. 2A). However, during the 52 weeks of ADA therapy, linear growth normalized in patients who initially had significant impairment at BL. This was evidenced by the median height velocity z-score improving from -3.25 at BL to -0.34 by 26 weeks, and further improving to +0.21 by 52 weeks (Fig. 2A). Indeed, by week 26, there was no significant difference in linear growth rate between the group with initial impairment compared with those with normal linear growth at BL (median height velocity z-score = -0.34 versus -0.07, $P = 0.555$). This normalization of growth rate was maintained at week 52 (median height velocity z-score = +0.21 versus -0.94, $P = 0.426$; Fig. 2A).

Patients who received high-dose ADA had greater median height velocity z-scores compared with patients who received low-dose ADA at both 26 and 52 weeks. Median height velocity z-score at 26 weeks was -0.02 for patients receiving high-dose ADA and -0.43 for patients randomized to low-dose ADA; median height velocity z-score at 52 weeks was +0.67 for the high-dose and -0.42 for the low-dose ADA group.

Patients receiving ADA without dose escalation had greater median height velocity z-scores compared with patients who required dose escalation to weekly ADA. Median height velocity at 26 weeks was +0.03 in patients without dose escalation and -1.25 in patients with dose escalation; median height velocity z-score at 52 weeks was 1.71 in patients without dose escalation and -1.36 in patients whose dose escalated ($P = 0.007$).

Subgroup analysis of patients with BL growth impairment demonstrated that patients who were responders to ADA induction therapy achieved significantly greater growth improvement by week 26 compared with nonresponders at week 4 (median height velocity z-score = +0.09 versus -2.92, $P = 0.023$; Fig. 2B). The numerical difference between week 4 responders and nonresponders persisted to week 52 (+0.68 versus -1.78, $P = 0.160$; Fig. 2C). A similar numerical pattern of improvement in linear growth by week 26 was observed when previous infliximab exposure was considered (median height velocity z-score by week 26: +0.11 versus -1.49, $P = 0.099$; and week 52: +1.27 versus -0.42, $P = 0.200$; in patients who were infliximab naive versus patients who were exposed, respectively). Patients treated with ADA with BL linear growth impairment experienced normalization of linear growth by weeks 26 and 52 regardless of BL disease severity (PCDAI <40 or ≥ 40) and regardless of corticosteroid use at BL (Fig. 2B, C). Of note, only a few of the patients who received corticosteroid therapy at study entry and showed linear growth impairment (Table 1) continued using corticosteroids at week 26 (17.2%, 5/29) and week 52 (6.9%, 2/29).

Biomarker Analysis

Median change from BL in BSAP was significantly increased with ADA treatment at week 26 both in patients with linear growth impairment (20.5 [-65.2, 171.3] μg/L; $P < 0.001$) and in those with normal growth at BL (14.7 [-37.4, 99.8] μg/L;

TABLE 1. Demographics and BL Characteristics for Patients with Linear Growth Impairment (Height Velocity Z-Score ≤ -1.0) or Without Growth Impairment (Height Velocity Z-Score > -1.0) at BL

	BL Growth Impairment	No BL Growth Impairment
	N = 73	N = 27
Male, n (%)	46 (63.0)	18 (66.7)
Chronological age, mean (SD), yr	12.0 (2.1)	11.9 (2.1)
Bone age, yr		
Mean (SD)	11.0 (2.1)	11.2 (2.4)
Median (range)	11.3 (3.0, 14.0)	11.6 (5.0, 14.0)
Difference between bone age and chronological age, mean (SD), yr	−1.0 (1.5)	−0.7 (1.3)
Weight, mean (SD), kg	36.5 (11.2)	39.6 (13.0)
Height, mean (SD), cm	144.6 (12.3)	146.8 (12.6)
Height velocity z-score, median (range)[a]	−3.25 (−7.9, −1.0)	0.88 (−0.8, 6.2)
Height z-score, median (range)	−1.10 (–3.5, 2.3)	−0.71 (−3.1, 1.6)
PCDAI score, mean (SD)	42.8 (6.7)	40.6 (6.4)
Disease duration, mean (SD), yr	2.4 (2.0)	2.3 (1.5)
CRP, median (range), mg/dL	1.38 (0, 16.8)	0.64 (0, 14.4)
Albumin, median (range), g/L	40 (27, 53)	40 (26, 47)
Concomitant medication use at BL, n (%)		
Corticosteroids	29 (39.7)	7 (25.9)
Immunomodulator (AZA, 6-MP, and MTX)	45 (61.6)	19 (70.4)
Previous infliximab use, n (%)	27 (37.0)	13 (48.1)

[a] $P < 0.001$ by Wilcoxon Rank Sum Test.
6-MP, 6-Mercaptopurine; AZA, azathioprine; CRP, C-reactive protein; MTX, methotrexate.

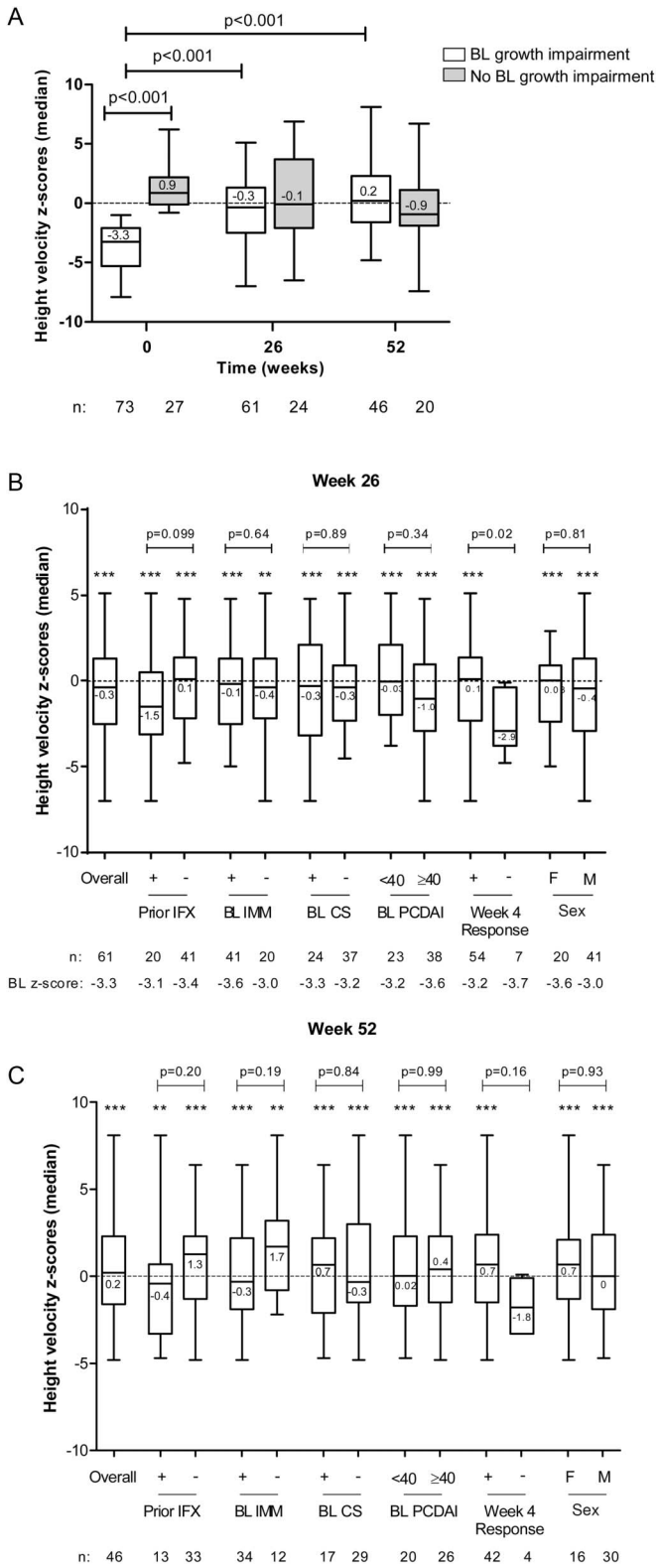


FIGURE 2. Median height velocity z-scores for patients treated with ADA with BL linear growth impairment (*white boxes*) and without linear growth impairment (*gray boxes*) at BL, weeks 26, and 52 (A). Median height velocity z-scores in subgroups of patients with BL linear growth impairment at week 26 (B) and week 52 (C). Subgroup analysis by previous infliximab (IFX) use, BL immunomodulator use (IMM), BL corticosteroid use (CS), BL disease severity (PCDAI), week 4 response, and sex. The n observed at each time point and the median height velocity z-scores at BL (B) for each subgroup are shown at the bottom of the figures. *P* values for differences in height velocity z-scores between patients with and without linear growth impairment at BL and for differences between subgroup strata were determined by the Wilcoxon rank sum test in figures (A–C). $^{*}P < 0.05$, $^{**}P \leq 0.01$, and $^{***}P < 0.001$ for within group median change from BL determined by the Wilcoxon signed rank test in figures (B) and (C). F, female; M, male.

$P = 0.005$; Fig. 3A). At week 52, significant median increases from BL in BSAP were observed with ADA treatment in patients with linear growth impairment (26.95 [−121.6, 148.0] μg/L; $P = 0.002$), but not in patients with normal growth at BL (2.10 [−72.5, 60.6] μg/L; $P = 0.956$; Fig. 3A).

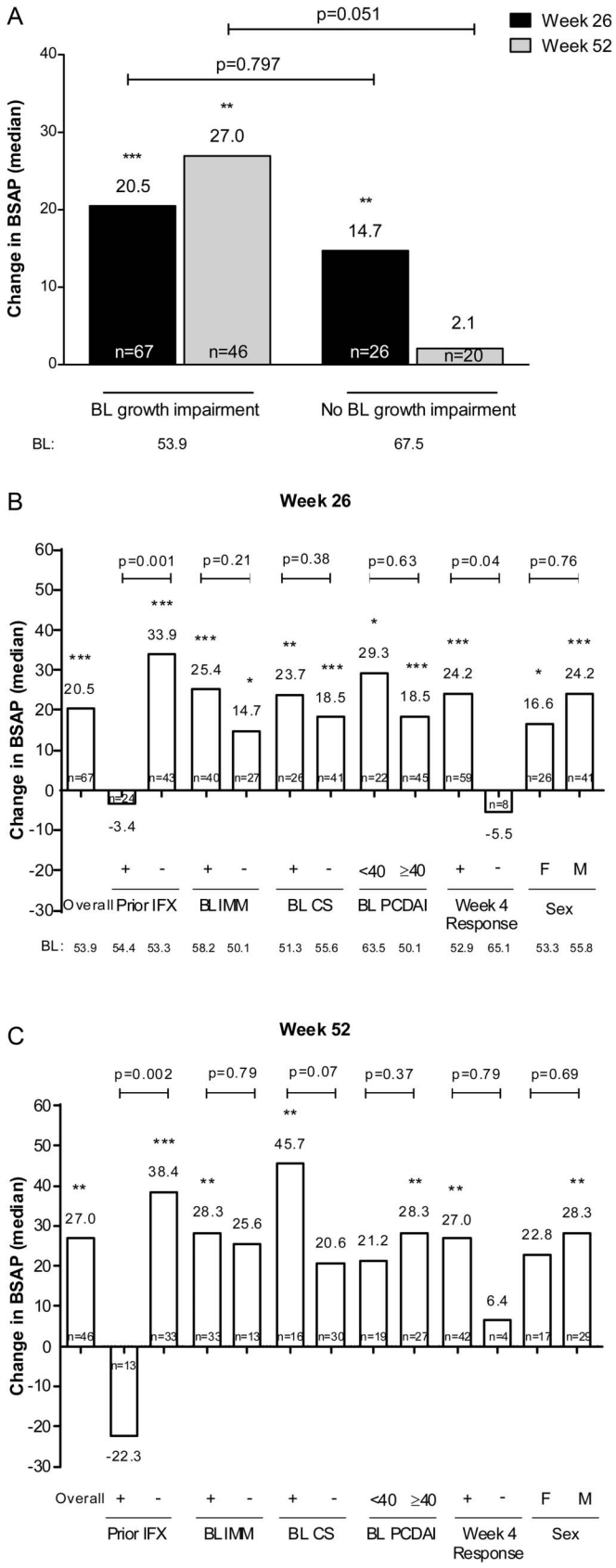
Subgroup analysis in patients with linear growth impairment at BL revealed that ADA was especially effective in patients who were infliximab naive. Median BSAP significantly improved in patients who were infliximab naive compared with patients who had experienced infliximab at both weeks 26 and 52 (Fig. 3B, C). Also, patients who responded to induction therapy by week 4 achieved significantly greater improvements in median BSAP compared with week 4 nonresponders at week 26 (Fig. 3B).

Predictors of Normalization of Growth Rate

Logistic regression analysis showed that week 4 response status was a significant predictor of linear growth normalization at week 26 (odds ratio 9.28 [95% confidence interval: 1.39–62.10]; $P = 0.022$; Table 2). At week 52, male patients were significantly more likely to exhibit normalization in height velocity than female patients (odds ratio 4.04 [95% confidence interval: 1.12–14.50]; $P = 0.032$), and ADA trough levels at week 4 after induction therapy were also a significant predictor of growth normalization (odds ratio 1.13 [95% confidence interval: 1.01–1.27]; $P = 0.033$). ROC curve analysis suggested that an ADA trough concentration of 10.9 μg/mL was the best cutoff for growth normalization in this patient population (area under the ROC curve, 0.605).

Association of Normalization of Growth Rate with Durable Remission and Response

Patients treated with ADA with linear growth impairment at BL who achieved and maintained durable remission throughout the study (defined by PCDAI ≤10 at ≥80% of visits after week 4) were significantly more likely to exhibit a normal growth rate at week 52 than patients without durable remission ($P = 0.023$ by the Fisher's exact test, N = 46). Median height velocity z-score and change from BL in height velocity z-score were significantly greater in patients with durable remission compared with patients without durable remission at weeks 26 and 52. These results were confirmed by analysis of clinical remission



status at weeks 26 and 52. Median height velocity z-score and change from BL in height velocity z-score were significantly greater in remitters compared with nonremitters at weeks 26 and 52 (Table 3). By contrast, there was no association between growth normalization at week 52 and achieving a durable response throughout the study, defined by a decrease in PCDAI ≥15 from BL at ≥80% of visits after week 4.

Change in Height Z-Score

In patients with BL growth impairment, median change from BL in height z-scores was 0.02 at week 26 and 0.19 at week 52. For patients without BL growth impairment, median change from BL in height z-scores was 0.05 at week 26 and 0.19 at week 52.

In patients with BL growth impairment, significantly greater improvement in median height z-score from BL was observed in remitters compared with nonremitters at weeks 26 and 52. In addition, change in median height z-score from BL tended to be more favorable in patients with durable remission compared with patients without durable remission at weeks 26 and 52 (Table 4).

Correlation of Growth Rate with PCDAI and ADA Trough Levels at Week 4

PCDAI weakly inversely correlated with height velocity z-scores at week 26 ($r^2 = -0.33$, $P = 0.017$) and week 52 ($r^2 = -0.38$, $P = 0.011$) in the Pearson's correlation analysis. Using a linear regression model, there was no correlation between week 4 ADA trough levels and height velocity z-scores at weeks 26 and 52 (data not shown).

DISCUSSION

The aim of pediatric CD therapy is to achieve remission, improve quality of life, and enable patients to attain full adult height potential. Anti-TNF therapy has been shown to improve height velocity in pediatric patients with CD.[11,12,22] This analysis examined the effect of maintenance ADA treatment on linear growth in the clinically important subset of pediatric patients with CD who entered the IMAgINE 1 study with physiologic growth

FIGURE 3. Median change from BL in BSAP (μg/L) to week 26 and week 52 for patients with and without linear growth impairment at BL (A). Median changes at week 26 *(black bars)* and week 52 *(gray bars)*. Median change in BSAP in subgroups of patients with linear growth impairment at BL at week 26 (B) and week 52 (C). Subgroup analysis by previous infliximab (IFX) use, BL immunomodulator (IMM) use, BL corticosteroid use (CS), BL disease severity (PCDAI), week 4 response, and sex. The n observed at each time point and BSAP values at BL are shown at the bottom of the graph. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. *P* values for within group median change from BL were determined by the Wilcoxon signed rank test in figures (A–C); *P* values for differences in BSAP between patients with and without linear growth impairment at BL and for differences between subgroup strata were determined by the Wilcoxon rank sum test in figures (A–C). F, female; M, male.

TABLE 2. Logistic Regression Analysis of Predictors of Achieving Normal Growth Rate (Height Velocity Z-Scores ≥0) in Patients Treated with ADA, Odds Ratios (95% Confidence Interval)

	Week 26 (N = 85)	Week 52 (N = 66)
Sex (male versus female)	2.34 (0.77–7.12)	4.04 (1.12–14.50)[a]
Bone age, yr	1.30 (0.90–1.88)	0.83 (0.54–1.29)
BL PCDAI	0.98 (0.90–1.07)	1.02 (0.92–1.14)
BL weight, kg	1.00 (0.94–1.07)	1.01 (0.93–1.11)
BL immunomodulator use (yes versus no)	0.92 (0.29–2.90)	0.29 (0.06–1.37)
BL corticosteroid use (yes versus no)	0.94 (0.29–3.01)	2.39 (0.54–10.70)
Disease duration, yr	0.96 (0.67–1.39)	1.17 (0.72–1.88)
BL CRP, mg/dL	0.88 (0.71–1.09)	1.03 (0.81–1.31)
Previous infliximab use (yes versus no)	0.42 (0.11–1.56)	0.33 (0.06–1.84)
Week 4 ADA trough levels	1.05 (0.97–1.14)	1.13 (1.01–1.27)[a]
Week 4 response	9.28 (1.39–62.10)[a]	3.57 (0.36–35.60)

[a]$P < 0.05$.
CRP, C-reactive protein.

TABLE 3. Median Z-Scores for Growth Rate in Patients Treated with ADA, Based on Remission Status (PCDAI ≤10; Durable if Achieved at ≥80% of Visits After Week 4)

	Week 26 (N = 52)	Week 52 (N = 44)
Height velocity z-score		
Remitters (n)	1.33 (23)	2.17 (27)
Nonremitters (n)	−0.78 (29)	−1.57 (17)
P value	0.01	0.001
Change from BL in height velocity z-score		
Remitters (n)	4.35 (23)	5.15 (27)
Nonremitters (n)	1.96 (29)	2.00 (17)
P value	0.026	0.018
Height velocity z-score		
With durable remission (n)	2.00 (12)	3.00 (9)
Without durable remission (n)	−0.39 (40)	−0.33 (35)
P value	0.040	0.006
Change from BL in height velocity z-score		
With durable remission (n)	4.86 (12)	5.78 (9)
Without durable remission (n)	2.30 (40)	3.04 (35)
P value	0.241	0.043

P value for differences among subgroups from the Wilcoxon Rank Sum Test.

potential. Height velocity z-score is regarded as the most sensitive measurement of growth in children.[10] ADA improved height velocity z-scores in patients with BL linear growth impairment at weeks 26 and 52, and this effect was especially profound in week 4 responders to ADA induction therapy.

Of note, the lack of improvement in standardized height velocity measures in patients without initial linear growth impairment provides evidence that the growth improvement observed is a result of the effectiveness of ADA for the treatment of pediatric patients with CD rather than a physiologic growth spurt in normally developing children. This is further corroborated by the significant relationship between clinical remission with ADA treatment and normalization of height velocity in patients with growth impairment at BL. Restoration of normal growth with ADA treatment in patients with growth impairment demonstrates success in achievement of a therapeutic goal.[8] Normalization of linear growth velocity over the course of this 52-week study had not yet resulted in a substantial change in height z-score that was not unexpected, as change in height z-score is a relatively insensitive measure over short time frames. Conversely, change in height velocity z-score is a more sensitive method for monitoring linear growth over relatively short time frames, such as 12 to 24 months.[23] However, statistically significant improvement was seen for median change in height z-score in patients who achieved remission compared with nonremitters at weeks 26 and 52.

In this study, height velocity z-scores were properly standardized by bone age. A limitation of the study was that patients' pubertal stage and midparental heights were not collected in the IMAgINE 1 trial. However, fluctuations related to puberty were greatly reduced by analyzing height velocity z-scores and by referring to bone age rather than calendar age in the standard height velocity tables for height velocity z-score calculations. Conversely, if changes in height z-score were calculated from

TABLE 4. Median Change from BL in Height Z-Scores in Patients Treated with ADA, Based on Remission Status (PCDAI ≤10; Durable if Achieved at ≥80% of Visits After Week 4)

	Week 26 (N = 59)	Week 52 (N = 44)
Remitters (n)	0.20 (24)	0.53 (27)
Nonremitters (n)	0 (35)	−0.08 (17)
P value	0.018	<0.001
With durable remission (n)	0.20 (12)	0.50 (9)
Without durable remission (n)	0.03 (47)	0.16 (35)
P value	0.166	0.074

P value for differences among subgroups from the Wilcoxon rank sum test.

age-based Center for Disease Control norms, aberrations in pubertal development would have led to spurious conclusions. We limited our analysis to patients who most probably had not exhausted their growth potential, i.e., females with a bone age ≤13 years and males with bone age ≤14 years. These cutoffs were chosen based on published literature showing that median bone age at menarche was 13.5 years for girls with CD,[16] whereas the median bone age at puberty for boys with CD is not well defined.

Our findings show that a majority of the children enrolled in the IMAgINE 1 trial who still had growth potential (73%) had significant linear growth impairment. In unselected populations, severe linear growth impairment occurs in approximately 20% to 30% of children and adolescents with CD and is marked by height less than one-third the percentile for age and height 2 SDs below the average for age or bone age 2 years less than chronological age.[2,24] Normal linear growth is marked by a height velocity z-score of zero. In the absence of a unique definition, in this study, we defined linear growth impairment as a height velocity z-score less than or equal to −1, which is the same cut point used by the PCDAI to indicate impaired linear growth velocity. The cutoff is also consistent with the definition of severe growth retardation used in a retrospective analysis of children with juvenile idiopathic arthritis and is in line with the mean height velocity z-score (−1.3) from a randomized trial of patients with pediatric CD who received growth hormone therapy for linear growth.[25,26] For this study, the median height velocity z-score of patients who met the definition of growth impairment was −3.25 at BL, suggesting that 99.9% of age- and sex-matched children would demonstrate a faster linear growth rate.[27] These data underline the severity of the linear growth impairment experienced in our cohort of pediatric patients with CD and the appropriateness of the chosen height z-score cutoff of ≤−1.0 as the definition of linear growth retardation.

Prolonged corticosteroid use has been associated with poorer growth outcomes.[28] Therefore, reduction of corticosteroid use is an important therapeutic goal in the management of pediatric CD. In this study, concomitant corticosteroid use at IMAgINE 1 BL did not demonstrate an influence on improvement in height velocity compared with patients without corticosteroids at BL. Of note, more than 80% (24/29) of patients treated with ADA with linear growth impairment and corticosteroid use at BL discontinued corticosteroids by week 26, and over 90% (27/29) of these patients discontinued corticosteroid use by week 52. Thus, the differences in terms of concomitant use of corticosteroids at BL may have balanced out by week 26, not exerting clinical effects afterward. In addition, subgroup analyses were carried out in patients with growth impairment, and corticosteroid use albeit being highly important might be accompanied by other risk factors for growth impairment. In addition, because physicians strive to restrict the application of corticosteroids in children because of the known negative influence on growth, use of concomitant corticosteroids at BL might not reflect the patients' actual most recent corticosteroid load because previous exposure to corticosteroids was not collected in a quantitative manner. Nevertheless, although not statistically different, the proportion of patients with concomitant corticosteroid use at BL was numerically greater in patients with impaired growth compared with patients with normal growth (~40% versus ~26%, respectively). Also, no consistent influence of disease severity on improvement of growth velocity was identified in contrast to other reports.[5] This might be explicable by the eligibility criteria of the IMAgINE 1 trial that selected patients with moderately to severely active CD at enrollment. Thus, the patients enrolled represented a relatively homogenous population in terms of high disease severity. These findings further highlight that patients with moderate and severe CD share a similar disease burden with regard to linear growth. The fact that increase in height velocity was particularly obvious in the subset of patients with early response to induction therapy at week 4, which has been identified as a predictor of therapeutic success with ADA,[12] further provides evidence of the efficacy of ADA for linear growth improvement.

Although patients who were infliximab naive tended to demonstrate larger growth improvement than patients who had experienced infliximab, the latter also achieved a statistically significant improvement from BL in median height velocity z-score that translated into a nearly normal growth rate in this particularly refractory patient group after 52 weeks of ADA treatment (median height velocity z-score at BL, −3.1 versus week 52 −0.4, $P = 0.01$). Numerical differences in height velocity z-scores at week 52 between patients with and without concomitant immunomodulators should be interpreted with caution because patients were not randomized by immunomodulator use at BL.

Studies have shown that boys with CD have a greater risk of developing growth failure,[29,30] even though girls present with more severe disease.[29] In this study, logistic regression analysis indicated that male sex statistically significantly predicted restoration of growth velocity at week 52, but both male and female patients achieved growth normalization based on median height velocity z-scores at weeks 26 and 52.

ADA trough levels after induction treatment at week 4 were statistically significantly but only weakly associated with achieving normal growth velocity at week 52. ROC curve analysis identified ADA trough concentration of 10.9 μg/mL as a potential cutoff value in the evaluated patient population; however, the accuracy of this predictor as measured by the area under the ROC curve was poor (0.605).

The observed improvement in height velocity z-scores is also supported by results from the analysis of BSAP, a biomarker of bone formation that has been shown to be reduced in children with CD.[31] Maintenance ADA treatment significantly increased BSAP serum levels at weeks 26 and 52 (a median increase of 20.5 and 27.0 μg/L compared with BL, respectively) in patients with BL linear growth deficiency, and also at week 26 in patients with normal growth velocity at BL. These results are generally consistent with findings from a randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF chimeric monoclonal antibody (the REACH trial), where treatment of children with CD with infliximab significantly increased BSAP (a

median increase in BSAP of 36.3 μg/L at week 10 compared with BL).[32] Hence, change in BSAP levels in pediatric patients with CD may be a good marker for monitoring response to treatment of skeletal disease.

In summary, ADA therapy significantly improved linear growth rate in pediatric patients with BL growth retardation in the IMAgINE 1 trial. Restoration of normal growth was significantly associated with clinical remission and was especially profound in week 4 responders.

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