

Perspectives on growth promoting treatment for patients with Turner syndrome in Japan

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Abstract. In Japan, anabolic steroid hormone (ASH) treatment for Turner syndrome (TS) to promote growth had been provided before GH therapy for TS was approved. ASH effectively improved the adult height (AH) of TS patients without spontaneous puberty but decreased the AH of TS patients with spontaneous puberty. Although GH therapy for TS was approved in 1991, the approved dosage remained 0.5 IU/kg/wk for GH-deficient TS patients and improved AH by approximately 7 cm. However, AH did not reach -2 standard deviations in healthy girls. In 1999, the requirement of GH deficiency was removed and a dose of 1.0 IU/kg/wk was approved. Although an increase in AH was expected, no reports showed significant improvements in AH at a high dose of GH. GH + ASH combination therapy was reevaluated and recommended for TS patients with gonadal failure and an extremely short stature or those who respond poorly to GH therapy. Although early estrogen replacement therapy is recommended to improve psychological quality of life and prevent osteoporosis, it lowered AH even at a low dose of ethinyl estradiol (25 ng/kg/d). The initiation of ethinyl estradiol at an extremely low dose (1–5 ng/kg/d) at a relatively young age successfully improved AH.

Key words: Turner syndrome, GH therapy, estrogen therapy, anabolic steroid hormone, adult height

Turner syndrome (TS) was first described in 1938 by Henry Turner as “a syndrome with infantilism, congenital webbed neck, and cubitus valgus” with 7 reported cases (1). Thereafter, in 1959, Ford *et al.* reported an X chromosome defect as the pathogenesis of the syndrome (2). The triad of TS consists of ovarian failure, short stature, and minor anomalies.

The frequency of TS is reportedly 1 of 2,000–2,500 girls. However, according to the chromosome screening of umbilical cord blood by Kuroki (3) and Maeda *et al.* (4) in Japan, the frequency is higher at around 0.7–2.1 of 1,000 girls. However, patients with TS are not frequently seen in the actual clinical setting, suggesting that a substantial number of TS patients do not exhibit short stature or ovarian failure in childhood.

In Japan, the use of GH therapy for TS was approved in 1991, although the growth promoting treatment of TS using anabolic steroid hormone (ASH) had already been performed.

Gonadal Function and ASH Therapy

In 1987, the 1st International Turner Syndrome Symposium was held in San Francisco, organized by R. Rosenfeld and M. Grumbach. Itsuro Hibi, Director

of the Department of Endocrinology and Metabolism at the National Children’s Hospital, participated in the symposium from Japan and reported that 13 of 61 TS patients (21.3%) aged 17 yr or older experienced spontaneous menarche (5). He also reported on adult height (AH) in relation to ASH therapy (stanozolol [Winstrol[®]], Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan) and gonadal function. A total of 45 TS patients did not experience spontaneous pubertal development after ASH therapy and reached AH with estrogen therapy. The mean AH in these 45 patients was 141.9 cm, whereas the corresponding height was 135.4 cm in 17 patients who had spontaneous pubertal development, showing a significant difference ($p < 0.01$). In addition, among the 17 patients who experienced spontaneous pubertal development, the mean AH was 131.6 cm in 11 patients who received ASH therapy, significantly lower than the corresponding height of 137.5 cm in the other 6 patients who did not receive ASH therapy (5).

At that time, Hibi had already indicated that normal gonadal function, i.e., sex hormones, would lower AH and that the administration of ASH in TS patients with normal gonadal function might result in a shorter AH. Indeed, aside from TS, this is consistent with the fact that adults with precocious puberty have

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a short stature (6) and that AH is shorter in patients with idiopathic short stature (ISS) who has been given ASH before puberty (7).

Regarding the gonadal function in patients with TS, Hibi reported at the 2nd International Turner Syndrome Symposium held in Frankfurt in 1990 that the cumulative frequency of spontaneous menarche was 21.3% (8). Since then, spontaneous onset of puberty has been reported in other countries (9–11). In Japan, Tanaka *et al.* analyzed the Turner Syndrome Research Collaboration (TRC) study and reported the frequencies of spontaneous breast development and spontaneous menarche (12). In that study, the frequency of spontaneous breast development was 36.3% (77/212), with frequencies of 20.3% (13/64) among patients with a karyotype of 45,X and 60.7% (17/28) among those with a 45,X/X mosaicism with no structural abnormalities. The frequency of spontaneous menarche was 14.6% (77/212), with frequencies of 6.3% (4/64) among those with a 45,X karyotype and 46.4% (13/28) among those with a 45,X/X mosaicism with no structural abnormalities.

Satoh *et al.* reported the results of ASH therapy in TS patients in the National Children's Hospital (13). Stanozolol (Winstrol[®]) 1 mg/d was given orally to 35 TS patients without spontaneous menarche. The mean age of patients at the initiation of stanozolol therapy was 12.09 ± 2.94 yr and the same at the initiation of cyclic estrogen-progesterone therapy (Kaufmann therapy) was 18.59 ± 1.37 yr. The mean AH was 142.4 cm. The height standard deviation (SD) score of TS standard was -0.2 SD before treatment, which significantly improved to +0.52 SD ($p < 0.05$) after treatment. This result significantly exceeded the AH of 139.1 cm among patients with untreated TS patients reported by Suwa *et al.* (14).

GH Therapy and Its Limitations

As mentioned previously, GH therapy for TS was approved by the Ministry of Health and Welfare of Japan in 1991. At that time, a dose of 1.0 IU/kg/wk had already been approved for TS in other countries. In Japan, two pharmaceutical companies conducted clinical trials using doses of 0.5 IU/kg/wk and 1.0 IU/kg/wk, and both trials resulted in better outcomes with 1.0 IU/kg/wk groups. However, the approved dosage remained the same as GH deficiency (GHD), i.e., 0.5 IU/kg/wk for GH-deficient TS patients.

Fujita *et al.* analyzed data of the Foundation for Growth Science database in Japan of GH therapy at 0.5 IU/kg/wk and reported on 258 TS patients who reached their AH by 2000 (15). At the initiation of GH therapy, the mean age was 12.0 yr and the mean height SD score was -3.6 SD. The mean age at the initiation of therapy was 17.0 yr for estrogen therapy and 18.3 yr for Kaufmann therapy. The mean age at the end of GH therapy was 17.7 yr, with a mean GH therapy duration of 5.6 yr. The mean AH was 145.7 cm, showing an improvement of approximately 7 cm as compared with

that of the untreated TS patients. However, it did not reach -2 SD of the AH SD score in healthy girls. Although there was no difference in AH according to the presence or absence of spontaneous breast development, AH was significantly lower in TS patients with spontaneous menarche than in those without (141.9 cm vs. 145.5 cm). According to their report, the age at the initiation of therapy was relatively high at 12.0 yr for GH therapy and 17.0 yr for estrogen therapy.

In 1999, the requirement of GH deficiency was removed and a new indication for GH therapy allowing a therapeutic dose of 1.0 IU/kg/wk (0.33 mg/kg/wk) for TS was approved. Along with the change in expression of the GH dose from international units to milligrams, the therapeutic dose of 0.35 mg/kg/wk was approved in Japan in 2000, paralleling the standard dose in Europe and the US. It was expected that a better AH would be achieved in TS patients on GH therapy. However, Takano *et al.* (16) compared the results of GH therapy between 0.5 IU/kg/wk and 1.0 IU/kg/wk groups in clinical trials in Japan and found that the mean AH was 142.2 ± 6.5 cm ($n = 15$) in the lower dose group and 144.3 ± 3.9 cm ($n = 15$) in the higher dose group, showing no significant difference. The improvement in height SD score from baseline to AH was 1.40 ± 0.80 SD and 1.40 ± 0.73 SD, respectively, also showing no significant difference. According to data from the National Children's Hospital (17), the mean AH was 144.5 ± 5.2 cm ($n = 48$) in the 0.5 IU/kg/wk group and 147.0 ± 4.1 cm ($n = 27$) in the 1.0 IU/kg/wk group; the AH was significantly higher in the latter. However, the therapeutic effect in terms of "AH minus predicted AH (PAH)" was 4.0 ± 5.3 cm for 0.5 IU/kg/wk and 3.8 ± 4.7 cm for 1.0 IU/kg/wk, showing no significant difference. Tanaka *et al.* (18) analyzed the TRC study and reported that the AH of 33 patients treated with 0.35 mg/kg/wk for 7.4 ± 3.6 yr was 145.8 ± 5.9 cm, showing no difference from the AH (145.7 ± 5.2 cm) of 258 patients treated with 0.5 IU/kg/wk reported by Fujita *et al.* (15).

GH therapy is reported to be effective for TS. **Figure 1** shows the growth velocity of children with short stature due to GHD (19), ISS (20), Noonan syndrome (21), achondroplasia (22), and TS (23) during the first year of GH therapy in clinical trials. The mean age at the initiation of therapy varied among the different trials: GHD, 8.02 ± 3.18 yr; ISS, 8.75 ± 1.91 yr; Noonan syndrome, 8.88 ± 2.64 yr; achondroplasia, 7.7 ± 1.8 yr at 0.5 IU/kg/wk and 7.2 ± 1.8 yr at 1.0 IU/kg/wk; and TS, 9.78 ± 3.39 yr at 0.5 IU/kg/wk and 9.60 ± 3.20 yr at 1.0 IU/kg/wk. Although a direct comparison was not possible due to the age discrepancy, the response of patients with TS was lower than those of GHD, ISS, or Noonan syndrome but was almost equal to that of patients with achondroplasia, a skeletal disorder, indicating the poor response of TS to GH therapy.

Reevaluation of ASH

GH + ASH combination therapy was performed even after the initial approval of GH therapy for TS

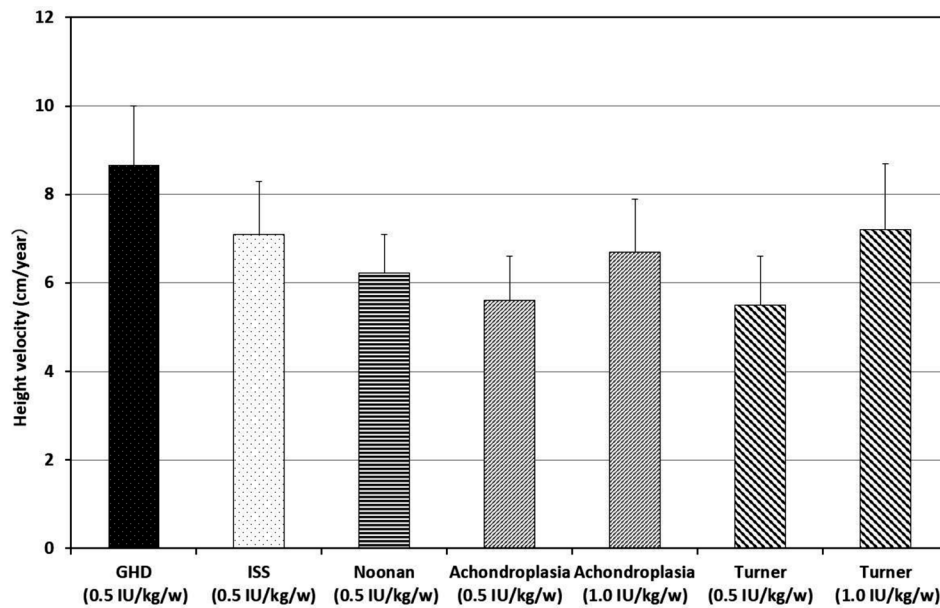


Fig. 1. First-year growth velocity during GH therapy in patients with GH deficiency (GHD), idiopathic short stature (ISS), Noonan syndrome, achondroplasia, or Turner syndrome. Numerals in parentheses are GH dose. (Reproduced with permission of the Japanese Association for Human Auxology from Tanaka T, *et al.* Adult height after growth hormone treatment (0.35 mg/kg/week) in patients with Turner syndrome: Turner Syndrome Research Collaboration (TRC) study. *J Jpn Ass Hum Auxo* 2018;24: 64–70)

in 1991. Tanaka *et al.* (17) compared the therapeutic effects of GH monotherapy and GH + ASH combination therapy (stanozolol [Winstrol®]) until AH was reached and reported no significant differences in mean AH (145.1 cm vs. 146.1 cm) although the therapeutic effect in terms of the difference from the predicted height at baseline was greater with the combination therapy (+2.7 cm vs. +6.9 cm). Oxandrolone is an ASH used in Europe and the US. Rosenfeld *et al.* (24) compared AH in TS patients who received no treatment, GH monotherapy, or GH + ASH combination therapy and reported that the combination therapy achieved a significantly better therapeutic effect (GH: 8.4 cm; GH + ASH: 10.3 cm).

ASH is a generic term for testosterone-derived synthetic steroids that have a higher anabolic action/androgen action ratio than that of testosterone. These derivatives include those that do and do not serve as an aromatase substrate; those that serve as an aromatase substrate have estrogenic activity. Derivatives that do not serve as an aromatase substrate include methenolone acetate (Primobolan®, Bayer Yakuin, Ltd, Osaka, Japan), stanozolol (Winstrol®), and oxandrolone. Human growth ends with the epiphyseal fusion of the long bones. During puberty, the bone age advances and epiphyseal fusion eventually occurs. The role of estrogen in epiphyseal fusion has been clinically demonstrated by the fact that male patients with estrogen receptor abnormality (25) and aromatase deficiency (26) continued to grow taller even after 20 yr of age and exceeded a height of 2 m due to a lack of epiphyseal closure.

In TS with ovarian failure, the bone age of patients on GH therapy alone advances slowly after the bone age of 10.5 yr and does not exceed 13 yr even after the

chronological age of 18 yr. However, on estrogen therapy, bone age advances with chronological age, resulting in epiphyseal fusion (27).

ASH administered to prepubertal boys with normal gonadal function induces precocious puberty (7). However, when ASH is administered during puberty, negative feedback acts on the central nervous system to decrease gonadotropin secretion, which in turn decreases testosterone, causing a decrease in estrogen, which is converted from testosterone through aromatization (28). As a result, the advancement of bone age slows and the duration of puberty is prolonged. Since ASH itself has a growth-stimulating effect, it is assumed that greater growth during puberty can be achieved with its use. In actuality, when GH monotherapy and GH + ASH combination therapy were compared in GHD boys, pubertal growth was significantly greater in those given combination therapy (25.4 cm vs. 31.5 cm, $p < 0.05$) (29).

As ASH has an androgenic effect, it causes adverse reactions such as voice changes, hirsutism, and increased muscularity in girls; therefore, its liberal use should be avoided. Likewise, a low dose of ASH is recommended for TS patients. As mentioned previously, the prepubertal administration of ASH to TS patients who will have spontaneous pubertal development induces puberty, resulting in a low AH (5). However, in recent years, three double-blind studies in Europe and the US demonstrated the benefit of GH + ASH combination therapy in TS patients with gonadal failure (30–32). In a review of these studies, Sas *et al.* (33) recommended considering the combined use of oxandrolone at a dose of 0.03–0.06 mg/kg/d in patients older than 8–10 yr with an extremely short stature or who respond poorly

to GH therapy because oxandrolone at doses up to 0.06 mg/kg/d causes no problematic adverse reactions. Moreover, the AH was higher by 2.3–4.6 cm with GH + ASH combination therapy than with GH monotherapy.

The commercial distribution of Winstrol® (13) was discontinued in Japan; therefore, Primobolan® (28) 2.5–5 mg/d is currently used. ASH treatment should be initiated in patients with ovarian failure in whom the follicle stimulating hormone (FSH) level has increased to 10 mIU/mL or higher after obtaining their consent to the therapy, based on the known risk of adverse reactions such as potential voice changes and hirsutism (34).

Estrogen Replacement Therapy

Estrogen therapy and Kaufmann therapy are necessary for TS patients with ovarian failure. Because gonadal function is not completely normal in TS patients with spontaneous menarche, the occurrence of early menopause requiring treatment is not rare. In the TRC study (12), estrogen therapy was subsequently required for 21 of 77 patients (27%) who had spontaneous breast development, and Kaufmann therapy was required later for 6 of 31 patients (19%) who had spontaneous menarche.

As mentioned previously, estrogen eventually causes epiphyseal fusion to determine the AH of the patient, and the initiation of estrogen replacement therapy at an early stage may cause a decrease in AH. Ross *et al.* (35) conducted a double-blind placebo-controlled study using GH, estrogen, and their placebos in 149 TS patients. The mean ages at the start of the study for double-placebo, estrogen-alone, GH-alone, and GH-estrogen groups were 7.5 ± 2.3 yr, 8.5 ± 2.7 yr, 8.2 ± 2.6 yr, and 9.3 ± 2.5 yr ($p = 0.041$), respectively, while the mean height SD scores

were -2.59 ± 0.96 , -3.01 ± 0.74 , -2.65 ± 0.91 , and -2.71 ± 0.81 ($p = 0.18$), respectively. The GH dose was 0.1 mg/kg three times per week. The doses of ethinyl estradiol were adjusted for chronological age and pubertal stage. The youngest dose was 25 ng/kg/d for children 5.0–8.0 yr. The average study period was 7.2 ± 2.5 yr. A total of 91 patients achieved AH with mean height SD scores of -2.81 ± 0.85 , -3.39 ± 0.74 , -2.29 ± 1.10 , and -2.10 ± 1.02 for the double-placebo, estrogen-alone, GH-alone, and GH-estrogen groups, respectively. **Figure 2** shows the height SD score at baseline and at AH for the four groups in the AH population. This finding indicates that combined GH and estrogen therapy increase AH more than GH-alone therapy but that estrogen-alone therapy initiated at the earlier age causes a lower AH SD score than no treatment, even at a low estrogen dose.

Regarding the relationship between AH and age at the initiation of estrogen therapy in TS patients on GH therapy, Chernausek *et al.* (36) compared AH in patients given estrogen monotherapy, GH + estrogen therapy initiated at a mean age of 12.3 yr, and the same combined therapy initiated at a mean age of 15 yr. The mean difference between AH and PAH as an index of the therapeutic effect was -0.6 cm, $+5.1$ cm, and $+8.4$ cm, respectively, in these three groups. Thus, the combination of GH + estrogen therapy administered at a later stage was associated with a significantly greater therapeutic effect. This result indicates that the more delayed the initiation of estrogen therapy, the higher the resultant AH.

However, delayed estrogen therapy prevents pubertal development, resulting in adverse psychosocial effects. In addition, the absence of estrogen at the appropriate time may result in future osteoporosis, whereas the early initiation of GH + estrogen replacement

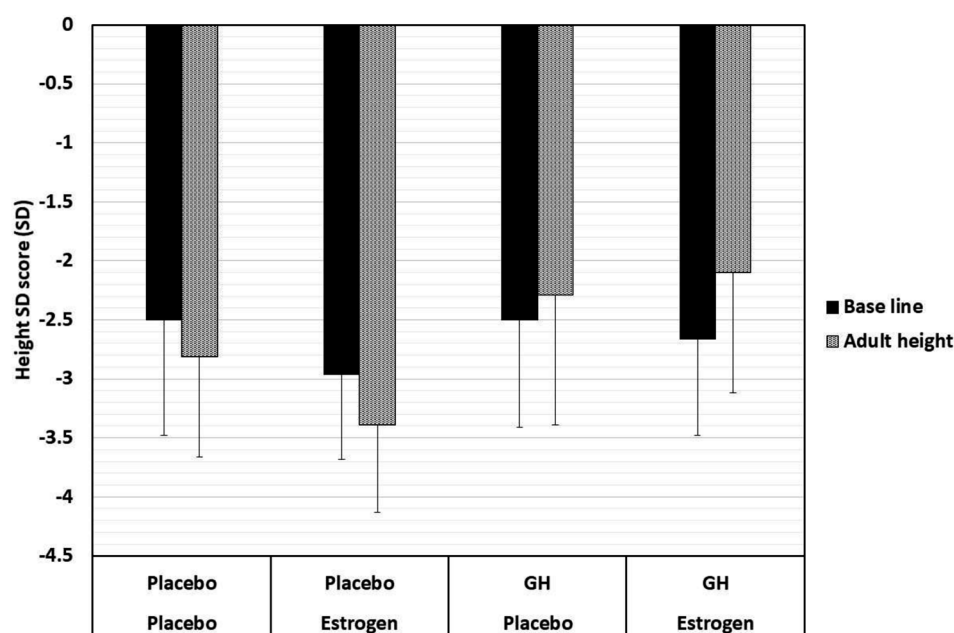


Fig. 2. Height standard deviation (SD) scores at baseline and at adult height in a double-blind placebo-controlled study of Turner syndrome (35).

therapy maintains an appropriate bone mineral density (BMD) and prevents bone fragility (37, 38). To prevent adverse psychosocial effects, it is recommended that estrogen therapy should be initiated without much delay from the age of pubertal development in healthy girls, although it is necessary to wait until their height reaches a certain level considering AH. The Turner Syndrome Consensus Study Group in the US observed spontaneous pubertal development in patients aged 10–11 yr using Tanner stages and blood FSH levels and recommended initiating low-dose estrogen therapy at the age of 12–13 yr in cases of no spontaneous pubertal development while the FSH level is increased (39).

In Japan, a guideline for estrogen replacement therapy has been issued. Tanaka analyzed the growth of TS patients from the initiation of estrogen therapy to AH and reported that estrogen therapy started at the age of 12–14 yr was associated with a height increase of about 10 cm until AH (40). The Japanese Society for Pediatric Endocrinology has issued a guideline for estrogen replacement therapy which recommends to start estrogen therapy at a low dose (Premarin[®]; Pfizer Japan Inc., Tokyo, Japan, 0.0625 mg p.o. or Estrana[®] tapes (Hisamitsu Pharmaceutical Co. Inc., Tosu, Japan) 0.09 mg to be changed every 2 day) at the age of 12–14 yr when the patient is about 140 cm in height with an AH goal of 150 cm and increasing the dose every 3–6 mo to reach the adult dose (Premarin[®] 0.625 mg or Estrana[®] tapes 0.72 mg) in about 2 yr, at which point the therapy should be converted to Kaufmann therapy (41). To comply with this guideline, patients are required to be 140 cm tall when they are 12–14 yr of age. However, based on analysis of data from the Foundation for Growth Science, Mochizuki *et al.* (42) reported that only 7.5% of 12-yr-old and 59.8% of 15-yr-old TS patients reached a height of 140 cm. In contrast, 29.5% of 12-yr-old and 85.6% of 15-yr-old TS patients reached a height of 135 cm. There has been no report on AH achieved in TS patients who were treated according to this guideline. The mean height increase in healthy girls during puberty is about 25 cm (43). A height increase of only 10 cm from the initiation of estrogen therapy to AH seems to reflect a failure of the therapeutic dose and regimen to imitate the development and progression of puberty in healthy girls.

Rosenfield *et al.* (44) reported on the course of TS in 7 patients who began receiving GH therapy before the age of 12 yr and started estrogen therapy at age 12.0–12.9 yr (Early group) or age 14.0–14.7 yr (Late group). There was no intergroup difference in height at 12 yr of age. Estrogen therapy was started as an intramuscular injection of estradiol depo 0.2 mg once a month, and the dose was increased every 6 mo. According to that report, the mean height gain in puberty (increase from the initiation of estrogen therapy to AH or near-adult height [NAH]) was significantly greater in the Early group (17.3 cm) than in the Late group (6.1 cm). The AH or NAH tended to be higher in the Early group than in the Late group, but the difference was not statistically significant. Patients in the Early group in

the National Cooperative Growth Study were treated with conjugated estrogen, and the mean height increase in puberty was 11.4 cm (44).

Although oral estrogen preparations exert their actions after being metabolized in the liver, intramuscular or patch preparations may exert their actions in different ways because they are directly absorbed into the blood. Torres-Santiago *et al.* (45) compared the effects of oral and patch preparations and concluded that the patch preparation is more physiological than the oral preparation. The estrogen concentration reached an extraordinarily high level immediately after oral administration despite no particular differences in body composition or lipid metabolism. Strategies for clinical studies to determine the superiority of one preparation over the other have also been proposed (46).

In the study by Ross *et al.* (35), while doses were adjusted for patient chronological age, the minimum dose in low-dose estrogen therapy was ethinyl estradiol 25 ng/kg/d. Hasegawa (47) started the administration of ethinyl estradiol at an extremely low dose of 1–5 ng/kg/d in 17 TS patients with a mean age of 11.6 yr (range, 9.8–13.7 yr) and a height of about 133 cm who had started to receive GH therapy at a mean age of 7.4 yr. The dose of ethinyl estradiol was increased every 6 mo by 8–10 ng/kg, 20–25 ng/kg, 50 ng/kg, and 100 ng/kg, and the mean AH reached 152.4 cm, exceeding 150 cm for the first time in Japan. The pubertal height gain was about 20 cm, similar to that of healthy girls with delayed puberty. However, there was no improvement in BMD. In his study, the timing of estrogen therapy initiation was the earliest ever in Japan, and the pubertal height gain was greater than that obtained in other studies. However, an even earlier initiation of estrogen therapy may be necessary to achieve BMD improvement.

Future Strategies for Growth Stimulating Treatment

Growth stimulation treatment for TS patients aims for the following: 1) early achievement of normal stature to improve psychosocial problems arising from a short stature; 2) initiation of estrogen replacement therapy in patients with ovarian failure without much delay from the age of pubertal development in healthy girls; and 3) achievement of a normal AH to facilitate adaptation to adult social life. The goal of AH should be set at over 150 cm. To this end, early diagnosis and early treatment are most important. Younger patients may not be of short stature as yet, and it is important to follow their clinical course. If there are any suspicious minor anomalies, chromosomal testing should be actively performed. However, even minor anomalies may not be present in patients with a 45,X/X mosaicism with no structural abnormalities.

If patients are of severely short stature or have a poor response to GH, ovarian failure (FSH > 10 mIU/mL) should be confirmed at about 11 yr of age, and Primobolan[®] therapy at a dose of 2.5 mg/d (beginning

with alternate-day administration if possible) should be considered after obtaining consent from the patients and their guardians.

Achieving an AH of 150 cm or higher can be expected when the protocol of oral ethinyl estradiol therapy is started at an extremely low dose of 1–5 ng/kg/d once the patients have reached a height of approximately 135 cm. However, treatment with extremely low doses of ethinyl estradiol is available only at institutions where it is possible for the pharmaceutical department to prepare such low doses. Although insufficient data are available, a generally feasible method is the application of one-fourth fraction of the patch preparation Estrana® tapes

of 0.09 mg replaced every other day as the initial dose. The dose should be doubled every 6 mo to a one-half fraction, one whole 0.09-mg tape, one 0.18-mg tape, one 0.36-mg tape, and one 0.72-mg tape. Thereafter, estrogen therapy should be changed to Kaufmann therapy (48).

Although the optimal treatment has not yet been established, these treatments are expected to facilitate improved quality of life in patients from an early age, preclude psychosocial problems during puberty, and normalize their AH.

Conflict of Interests: The authors declare no conflicts of interest.

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