

Growth During Tocilizumab Therapy for Polyarticular-course Juvenile Idiopathic Arthritis: 2-year Data from a Phase III Clinical Trial

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ABSTRACT. Objective. Evaluate growth in patients with polyarticular-course juvenile idiopathic arthritis (pcJIA) treated with tocilizumab (TCZ) for up to 2 years in a phase III trial.

Methods. Patients with pcJIA lasting at least 6 months and inadequate response to methotrexate received open-label TCZ intravenously every 4 weeks (randomly assigned to 8 or 10 mg/kg if they weighed < 30 kg; received 8 mg/kg if they weighed ≥ 30 kg) for 16 weeks. Patients with JIA American College of Rheumatology 30 response at Week 16 were randomly assigned to TCZ or placebo for 24 weeks, with an open-label extension through Week 104. Mean ± SD height velocity (cm/yr) and World Health Organization (WHO) height SD score (SDS) were measured in patients receiving ≥ 1 dose of TCZ who did not receive growth hormone and in patients whose baseline Tanner stage was ≤ 3.

Results. The study included 187 of 188 patients (99.5%) with mean WHO height SDS -0.5 ± 1.2 , which was unrelated to age or disease duration (Spearman rank correlations $r = 0.08$ and $r = -0.12$, respectively). There were 123 patients at Tanner stage ≤ 3 at baseline, among whom 103 completed the study with 2 years of height SDS data. Mean height SDS increased from baseline to year 2 ($+0.40$, $p < 0.0001$). In 74 of 103 patients (72%), height SDS was greater than at baseline, and mean height velocity was 6.7 ± 2.0 cm/year.

Conclusion. Among patients with pcJIA at Tanner stage ≤ 3 at baseline, 72% (74/103) had increased height SDS at the end of the study. (J Rheumatol First Release July 1 2018; doi:10.3899/jrheum.170326)

Key Indexing Terms:

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Juvenile idiopathic arthritis (JIA) is a group of arthritides encompassing several forms of chronic arthritis with an onset before 16 years of age¹. The effect of chronic arthritis on bone and joint development often results in impaired growth in children, ranging from a mild decrease in growth velocity to severely short stature. Patients with polyarticular-course JIA (pcJIA), and to a greater extent, systemic JIA (sJIA), experience impaired growth^{2,3,4,5,6}. In patients with JIA, prolonged use of glucocorticoids has been associated with growth retardation⁷. Indeed, in a retrospective analysis, significant loss of height was positively correlated with duration of prednisone therapy, and even after the discontinuation of glucocorticoids, about 30% of patients with JIA did not achieve catch-up growth⁸. Given that significant growth retardation is also observed in steroid-naïve children with sJIA and pcJIA, glucocorticoids are not solely responsible for impaired growth in patients with JIA⁹. A number of other factors contribute to growth retardation in JIA, including high disease activity and severity, disease duration, age at onset, malnutrition, genetic predisposition, demographics, and inflammation. Improvement in growth velocity and the attainment of normal height have been observed with improved disease control and reduced glucocorticoid dosing^{5,10,11,12}.

The influence of proinflammatory cytokines on the pituitary-derived growth hormone insulin-like growth factor-1 (IGF-1) axis in growth retardation has been postulated^{4,13}. Interleukin 6 (IL-6) appears to be the major proinflammatory cytokine involved in growth retardation in patients with JIA. A 50% to 70% reduction in growth rate was observed in transgenic mice expressing high levels of circulating IL-6 compared with nontransgenic littermates. This growth defect, partially reversed by administration of an anti-IL-6 receptor antibody, was associated with low levels of IGF-1¹⁴. Overexpression of IL-6 also led to

osteopenia with accelerated bone reabsorption, reduced bone formation, and defective ossification, indicating that IL-6 is an important mediator of bone homeostasis¹⁵. A statistically significant inverse correlation between growth velocity and serum IL-6 levels has been shown in patients with JIA³. IL-6 levels are markedly elevated in the serum and synovial fluid of patients with pcJIA and sJIA and have been correlated with disease activity and reduced growth^{3,16,17}. Two pivotal phase III trials, TENDER¹⁸ and CHERISH¹⁹, have demonstrated the efficacy of the anti-IL-6 receptor- α antibody tocilizumab (TCZ) in treating the signs and symptoms of sJIA and pcJIA. A posthoc analysis conducted in the TENDER study population demonstrated that TCZ promoted significant catch-up growth in patients with sJIA and improvement of laboratory markers associated with growth and bone homeostasis⁵. The aim of the present posthoc analysis was to evaluate growth rates in patients with pcJIA treated with TCZ in the 2-year CHERISH trial.

MATERIALS AND METHODS

Study design. The phase III CHERISH trial (ClinicalTrials.gov, NCT00988221) was conducted by members of the Paediatric Rheumatology International Trials Organisation (PRINTO)²⁰ and the Pediatric Rheumatology Collaborative Study Group (PRCSG) to evaluate the efficacy and safety of TCZ in patients with pcJIA. Patients received intravenous TCZ every 4 weeks, dosed according to body weight [BW; 8 mg/kg for BW \geq 30 kg or randomly assigned (1:1) to receive 8 mg/kg or 10 mg/kg for BW < 30 kg]. The trial consisted of 3 parts: a 16-week, open-label, lead-in period (Part 1); a 24-week, randomized, double-blind, placebo-controlled, withdrawal phase for patients who achieved at least a JIA–American College of Rheumatology 30 (ACR30) response during Part 1 (Part 2); and a 64-week, open-label extension (Part 3). Patients who experienced a JIA flare in Part 2 could escape to open-label TCZ. The study design and the full methodology of the CHERISH trial have been described¹⁹. The trial was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines and with local requirements. Informed consent from a parent or guardian and assent from the patient if applicable were obtained for all patients. The trial was approved by the institutions' Research Ethics Boards (the approval number for the principal trial site 165340 was 73/2009).

Patients. Eligible patients were 2 to 17 years of age and had pcJIA. The term pcJIA refers to rheumatoid factor–positive or –negative polyarticular JIA or extended oligoarticular JIA according to the International League of Associations for Rheumatology criteria²¹. Patients had to have disease for at least 6 months, inadequate response or intolerance to methotrexate (MTX), and at least 5 active joints at baseline. Stable doses of nonsteroidal anti-inflammatory drugs, glucocorticoids, and MTX were permitted. Patients could not have been receiving oral glucocorticoids at the baseline visit, or if they were receiving oral glucocorticoids at that time, the dose had to have been stable (\leq 0.2 mg/kg/day prednisone or 10 mg/day, whichever was lower) for at least 4 weeks before and including the baseline visit. Glucocorticoid doses could be tapered in Part 3.

Assessments. Height was assessed at screening and baseline, at 2, 4, 8, 12, 16, 20, and 24 weeks, and every 4 weeks thereafter through Week 104. Increases in growth over time were assessed using height SD scores (SDS) and height velocity (cm/yr). Height SDS was calculated as:

$$\frac{(\text{observed height} - \text{mean value of the reference population})}{\text{SD of the reference population}}$$

The reference population was derived from age- and sex-matched World

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Health Organization (WHO) norms²². Height SDS > 0 indicated patients were above the mean height expected for their age and sex, whereas height SDS < 0 indicated patients were below the mean height expected for their age and sex. Height velocity was calculated as:

$$\frac{(\text{Year 1 or Year 2 height assessment} - \text{baseline height assessment})}{(\text{no. days between assessments} \div 365.25)}$$

For this exploratory analysis, growth was assessed in a subset of patients who received ≥ 1 dose of TCZ and did not receive growth hormone during the study. Because patients at Tanner stage ≤ 3 represented children with the highest potential for growth, additional growth analyses for some assessments were performed in patients at Tanner stage ≤ 3 at baseline for whom data were available at baseline, Year 1, and Year 2 (completer analysis, i.e., analysis of patients who completed the full 2 yrs). Height SDS at 2 years was also assessed in the subset of patients who had height SDS < -2 at baseline, representing patients with the greatest growth impairment.

Tanner stage was determined at selected visits during the study in accordance with published methods²³. Given that genitalia growth and breast development may precede the growth of pubic hair, the genitalia score was used if pubic hair and genitalia scores were different in boys, and the breast development score was used if pubic hair and breast development scores were different in girls²³. Tanner stage 1 indicates prepubertal development, and stages 2 to 5 indicate increasing sexual maturation.

Statistical analysis. Mean \pm SD was determined for height velocity and height SDS unless stated otherwise. The relationship between height SDS at baseline and age or disease duration was evaluated using Spearman rank correlation (*r*). Change in height SDS from baseline to Week 104 was assessed by 2-sided paired *t* test. *P* < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics. In total, 188 patients were enrolled in the CHERISH study, and 187 (99.5%) of those were included in our current analysis; 1 patient received growth hormone and was excluded from the analysis. During Part 2 of the study, 84 of 187 patients were randomly assigned to receive placebo and 3 of these patients discontinued before receiving a single dose; 39 of 81 patients (48.1%) experienced a JIA flare and escaped to TCZ before the end of Part 2 (Week 40)¹⁹. Improvements in all JIA ACR core components with TCZ treatment were reported at Week 40¹⁹ and were maintained through Week 104²⁴.

Baseline characteristics of the subset of patients (*n* = 187) who received TCZ and did not receive growth hormone (Table 1) were similar to those of the total study population¹⁹. Among 86 of 187 patients (46%) who were receiving oral glucocorticoids at baseline, the mean dose at baseline was 0.13 mg/kg/day. In total, 123 of 187 patients (66%) were at Tanner stage ≤ 3 at baseline. Baseline height SDS was not related to age or disease duration (Spearman rank correlation *r* = 0.08 and *r* = -0.12, respectively; Supplementary Figure 1A and 1B, available with the online version of this article).

Growth characteristics before and during TCZ treatment. At baseline, the mean height SDS was -0.5 among the patients who received TCZ and did not receive growth hormone; 30% (56/187) of patients had a height SDS < -1, and 12% (22/187) had a height SDS < -2 (Table 1). During 2 years of TCZ treatment, 55.9% (19/34) of male and 61.7% (74/120) of

Table 1. Baseline demographics and growth characteristics. Data are mean \pm SD unless otherwise noted.

Characteristics	Growth Analysis Subset ^a , <i>n</i> = 187
Female, <i>n</i> (%)	143 (76)
Age, yrs	11.0 \pm 4.0
Tanner stage ≤ 3 , <i>n</i> (%)	123 (66)
Duration since pcJIA diagnosis, yrs	4.2 \pm 3.7
Height SDS (WHO)	-0.5 \pm 1.2
< -1, <i>n</i> (%)	56 (30)
< -2, <i>n</i> (%)	22 (12)
BMI SDS (WHO)	0.1 \pm 0.1

^a Patients who received ≥ 1 dose of TCZ and did not receive growth hormone. BMI: body mass index; pcJIA: polyarticular-course juvenile idiopathic arthritis; SDS: standard deviation score; TCZ: tocilizumab; WHO: World Health Organization.

female patients experienced height velocities greater than the mean height velocity for their respective ages. There was no evident difference in 2-year height velocity in the 81 patients who received placebo for a mean duration of about 18 weeks in Part 2 of the trial (Supplementary Table 1, available with the online version of this article) compared with those who received TCZ continuously (Figure 1A and 1B). Overall, the mean height SDS at weeks 52 and 104 were -0.3 \pm 1.1 and -0.2 \pm 1.1, respectively. The mean height SDS increased by +0.3 from baseline to Year 2 in patients who had height SDS data at both timepoints (*n* = 154).

Among patients at baseline Tanner stage ≤ 3 (*n* = 123), 103 had data to Week 104 of the study. In these patients, mean height SDS increased significantly from baseline at -0.6 \pm 1.1 to Year 1 at -0.4 \pm 1.2 and to Year 2 at -0.2 \pm 1.1 (*p* < 0.001 at both timepoints; Figure 2A and 2B; Supplementary Table 2, available with the online version of this article). Thus, mean height SDS increased by 0.4 from baseline to Year 2. At Week 104, height SDS increased compared with baseline in 74 of 103 of these patients (72%); the mean height velocity in these 103 patients was 6.7 \pm 2.0 cm/year during the 2-year period. These results in patients at baseline Tanner stage ≤ 3 were consistent with observations for the entire growth population (Supplementary Figure 2 and Supplementary Table 2). Among 11 patients who were at Tanner stage ≤ 3 and had height SDS < -2 at baseline, height SDS was improved in 8 patients at Year 2 (*p* = 0.012), with a mean increase in height SDS of 0.57 (Table 2).

DISCUSSION

At baseline, height SDS was below the 50th percentile in a large proportion of patients with pcJIA enrolled in the CHERISH trial. Overall, growth profiles improved in patients treated with TCZ through the 2 years of the study, with a mean increase in height SDS of +0.3 from baseline to Year 2 and +0.4 in patients at Tanner stage ≤ 3 at baseline. Most (72%) of the patients at Tanner stage ≤ 3 at baseline had increased height SDS at the end of the study (Yr 2), and most

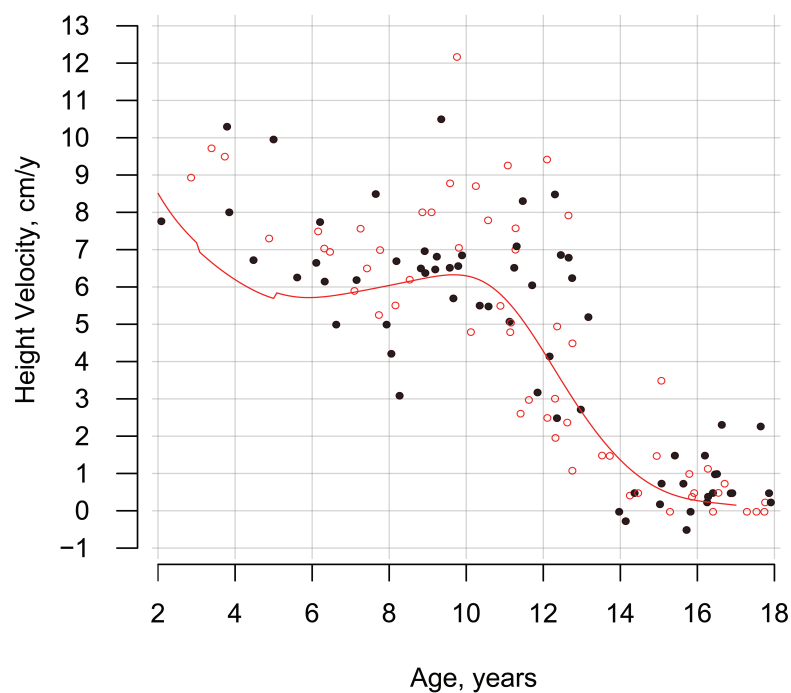
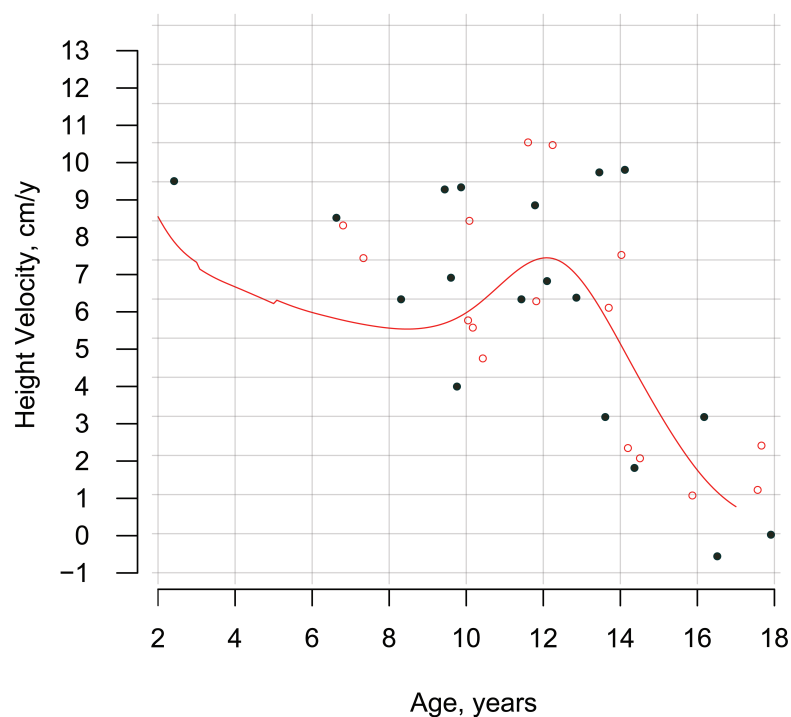
A**B**

Figure 1. Height velocity during 2 years versus baseline age in (A) girls ($n = 120$) and (B) boys ($n = 34$) according to randomization to placebo or TCZ treatment during Part 2. Actual height velocities are a function of age and pubertal status. Solid red curves represent the expected 2-year annualized height velocities based on World Health Organization norms. Eighty-four patients were randomly assigned to receive placebo during the Part 2 withdrawal phase; about 50% of those patients escaped to TCZ before Week 40. Red open circles represent patients who were randomly assigned to the TCZ treatment group during Part 2 (61 girls, 16 boys) and who received TCZ continuously for 2 years. Black dots represent patients who were randomly assigned to the placebo group during Part 2 (59 girls, 18 boys). TCZ: tocilizumab.

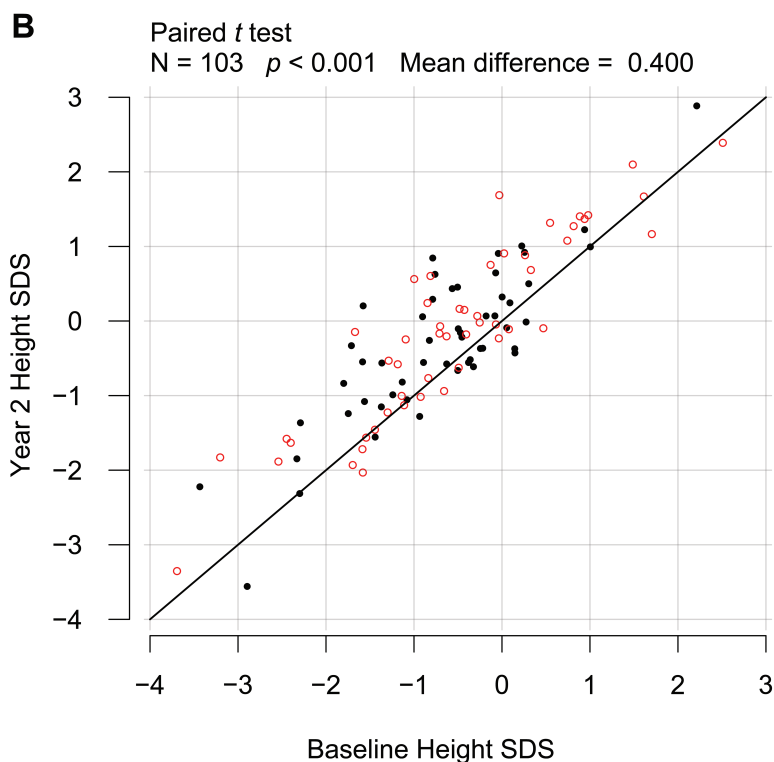
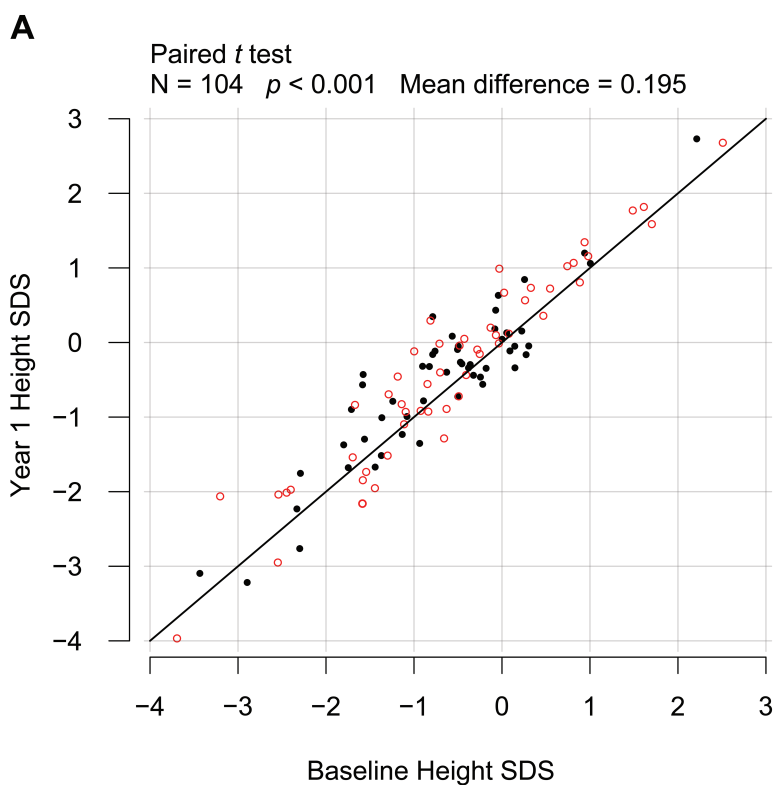


Figure 2. Baseline height SDS versus height SDS at (A) Year 1 and (B) Year 2 in patients at baseline Tanner stage ≤ 3 ($n = 103$). Eighty-four patients were randomly assigned to receive placebo treatment during the Part 2 withdrawal phase; about 50% of those patients escaped to TCZ before Week 40. Black diagonal line represents no change in height SDS. Black dots represent patients randomly assigned to placebo in Part 2. Red open circles represent patients who received TCZ continuously. SDS: standard deviation score; TCZ: tocilizumab.

Table 2. Height SDS for patients at baseline Tanner stage ≤ 3 and baseline height SDS < -2 (n = 11).^a

Baseline Age, Yrs/sex	Baseline Height SDS	Year 1 Height SDS	Year 2 Height SDS
8/female	-2.879	-3.203	-3.545
11/female	-2.314	-2.218	-1.833
10/female	-2.530	-2.936	NA
14/male	-3.417	-3.082	-2.209
10/female	-2.524	-2.024	-1.870
12/female	-3.186	-2.049	-1.815
10/female	-2.430	-1.999	-1.566
12/male	-2.282	-2.749	-2.299
7/female	-2.384	-1.960	-1.619
12/female	-2.273	-1.740	-1.350
8/female	-3.676	-3.954	-3.339
Mean height SDS \pm SD	-2.72 \pm 0.497	-2.54 \pm 0.694	-2.14 \pm 0.741

^a Eleven patients had baseline and Year 1 data, and 10 patients had baseline and Year 2 data. NA: not available; SDS: standard deviation score.

male and female patients also experienced increased height velocities. In a similar growth analysis of patients with sJIA in the TENDER trial, catch-up growth was observed over 2 years of treatment with TCZ⁵. Patients in the TENDER trial had a lower height SDS at baseline (-2.2), which was indicative of more severe growth impairment in patients with sJIA² and was likely attributed to higher inflammatory burden, greater need for longterm glucocorticoid therapy, or both. In the CHERISH growth analysis, 8 of the 11 patients who had height SDS < -2.0 at baseline had markedly improved height SDS at Year 2, suggesting that patients with pcJIA who had the most severe growth impairment experienced growth improvement. In the TENDER trial, the mean increase in height SDS from baseline to Year 2 was +0.3 in patients at Tanner stage ≤ 4 at Year 2, possibly indicative of the lower baseline height SDS and the greater potential for catch-up growth. Nevertheless, in both studies, the mean height SDS was significantly increased over 2 years of TCZ treatment.

In the TENDER trial, multiple regression analysis revealed a relationship between height velocity during Year 1 and age at baseline and average glucocorticoid dose during Year 1 in patients with sJIA. The relationship with age was attributed to the higher growth potential in younger children, suggesting that early intervention is required to maximize therapeutic benefit on growth⁵. The correlation with glucocorticoid dose would be expected given the effect of glucocorticoids on growth impairment^{5,25}. Multiple regression analysis was investigated for the present CHERISH study, but the resultant total R^2 value (0.24) was not considered large enough to be clinically relevant; this might have resulted from the normal growth trajectories observed for patients with pcJIA treated with TCZ in CHERISH compared with the catch-up growth observed in TENDER for patients with sJIA treated with TCZ who had overall short stature at baseline⁵. In addition, 1 important difference was that fewer

patients were receiving glucocorticoids at baseline in CHERISH (46%) than in TENDER (90%). A limitation of our study might be the exclusion of patients receiving high doses of glucocorticoids in CHERISH, which could have affected the overall baseline height SDS of the study population because patients receiving higher doses of glucocorticoids would likely have experienced more severe growth impairment as a result of this treatment. Therefore, growth patterns during the study might have been influenced by glucocorticoid dosing at baseline and glucocorticoid tapering during the study as well as by the effect of TCZ treatment. The exclusion of patients who did not achieve JIA ACR30 response after Week 16 in CHERISH might have led to a selection bias for patients who had greater growth potential while receiving TCZ treatment.

A further limitation compared with the TENDER trial is the lack of analysis of laboratory variables, including IGF-1 levels and markers of bone turnover. In the TENDER analysis, TCZ treatment was associated with normalization of IGF-1 levels, and baseline levels of osteocalcin (a marker of bone formation) and C-telopeptide of type I collagen (a marker of bone resorption) were related to levels of C-reactive protein (CRP), a marker of inflammation. It remains to be determined whether TCZ has an effect on markers of growth or bone turnover in patients with pcJIA; however, given the reduction in CRP in CHERISH¹⁹, it is reasonable to expect that there might be a similar relationship with bone turnover and IGF-1.

Most patients with pcJIA in the CHERISH study at baseline Tanner stage ≤ 3 experienced increased height SDS at the end of Year 2, consistent with improved growth profiles previously reported for patients with sJIA treated with TCZ. Overall, patients with pcJIA experienced adequate or improved growth over 2 years of treatment with TCZ, particularly those whose growth impairment at baseline was greatest.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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