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ORIGINAL ARTICLE

Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty

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Summary

Objective We investigated whether inhibition of oestrogen biosynthesis with the aromatase inhibitor, letrozole, during adolescence improves near-final height in boys with constitutional delay of puberty.

Patients and methods Seventeen boys with constitutional delay of puberty were randomized to receive testosterone (T) enanthate (1 mg/kg i.m.) every 4 weeks for 6 months in combination with placebo (Pl, $n = 8$), or the aromatase inhibitor letrozole (Lz, 2·5 mg/day orally) ($n = 9$), for 12 months. After treatment, patients were followed up until near-final height. Height discrepancy was calculated as near-final height minus mid-parental target height.

Measurements The primary end point was the difference in near-final height between the groups treated either with T + Pl or T + Lz. Secondarily, height discrepancy and gain in height standard deviation score (SDS) were analysed in both groups.

Results Boys treated with T + Lz reached a higher mean near-final height than did boys on T + Pl (175·8 *vs.* 169·1 cm, respectively, $P = 0{\cdot}04$). In T + Lz-treated boys, mean near-final height did not differ from their mid-parental target height (175·8 *vs.* 177·1 cm, $P = 0{\cdot}38$), whereas in T + Pl-treated boys, mean near-final height was lower than mid-parental target height (169·1 *vs.* 173·9 cm, $P = 0{\cdot}007$). T + Lz-treated boys had a greater increment in height SDS over the pretreatment height SDS than T + Pl-treated boys (+1·4 SDS *vs.* +0·8 SDS, $P = 0{\cdot}03$).

Conclusions Our findings indicate that in adolescent boys an increase in adult height can be attained by use of aromatase inhibitors.

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Introduction

Oestrogens are essential in bone maturation, growth plate fusion, and cessation of longitudinal growth in both sexes.[1] This relatively recent finding has led to attempts to develop a new treatment modality to improve final height in some growth disorders, by use of aromatase inhibitors.[2–5] By blocking oestrogen biosynthesis, these compounds delay bone maturation and improve predicted adult height (PAH) in boys.[2,6,7] Thus far, no data have been reported on effects of aromatase inhibitor treatment on final adult height, leaving the efficacy of aromatase inhibition in increasing final adult height unclear.

We reported in 2001 that a 1-year treatment with the aromatase inhibitor letrozole (Lz), in combination with low-dose testosterone (T), effectively delayed bone maturation in boys with constitutional delay of puberty, with minor effects on growth velocity.[6] Consequently, PAH increased by 5·1 cm. Here we report the near-final height data of this prospective, randomized, placebo-controlled study.

Methods

Inclusion criteria and baseline characteristics of the 23 boys with constitutional delay of puberty randomly assigned to receive either Lz or placebo (Pl) have been reported in detail.[6] In short, diagnosis of constitutional delay of puberty was defined as a Tanner genital (G) or pubic hair (P) stage observed at an older age than the mean +2 SD for healthy Finnish boys, or a testis volume of less than 4 ml after 13·5 years of age. However, as indicated by the increased mean concentrations of testosterone in the treatment groups at baseline,[6] some of the boys were already at early or mid puberty at the start of the study. Of the 23 boys recruited, 19 (9 on T + Lz, 10 on T + Pl) completed the initial 18-month follow-up. Of these 19 boys, 17 (9 on T + Lz, 8 on T + Pl) completed the follow-up until near-final height, and constitute the population of the current study. In this population, 7 out of 9 and 7 out of 8 boys in the T + Lz and T + Pl groups, respectively, had a family history of delayed puberty. The two boys lost to follow-up received T + Pl. At 18 months after the start of the study, the mean PAH of those T + Pl-treated boys who completed the initial 18-month follow-up ($n = 10$) was comparable to the respective mean of those T + Pl-treated boys who completed the follow-up until near-final height ($n = 8$) (175·2 *vs.* 173·3 cm, respectively).

The participants received one of the two treatments: T at a dose of 1 mg/kg i.m. every 4 weeks for 6 months in combination with placebo (Pl) for 12 months ($n = 8$); or T (as above) in combination with Lz

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Table 1. Baseline characteristics of the boys with constitutional delay of puberty treated with testosterone (T) and placebo (Pl), or T and letrozole (Lz), during adolescence. Values are means (SD), except for Tanner genital (G) and pubic hair (P) stages of puberty, which are medians (range). BA, bone age. Bone age delay was calculated as calendar age minus bone age

	T + Pl-treated boys ($n = 8$)	T + Lz-treated boys ($n = 9$)
Age (years)	14·8 (0·9)	15·2 (0·8)
Bone age delay (years)	2·3 (0·8)	2·2 (0·3)
Stage of puberty		
G	2 (2–3)	2 (2)
P	1 (1–2)	1 (1–2)
Height (SDS)	−2·0 (0·7)	−1·8 (0·7)
Predicted adult height (cm)	173·7 (6·5)	177·1 (5·4)
Mid-parental target height (cm)	173·9 (4·0)	177·1 (4·1)

Table 2. Concentrations of serum FSH, LH, testosterone, and oestradiol during the initial follow-up of 18 months in groups treated with testosterone and placebo (T + Pl) or testosterone and letrozole (T + Lz). Values are arithmetic means (SD) or geometric means. *P*-value refers to difference between treatment groups. *($P < 0·05$), †($P < 0·01$), and ‡($P < 0·001$) refer to within-group changes from the baseline value

	T + Pl-treated boys ($n = 8$)	T + Lz-treated boys ($n = 9$)	*P*
S-FSH (IU/l)			
0 months	2·7 (1·3)	3·5 (2·3)	0·77
5 months	0·8 (1·3)†	9·3 (8·7)*	0·01
12 months	3·9 (1·8)	7·4 (4·0)†	0·04
18 months	4·4 (2·0)*	4·3 (2·6)	0·94
S-LH (IU/l)			
0 months	1·9 (1·0)	2·5 (1·2)	0·59
5 months	0·7 (1·1)*	7·8 (4·9)†	0·002
12 months	2·3 (1·0)	7·2 (4·5)†	0·009
18 months	3·4 (1·4)*	3·5 (1·4)	0·80
S-testosterone (nmol/l)			
0 months	11·7 (9·3)	8·3 (11·1)	0·50
5 months	18·8 (10·3)	64·6 (43·8)†	0·01
12 months	21·6 (11·7)‡	57·8 (8·7)‡	< 0·0001
18 months	17·8 (7·9)‡	17·7 (5·7)	0·99
S-oestradiol (pmol/l)			
0 months	17·6 (10·6)	11·3 (8·9)	0·20
5 months	30·6	9·1	0·002
12 months	50·2 (27·4)‡	8·1 (2·1)	0·003
18 months	41·1 (26·3)‡	37·8 (14·4)‡	0·75

at a dose of 2·5 mg/d orally for 12 months ($n = 9$). No significant differences in baseline characteristics were found between the two groups (Table 1). No boy had had a pubertal increase in growth velocity before start of treatment.

The treatment-induced changes in serum concentrations of FSH, LH, T, and oestradiol among the boys who completed the initial follow-up of 18 months have been reported in detail previously.[6] The changes in hormonal measures were similar among those who completed the follow-up until near-final height (Table 2). Lz effectively inhibited oestrogen synthesis, as indicated by the low oestradiol and high gonadotrophin and T concentrations in the T + Lz group during the treatment. At baseline, and 6 months after the cessation of treatments (at 18 months), the concentrations of gonadotrophins, T, or oestradiol did not differ between the groups. As reported earlier,[6] boys treated with T + Pl grew slightly faster than boys on T + Lz during the first 5 months of treatment (9·9 *vs.* 7·1 cm/year, $P = 0·03$). Thereafter, no differences in growth velocities existed between the treatment groups. Bone age progression, determined by the method described by Bailey and Pinneau,[8] was slower in the T + Lz-treated.[6] Consequently, after the initial follow-up period of 18 months, PAH had increased by 5·1 cm in those who received T + Lz, with no change in PAH in those on T + Pl.[6]

The boys were considered to be at near-final height if bone age was greater than or equal to 15·75 years. According to the tables of Bailey and Pinneau, at this bone age boys with the average tempo of pubertal maturation have achieved 97·9% of their final adult height. For statistical analyses, Student's *t*-test was used as appropriate. Statistical analyses concerning near-final heights were conducted after logarithmic transformation of the data; means of near-final heights refer to geometric means. The Pearson correlation coefficient was used for analysing the correlation between post-treatment PAH and near-final height. Height discrepancy was calculated as near-final height minus mid-parental target height.

Before the initiation of treatment, written informed consent was obtained from the boys and their guardians. The protocol was approved by the ethics committee of the Hospital for Children and Adolescents and by the National Agency for Medicines.

Results

At near-final height, mean ages of the T + Pl- and T + Lz-treated boys were 18·2 (range 17·1–19·1) and 19·2 (17·7–20·2) years, respectively, and mean bone ages were 16·7 (15·75–18·0) and 16·9 (15·75–17·5) years, respectively. Thus, at near final height, bone ages were still delayed in both groups, but the mean difference between chronological age and bone age was greater in the T + Lz-treated boys (2·2 *vs.* 1·5 years, $P = 0·04$). The T + Pl-treated boys reached a mean near-final height of 169·1 cm, while the respective mean of the T + Lz-treated boys was 175·8 cm ($P = 0·04$). The near-final height of the T + Pl-treated boys was lower than their mid-parental target height (169·1 *vs.* 173·9 cm, respectively, $P = 0·007$), whereas in the T + Lz-treated boys, near-final height did not differ from their mid-parental target height (175·8 *vs.* 177·1 cm, respectively; $P = 0·38$; Fig. 1a). A borderline difference in height discrepancy was found between the T + Pl and T + Lz groups (−4·8 *vs.* −1·2 cm, respectively, $P = 0·06$). Near-final height standard deviation score (SDS) was higher than pretreatment height SDS in all patients (Fig. 1b). However, at near-final height, the gain in height SDS over the pretreatment height SDS was greater in T + Lz-treated boys than in T + Pl-treated boys (+1·4 *vs.* +0·8 SDS, $P = 0·03$; Fig. 1b).

As previously reported,[6] an increase in PAH occurred at 18 months after start of treatment (post-treatment PAH) in T + Lz-treated boys. This treatment effect was well preserved until near-adult height: post-treatment PAH correlated strongly with near-final height (Fig. 2; $r = 0·91$, $P < 0·0001$). The Bailey-Pinneau prediction

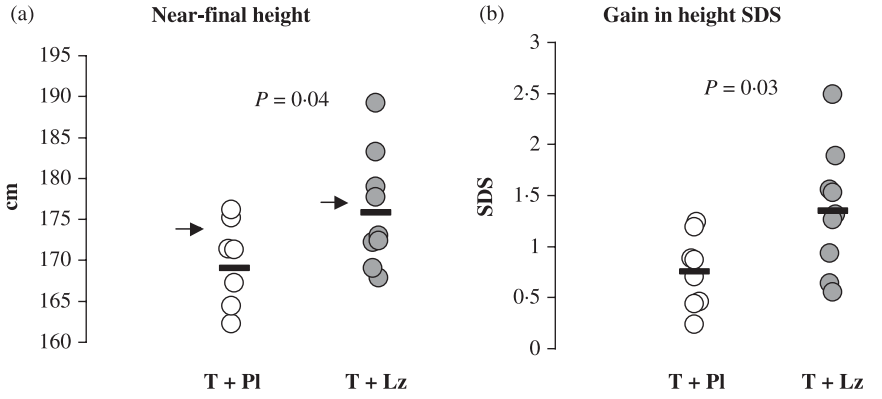

Fig. 1 Near-final height (a) and gain in height standard deviation score (SDS) (b) in boys with constitutional delay of puberty treated during adolescence either with a combination of testosterone and letrozole (T + Lz), or testosterone and placebo (T + Pl). Gain in height SDS was calculated as height SDS at near-final height minus pretreatment height SDS. Black arrow, mean mid-parental target height; black bar, mean.

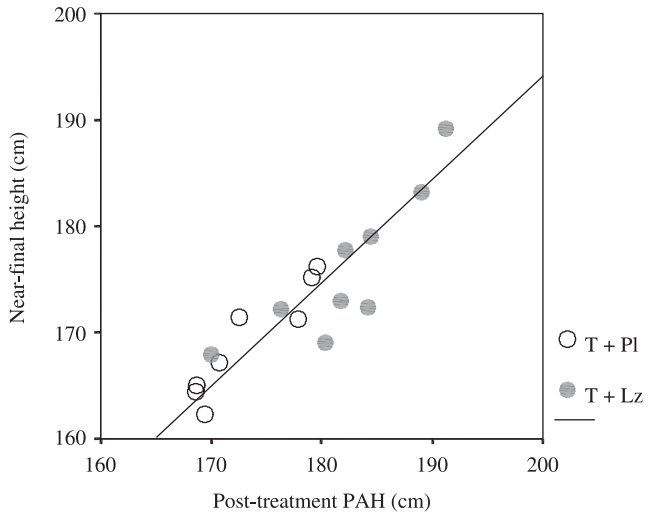

Fig. 2 Correlation between predicted adult height (PAH) at 18 months after start of treatment and near-final height in boys with constitutional delay of puberty treated during adolescence either with combination testosterone and letrozole (T + Lz), or testosterone and placebo (T + Pl).

method seemed to overestimate slightly final adult height, since PAHs were greater than near-final heights in both groups.

Discussion

At near-final height, the T + Lz-treated boys were taller than the T + Pl-treated boys, and reached a near-final height comparable to their mid-parental target height, whereas those treated with T + Pl did not. Moreover, boys treated with T + Lz had significantly greater increase in height SDS over the pretreatment level. These findings support our hypothesis that an increase in final adult height can be attained by inhibiting oestrogen action with an aromatase inhibitor in boys with constitutional delay of puberty, who often do not fully exploit their genetic growth potential.[9–12] Remarkably, the delay in bone maturation achieved during treatment with Lz was not overshadowed by faster progression of bone maturation after cessation of treatment, as indicated by the more delayed bone age at near-final height in those who received T + Lz. This supports the concept that, in adolescent boys, treatment with a potent aromatase inhibitor preserves growth potential and leads to greater final adult height by prolonging the period of growth.

Comparison of mean gains in height SDS over the pretreatment level between the T + Lz and T + Pl groups suggests that 1-year treatment with Lz produced a mean increment of 0·6 SDS in near-final height. As for comparison to other treatment modalities aiming at increasing final adult height, this effect of 0·6 SDS increase is similar to what has been achieved with long-term GH or GnRH-agonist treatments in children with short stature. GH treatment in peripubertal children with idiopathic short stature (ISS) for 4·4 years resulted in 0·5 SDS greater final adult height than treatment with placebo.[13] Similarly, suppression of gonadotrophin secretion with a GnRH-agonist, for a mean duration of 3·5 years, in short adolescents with normally timed puberty resulted in prolonged duration of linear growth, but only 0·6 SDS increase in final adult height.[14] Thus, in comparison with GH and GnRH-agonist treatments, Lz appears to possess at least comparable efficacy in increasing final adult height. Lz treatment appears to be equally effective in conditions other than constitutional delay of puberty; in our recently published randomized controlled trial, we observed a 0·9 SDS (5·9 cm) increase in PAH after 2-year treatment with Lz in boys with ISS.[7]

Of importance in clinical practice, aromatase inhibitors lack several unfavourable features of GnRH-agonist treatment. While aromatase inhibitor treatment inhibits the pubertal increases in oestradiol and IGF-I concentrations, pubertal growth velocity is not obviously affected by the treatment.[6,7] This suggests that androgens, at least in high concentrations, have direct growth-promoting effects in the growth plate. In support of this concept, androgen receptors have been localized in human growth plate chondrocytes,[15] and treatment with a nonaromatizable androgen, dihydrotestosterone, has been shown to stimulate ulnar growth in boys.[16] In addition, as evaluated by dual-energy X-ray absorptiometry (DEXA), bone mass accrual is not impaired in pre-, early- or mid-pubertal boys during aromatase inhibitor treatment.[7] Further, of importance to adolescent boys, the treatment does not adversely affect body composition,[7,17] or suppress the development of physical signs of puberty.[6,7]

Modern potent aromatase inhibitors provide a promising tool to improve final adult height in various disorders that affect growth. However, the number of patients recruited to the current study was limited by the experimental nature of the treatment, and therefore larger studies are needed to confirm the efficacy of aromatase inhibition in increasing final adult height. Since aromatase inhibition

stimulates gonadal androgen secretion in pubertal boys, careful follow-up of progression of puberty and of high-density lipoprotein cholesterol level are indicated in adolescent males receiving aromatase inhibitor treatment.[18,19] Moreover, the effects of long-term aromatase inhibitor treatment on maturing spermatogenesis, bone health, carbohydrate and lipid metabolism, and cognitive function remain inadequately characterized. Therefore, before the safety of aromatase inhibitors in children and adolescents is established in larger long-term follow-up studies, we recommend using these compounds in growth indications only in research setting.

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References

1 Cutler, G.B. Jr (1997) The role of estrogen in bone growth and maturation during childhood and adolescence. *Journal of Steroid Biochemistry and Molecular Biology*, **61**, 141–144.

2 Leschek, E.W., Jones, J., Barnes, K.M., Hill, S.C. & Cutler, G.B. Jr (1999) Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *Journal of Clinical Endocrinology and Metabolism*, **84**, 175–178.

3 Feuillan, P.P., Jones, J. & Cutler, G.B. Jr (1993) Long-term testolactone therapy for precocious puberty in girls with the McCune–Albright syndrome. *Journal of Clinical Endocrinology and Metabolism*, **77**, 647–651.

4 Merke, D.P., Keil, M.F., Jones, J.V., Fields, J., Hill, S. & Cutler, G.B. Jr (2000) Flutamide, testolactone, and reduced hydrocortisone dose maintain normal growth velocity and bone maturation despite elevated androgen levels in children with congenital adrenal hyperplasia. *Journal of Clinical Endocrinology and Metabolism*, **85**, 1114–1120.

5 Mauras, N., Welch, S., Rini, A. & Klein, K.O. (2004) An open label 12-month pilot trial on the effects of the aromatase inhibitor anastrozole in growth hormone (GH) -treated GH-deficient adolescent boys. *Journal of Pediatric Endocrinology and Metabolism*, **17**, 1597–1606.

6 Wickman, S., Sipila, I., Ankarberg-Lindgren, C., Norjavaara, E. & Dunkel, L. (2001) A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial. *Lancet*, **357**, 1743–1748.

7 Hero, M., Norjavaara, E. & Dunkel, L. (2005) Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism*, **90**, 6396–6402.

8 Bayley, N. & Pinneau, S.R. (1952) Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. *Journal of Pediatrics*, **40**, 423–441.

9 Crowne, E.C., Shalet, S.M., Wallace, W.H., Eminson, D.M. & Price, D.A. (1990) Final height in boys with untreated constitutional delay in growth and puberty. *Archives of Disease in Childhood*, **65**, 1109–1112.

10 Albanese, A. & Stanhope, R. (1995) Predictive factors in the determination of final height in boys with constitutional delay of growth and puberty. *Journal of Pediatrics*, **126**, 545–550.

11 Albanese, A. & Stanhope, R. (1993) Does constitutional delayed puberty cause segmental disproportion and short stature? *European Journal of Pediatrics*, **152**, 193–196.

12 LaFranchi, S., Hanna, C.E. & Mandel, S.H. (1991) Constitutional delay of growth: expected versus final adult height. *Pediatrics*, **87**, 82–87.

13 Leschek, E.W., Rose, S.R., Yanovski, J.A., Troendle, J.F., Quigley, C.A., Chipman, J.J., Crowe, B.J., Ross, J.L., Cassorla, F.G., Blum, W.F., Cutler, G.B. Jr & Baron, J. (2004) Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3140–3148.

14 Yanovski, J.A., Rose, S.R., Municchi, G., Pescovitz, O.H., Hill, S.C., Cassorla, F.G. & Cutler, G.B. Jr (2003) Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *New England Journal of Medicine*, **348**, 908–917.

15 Abu, E.O., Horner, A., Kusec, V., Triffitt, J.T. & Compston, J.E. (1997) The localization of androgen receptors in human bone. *Journal of Clinical Endocrinology and Metabolism*, **82**, 3493–3497.

16 Cassorla, F.G., Skerda, M.C., Valk, I.M., Hung, W., Cutler, G.B. Jr & Loriaux, D.L. (1984) The effects of sex steroids on ulnar growth during adolescence. *Journal of Clinical Endocrinology and Metabolism*, **58**, 717–720.

17 Mauras, N., O'Brien, K.O., Klein, K.O. & Hayes, V. (2000) Estrogen suppression in males: metabolic effects. *Journal of Clinical Endocrinology and Metabolism*, **85**, 2370–2377.

18 Raivio, T., Dunkel, L., Wickman, S. & Janne, O.A. (2004) Serum androgen bioactivity in adolescence: a longitudinal study of boys with constitutional delay of puberty. *Journal of Clinical Endocrinology and Metabolism*, **89**, 1188–1192.

19 Wickman, S., Saukkonen, T. & Dunkel, L. (2002) The role of sex steroids in the regulation of insulin sensitivity and serum lipid concentrations during male puberty: a prospective study with a P450-aromatase inhibitor. *European Journal of Endocrinology*, **146**, 339–346.