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Using change in predicted adult height during GnRH agonist treatment for individualized treatment decisions in girls with central precocious puberty

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Abstract

Objectives: It is important to understand what variables influence change in predicted adult height (PAH) throughout GnRHa treatment for central precocious puberty (CPP) to individualize treatment decisions and optimize care.

Methods: Changes in PAH, chronological age (CA), bone age (BA), BA/CA, and height velocity (HV) were evaluated in girls with CPP throughout treatment with leuprolide acetate (n=77). A second analysis focused on changes in the 3 years preceding the first observed BA of ≥12 years. Relationships were characterized using plot inspection and linear mixed-effects analyses. Association between treatment duration and last assessed PAH was examined using multiple linear regression models.

Results: BA/CA and HV showed a nonlinear change during treatment, with the largest changes and improvement in PAH observed in the first 6–18 months. Rate of BA advancement tended to decrease more slowly in girls initiating treatment at a younger BA. On-treatment change in PAH was predicted by concurrent BA/CA change, HV, and BA, as well as CA at treatment initiation. Last assessed PAH was positively associated with longer treatment durations (primary/exploratory models cut-offs of ≥33/≥55 months).

Conclusions: These findings support individualized monitoring during GnRHa treatment. Initial response should be interpreted with caution until 6–18 months after treatment initiation and failure should not be assumed based on continued bone maturation in girls starting therapy at a younger age. Treatment cessation should not be automatically based on a diminishing change in PAH or HV, as ongoing treatment may result in continued increase or maintenance of PAH.

Keywords: bone age; central precocious puberty; duration of therapy; height velocity; leuprolide; predicted adult height.

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Introduction

Gonadotropin-releasing hormone agonist (GnRHa) therapy is the standard of care for treatment of central precocious puberty (CPP). One goal of GnRHa therapy is to slow the rate of bone maturation while maintaining an adequate height velocity (HV) in order to maximize the impact on adult height (AH) [1, 2]. Decisions to discontinue GnRHa therapy have commonly been based on predetermined single-variable factors, such as bone age (BA) of >12 years, chronological age (CA) of >10 years, or slower HV, assuming additional height benefit is not anticipated [1, 3–7]. Because many factors contribute to height outcomes and further height gain has been reported with continued treatment beyond these single-variable cutoffs, no single factor should be used as the basis for deciding to discontinue GnRHa treatment [1, 8]. Prior research informing these decisions focused on change in predicted AH (PAH) from the start to end of treatment and compared

to AH [6, 7, 9–11]. Less is known about the impact of the rate of change in PAH during the course of treatment.

This study characterized changes in PAH during the course of GnRHa therapy and the relationship to concurrent changes in CA, BA, BA/CA ratio, and HV. The goal was to extend our previous work to inform individualized treatment decisions [8], by assessing changes in PAH as treatment progresses, in relation to the other variables.

Methods

Patients

We evaluated GnRHa-naïve and non-naïve girls with CPP who received leuprolide acetate (LUPRON DEPOT-PED®, AbbVie, North Chicago, IL) treatment for at least 24 weeks in either of two Phase 3 open-label multicenter clinical trials and who had at least one post-baseline BA measurement (Study 1, NCT00660010 [12]; Study 2, NCT00635817 and NCT00667446 [13]). The research related to human use complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. Institutional Review Board approval of the study protocols was obtained for each study site and written informed consent was provided by each patient and their parent or legal guardian, with child assent being obtained as appropriate.

As previously reported, at enrollment patients were <9 years in CA and (if GnRHa-naïve) with Tanner stage for breasts ≥2 by CA of 8 years, BA advanced ≥1 year beyond CA, GnRH-stimulated luteinizing hormone (LH) peak of ≥8 [13] or 10 [12] U/L, and without adrenal/thyroid pathology or prior therapy with medroxyprogesterone acetate. Leuprolide acetate intramuscular injection was administered in Study 1 as a 1-month depot with weight-based dosing of 7.5, 11.25, or 15 mg with treatment cessation at the discretion of the investigator [12] and in Study 2 as a 3-month depot at 11.25 or 30 mg for up to 3.5 years [13]. The trial populations were combined for this analysis, which sought to assess impact of changes in CA, BA, and HV on PAH while on treatment, without considering drug or dose effect.

Variables

BA, determined by a central reader using hand/wrist radiography and the FELS method, was obtained approximately every 6 months from treatment initiation until end of on-treatment follow-up. PAH was calculated by dividing actual height with the average percentage of AH associated with concurrent BA per the Bayley-Pinneau method [14]. A unique BA was matched with a single height measurement obtained within a time window of ≤30 days before to ≤90 days after BA assessment. Annualized HV was calculated as height increase (cm) from one BA-matched measurement to the next. Treatment duration was defined as time from start of treatment to each PAH time point. Mid-parental height (MPH) was calculated as the father's height (minus 13 cm) averaged with the mother's height.

Statistical analyses

This investigation evaluated 2 groups. Group 1 included GnRHa-naïve girls with data analyzed from the start of treatment until their last on-treatment assessment. Group 2 included GnRHa-naïve or non-naïve girls with data analyzed over the 3 treatment years preceding their first observed BA of ≥12 years. Plots were inspected to visualize changes in BA, BA/CA, HV, and PAH over time in Group 1 and changes in HV over time as well as changes in PAH in relation to BA/CA in Group 2.

Linear mixed-effects models examined average change in PAH between 2 consecutive time points during treatment (dependent variable) in Group 1. The base model included treatment duration (i.e., time) and its square term to account for non-linear (quadratic) change in PAH over time. Covariates were: change in BA/CA, HV, age at treatment initiation, BA, baseline height, baseline PAH, and MPH. Each of the covariates was first added separately to the base model to explore their relationship with change in PAH (while adjusting for time). Next, the final linear mixed-effects model used forward selection to add the covariate that maximized model prediction in each forward step. Beginning with time and square of time (i.e., base model), covariates were added in the order listed above until the stopping criterion of $p>0.05$ was reached. Individual patient plots were used to visualize key relationships in the final model.

To further evaluate the effect of treatment duration on PAH in Group 1, three multiple linear regression models were built, each using last assessed on-treatment PAH as the dependent variable and the same covariates as independent variables (i.e., treatment duration; MPH; race/ethnicity; and baseline BA, age, HV, height, and PAH). However, treatment duration was examined as a binary covariate with a cut-off of ≤33 vs. >33 months (the median treatment duration in Group 1) in Model 1 (primary analysis), and as a continuous covariate with a monthly increase in Model 2 (secondary analysis). Then, an exploratory classification and regression tree (CART) analysis was conducted to identify an "optimal" cut-off for treatment duration to separate girls with good PAH performance from others. Model 3 assessed treatment duration as a binary covariate with a CART-suggested cut-off.

SAS version 9.4 for UNIX (SAS Institute, Cary, NC) was used for these analyses, with a statistical significance threshold of $p<0.05$.

Results

Subjects

Group 1 included 77 girls with a mean CA of 7.0 ± 1.7 years (range 1–9 years), mean BA of 10.5 ± 1.9 years (range 2.5–12.7) at onset of treatment (Table 1) and median treatment duration of 33 months (range, 6–118 months). Group 2 included 56 girls with mean CA of 7.6 ± 1.3 years (range 3–10) and mean BA of 10.9 ± 1.1 years (range 6.6–12.0) at the onset of treatment (Table 1).

Table 1: Patient characteristics at baseline.

Characteristic	Group 1 n=77[a]	Group 2 n=56[a]
Race or ethnicity, n (%)		
White/Caucasian	47 (61.0)	33 (58.9)
Black/African descent	18 (23.4)	14 (25.0)
Hispanic/Latinx	8 (10.4)	3 (5.4)
Asian	1 (1.3)	2 (3.6)
Multiracial or multiethnic	3 (3.9)	4 (7.1)
CA, years		
Mean (SD)	7.0 (1.7)	7.6 (1.3)
Range	1–9	3–10
Tanner breast stage, n (%)		
1	1 (1.3)[b]	3 (5.4)[c]
2	13 (16.9)	12 (21.4)
3	46 (59.7)	30 (53.6)
4	16 (20.8)	10 (17.9)
5	1 (1.3)	1 (1.8)
Weight, kg		
Mean (SD)	35.5 (10.4)	37.0 (9.3)
Range	13.0–63.8	19.4–63.3
Height, cm		
Mean (SD)	133.8 (13.9)	136.2 (9.8)
Range	84.6–154.7	109.9–151.9
Height standardized score		
Mean (SD)	1.6 (1.12)	1.3 (1.2)
Range	–1.3–3.4	1.3 (–1.2 – 3.4)
PAH, cm		
Mean (SD)	156.8 (7.4)	156.4 (7.6)
Range	135.7–171.2	135.7–169.7
MPH, cm		
Mean (SD)	163.4 (7.0)	163.7 (5.8)
Range	138.3–175.6	144.6–172.6
BA, years		
Mean (SD)	10.5 (1.9)	10.9 (1.1)
Range	2.5–12.7	6.6–12.0
BA/CA		
Mean (SD, range)	1.5 (0.3)	1.4 (0.2)
Range	1.2–2.9	1.0–2.1
HV, cm/year		
Mean (SD)	10.0 (3.8)	9.0 (3.6)
Range	1.3–21.2	2.5–18.8

Change in BA, BA/CA, HV, and PAH with increasing treatment duration

Group 1 plots revealed that changes in BA, BA/CA, and rate of change in PAH over time were nonlinear during treatment. Change in BA tended to decrease as treatment progressed, with the largest changes observed during the first year of therapy (Figure 1). Further, girls who started treatment at a younger BA tended to initially advance their BA closer to one year per treatment year, compared to those with an older BA, who typically had more rapid decrease in rate of BA change over time (Figure 1). The most rapid rate of change in mean BA/CA was observed during the 6 to 18 months of treatment, followed by subsequent slowing of rate of change in mean BA/CA with longer duration of treatment (Figure 2A). Mean BA/CA decreased from 1.5 at baseline (n=76) to 1.1 at 5 years on treatment (n=8; Figure 2A).

Mean HV decreased rapidly in the first year of treatment, with the rate of change slowing thereafter (Figure 2B). The mean annualized rate of change in PAH was 0.4 cm at 0–6 months, increasing to 4.8 cm at 6–12 months, and 3.7 cm at 12–18 months, followed by a more consistent rate of change with continued treatment (Figure 2C). Despite the eventual decrease in annualized rate of PAH change over time, a mean rate of zero (indicating no further increase in PAH) was not observed over 5 years of on-treatment follow-up.

Group 2 plots examining the 3 years of treatment preceding their first observed BA of ≥12 years showed that the change in BA/CA decreased and the change in PAH increased (Figure 3A). As the BA/CA change approached zero, the PAH change approached zero, implying a stable PAH at this point. HV was observed to be stable during the 3 years of treatment preceding the first observed BA of ≥12 years and slower rates of growth appeared to be random and non-persistent (Figure 3B). In other words, ongoing treatment approaching and surpassing a BA of 12 years was not related to lower HV.

[a]Group 1 included GnRHa-naïve girls with data analyzed from start of treatment; n=77 with the following exceptions: weight, BA, and BA/CA, n=76; PAH, n=67; MPH, n=70, and HV, n=73. Group 2 included girls with data analyzed over the 3 treatment years preceding the first observed BA of ≥12 years; n=56 with the following exceptions: weight, n=55; height, n=54; PAH=51; MPH, n=50; and HV, n=52. [b]A one-year-old was enrolled in the trial with breast at Tanner stage 1 based on qualifying peak stimulated luteinizing hormone (84.7 IU/L) and estradiol (90 pg/mL). [c]Patients with Tanner breast stage <2 were enrolled in Study 2, if they were not naïve to GnRHa therapy. BA, bone age; CA, chronological age; HV, height velocity; MPH, mid-parental height; PAH, predicted adult height; SD, standard deviation.

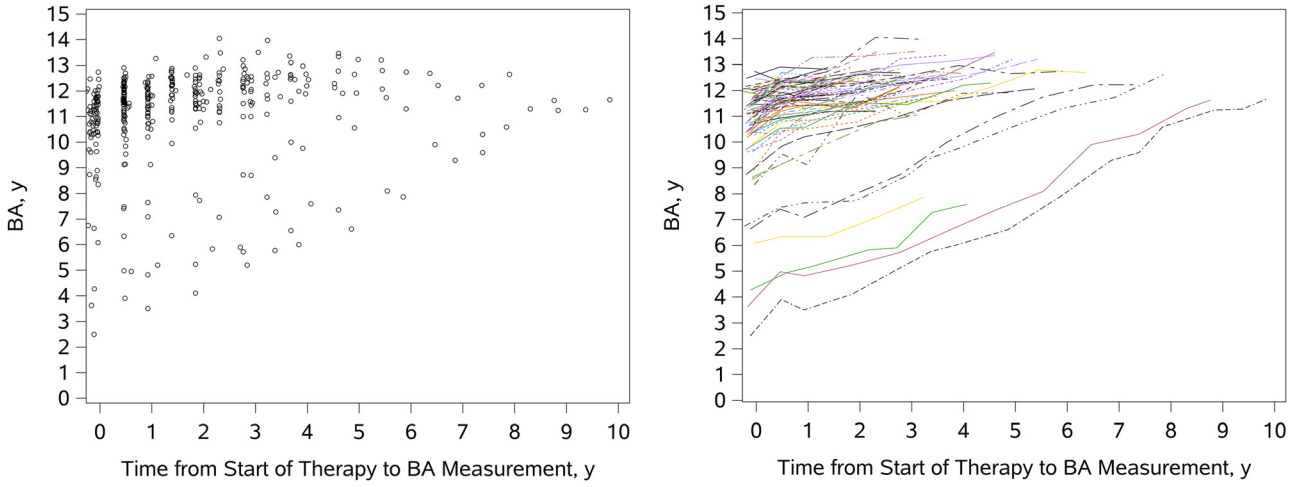

Figure 1: Individual patient plots illustrating changes in BA over time from start of therapy to BA measurements in Group 1*. *Group 1 included GnRHa-naïve girls with data analyzed from start of treatment. BA, bone age; y, year.

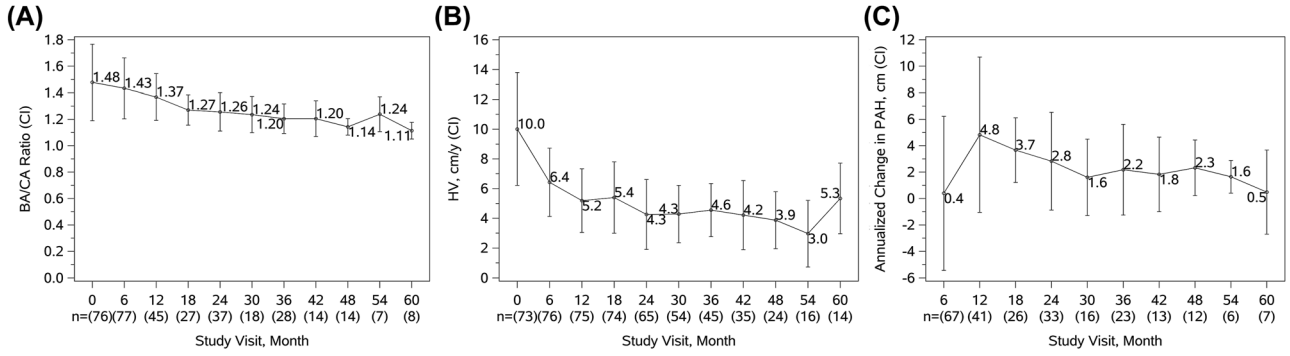

Figure 2: Mean BA/CA (A), mean HV (B) and mean annualized change in PAH (C) over time since start of therapy in Group 1*. Error bars reflect standard deviation. *Group 1 included GnRHa-naïve girls with data analyzed from start of treatment. BA, bone age; CA, chronological age; CI, confidence interval; HV, height velocity; PAH, predicted adult height.

Relationships between change in PAH and potential predictive variables

In Group 1, there was a significant association between change in BA/CA and change in PAH in the initial linear mixed-effects model adjusting for treatment duration (Supplementary Table 1: p<0.0001); this was also evident in the individual patient plot (Figure 4A). A weaker, but still significant, association was found between HV and change in PAH (p=0.0247; Figure 4B). In contrast, no relationship was found between change in PAH and BA (p=0.3373; Figure 4C) or the remaining variables (Supplementary Table 1: CA at treatment initiation, baseline height, baseline PAH, or MPH).

Forward-selection (starting from a base model including only treatment duration and its square term) determined that incorporation of concurrent BA/CA change, HV and BA, as well as CA at treatment initiation significantly improved the model's ability to predict change in PAH between consecutive time points (Table 2). In this analysis, the average change in PAH increased with longer treatment duration. BA and change in BA/CA were negatively associated with average change in PAH: for a year increase in BA, average change in PAH decreased by 0.53 cm (p=0.0008) and for a 0.1 decrease in change in BA/CA, average change in PAH increased by 4.55 cm (p<0.0001). Average change in PAH increased by 0.48 cm for every 1-cm/year

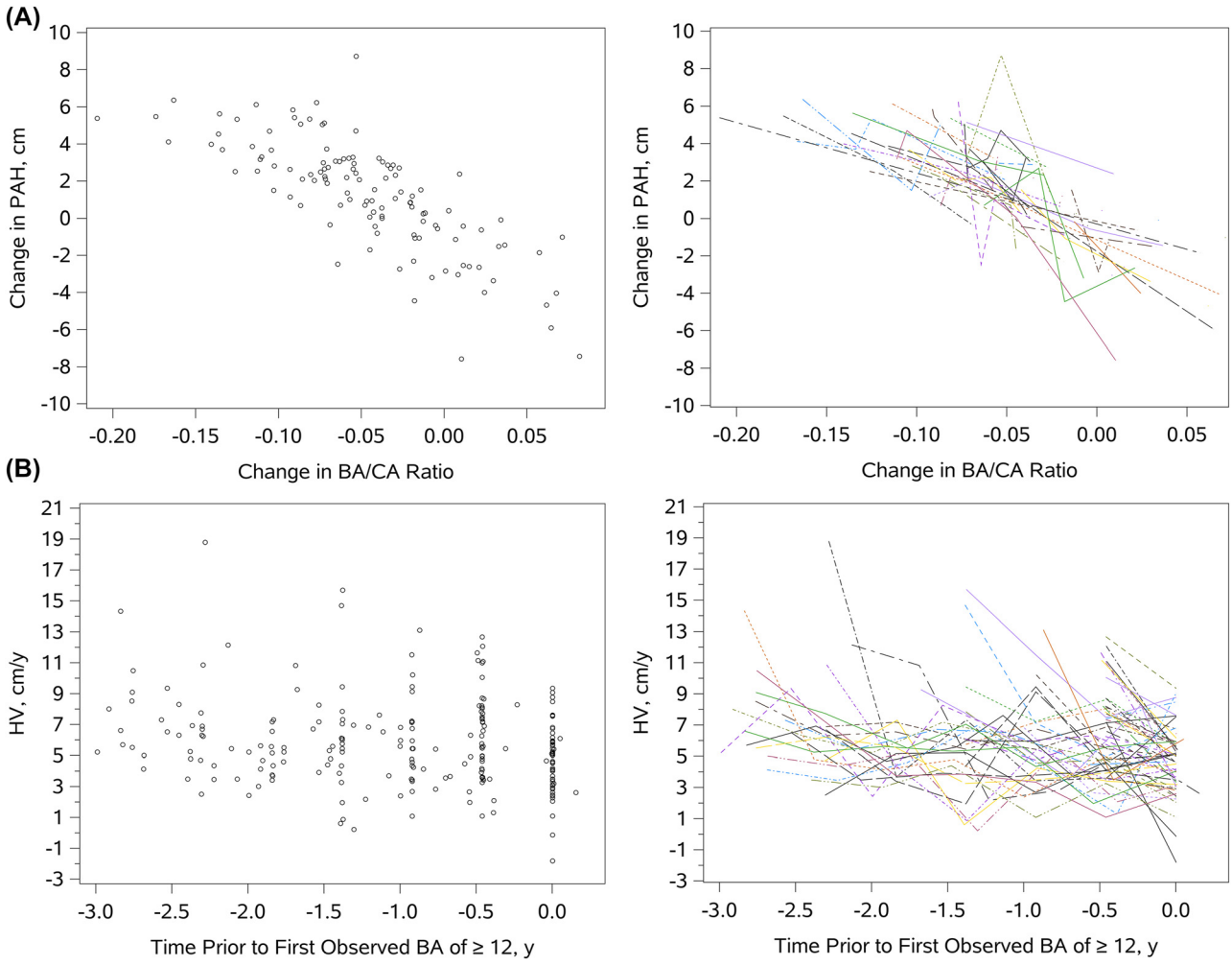

Figure 3: Individual patient plots illustrating changes in PAH in relation to changes in BA/CA (A) and HV over time (B) during the 3 years preceding BA of ≥12 years in Group 2*. Time (x-axis) of 0 in plot B indicates the first observed BA of ≥12 years. *Group 2 included girls with data analyzed over the 3 treatment years preceding the first observed BA of ≥12 years. BA, bone age; CA, chronological age; HV, height velocity; PAH, predicted adult height; y, year.

increase in HV ($p<0.0001$) and by 1.01 cm for every 1-year increase in CA at treatment initiation ($p<0.0001$). Addition of baseline height, baseline PAH, and MPH did not improve the predictive ability and were excluded from the final model.

Impact of treatment duration on final PAH

In the three multiple regression models in Group 1, the last assessed PAH near the end of on-treatment follow-up was found to be positively associated with longer duration of treatment in the primary (Model 1), secondary (Model 2), and exploratory (Model 3) analyses (Supplementary Table 2). Median treatment duration was 33 months and was used as the cut-off to dichotomize short vs. long treatment duration in the primary Model 1, which suggested a trend toward association of longer duration with increased final PAH (i.e., treatment duration beyond 33 months was associated with 1.82 cm increase in last observed PAH; $p=0.0531$). This trend was supported by results of the secondary Model 2, which analyzed treatment duration as a continuous variable and identified a significant positive association of increased treatment duration and increased final PAH (i.e., a one-month increase in treatment duration was associated with 0.08 cm increase in last observed PAH; $p=0.0040$). Lastly, the CART-based exploratory Model 3 identified a treatment duration of 55 months as a cut-off for short vs long treatment duration, with longer duration associated with increased PAH (i.e., treatment duration beyond 55 months was associated with 3.79 cm increase in last observed PAH; $p=0.0259$).

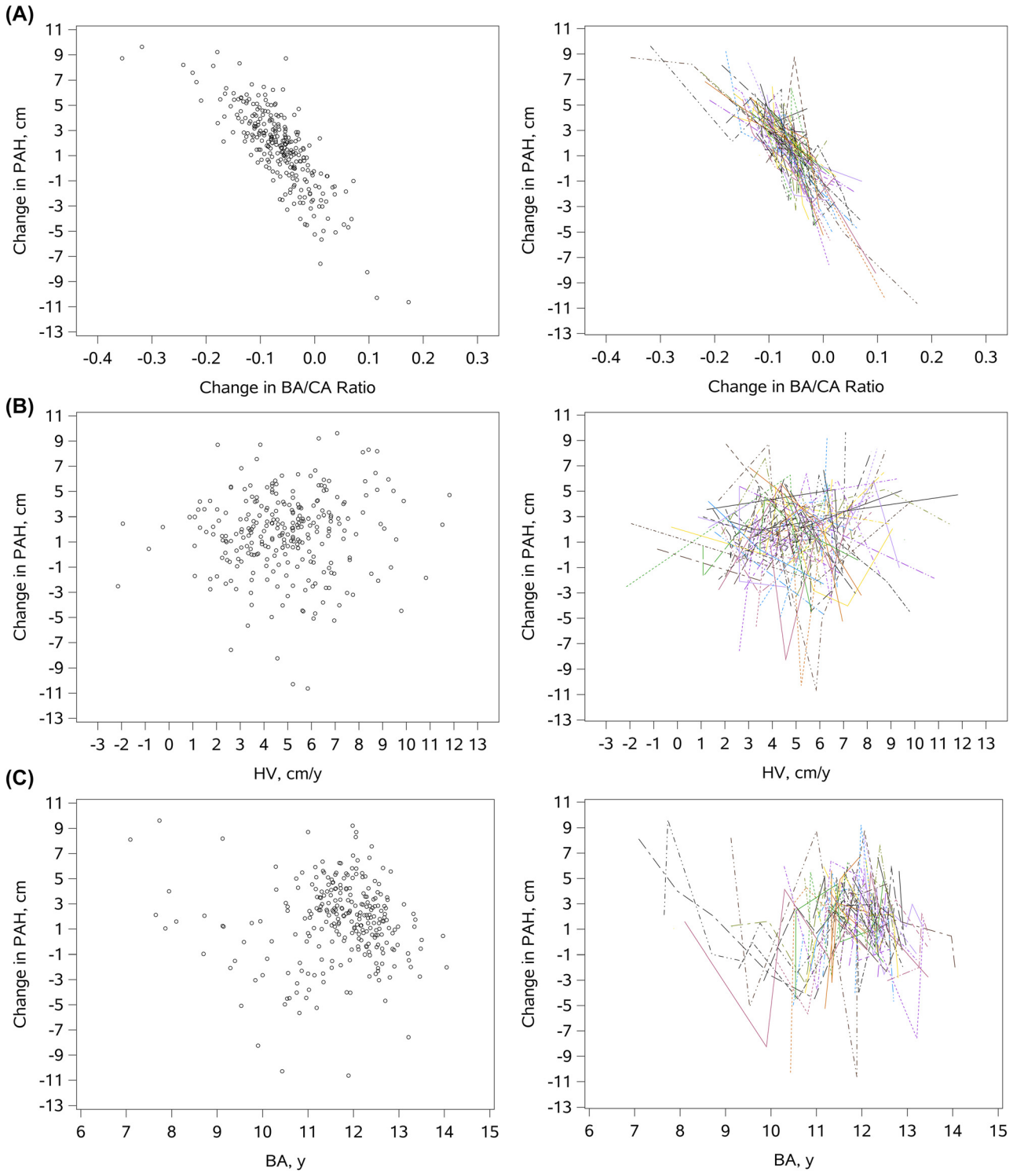

Figure 4: Individual patient plots illustrating on-treatment changes in PAH in relation to change in BA/CA (A), HV (B), and BA (C) in Group 1*. *Group 1 included GnRHa-naïve girls with data analyzed from start of treatment. BA, bone age; CA, chronological age; HV, height velocity; PAH, predicted adult height; y, year.

Table 2: Effect of the forward-selected independent variables on change in PAH between two consecutive time points during treatment in Group 1[a].

Independent Variable[b], Unit of Increase	Dependent Variable Estimate (SE), cm	p-Value
Treatment duration at measurement, since start of treatment	0.34 (0.168)	0.0461
Treatment duration squared at measurement, since start of treatment[c]	0.06 (0.021)	0.0076
Change in BA/CA at measurement, −0.1 y/y	4.55 (0.167)	<0.0001
HV at measurement, 1 cm/y	0.48 (0.051)	<0.0001
CA at treatment initiation, 1 y	1.01 (0.132)	<0.0001
BA at measurement, 1 y	−0.53 (0.157)	0.0008

[a]Group 1 included GnRHa-naïve girls with data analyzed from start of treatment. [b]Variables are listed in the order in which they were included in the final model using forward selection, starting with the base model with treatment duration and its square term; addition of baseline height, baseline PAH, and MPH did not improve predictive ability and were excluded from the final model. [c]Square term of treatment duration was used to account for nonlinear (quadratic) change in PAH over time. BA, bone age; CA, chronological age; HV, height velocity; MPH, mid-parental height; PAH, predicted adult height; SE, standard error; year, y.

Discussion

As previously reported, relying on CA, BA, or HV as a single variable is not sufficient to predict AH, consistent with the understanding that the impact of treatment on AH is multifactorial [1, 8]. We demonstrate how changes in BA/CA and HV, and therefore, changes in PAH vary based on the time since treatment initiation and CA. The BA/CA ratio changed in a nonlinear fashion over time, with the largest change (largest improvement in PAH) observed between 6 and 18 months of treatment. Change in HV was also nonlinear, with the largest decrease observed during the initial 12 months of treatment. Pre-treatment PAH is also sometimes considered as a single variable in assessing treatment potential; however, in our models, this was not a significant factor affecting improvements in PAH.

Based on our measurements, an initial modest treatment response is not necessarily of concern, as the BA/CA does not decrease and PAH does not increase significantly until at least 6 months of treatment. This is consistent with a lag of impact of sex steroids on BA advancement [15]. In contrast, the greater change in BA/CA and HV from 6 to 12 months of GnRHa exposure, especially in older children, appears to be an important indicator of treatment effect.

The rate of change in PAH during treatment was observed to be greater on average in girls who initiated therapy at an older CA in the multivariate model. This suggests that older girls with CPP who (1) are at a CA nearing normal onset of puberty and (2) have a BA in the pubertal range, experience more rapid decreases in bone maturation with treatment. In contrast, bone maturation continued in younger girls at a year-to-year rate. This aligns with typical growth patterns observed prior to and during puberty and the physiological changes occurring in the growth plate [15–17]. Older girls with CPP at CA nearing growth plate fusion may experience slowing down of growth plate senescence with the onset of GnRHa treatment and suppression of estrogen secretion [15–17]. This may result in a more rapid decrease in the rate of bone maturation, compared to younger girls not approaching growth plate senescence [15–17]. Girls nearing a typical age for puberty have a steeper deceleration of BA maturation, improve PAH faster [8], and require ongoing treatment to maintain this PAH improvement. Clinicians should not be too concerned that in treated younger girls the BA advances at approximately 1 year per year, as this still reflects slower bone maturation compared to the accelerated maturation prior to therapy initiation. Furthermore, once the younger girls reach a typical age for puberty, rate of bone maturation further decreases [15–17].

PAH was observed to continue to improve after the first year, even up to 5 years of treatment, albeit to a lesser degree. With more prolonged treatment, the rate of change of the variables slows. However, PAH continues to increase, as long as BA/CA continues to decrease (or stabilize) and an adequate HV is maintained, indicating maintenance of PAH with ongoing treatment. Therefore, it can be expected that if treatment is stopped upon stabilization of BA/CA, unless BA is very advanced and approaching complete growth plate fusion [15–17], BA/CA will again increase [11] and PAH will decline. This would support added value to ongoing treatment to improve or maintain height potential beyond a BA of 12 years [8, 18, 19]. In our analysis of the 3 years preceding the first observed BA of ≥12 years, HV did not appear to consistently decrease. As such, patients do not consistently reach the end of their growth potential. The continued PAH improvement with longer treatment duration, independent of BA, is consistent with our prior analysis of a subset of this study population [8] as well as with other reports [1, 4, 9, 11, 19–25]. In a previous study, we have shown the importance of individualized decisions on when to stop GnRHa treatment, because PAH can still improve by as much as an additional 4.8 cm even if CA is >10 years or BA is >12 years, with a decreasing or stable BA/CA and increasing or stable HV [8].

There is also a tendency to discontinue treatment based on stabilization in PAH alone [1]. However, despite

the smaller changes in PAH over time that we observed, the change in PAH did not reach a rate of zero. Others have reported the positive relationship between PAH and duration of treatment [8, 18, 19], with the multivariate models in the present study further supporting this relationship and showing significantly greater PAH at the end of follow-up with treatment duration beyond the median duration of 33 months or model-derived duration of 55 months. Continued treatment is therefore important to achieve further PAH improvement, or to, at least, maintain the improvements gained [1, 4, 9, 11, 20–22, 25]. This is certainly the case in younger children who tend to reach their mean PAH target during therapy [1] but who may benefit from a treatment extension to avoid a rebound increase in BA/CA [11] and loss of PAH. Finally, individual patients with an advanced BA at the onset of treatment may still experience a desirable treatment effect [18].

Strengths of this study include modelling an average on-treatment change in PAH as treatment starts and progresses (as opposed to reporting only on total PAH change). From the data obtained with the models utilized, better-informed decisions can be made, based on the patterns of change of the variables measured. Additional strengths included examining a long-term treatment course (median 2.75 years [33 months]; range, 6–118 months) and drawing from two trials, thus ensuring larger sample size and increased patient heterogeneity. A potential limitation of this study was that only PAH during treatment is reported. However, we previously published an analysis of a large subset of patients included in Group 1 of this study cohort, with data through AH [8]. In that prior work, most girls reached an AH similar to their PAH near the end of treatment and similar to their MPH, supporting the accuracy of current PAH analysis [8]. In this prior analysis, treatment was not automatically stopped at CA of 10 years or BA of 12 years (end of treatment mean CA: 11.5 years [range 10–14 years] and BA: 13 years [12–16 years]), and the results showed that PAH and AH were comparable, in contrast to the decreased height often observed if treatment is stopped at younger CA or BA [8]. A limitation true for all studies, including these with CPP patients, is that BA and PAH [14] measures are not precise and vary according to the methodology of BA assessment. The analyses done in this study account for this to some degree by (1) relying on BA determination done by a central reader and (2) by following PAH determination longitudinally. The latter addresses variability in PAH due to the potential error introduced by the difficulty to predict the pubertal growth spurt. Lastly, it should be noted that one of the trials included in this study took place in 1991–2009 (Study 1) [12] and the other in 2008–2013 (Study 2) [13]; however, the current investigation was not assessing specific drug dosing effects, but rather the relationship between key clinical variables.

In conclusion, these data support individualized monitoring of variables during GnRHa treatment. Changes in PAH vary depending on CA and time since initiation of treatment [1, 8]. Treatment response from 6 to 12 months post treatment initiation is more critical than the initial 6 months; outcomes in the first 6 months are not necessarily indicative of adequate treatment effect. Likewise, the continued steady advancement of BA in younger girls does not reflect lack of treatment efficacy, as a more robust decline in BA maturation is observed closer to a pubertal BA. Smaller changes in PAH and rate of BA advancement later in treatment do not necessarily reflect failure of continued treatment efficacy either, but rather ongoing slow improvement or maintenance of PAH. Our statistical models support that GnRHa treatment for at least the duration of 33 months (derived from Group 1 median treatment duration) or CART model-derived duration of 55 months conveys the most potential for improving and maintaining PAH, and therefore, improving AH of girls with CPP.

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Competing interests: AbbVie participated in the data collection; analysis and interpretation of data; and writing, reviewing, and approval of the manuscript for submission. No authors received payment or other compensation related to this work. Marcela Vargas Trujillo is a consultant for AbbVie and has received compensation for giving talks for Tolmar Pharmaceuticals in 2022. Karen Klein is a consultant for AbbVie and has been paid for participating in speaker bureaus and educational presentations for AbbVie and has had travel/accommodations paid for by AbbVie. Peter A Lee is a consultant and on the speaker bureau for AbbVie. Kent Reifschneider has been a consultant for AbbVie, Endo Pharma (2020), Ascendis and Novo Nordisk (2020) and on the speaker bureau for Ascendis and AbbVie (2021); he is currently a principal investigator for Ascendis. Philippe F. Backeljauw has been a consultant for Novo Nordisk,

Novartis/Sandoz, Ascendis Pharma, BioMarin Pharmaceutical, Tolmar Pharmaceuticals, Cavalry Bioventures, and Ipsen, and currently receives research support from Novo Nordisk, Novartis, and Ipsen. Sanja Dragnic, Stephen Van Komen, Jun Yu, and are employees of AbbVie and may own AbbVie stock and/or stock options.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The research related to human use has complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. Institutional Review Board approval of the study protocols was obtained for each study site and written informed consent was provided by each patient and their parent or legal guardian, with child assent being obtained as appropriate.

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