Title

Importance of individualizing treatment decisions in girls with central precocious puberty when initiating treatment after age 7 years or continuing beyond a chronological age of 10 years or a bone age of 12 years

Journal

Journal of Pediatric Endocrinology and Metabolism, 34(6)

ISSN

0334-018X

Authors

Trujillo, Marcela Vargas

Dragnic, Sanja

Aldridge, Petra

et al.

Publication Date

2021-06-01

DOI

10.1515/jpem-2021-0114

Peer reviewed

Marcela Vargas Trujillo*, Sanja Dragnic, Petra Aldridge and Karen O. Klein

Importance of individualizing treatment decisions in girls with central precocious puberty when initiating treatment after age 7 years or continuing beyond a chronological age of 10 years or a bone age of 12 years

https://doi.org/10.1515/jpem-2021-0114
Received December 18, 2020; accepted February 22, 2021; published online April 15, 2021

Abstract

Objectives: Gonadotropin-releasing hormone agonist treatment is important for optimal growth in girls with central precocious puberty (CPP). Data are lacking regarding benefit to height outcome when treatment is started after chronological age (CA) of 7 years, and if continued beyond CA of 10 years or bone age (BA) of 12 years.

Methods: Forty-eight girls with CPP were treated with monthly leuprolide depot. Change in predicted adult height (PAH) during treatment was assessed. Changes in PAH and growth velocity were compared between girls initiating treatment at CA <7 vs. ≥7 years, and BA ≥12 vs. BA <12 years.

Results: Mean baseline CA was 6.8 years, BA, 10.2 years; and PAH, 156.4 cm. BA/CA ratio decreased from pretreatment values, averaging 1.5 to 1.2 at the end of treatment. Proportion of girls with >5 cm PAH change during treatment was similar, and PAH increased throughout treatment in most girls, regardless of age at treatment initiation. PAH continued to increase in 16/19 girls who continued treatment after BA of 12 years, and also in 16/22 girls who continued treatment after CA of 10 years.

Conclusions: PAH improved in most girls who initiated treatment after CA of 7 years. It continued to improve in most girls with longer treatment, even past BA of 12 years or CA of 10 years, which suggests that no absolute CA or BA limit should define initiation or end of treatment. Treatment plans need to be individualized, and neither treatment initiation nor cessation should be based on BA or CA alone.

Keywords: bone age; central precious puberty; final height; leuprolide treatment; predicted adult height growth velocity.

Introduction

Central precocious puberty (CPP) occurs when the hypothalamic-pituitary-gonadal axis is prematurely activated, leading to an increase in gonadal steroid hormone secretion [1]. As a result, the affected child develops secondary sexual characteristics earlier than is typical, and experiences accelerated bone maturation and premature fusion of epiphyseal growth plates, with consequent reduction of adult stature [1–6].

The current standard of care for treating CPP is gonadotropin-releasing hormone agonist (GnRHa) therapy [7]. The primary goals for GnRHa treatment in CPP are to suppress the physical changes of puberty and to improve final height outcome [7]. It has been suggested that there is no further benefit to height outcome when treatment is continued after a bone age (BA) of 12 years [8–12], and there are conflicting reports on whether there is benefit from starting treatment at chronological age (CA) ≥7 years [2, 4, 13–17]. The mean CA of GnRHa treatment discontinuation reported in a consensus statement ranged from 10.6 to 11.6 years, and mean BA at discontinuation ranged from 12.1 to 13.9 years [7]. However, there is high variability in the increases in adult height, which is dependent on the age of the child at the time of treatment initiation [16]. Adult height outcome is multifactorial and the present analysis was conducted to assess whether girls diagnosed with CPP receive adult height benefit from GnRHa treatment when

***Corresponding author: Marcela Vargas Trujillo**, MD, Rady Children's Hospital, 3020 Children's Way, MC 5103, San Diego, CA 92123, USA; and Department of Pediatrics, University of California, San Diego, CA, USA, Phone: (858) 966 4032, E-mail: mvargas1@rchsd.org
Sanja Dragnic, AbbVie, North Chicago, IL, USA
Petra Aldridge, Covance, Inc., Princeton, NJ, USA
Karen O. Klein, Rady Children's Hospital, San Diego, CA, USA; and Department of Pediatrics, University of California, San Diego, CA, USA

treatment is initiated after CA of 7 years, and when treatment is continued after BA of 12 years or CA 10 years.

Methods

Study population

The population included in this study consisted of girls who enrolled in a previously published, open-label, long-term trial of monthly depot leuprolide acetate (7.5, 11.25, or 15 mg based on weight) (Lupron Depot®, AbbVie, North Chicago, IL) [18]. Inclusion criteria included: onset of breast development before CA 8 years; peak GnRH-stimulated luteinizing hormone (LH) ≥10 U/L; CA of <9 years at study entry; BA advanced ≥1 year beyond CA; and no evidence of adrenal or thyroid pathology. Girls were excluded from the study if they had received irradiation to the central nervous system or prior therapy with medroxyprogesterone acetate and/or any previous GnRH analog. Girls were also excluded if they had <24 weeks of treatment.

Study protocol

Study procedures have been described previously [18]. Briefly, leuprolide acetate depot was administered intramuscularly every 28 days. Study visits for safety and efficacy assessments occurred at weeks 4, 8, 12, 24, 36, 48 and then every 6 months until the study drug was discontinued. The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. Institutional Review Board approval was obtained at each site where the original study was conducted, and written informed consent was provided by the subject and the subject's parent and legal guardian.

Study variables

The following variables were collected: medical history, including a six-month historical height; physical examination, including height, weight and pubertal staging of breasts and pubic hair using a modified Tanner method with palpation of breast tissue [19] and BA, as measured by radiograph of left wrist and determined by the FELS method [20].

Final height was defined as height associated with a growth velocity (GV) less than 1 cm/year or a BA ≥14 years. Bone age was measured annually until the end of treatment. The ratio of BA to CA was computed from measurements made at start of study and at weeks 24 and 48, and then every 12 months throughout treatment. Change in BA/CA ratio over time was calculated for each study visit.

Predicted adult height (PAH) was computed by dividing a girl's height by the average percentage of mature height associated with a given BA based on tables published by Bayley and Pinneau [21].

Statistical analysis

Correlations between variables were assessed by linear regression. Changes over time in PAH, BA and BA/CA ratio from baseline were compared using paired *t* tests. Changes in PAH during treatment, PAH–mid-parental height (MPH), final height–MPH, and height standardized score (HSS) were summarized for girls who started treatment at CA <7 vs. ≥7 years.

The change in BA/CA ratio and PAH were summarized for girls who discontinued treatment at BA <12 vs. ≥12 years. Values are presented as mean ± SD unless noted otherwise. Software used was SAS version 9.4 for UNIX (SAS Institute, Cary, NC).

To evaluate the influence of BA on the rate of change in PAH, a subset of 38/48 girls were also evaluated over one year of treatment, independent of chronological age or stage of treatment.

Changes in PAH over one year were analyzed using the last available BA with a previous BA 1 year earlier ±4 months. This data is referred to as "evaluated over one year" throughout the results and discussion.

Results

Subject characteristics

Baseline characteristics of the girls are summarized in Table 1. Mean treatment duration was 3.9 ± 2.0 (range, 1.1–9.8) years. Mean age at end of treatment was 11.5 ± 0.97 (range, 9.8–14.1) years. Mean BA at end of treatment was 12.7 ± 0.94 (range, 11.5–16.4) years. GnRH-stimulated peak LH was suppressed to <1.75 IU/L in ≥93.6% girls for all timepoints past week 12 of treatment.

Bone age/chronological age ratio

Ratio of BA/CA decreased consistently throughout the treatment from pretreatment values, averaging 1.5 ± 0.30 at baseline to 1.2 ± 0.11 at last assessment (Figure 1). All 38 subjects who were evaluated over one year had a decrease in BA/CA during that year, from 1.2 ± 0.1 to 1.1 ± 0.1 independent of CA at the assessment, demonstrating the consistency of decrease in BA/CA during continued treatment. Fifteen girls reached a point with a BA <1 year beyond CA; 9/15 of those had a BA >12 years.

Growth velocity

Growth velocity declined from a mean baseline value of 10.6 ± 3.4 (range, 5.5–21.2) cm/year to 3.7 ± 1.8 (range, –1.9 to 7.6) cm/year during treatment. Five out of twelve girls with GV <4 cm/year continued to have improvement in PAH over the following year.

Predicted adult height

Predicted adult height continued to increase with longer duration of treatment (Figure 2A) in almost all girls (45/48)

Table 1: Subject characteristics at baseline.

Characteristic	Baseline (n=48)
Race, n, %	
White	30 (62.5)
African American	11 (20.8)
Asian	8 (16.7)
Ethnicity, n, %	
Hispanic	8 (16.7)
Not Hispanic	40 (83.3)
CA, mean (SD), years	6.8 (1.9)
Range, years	1.0, 9.0
Weight, n	46
Mean (SD), kg	33.8 (9.7)
Range, kg	13.0–52.2
Height, n	46
Mean (SD), cm	131.6 (15.1)
Range, cm	84.6, 154.7
HSS, mean (SD)	1.6 (1.2)
Range	−1.3 to 3.4
Tanner stage (breast), n (%)	
1	1[a] (2.1)
2	9 (18.8)
3	24 (50.0)
4	13 (27.1)
5	1 (2.1)
Growth velocity, n	44
Mean (SD), cm/year	10.6 (3.4)
Range, cm/year	5.5–21.2
BA, n	47
Mean (SD), years	10.2 (2.2)
Range, years	2.5–12.1
BA/CA, n	47
Mean (SD)	1.5 (0.3)
BA – CA, n	47
Mean (SD), years	3.0 (0.8)
Range, years	1.4–4.5
PAH, n	39
Mean (SD), cm	156.4 (8.4)
Range, cm	135.7–171.2
MPH, n	44
Mean (SD), cm	163.8 (7.2)
Range, cm	138.4–175.8

BA, bone age; CA, chronological age; HSS, height standardized score; MPH, mid-parental height; PAH, predicted adult height.[a]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).

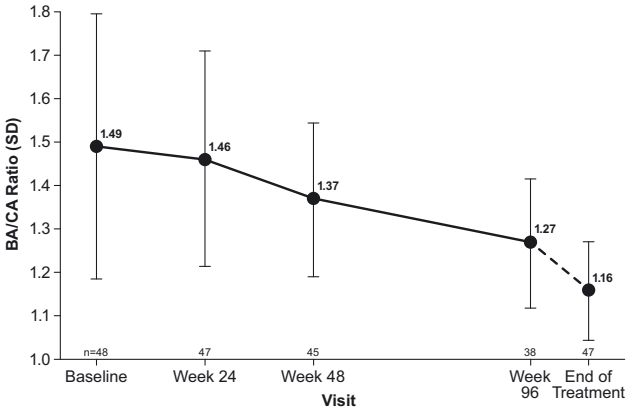

Figure 1: Change in mean BA/CA ratio during treatment.
BA, bone age; CA, chronological age.

regardless of age at treatment initiation or age during treatment (p<0.001) (Figure 2B and C). Two of the girls who did not have an increase in PAH with treatment had very tall PAH at start of treatment and reached their MPH.

The majority of girls (91%, 30/33) who initiated treatment at CA ≥7 years showed improvement in PAH. (Figure 2C). Girls with treatment initiation at CA <7 years had slightly greater increase in PAH during treatment, and greater change in final height – MPH than girls with treatment initiated at ≥7 years. Similar proportions of girls in both groups experienced PAH improvements >5 cm, although the sample size was too small to reach statistical significance (Table 2). Mean PAH continued to increase in 16/19 girls who continued treatment after a BA of 12 years, (range 0.5–4.8 cm) over the following year. The three girls who did not show improvement of PAH with treatment were either already at or near their MPH or exhibited poor growth velocity. To investigate the influence of continuing treatment after a BA of 12 years, the two groups of girls (<12 and ≥12 years) were compared. The mean change in PAH during treatment was greater in the BA ≥12-year group (6.5 cm) than in the BA <12-year group (3.9 cm) (Table 3).

Twenty-nine of the thirty-eight (76.3%) girls evaluated over one year showed increases in PAH during that year. This was not dependent on whether CA equaled BA, the rate of BA advancement during that year, the GV during that year, or baseline PAH. Predicted adult height increase over 1 year of treatment averaged 1.77 ± 2.21 (range, −2 to 8.47) cm and was very similar for those with BA ≥12 years and those with BA <12 years. Similarly, mean PAH continued to increase in 16/22 girls who continued treatment after a CA of 10 years (0.14–8.47 cm).

Final height

Thirty girls were followed up until they reached their final height. On average, the girls reached a final height of 162.54 ± 7.35 (range, 146.47–176.11) cm, which was similar to the PAH attained during treatment (162.39 ± 8.38 cm) (Figure 3). However, 16 girls had a decrease from their greatest PAH during treatment to final height by an average of 2.33 ± 3.14 cm. Seventeen of the twenty nine with MPH recorded met or surpassed their MPH.

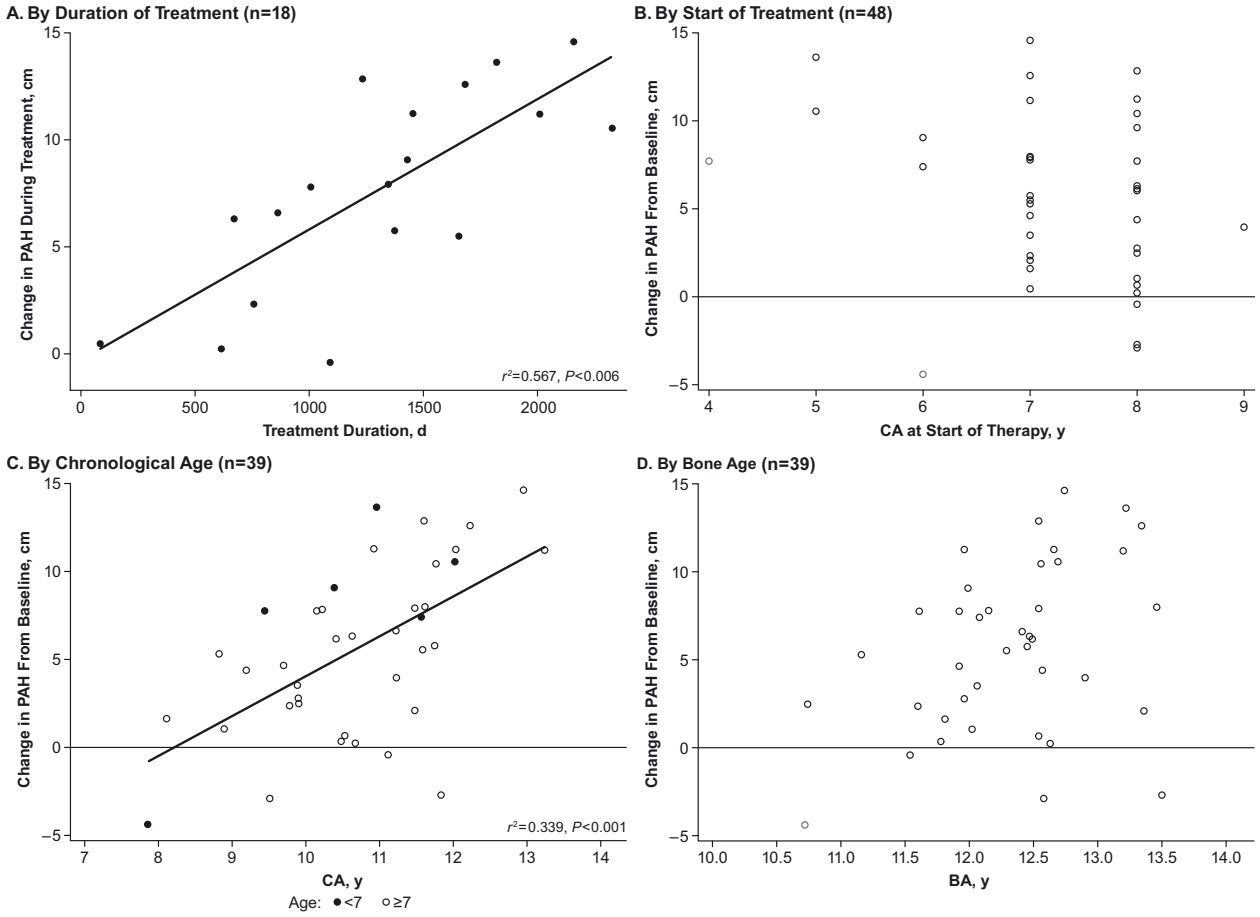

Figure 2: Change in PAH by duration of treatment (A), chronological age at start of treatment (B), age during treatment (C), and bone age (D), Solid dots indicate CA <7 at start of treatment, open circles indicate CA ≥7 at start of treatment. BA, bone age, CA. Chronological age; PAH, predicted adult height.

Table 2: Comparison of girls with CA <7 and ≥7 years at treatment onset.

Characteristic	<7 years at treatment start (n=11)	≥7 years at treatment start (n=37)
Change in PAH during treatment, n	6	33
Mean (SD), cm	7.3 (6.2)	5.3 (4.6)
Range, cm	−4.4 to 13.6	−2.9 to 14.6
≥5-cm change in PAH, n, %	5 (45.5)	17 (45.9)
Final height – MPH, n	4	22
Mean (SD), cm	−4.2 (4.4)	−1.6 (7.9)
Range, cm	−10.4 to 0	−15.3 to 21.0
Change in HSS	6	33
Mean (SD)	−1.1 (0.8)	−0.6 (0.6)
Range	−2.5 to −0.2	−2.3 to 0.2

CA, chronological age; HSS, height standardized score; MPH, mid-parental height; PAH, predicted adult height.

Table 3: Comparison of girls With BA <12 years vs ≥12 years at assessment.

Characteristic	<12 years at assessment	≥12 years at assessment
BA, n	16	31
Mean (SD), years	11.4 (1.1)	12.6 (0.4)
Range	7.6–12.0	12.0–13.5
BA/CA, n	16	31
Mean (SD)	1.2 (0.1)	1.1 (0.1)
Range	1.0–1.5	1.0–1.4
Change in PAH during treatment,	13	26
Mean (SD), cm	3.9 (4.3)	6.5 (4.9)
Range	−4.4 to 11.3	−2.9 to 14.6

BA, bone age; CA, chronological age; GV, growth velocity; PAH, predicted adult height.

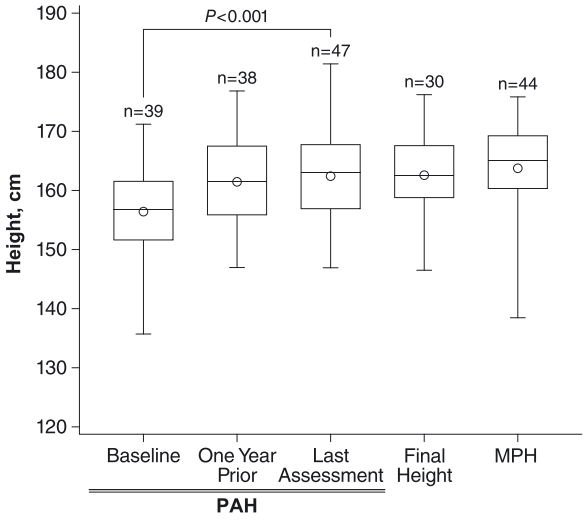

Figure 3: Predicted adult height during treatment, final height and mid-parental height.
MPH, mid-parental height; PAH, predicted adult height.

Discussion

The present study addresses two key areas regarding height outcome after GnRHa treatment in girls with CPP. One is whether there is additional height gain when continuing treatment after a BA of 12 years, and the other is whether there is height gain when onset of treatment is at CA>7 years. This study focused on girls because larger studies are needed to answer similar questions in boys. The data presented here represent one of the largest studies with long-term follow-up of girls with CPP treated with leuprolide. The girls also started treatment at an earlier age than those in many recent studies, at a mean of 6.8 years.

With adequate treatment, the rate of BA maturation decreases and CA approaches BA over time. As long as linear growth is adequate, PAH continues to improve. In the present study, BA/CA ratio improved continuously during treatment. PAH continued to increase during treatment in almost all girls, including those with a BA of 12 years. The continued improvement in PAH throughout treatment independent of BA is consistent with a longer duration of treatment improving height outcome, which has been previously shown [22–24].

Most previous reports suggest that, on average, girls do not reach their PAH at the end of treatment [4, 15, 25]. Interestingly, on average this cohort did reach their PAH achieved during treatment. It is not possible to estimate what would have happened to final height if a particular girl had stopped treatment earlier. For those who did not reach PAH by end of treatment, might they have done better with earlier cessation of treatment? It is however also possible that the continued treatment allowed them to reach the height they did.

The high variability in range of change of PAH over time emphasizes the multifactorial influences on height and the importance of individualizing treatment decisions. In general, it is reasonable to continue treatment until PAH is close to MPH and growth is still reasonable. In the present study, some girls continued to have improvement of their PAH despite slow growth velocity. This highlights the importance of looking at all variables in the decision regarding cessation of treatment. If BA indicates growth potential and PAH is improving, even GV alone may not dictate the cessation of treatment. If GV continues to slow down, CA is nearing BA and PAH is not improving, then discontinuation of treatment is reasonable.

Some studies suggest that PAH is not improved if girls start treatment after CA of 6 or 7 years [15], whereas others suggest improvement in this age group [2, 4, 14, 17, 26, 27] even if treatment is started beyond age 8 years [28]. There are several key variables that determine who benefits from treatment. Some girls initiate puberty before a CA of 7 years but do not receive treatment until they are older than 7 years. These girls may have different outcomes from treatment than girls who start puberty after a CA of 7 years. Additionally, girls with rapid progression of puberty have lower height outcomes than those with slow progression who may not need treatment. As clinicians evaluate whether to treat someone after a CA of 7 years, it is important to determine age of onset of puberty and rate of progression of puberty. In the present study with strict inclusion criteria, girls who initiated treatment after a CA of 7 years had improvements in PAH similar to those who initiated treatment at a younger age.

In a recent review, Kaplowitz et al. suggested discontinuing GnRHa no later than a CA of 10 years, with exceptions made in rare cases of severe psychosocial stress and, perhaps, a very low PAH [10]. In the present study, mean CA at the end of treatment was 11.5 years. The data suggesting no further increase in height with treatment continuation after a CA of 10 years was based on an algorithm, not patient data. One difficulty in suggesting a CA or BA at which to stop treatment is that PAH often decreases after treatment discontinuation, so a determination of those at risk to lose benefit is not straightforward, leaving the emphasis on the clinician to individualize treatment decisions by carefully looking at height, GV, rate of BA progression, estimates of PAH and MPH. Our data support benefit in height outcomes with continued treatment after a BA of 12 years in most girls. Many children will achieve the desired outcome when treatment is stopped at a CA of 10

years or a BA of 12 years, but others benefit from continued treatment. When PAH is particularly short, or family heights particularly tall, this is an important consideration. For example, a girl with a CA of 10 years and BA of 10 years has more growth potential than a girl with a CA of 10 years and BA of 12 years. The latter child may wish to remain on treatment longer to continue to slow the rate of bone maturation. Similarly, two children, each aged 10 years, but with different heights, 152 and 137 cm, may have different treatment plans.

It should also be noted that the Kaplowitz et al. review considered cost-effectiveness [10]. Although cost containment is important in medicine, treatment goals to optimize height consistent with genetic potential is appropriate in girls with CPP. Once a girl has undergone treatment for many years, anticipating optimal height outcome is appropriate for her and her family. It is the clinician's role to give reasonable expectations and cautions about PAH and help a family make decisions based on cost benefit. The review by Kaplowitz et al. also reasons that since onset of menses occurs on average 18 months after cessation of treatment, a girl who stops treatment at 10 years would have menses at an average age of 11.5 years. The caution with this reasoning is that girls may start menses earlier, by 3–12 months after discontinuation of treatment.

A limitation of the present study, like most studies in children with CPP, is the small sample size, and that there are not enough children with each combination of variables to develop a prediction model for who benefits from longer duration of treatment and who does not, nor to determine set guidelines for a particular CA or BA at which to discontinue treatment. Some of the subgroup analyses involve very small numbers of girls, preventing meaningful statistical testing. Another limitation is that not all parental heights were measured in clinic. Additionally, we hypothesize that continued treatment maintains or improves PAH in most girls, but it is impossible to actually know how they would have grown if treatment had been stopped sooner. Likewise, it is impossible to predict how girls with onset of treatment at 7–8 years would have grown without treatment.

In conclusion, the present study confirms that rate of bone maturation slows and PAH improves with leuprolide acetate treatment. Girls who had initiation of treatment at a CA between 7 and 8 years had improvement in PAH at least as great as those initiating treatment before a CA of 7 years. Continuation of treatment after a CA of 10 years and a BA of 12 years led to continued increase in PAH in almost all girls. On average, final height reached PAH during treatment. Initiation of treatment despite a CA of ≥7 years and continuation of treatment after a BA of ≥12 years should be considered in some girls, with the aim of attaining optimal growth, especially in girls with a greater predicted height deficit. Treatment decisions should be individualized, and initiation or cessation of treatment should not be based on BA or CA alone.

Acknowledgments: Editorial support was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY). Funding for this support was provided by AbbVie (North Chicago, IL).

Research funding: This study was funded by AbbVie Inc.

Author contributions: AbbVie participated in the data collection; analysis and interpretation of data; and writing, reviewing, and approval of the manuscript for submission. The authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: 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 but has received no payment related to this work. Marcela Vargas is a consultant for AbbVie and has received no payment for this work. Sanja Dragnic is an employee of AbbVie and owner of AbbVie stock and/or stock options. Petra Aldridge is an employee of Covance, Inc., and is working as a contractor for AbbVie.

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

Ethical approval: The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. Institutional Review Board approval was obtained at each site where the original study was conducted, and written informed consent was provided by the subject and the subject's parent and legal guardian.

References

1. Lee PA. Central precocious puberty. An overview of diagnosis, treatment, and outcome. Endocrinol Metab Clin N Am 1999;28: 901–18, xi.
2. Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. Hum Reprod Update 2004;10:135–47.
3. Menon PS, Vijayakumar M. Precocious puberty–perspectives on diagnosis and management. Indian J Pediatr 2014;81:76–83.
4. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, et al. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. J Clin Endocrinol Metab 1999;84:1973–8.

5. Lebrethon MC, Bourguignon JP. Management of central isosexual precocity: diagnosis, treatment, outcome. Curr Opin Pediatr 2000;12:394–9.
6. Mul D, Hughes IA. The use of GnRH agonists in precocious puberty. Eur J Endocrinol 2008;159:S3–8.
7. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Group E-LGACC, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123: e752–62.
8. Eugster EA, Clarke W, Kletter GB, Lee PA, Neely EK, Reiter EO, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. J Clin Endocrinol Metab 2007;92:1697–704.
9. Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol 2016;174:R79–87.
10. Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-effective gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. Horm Res Paediatr 2018; 90:1–7.
11. Mul D, Oostdijk W, Otten BJ, Rouwe C, Jansen M, Delemarre-van de Waal HA, et al. Final height after gonadotrophin releasing hormone agonist treatment for central precocious puberty: the Dutch experience. J Pediatr Endocrinol Metab 2000;13:765–72.
12. Partsch CJ, Heger S, Sippell WG. Treatment of central precocious puberty: lessons from a 15 years prospective trial. German Decapeptyl Study Group. J Pediatr Endocrinol Metab 2000;13:747–58.
13. Franzini IA, Yamamoto FM, Bolfi F, Antonini SR, Nunes-Nogueira VS. GnRH analog is ineffective in increasing adult height in girls with puberty onset after 7 years of age: a systematic review and meta-analysis. Eur J Endocrinol 2018;179:381–90.
14. Micillo M, Salerno M, Officioso A, Perna E, Gasparini N, Pisaturo L, et al. Near final height after GnRH agonist treatment in central precocious puberty. J Pediatr Endocrinol Metab 2000;13:787–90.
15. Oerter KE, Manasco P, Barnes KM, Jones J, Hill S, Cutler GB Jr. Adult height in precocious puberty after long-term treatment with deslorelin. J Clin Endocrinol Metab 1991;73:1235–40.
16. Chen M, Eugster EA. Central precocious puberty: update on diagnosis and treatment. Paediatr Drugs 2015;17:273–81.
17. Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler GB Jr. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. J Clin Endocrinol Metab 2001;86:4711–6.
18. Neely EK, Lee PA, Bloch CA, Larsen L, Yang D, Mattia-Goldberg C, et al. Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. Int J Pediatr Endocrinol 2010;2010:398639.
19. Tanner J. Growth at adolescence. With a general consideration of the effects of hereditary and environmental factors upon growth and maturation from birth to maturity, 2nd ed. Oxford, UK: Blackwell Scientific; 1962.
20. Roche AF, Chumlea WC, Thissen D. Assessing the skeletal maturity of the hand-wrist: FELS method. Springfield, IL: Charles C Thomas Pub Ltd; 1988.
21. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423–41.
22. Li P, Li Y, Yang CL. Gonadotropin releasing hormone agonist treatment to increase final stature in children with precocious puberty: a meta-analysis. Medicine 2014;93:e260.
23. Nabhan ZM, Feezle LK, Kunselman AR, Johnson NB, Lee PA. Normal adult height among girls treated for central precocious puberty with gonadotropin-releasing hormone analog therapy. J Pediatr Endocrinol Metab 2009;22:309–16.
24. Poomthavorn P, Suphasit R, Mahachoklertwattana P. Adult height, body mass index and time of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing hormone analogue treatment. Gynecol Endocrinol 2011; 27:524–8.
25. Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Antoniazzi F, et al. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. Eur J Endocrinol 1999;141:140–4.
26. Bereket A. A critical appraisal of the effect of gonadotropin-releasing hormone analog treatment on adult height of girls with central precocious puberty. J Clin Res Pediatr Endocrinol 2017;9: 33–48.
27. Bertelloni S, Massart F, Einaudi S, Wasniewska M, Miccoli M, Baroncelli GI. Central precocious puberty: adult height in girls treated with quarterly or monthly gonadotropin-releasing hormone analog triptorelin. Horm Res Paediatr 2015;84: 396–400.
28. Lee HS, Yoon JS, Park KJ, Hwang JS. Increased final adult height by gonadotropin-releasing hormone agonist in girls with idiopathic central precocious puberty. PloS One 2018;13:e0201906.