Final Height in Pubertal Short Stature Boys Treated with GH Combination with Letrozole: A retrospective study

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Research

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Abstract

Background

The growth potential of pubertal short stature boys is limited by the effect of estrogen on epiphyseal fusion. This study aims to identify the efficacy and safety of growth hormone (GH) combination with letrozole on final adult height (FAH) in pubertal short stature boys.

Methods

This is a retrospective study. Among pubertal short stature boys who treated with GH and letrozole were be followed up in our hospital, 20 cases reached FAH.

Results

Baseline chronological age were 12.12±1.14yr, bone age were 13.00±0.93yr. The treatment duration was 1.94±0.67yr. The height standard deviation score for bone age was increased from -1.46±0.51 to -0.12±0.57 ($p<0.000$). The predicted FAH before treatment, predicted FAH after treatment, FAH, and genetic target height were 161.02 ±4.12 cm, 172.11±4.20 cm, 172.67±2.72cm and 167.67±3.56 cm, respectively. There was significant differences between predicted FAH before treatment and after treatment ($p<0.000$), as well as predicted FAH before treatment and genetic target height ($p<0.000$).The predicted FAH after treatment was higher than that of genetic target height ($p<0.001$), as well as FAH and genetic target height ($p<0.000$).

Conclusions

The GH combination with letrozole can enhance the FAH in pubertal short stature boys. No significant side effects were observed.

Introduction

In recent years, how to improve the final adult height (FAH) of pubertal short stature boys has attracted the close attention of many experts in pediatric endocrinology and related fields. Among them, the focus is the close relationship between estrogen and bone age. High levels of estrogen in puberty can lead to premature epiphyseal closure, which makes FAH unsatisfactory. Gonadotropin-releasing hormone analogue (GnRHa) is an effective medication approved to inhibit hypothalamic-pituitary-gonadal axis (HPGA) in children, which can control gonadal development and lower estrogen levels. Under the guideline [1], the indication of GnRHa application in boys is that the bone age is less than 12.5 years old, and the cautious indication is that the bone age is more than 12.5 years old. However, when the bone age is more than 13.5 years old, the effect of GnRHa treatment alone on improving FAH is not significant, so pubertal short stature boys with large bone age are not suitable to use GnRHa treatment only.

Letrozole is one of the third generation aromatase inhibitors, and it can inhibit estrogen production more than 99.1% in vivo [2]. The main clinical indications are anti-cancer, especially for early postmenopausal hormone-positive breast cancer patients and late postmenopausal breast cancer patients who are ineffective in anti-estrogen therapy [3]. At present, the words "can be used for children" have not been found in the instructions of letrozole, but in fact, in recent years, more and more studies for letrozole have been carried out in pediatrics, especially in pediatric endocrine clinical application. For example, it has been applied in some endocrine diseases in children (gynecomastia, growth hormone deficiency, idiopathic short stature and congenital adrenal hyperplasia, etc.) [4-7]. Comparison with GnRHa, the advantage of letrozole is that it only inhibits the production of estrogen in vivo and does not inhibit the normal development of child. It can make the children have pubertal psychology as same as normal children. In recent years, the clinical application of GH combination with letrozole in the treatment of pubertal short stature boys has gradually increased, but few cases have been followed up to FAH.

Subjects And Methods

Study subjects. This study was approved by the Ethics Committee of our hospital. From August 2009, among pubertal short stature boys treated with GH combination with letrozole, twenty cases were be followed until they reach final adult height. Informed consent was obtained from their parents before treatment. The referenced diagnostic criterias were as follows: Normal puberty is defined as gonadal development began after 9 years old, with testis (>4 mL). There are the evidence for activated HPGA from GnRHa

stimulation test, or single serum gonadotropin level [1]. Short stature and short stature of predicted FAH(PFAH) is defined as height or PFAH below the third percentile of growth curve of healthy children at the same age and gender [8]. FAH is defined as epiphyseal closure on hand-wrist bone age x-ray and no change (<1 cm) in height for 12 months [9]. Residual growth capacity 1 is defined as PFAH before treatment (PFAH1) minus pre-treatment height. Residual growth capacity 2 is defined as PFAH after treatment (PFAH2) minus pre-treatment height. And final residual growth capacity is defined as FAH minus pre-treatment height [10]. The exclusion criteria were as follows: prepuberty, asymmetric short stature (such as achondroplasia, et al.), severe acute and chronic liver or kidney diseases and tumor.

Examination, treatment and monitoring. HPGA were all activated before treatment. And the indicators of physical measurement (such as weight, height and testicular development), blood biochemical indexes (liver function, kidney function, electrolyte), glycometabolism indexes (glycosylated hemoglobin, oral glucose tolerance test, insulin release test), IGF-1, IGF-BP3, tumor indexes (alpha-fetoprotein, chorionic gonadotropin), MRI (pituitary gland), B ultrasonography (upper abdomen, thyroids, adrenal gland) and bone age were evaluated. After evaluation, 20 cases were treated with GH (GH, 0.15-0.20 IU/kg.d, subcutaneous injection) and letrozole tablets (2.5 mg/per day, oral). During the period of treatment, the indicators of physical measurement, blood biochemistry, glucose metabolism, IGF-1, IGF-BP3 and bone age were monitored regularly. THt is calculated by (parent's height + 13)/2±5cm.

Statistical analysis. SPSS19.0 was used to analyze the data. The paired *t* test and Wilcoxon Signed-Rank test were used to compare the data between the two groups. A two-tailed *P* value < 0.05 was considered to indicate statistical signifcance in all analyse.

Results

Baseline characteristics

At the beginning of the study, the chronological age were 12.12±1.14yr and 13.00±0.93yr, respectively. At the end of the study, the chronological age were 14.06±1.28yr and14.41±1.31yr. The treatment course was 1.94±0.67yr and growth velocity was 9.32±2.28cm per year. Table 1 and Table 2.

Comparison for indexes

The serum estradiol decreased from 21.731±16.870pg/ml to 13.000±12.472pg/ml (*Z*=-2.054, p=0.040). The testosterone increased from 2.167±1.692ng/ml to 6.807±2.339ng/ml (*Z*=-2.213, p=0.027). After treatment, the range of testosterone was 2.13-11.28ng/ml, and no hypertestosteronemia was observed [11].

The height increased from 148.20±6.87cm to 165.53±4.10cm (*t*=-14.012, p<0.000), and height standard deviation score (SDS) for bone age from -0.43±0.87 to 1.53±0.64 (*t*=-12.007, p<0.000). The PFAH1, PFAH2, FAH, and target height (THt) were 161.02 ±4.12 cm, 172.11±4.20 cm, 172.67±2.72cm and 167.67±3.56 cm, respectively.There was significant differences between PFAH1 and PFAH2 (*t*=-10.831, p<0.000), as well as PFAH1 and THt (*t*=-5.814, p<0.000). PFAH2 was higher than that of THt (*t*=-3.940, p<0.001), as well as FAH and THt (*t*=5.714, p<0.000). The PFAH1-THt, PFAH2-THt and FAH-THt were -6.65±5.11cm, 4.44±5.03cm and 5.00±3.91cm, respectively. There was significant differences between PFAH1-THt and PFAH2-THt (*t*=-10.831, p<0.000), as well as PFAH1-THt and FAH-THt (*t*=-13.372, p<0.000). There was no difference between PFAH2-THt and FAH-THt (*t*=-0.625 p<0.540).

Residual growth capacity 1, residual growth capacity 2 and final residual growth capacity were 12.83±5.54cm, 23.91±8.16cm and 24.47±6.70cm, respectively. There was significant difference between residual growth capacity 1 and residual growth capacity 2 (*t*=-10.831, p<0.000), as well as residual growth capacity 1 and final residual growth capacity (*t*=-13.372, p<0.000). There was no difference between residual growth capacity 2 and final residual growth capacity (*t*=0.625, p<0.540).

Safety and tolerability

One case with single ankle and metatarsal fracture (refused to take vitamin D and calcium tablets), 1 case of scoliosis (21 degrees, no posterior and lateral radiographs of the spine before treatment); 2 cases with hypothyroidemia (recovered after withdrawal); 2 cases with insulin resistance before treatment (no deterioration during the course of treatment, and be recovered after withdrawal); 5 cases with insulin resistance during the course of treatment (be recovered after withdrawal).

Discussion

The biggest problem faced by pubertal short stature boys is limited growth potential. The treatment goal is to exploit their residual growth ability and make the children obtain satisfactory height (close to THt). At present, there is little literatures on GH combined with letrozole in the treatment of adolescent short boys followed up to FAH. In pubertal boys with severe idiopathic short stature, GH(0.13U/kg·d), or combination treatment (aromatase inhibitor/GH) for the next 24 months. Subjects were then randomized to treatment with GH and one kind of aromatase inhibitor (n=25, anastrozole or letrozole—balanced 1:1) . The mean height gain at 24 months was 18.9±0.8cm, and the absolute change in height from baseline at near FAH was 22.5±1.4cm [6]. In our study, 20 cases reached FAH. Although 25 cases in the above study were all near FAH, none of FAH. In our study, GH dosage (0.15-0.2U/kg.d) was slightly higher than that of the above study considering the maximum residual growth capacity. But the dose of GH in our study was within the recommended guidelines of GH usage [12]. The treatment duration was 1.94±0.67yr, and mean height gain was 17.34±5.53cm. If calculated by 24 months, the net height gain was 17.9 cm, which was close to the 24 months height gain (18.9 cm) of the above study. In our study, the net height gain was 24.47±6.70cm at FAH, which was close to that of near FAH (22.5±1.4 cm) in above study. However, unlike the above reports, the end point of our study was FAH. In our study, the effect of GH combined with letrozole alone on FAH was observed, and we aimed to avoid the interference of mixed factors of letrozole and anastrozole. And they have different inhibitory rates on estrogen (letrozole >99.1%, anastrozole 97.3%) [2]. In terms of the number of GH combined with letrozole, there were 20 cases in our study, while there was only 12-13 cases in the above study .

In 2017, a study reported that 96 adolescent boys were divided into 4 groups. The height SDS of anastrozole, GH combined with anastrozole, letrozole, GH combined with letrozole were 0.8±0.7, 0.7±0.7, 0.3±0.5 and 1.2±0.8, respectively. There were 22 cases of near FAH and no cases of FAH. And there was significant differences among these groups and no side effects were found. GH combined with letrozole can maximize near FAH [13]. Compared with 9 cases of NFAH achieved by GH combined with letrozole in the literature [13], there were no differences for indexes before treatment such as between bone age [(13.28±1.09)y & (13.00±0.93)y], height [(152.17±6.99)cm & (148.20±6.87)cm] between that of our study and the above study (13), [(Z=-1.182, p=0.237)&(t=1.432, p=0.163)]. But the PFAH1 (161.02±4.12cm) before therapy in our study was lower than that of the above study (170.27±2.35cm) (t=6.251, p<0.000). And the THt (167.67±3.56cm) before therapy in our study was lower than that of the above study (172.89±4.53cm) (t=3.357, p=0.002). But there was no significant difference of NFAH in above study and FAH in our study (174.58±7.01cm&172.67±2.72cm), (t=0.793, p=0.448). So it indicated that there was the same efficacy between our study and the above study [13].

Compared with 5 cases of NFAH achieved by letrozole in the literature [13], there were no differences for indexes before treatment such as between bone age [(13.60±0.78)y & (13.00±0.93)y], height [(157.30±5.82)cm & (148.20±6.87)cm] between that of our study and the above study [13], [(t=-1.336, p=0.195)&(t=-1.336, p=0.195)]. But the PFAH1 (161.02±4.12cm) before therapy in our study was lower than that of the above study (174.16±1.11cm) (t=-6.965, p<0.000). And the THt (167.67±3.56cm) before therapy in our study was lower than that of the above study (176.20±1.92cm) (t=-5.113, p<0.000). But there was the same efficacy between our study and the above study [13], and there was no difference for NFAH in above study and FAH in our study [171.06±2.33cm&172.67±2.72cm], (t=-1.207, p=0.240), so it indicated that the GH combined with letrozole was superior than that of letrozole alone.

Compared with 3 cases of near FAH achieved by GH combined with anastrozole in the literature [13], there were no differences for bone age before treatment between [(13.33±0.29)y & (13.00±0.93)y] between that of our study and the above study, (Z=-1.189, p=0.234). And the height (148.20±6.87cm) before therapy in our study was lower than that (152.83±7.08cm) of the above study (t=-1.087, p=0.289), as well as the PFAH1 (161.02±4.12cm) in our study and that (172.00±6.03cm) of the above study(t=-4.088, p=0.001), and the THt (167.67±3.56cm) in our study and that (174.50±2.60cm) of the above study(Z=2.332, p=0.020). However, there was the same efficacy between our study and the above study [13], and there was no difference for NFAH in above study and FAH in our study [168.83±5.86cm&172.67±2.72cm], (t=-1.115, p=0.375), so it indicated that the GH combined with letrozole was superior than that of letrozole alone, while the number of cases was limited and further study need be researched.

Compared with 5 cases of near FAH achieved by anastrozole in the literature [13], there were no differences for indexes before treatment such as between bone age [(12.60±0.65)y &(13.00±0.93)y], height [(149.00±5.76)cm & (148.20±6.87)cm] between that of our study and the above study (13), [(t=0.474, p=0.640)&(t=-0.163, p=0.872)]. But the PFAH1 (161.02±4.12cm) before therapy in our study was lower than that of the above study (173.84±6.55cm) (t=-2.622, p=0.015). And the THt (167.67±3.56cm) before therapy in our study was lower than that of the above study (171.75±2.96cm) (Z=-1.360, p=0.174). But there was the same efficacy between our study and the above study (13), and there was no difference for near FAH in above study and FAH in our study

[172.80±5.12cm&172.67±2.72cm], (*t*=0.083, p=0.935), so it indicated that the GH combined with letrozole was superior than that of anastrozole alone.

Letrozole can significantly inhibit bone age progress and improve FAH in adolescent short boys. In a prospective, double-blind, randomized, placebo-controlled clinical study, thirty-one boys, aged 9.0-14.5 yr, with idiopathic short stature were studied.The boys were treated with the aromatase inhibitor letrozole (2.5 mg/d) for 2 yr. The main outcome measure was the change in PAH after 24 months of treatment. The level of serum testosterone in letrozole group was significantly higher than that in control group. After 2 years of treatment, the range of serum testosterone entering puberty was 17.3-1385 ng/dl, while the level of serum estradiol was similar to that before treatment [14]. In this study, testosterone [(6.807+2.339) ng/ml, ranging from 2.13 to 11.28ng/ml] after treatment was higher than thatof before treatment [(2.167+1.692) ng/ml, ranging from 0.19 to 5.33ng/ml]. Serum estradiol (13.000+12.472) pg/ml was significantly lower than before treatment (21.731+16.870) pg/ml. The bone age minus chronological age changed from 0.88±0.83 to 0.35±1.34. It indicated that letrozole prevented the conversion of testosterone to estradiol, and promoted the slow growth of bone age, and gradually shortened thebone age minus chronological age, and it provided the opportunity for FAH, and serum testosterone were in normal range.

It indicated that GH combined with GnRHa did not yet improve FAH in adolescent short boys. Thirty-two adolescents with Tanner stage 2-3, age and bone age (BA) less than 12 yr for girls or less than 13 yr for boys, height SDS less than -2.0 SDS or between -1.0 and -2.0 SDS plus a PAH less than -2.0 SDS were randomly allocated to receive GH plus GnRHa (n=17) or no treatment (n=15) for 3 yr. FAH was assessed at the age of 18 yr or older in girls or 19 yr or older in boys.FAH was no difference between treatment and control groups. Mean lumbar spine bone mineral density and bone mineral apparent density tended to be lower in treated boys. GH plus GnRHa can not be considered routine treatment for children with idiopathic short stature [15].

Among the common side effects of GH, scoliosis progression during GH therapy appears due to rapid growth rather than as a direct side effect of GH. Scoliosis is observed in ~ 0.2% of children with idiopathic short stature or idiopathic growth hormone deficiency treated with GH [16 -17]. In our study, there was a case of scoliosis with a growth rate of 10.9 cm/year. It was considered that the growth rate of scoliosis was related to its rapid growth. However, it was regrettable that the child had not received anteroposterior and lateral spine radiographs before treatment, so it was necessary to do anteroposterior and lateral spine radiographs before GH.

In addition to the common side effects of GH, many scholars have paid attention to the side effects of letrozole in short-stature boys, but there is some controversy. In a survey in 2015, in order to assess the effects of aromatase inhibitors in male children and adolescents with short stature, the author searched the Cochrane Library (2014, Issue 7), MEDLINE, EMBASE, and the World Health Organization ICTRP trial register from their inception until August 2014. Four RCTs involving 207 participants (84 on interventions) were in the review. Trials included males with constitutional delay of growth and puberty, idiopathic short stature, and GH deficiency. A significant proportion (45%) of prepubertal boys with idiopathic short stature treated with letrozole developed mild morphological abnormalities of their vertebrae, compared with none in the placebo group [18]. The incidence of vertebral deformation in children with idiopathic short stature increased after letrozole was used, but there was the similar incidence between letrozole group and control group, so it may be other reasons for the vertebral deformation [19]. Vertebral deformities do not occur in boys with delayed puberty treated with letrozole for one year [20]. No case with abnormal vertebral morphology was found in our study. Therefore, the effect of letrozole on skeletal system needs further study.

Conclusion

GH combined with letrozole can improve the final residual growth ability of pubertal short stature boys, improve their FAH, and serum testosterone were in normal range. And the safety of the effect of letrozole on vertebral deformation, and so on, need be studied further.

Abbreviations

THt:Target height; GH: Growth hormone; FAH: Final adult height;GnRHa:Gonadotropin-releasing hormone analogue; HPGA: Hypothalamic-pituitary-gonadal axis; PFAH: Predicted final adult height

Declarations

Studies involving animals must include a statement on ethics approval

Not applicable.

Authors' Contributions

Y.P.M. and Z.J.X. contributed to the study conception and design; data acquisition, analysis, and interpretation; and drafting and critical revision of the manuscript. R.F.J and B.Y.X. contributed to the data collection, partial data analysis and partial revision of the manuscript. B.T. contributed to the data collection. All authors provided final approval and agree to be accountable for all aspects of the work.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available

from the corresponding author on reasonable request.

Declarations

Ethical clearance was obtained from Affiliated Hospital of Jiangnan University. During data collection, written informed consent was obtained from each child family after briefly explaining the purpose, risk,and benefit of the study. All the procedure and purpose were told to the child, and verbal assent was also obtained from each child before any data collection and anthropometric measurements. Confidentiality of data was maintained by avoiding personal identifiers.

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

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Tables

Table 1. Clinical and laboratory data of 20 cases at the beginning of the study

No.	Age(y)	Height(cm)	Bone age(y)	height SDS for bone age	testis volume(ml)	testosterone(ng/ml)	estradiol (pg/ml)	Target height (cm)
1	13.2	148.1	13.9	-2.37	25.0	2.08	21.00	166.5
2	13.2	158.0	14.4	-1.42	25.0	3.22	25.00	166.5
3	11.0	148.5	13.4	-1.83	10.0	2.16	26.00	165.8
4	13.3	140.3	12.9	-2.42	6.0	0.77	39.00	168.5
5	10.8	144.7	12.3	-1.28	16.0	4.96	54.00	165.0
6	11.8	143.5	12.6	-1.66	8.0	0.58	6.00	167.5
7	11.8	143.7	12.4	-1.49	6.5	0.93	1.00	173.0
8	12.2	146.4	12.7	-1.36	8.0	3.51	69.00	169.0
9	11.7	154.0	12.8	-0.55	15.0	1.59	7.00	167.5
10	11.1	153.4	13.1	-0.87	18.0	0.48	17.28	168.0
11	11.2	143.8	12.4	-1.47	4.5	1.61	30.00	165.0
12	14.3	159.0	14.1	-1.01	20.0	5.33	25.0	166.0
13	12.5	148.5	13.2	-1.58	21.0	5.20	9.00	161.2
14	10.8	147.0	13.0	-1.62	10.5	1.91	13.0	176.4
15	14.1	158.1	15.1	-1.83	10.0	4.29	18.3	171.3
16	11.9	141.5	12.1	-1.51	8.0	0.62	3.0	169.7
17	12.6	153.8	13.4	-1.13	8.0	2.04	19.0	165.5
18	11.1	135.0	10.8	-1.45	4.0	0.19	9.0	167.5
19	10.5	140.1	12.3	-1.88	6.0	0.22	26.0	162.0
20	13.2	156.5	13.0	-0.39	18.0	1.64	17.0	171.5

SDS: Standard deviation score.

Table 2. Clinical and laboratory data of 20 cases at the end of the study

No.	Age(y)	Height(cm)	Bone age(y)	height SDS for bone age	testis volume(ml)	testosterone(ng/ml)	estradiol (pg/ml)	treatment course(y)	growth velocity(cm/y)
1	15.3	162.5	14.2	-0.59	25.0	6.74	1.00	2.1	6.9
2	15.3	171.5	15.7	0.06	25.0	3.54	0.00	2.1	6.4
3	11.9	159.2	14.5	-1.30	20.0	7.14	16.00	0.9	11.9
4	15.5	163.0	13.4	0.08	25.0	7.25	23.00	2.2	10.3
5	12.6	161.5	14.6	-1.01	15.0	6.87	10.00	1.8	9.3
6	15.0	167.5	16.2	-0.69	21.0	11.28	0.00	3.2	7.5
7	14.0	168.8	14.7	0.01	20.0	2.13	5.00	2.2	11.4
8	14.2	167.5	14.1	0.17	15.0	7.16	17.00	2.0	10.6
9	12.8	166.5	13.5	0.46	21.0	7.10	0.00	1.1	11.4
10	12.0	164.7	13.9	-0.10	18.0			0.9	12.6
11	13.2	165.4	12.9	0.84	25.0	10.19	14.00	2.0	10.8
12	15.6	167.0	15.4	-0.60	20.0	4.46	12.0	1.3	6.2
13	15.3	166.0	14.3	-0.20	25.0	3.22	12.0	2.8	6.3
14	12.3	165.2	14.0	-0.10	25.0	7.14	0.0	1.5	12.1
15	16.0	168.5	18.3	-0.69	15.0	10.39	36.0	1.9	5.5
16	14.5	166.9	14.0	0.14	25.0	7.60	8.0	2.6	9.8
17	14.0	169.0	14.9	-0.08	20.0	7.79	5.0	1.4	10.9
18	13.6	153.6	12.1	0.15	15.0	5.81	14.0	2.5	7.4
19	13.5	165.8	13.9	0.06	25.0	6.57	39.0	3.0	8.6
20	14.5	170.5	13.5	0.99	25.0	6.96	35.0	1.3	10.8

SDS: Standard deviation score.

Supplementary Files

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- MedicalethicscommitteenotificationYapingMa.pdf