Clinical Investigation

Combined Treatment with Gonadotropin-releasing Hormone Analog and Anabolic Steroid Hormone Increased Pubertal Height Gain and Adult Height in Boys with Early Puberty for Height

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Abstract. Twenty-one boys with a height of 135 cm or less at onset of puberty were treated with a combination of GnRH analog and anabolic steroid hormone, and their pubertal height gain and adult height were compared with those of untreated 29 boys who enter puberty below 135 cm. The mean age at the start of treatment with a GnRH analog, leuprorelin acetate depot (Leuplin®) was 12.3 yr, a mean of 1.3 yr after the onset of puberty, and GnRH analog was administered every 3 to 5 wk thereafter for a mean duration of 4.1 yr. The anabolic steroid hormone was started approximately 1 yr after initiation of treatment with the GnRH analog. The mean pubertal height gain from onset of puberty till adult height was significantly greater in the combination treatment group (33.9 cm) than in the untreated group (26.4 cm) (p<0.0001). The mean adult height was significantly greater in the combination treatment group (164.3 cm) than in the untreated group (156.9 cm) (p<0.0001). The percentage of subjects with an adult height of 160 cm or taller was 90.5% (19/21) in the combination treatment group, and it was 13.8% (4/29) in the untreated group (p<0.0001). Since growth of the penis and pubic hair is promoted by the anabolic steroid hormone, no psychosocial problems arose because of delayed puberty. No clinically significant adverse events appeared. Combined treatment with GnRH analog and anabolic steroid hormone significantly increased height gain during puberty and adult height in boys who entered puberty with a short stature, since the period until epiphyseal closure was extended due to deceleration of the bone age maturation by administration of the GnRH analog and the growth rate at this time was maintained by the anabolic steroid hormone.

Key words: gonadotropin-releasing hormone analog, anabolic steroid hormone, early puberty for height, adult height

Introduction

It has been reported that the height at onset of puberty has the closest relation with adult height among the clinical factors before puberty in patients with idiopathic short stature (ISS) (1–3) or growth-hormone deficient short stature (GHD). We followed the natural growth of 46

boys with a chief complaint of short stature until they reached their adult height and demonstrated that the height at onset of puberty strongly correlated with the adult height (r=0.782, p<0.0001) (3). When the height at onset of puberty exceeded 135 cm, the percentage of the patients with an adult height of 160 cm or more was 88% (15/17). The percentage of patients with a height at puberty of 135 cm or less and an adult height of 160 cm or more was 14% (4/29). The same tendency was also reported in patients with growth hormone deficiency (GHD). The correlation coefficient between height at onset of puberty and adult height was strongly positive in boys (r=0.60, p<0.01) and in girls (r=0.79, p<0.01) with GHD (4). Therefore, when children enter puberty with a short stature, their adult heights remain short in both short children without treatment and GHD even if they undergo growth hormone (GH) treatment. We designated this group of children as early puberty for height, which refers to relative precocious puberty with high possibility of a short adult height.

In children who enter puberty with a short statue, combined gonadotropin-releasing hormone (GnRH) analog and GH treatments have been used concomitantly to increase pubertal height gain. Although a sufficiently long-term combined treatment is reported to increase pubertal height gain and adult height in both GHD and ISS (5), its effect is still controvercial (6–12). Since GH is expensive in Japan and is not indicated for ISS, GH and GnRH analog cannot be used in combination for ISS at present because of mainly economical reasons. Administration of GnRH analog might cause psychosocial problems in patients due to arrested pubertal maturation.

The growth promoting effects of anabolic steroid hormones are well known. However, because of early induction of puberty when they are used in prepuberty, they can only be used for Turner syndrome with ovarian failure. Satoh and Yokoya (13) used a combined GnRH analog and anabolic steroid treatment in two boys who

entered puberty with a short stature and showed improvement in their adult heights. Since anabolic steroid hormone acts as a male sex hormone (androgen) and promotes maturation of the external genitalia other than the testes, it is unlikely to cause psychosocial problems due to late maturation of puberty caused by GnRH analog.

We treated boys who entered puberty at short stature with a combination of GnRH analog and anabolic steroid hormone and compared the effects on their pubertal height gain and adult height with those of untreated boys with early puberty for height.

Subjects and Methods

Based on the observation of the natural growth of children with early puberty for height described above (3), the combination treatment group consisted of 21 boys with a height of 135 cm or less at onset of puberty. Twenty-nine untreated boys with a height of 135 cm or less at onset of puberty served as a historical control group (3). Subjects in both groups had neither growth hormone deficiency nor other endocrine disorders. Boys in the combination treatment group had received no treatment before entry. Table 1 shows the clinical characteristics at birth and parents' heights of both groups. In the combination treatment group, the period of gestation was significantly shorter, and the fathers were significantly taller than those of the untreated group. The target height was also significantly greater in the combination treatment group, reflecting the height of the fathers.

Treatment was started in the combination treatment group after consent was obtained. In the combination treatment group, the mean age at the start of treatment with GnRH analog, leuprorelin acetate depot (Leuplin®) was 12.3 yr, a mean of 1.3 yr after the onset of puberty, and it was administered every 3 to 5 wk thereafter. The mean initial dose was 62 µg/kg (Table 2).

Table 1 Clinical factors at birth and parents' heights

	No TX	Combined TX	M-U test
Gestational age (wk)	39.1 ± 2.2	37.0 ± 3.6	p<0.05
Birth length (cm)	48.5 ± 2.7	45.1 ± 5.7	NS
Birth weight (g)	2,956 ± 472	2,449 ± 838	NS
Father's height (cm)	162.2 ± 5.0	166.9 ± 5.6	p<0.05
Mother's height (cm)	151.3 ± 4.6	153.6 ± 3.3	NS
Target height (cm)	163.3 ± 3.3	166.6 ± 3.5	p<0.01

Every 3 mo, bone age, gonadotropins and testosterone were measured. When the LH concentration exceeded 0.5 mIU/ml, the dose of GnRH analog was increased. The mean age at the cessation of GnRH analog treatment was 16.4 yr, the mean treatment period was 4.1 yr and the mean dose at the cessation of treatment was 60.8 μg/kg. Progression of the bone age during GnRH analog treatment was limited to a mean of 0.6 yr/year.

The anabolic steroid hormone was started approximately 1 yr after initiation of treatment with the GnRH analog. The anabolic steroid used was stanozolol (Winstrol®) 2 mg in 18 patients and metenolone acetate (Primobolan®) 5 mg in 3 patients. As the growth rate decreased, the doses were increased. The age at the cessation of anabolic steroid hormone was a mean of 16.7 yr, and the mean treatment period was 3.4 yr (Table 2). The dose of the anabolic steroid at the cessation was 2 mg in 4 patients and 4 mg in 6 patients for stanozolol and 10 mg in 3 patients, 15 mg in 7 patients and 20 mg in 1 patient for metenolone acetate.

The adult height age was defined as the age when the annual growth rate was 1 cm or less, and the height at that time was defined as the adult height.

The Mann-Whitney test was used for the comparison between the combination treatment group and the untreated group. Growth during puberty was compared using ANOVA in which the age of puberty was adjusted. The difference between adult height and the target height was tested by the sign test. Comparison of percentages

Table 2 Clinical characteristics of treatment group

	Combined treatment
At start of GnRHa	
Age (yr)	12.3 ± 1.1
Height (cm)	140.4 ± 6.3
Bone age (yr)	12.6 ± 1.2
Dose of GnRHa (μg/kg)	62.6 ± 10.1
At start of AH	
Age (yr)	13.3 ± 1.4
Height (cm)	145.5 ± 6.0
At cessation of GnRHa	
Age (yr)	16.4 ± 1.2
Height (cm)	159.7 ± 2.9
Bone age (yr)	14.9 ± 0.5
Dose of GnRHa (μg/kg)	60.8 ± 32.9
GnRHa treatment years (yr)	4.1 ± 1.1
At cessation of AH	
Age (yr)	16.7 ± 1.3
Height (cm)	161.1 ± 3.0
AH treatment years (yr)	3.4 ± 0.9
ΔBA/ΔCA during GnRHa	0.6 ± 0.2

GnRHa: GnRH analog. AH: anabolic steroid hormone. ΔBA/ΔCA: Δbone age/Δchronological age.

was tested by the χ^2 test.

Results

Table 3 shows a comparison of the clinical factors at onset of puberty and at the adult height in the untreated and combination treatment groups. The heights at onset of puberty showed no differences between the two groups, but the

Table 3 Clinical characteristics at onset of puberty and at adult height

	No Treatment	Combined treatment	Significance
Age at onset of puberty			
Age (yr)	12.1 ± 0.8	11.0 ± 0.9	p<0.001
Height (cm)	130.5 ± 3.2	130.4 ± 3.7	NS
Height SDS (SD)	−2.46 ± 0.60	−1.68 ± 0.44	p<0.0001
Age at adult height (cm)			
Age (yr)	17.9 ± 1.0	18.8 ± 1.8	NS
Adult height (cm)	156.9 ± 2.7	164.3 ± 3.6	p<0.0001
Adult height SDS (SD)	−2.41 ± 0.49	−1.09 ± 0.64	p<0.0001
Pubertal height gain (cm)	26.4 ± 2.9	33.9 ± 4.8	p<0.0001
Change in height SDS from onset			
of puberty till adult height (SD)	0.05 ± 0.59	0.59 ± 0.83	p<0.05
Period from onset of puberty till adult height (yr)	5.8 ± 1.0	7.9 ± 1.4	p<0.0001
Target height-Adult height (cm)	6.3 ± 3.2	2.3 ± 4.5	p<0.005

age at onset of puberty was significantly younger in the combination treatment group. However, the adult height age was older in the combination treatment group, although the difference was not significant. The mean duration from onset of puberty till adult height was significantly longer in the combination treatment group (7.9 yr) than in the untreated group (5.8 yr). Figure 1 shows the relation between the height at onset of puberty and the adult height in the untreated group and the combination treatment group. The mean adult height was significantly taller in the combination treatment group (164.3 cm) than in the untreated group (156.9 cm, p<0.0001; Table 3).

The percentage of subjects with an adult height of 160 cm or taller was 90.5% (19/21) in the combination treatment group and it was 13.8% (4/29) in the untreated group. The percentage was significantly higher in the combination treatment group (p<0.0001).

Figure 2 shows the relation between age at onset of puberty and adult height in the untreated group and combination treatment group. The mean pubertal height gain from onset of puberty till adult height was significantly greater in the combination treatment group (33.9 cm) than in

the untreated group (26.4 cm, p<0.0001: Table 3). The combination treatment group showed earlier onset of puberty, and in ANOVA in which the age of puberty was adjusted, there was still a significant difference (p<0.001).

The height difference between the target height and the adult height was significantly less in the combination treatment group than in the untreated group (Table 3). The adult height in the combination treatment group showed no significant difference from the target height, while that in the untreated group was significantly shorter than the target height (p<0.001).

During combined treatment, the size of the penis and appearance of pubic hair progressed due to administration of the anabolic steroid hormone. The testes gradually increased in size but did not maturate until they reached adult size during treatment. Adverse events of the anabolic steroid hormone included complaints of early onset of secondary sex characteristics such as a change in voice and growth of pubic hair in four boys and increased ALT and AST in one obese boy.
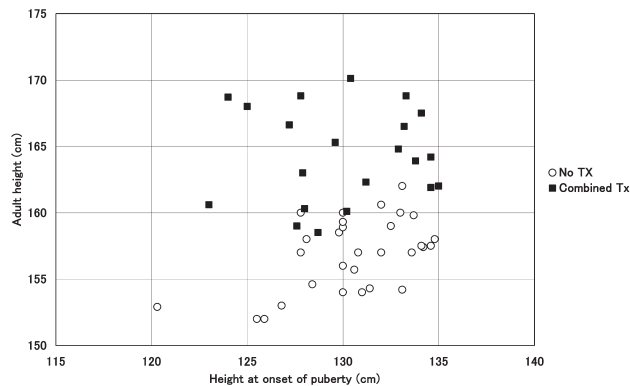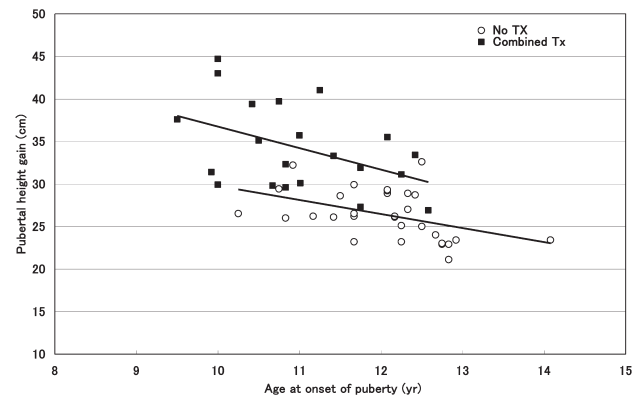
Fig. 1 Relation between height at onset of puberty and adult height in the untreated group and the combination treatment group.
Figure 1 shows the relation between the height at onset of puberty and the adult height in the untreated group and the combination treatment group. The mean adult height was significantly taller in the combination treatment group (164.3 cm) than in the untreated group (156.9 cm, p<0.0001; Table 3).

Fig. 2 Relation of age at onset of puberty and adult height in the untreated group and combination treatment group.
Figure 2 shows the relation between age at onset of puberty and adult height in the untreated group and combination treatment group. The mean pubertal height gain from onset of puberty till adult height was significantly greater in the combination treatment group (33.9 cm) than in the untreated group (26.4 cm, p<0.0001; Table 3). The combination treatment group showed earlier onset of puberty, and in ANOVA in which the age of puberty was adjusted, there was still a significant difference (p<0.001).

Discussion

In Japan, the minimal desired adult height is 160 cm for boys, which is equivalent to a adult height SD score of −1.86 SD. Scientifically, the normal height is above −2SD (159.2 cm), but in clinical practice, whether or not the height exceeds 160 cm has a major impact on the psychosocial QOL (quality of life) of the patient and parents. Therefore, the critical adult height in this study was taken as 160 cm.

We have already demonstrated increased pubertal height gain and improvement of adult height by combination treatment of a GnRH analog and GH in GHD children (12). Since use of an untreated control group of children with a short stature at onset of puberty who want a greater adult height presents an ethical problem, we used a historical control as the control group. Because the secular trend was already completed 20 yr ago in Japan, the current mean adult height does not differ from that in the historical control.

As was clear from the historical control group, a strong positive correlation is present between the height at onset of puberty and adult height. Therefore, there is a very high possibility that the adult height might also remain short when a child enters puberty with a short stature. In particular, when boys enter puberty with a height of 135 cm or less, about 90% will have an adult height of less than 160 cm.

The therapeutic dose for GHD in Japan is 0.175 mg/kg/wk, and we have reported that even when children with idiopathic short stature were treated with this dose of GH, the mean pubertal height gain in the GH-treated group (24.8 cm) was not significantly different from that in the untreated group (26.8 cm) (14). Zucchini et al. (15) retested GHD subjects, who had been diagnosed before puberty and were treated with

GH, after entering puberty and showed that the withdrawal of GH therapy from subjects who showed a normal GH response to a provocative test was not associated with a catch-down growth. There was no significant difference in the adult height between subjects who continued GH treatment and those who withdrew from treatment. These facts suggested that pubertal height gain was mainly regulated by sex steroid hormone rather than additional GH.

Since height at onset of puberty and adult height show a strong positive correlation in GHD, it is important to increase the height by onset of puberty through early diagnosis and GH treatment so that a satisfactory adult height can be achieved. Whether or not increasing the dose of GH in patients with GHD who enter puberty with a short stature can increase pubertal height gain is under investigation. Stanhope et al. (16) randomly assigned 32 GHD patients who had reached puberty to a group treated with 15 IU/kg/m^2 of GH and a group treated with double the dose, 30 IU/kg/m^2, and treated them until they reached adult height. The rate of growth during puberty did not differ in the two groups, and there was also no difference in adult height between the two groups. Albertsson-Wikland et al. (17) divided boys with GHD into a group treated with 0.1 IU/kg/d of GH and a group treated with a double dose of 0.2 IU/kg/d after entering puberty and reported that the SD improvement rate in puberty was 0.7 SD in both groups, showing no difference between the groups.

Only one report showed that growth in puberty increased in children treated with higher doses of GH during puberty. Mauras et al. (18) administered a very high dose of 0.7 mg/kg/wk to GHD patients and found that the mean adult height was 4.6 cm greater than in the group given 0.3 mg/kg/wk, but this cannot serve as a reference because the dose was four times higher than that used for GHD in Japan, and such a high dose cannot be used.

Combined GH and GnRH analog treatment is another method for increasing pubertal height gain in children who enter puberty with a short stature. Gonadal suppression therapy using a GnRH analog is a method for improving adult height by prolonging the period of growth by delaying advancement of bone age and epiphyseal fusion by inhibition of gonadotropin and sex hormones. Advancement of bone age and epiphyseal maturation during puberty is sex hormone dependent, especially estrogen dependent, in both men and women. This has been proven by the observations that the bone age maturation decelerates in Turner syndrome with ovarian failure (19) and that the bone age was arrested without epiphyseal fusion in a man with estrogen receptor abnormality (20) and in men with aromatase deficiency (21) even when the men were over 20 yr of age and their heights exceeded 200 cm.

Although it has been reported that adult height is improved with only GnRH analog treatment in children of short stature (22), it is theoretically difficult to improve adult height with the GnRH analog alone. The reason for this is that GnRH analog decelerates bone age maturation and elongates the period of pubertal growth, but the sex hormone-dependent growth velocity during puberty is also reduced. Therefore, it is necessary to administer growth-promoting agents such as GH (20) to improve adult height in combination with a GnRH analog. Combination treatment with GH and a GnRH analog is performed not only in patients with GHD (6–12) but also in those with ISS (23–27). Although the results are under discussion, adequate effects can be expected when long-term combination treatment is performed for 3 yr or longer (5).

The subjects of this study (combination treatment group) entered puberty earlier than healthy Japanese boys with a mean age at onset of puberty of 11.5 yr (28), despite the fact that children with short stature tend to show delayed puberty onset (1). Thus, the subjects tended to show relatively early onset of puberty, while their

heights at onset of puberty were short. Therefore, the subjects were considered to have shorter adult heights, since the height at onset of puberty has a close relation with adult height. When a GnRH analog and anabolic steroid hormone were administered for long periods with means of 4.1 yr and 3.4 yr, respectively, to these patients, height gain during puberty increased, and adult height reached 160 cm or greater in approximately 90% of the patients. Nine patients grew to heights of 165 cm or greater. The results demonstrated that combination treatment increased pubertal height gain through the deceleration of bone age maturation by the GnRH analog and maintenance of growth velocity by the anabolic steroid hormone.

There is a significant negative correlation between age at onset of puberty and pubertal height gain (29). Since the age of onset of puberty was younger in the combination group than in the control group, the combination treatment group was expected to show greater pubertal height gain. However, the pubertal height gain was much greater than expected even after the age at onset of puberty was adjusted. Adult height showed no significant difference from the target height in the combination treatment group, while it was significantly shorter than the target height in the untreated group.

Anabolic steroid hormones are testosterone derivatives, and some of them are converted into estrogens by aromatization due to the action of aromatase. However, stanozolol and metenolone acetate, which were used in this study, are not aromatase substrates and therefore do not promote advancement of bone age. Oxandrolon, which also is not affected by aromatase, has been reported to show effects in Turner syndrome when used concomitantly with GH (30). Such anabolic steroids have an inhibitory effect on gonadotropin secretion from the pituitary gland via feedback to the central nervous system, which means that they also inhibit secretion of testosterone and can be expected to result in slower advancement of bone age (31).

Treatment with a combination of GH and GnRH analog improves adult height when administered over a long period, but there are also concerns about reduction of psychosocial QOL due to interrupted maturation of secondary sex characteristics and retardation of bone mineral density increase due to inhibition of sex hormones. However, since anabolic steroids act as male hormones and elevate bone mineral density, secondary sex characteristics are not retarded by treatment with a combination of GH and GnRH analog, and maturation of secondary sex characteristics such as development of the penis and pubic hair and voice change have been confirmed. Therefore, no psychosocial problems due to delayed puberty in children have been observed. Also anabolic steroid hormones increase bone mineral density. The bone mineral density could not be measured because DEXA was not available in our facility at initiation of treatment. However, after the introduction of DEXA, the bone mineral density measurements in most patients in the combination treatment group showed values within the normal range. There have been sporadic cases of adverse events such as early voice change and increased acne.

It is possible to increase pubertal height gain in girls who enter puberty with a short stature using the combination of a GnRH analog and anabolic steroid hormones. However, because of the side effect of voice change and increased hair in some girls caused by anabolic steroid hormone even at a low dose and the difficulty in maintaining growth rate during a combination treatment in some girls, the effect on adult height is not as satisfactory as demonstrated in boys. When the height at onset of puberty was below 132.5 cm, the percentage of the girls with an adult height of 150 cm or more was 17.2% (3). The percentage of girls with an adult height of 150 cm or more was 43.2% in girls who entered puberty with a height of less than 132.5 cm and received the combination treatment for a mean period of 3.6 yr (unpublished data). Therefore, the combination treatment is not recommended

in girls except for those who desire strongly to be taller even though their voices may change.

In conclusion, when boys who enter puberty with height of 135 cm or less were administered GnRH analog and an anabolic steroid for long periods, an adult height of at least 160 cm was achieved in 90.5% of all subjects. Height gain during puberty was significantly greater, since the period until epiphyseal closure was extended due to deceleration of the bone age maturation by administration of the GnRH analog and the growth velocity at this time was maintained by the anabolic steroid hormone. Since growth of the penis and pubic hair is promoted by the anabolic steroid hormone, no psychosocial problems due to delayed puberty occurred. No clinically significant adverse events appeared.

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