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Review

Growth Hormone Treatment to Final Height in Turner Syndrome: Systematic Review

Tommaso Aversa [1,2], Alessandra Li Pomi [1,2], Giorgia Pepe [1,2], Domenico Corica [1,2], Maria Francesca Messina [1,2], Roberto Coco [1,2], Fabio Sippelli [1,2], Chiara Ferraloro [1,2], Giovanni Luppino [1,2], Mariella Valenzise [1,2], Malgorzata Gabriela Wasniewska [1,2,*]

[1] *Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy*
[2] *Pediatric Unit, "G. Martino" University Hospital, Messina, Italy*

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ABSTRACT

Purpose: Turner syndrome (TS) is the most common sex chromosomal abnormality found in female subjects. It is a result of a partial or complete loss of one of the X chromosomes. Short stature is a hallmark of TS. Attainment of adult height (AH) within the normal range for height within the general female population represents the usual long-term goal of growth hormone (GH) treatment. The aim of this systematic review was to understand the efficacy of GH therapy on AH of patients with TS.

Methods: The literature review yielded for analysis 9 articles published from 2010 to 2021. Using the data from this literature search, the goal was to answer 5 questions: (1) What is the efficacy of GH on AH of girls with TS?; (2) Is AH influenced by the age at initiation of GH treatment?; (3) What is the optimal dose of GH to improve AH?; (4) Can the timing of either spontaneous or induced puberty influence AH?; and (5) Can the karyotype influence AH in patients with TS?

Findings: GH therapy and adequate dose could enable patients with TS to achieve appropriate AH compared with the possible final height without therapy. The greatest increase in height during GH therapy occurs in the prepubertal years, and if therapy is continued to AH, there is no further increase. Furthermore, karyotype did not show a predictive value on height prognosis and did not affect the outcome of GH administration or the height gain in girls with TS.

Implications: Even if GH therapy is safe, close monitoring is indicated and recommended. Further evidence is needed to understand what other parameters may influence AH in patients undergoing GH therapy.

Introduction

Turner syndrome (TS) is the most common sex chromosomal abnormality found in female subjects, with a prevalence of ~1 in 2000 to 1 in 2500 live female births.[1] It is a result of a partial or complete loss of one of the X chromosomes and, depending on the level of mosaicism (the proportion of affected cells to healthy ones), it can vary in severity. Short stature and primary ovarian failure (POF) are the hallmarks of TS, although it can also manifest with cardiac and renal anomalies, autoimmune disorders, and hearing loss.[2]

Short stature is the most constant finding in patients with TS. Attainment of adult height (AH) within the normal range for the general female population represents the usual long-term goal of growth hormone (GH) treatment in individuals with TS.[2]

The first short-term (1 year) placebo-controlled study of pituitary-derived human GH in TS was initiated in 1984 but was aborted the next year when pituitary GH was withdrawn from all human use.[3] Nevertheless, this trial formally showed the proof of concept that GH could significantly increase height velocity in TS.

It was widely accepted for many years that children with TS should be regularly treated with GH. In past years it had been shown that, in childhood, GH treatment with doses higher than those used in GH deficiency could improve AH in these patients.[4–6] The last international guidelines of 2016 recommended initiating GH treatment early (~4–6 years of age, and preferably before 12–13 years of age) if the child already has evidence of growth failure, using a GH dose of 45–50 μg/kg per day increasing to 68 μg/kg per day if AH potential is substantially compromised. Attainment of AH within the normal range

* Address correspondence to: Malgorzata Gabriela Wasniewska, Department of Human Pathology of Adulthood and Childhood, University of Messina, Via Consolare Valeria 1–98125, Messina, Italy.
E-mail address: mwasniewska@unime.it (M.G. Wasniewska).

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for height within the general female population represents the usual long-term goal of GH treatment in patients with TS. Moreover, short stature in TS might be treated with GH alone or with oxandrolone (a non-aromatizable androgen), with the goal of increasing AH but, due to the undesirable effect of masculinization, this combination is not common.[2]

Although GH therapy is conventionally indicated in patients with TS, results are not always achieved. For example, the diagnosis of TS is often at an advanced age and the initiation or duration of GH therapy may not be sufficient to achieve an appropriate AH. In fact, it should be noted that >20% of girls with TS are diagnosed beyond the age of 11 years with a severe height deficit and pubertal delay. Given the broad variation in potential outcome, substantial effort has been expended to define pre-treatment and treatment-related variables associated with greater AH or greater height gain from baseline to AH.

The aim of the present article was to summarize the recent literature (from the last 12 years) concerning evaluation of AH in the setting of TS treated with GH and to establish which factors should be taken into consideration during GH treatment. Using data from the present literature search, our goal was to find answers to the following 5 questions: (1) What is the efficacy of GH on AH of girls with TS?; (2) Is AH influenced by the age at initiation of GH treatment?; (3) What is the optimal dose of GH to improve AH?; (4) Can the timing of either spontaneous or induced puberty influence AH?; and (5) Can the karyotype influence AH in patients with TS?

Materials and Methods

The literature included in the review was identified by 6 independent investigators (T.A., A.L.P., R.C., F.S., C.F., and G.L.) principally using an automated literature search for English language papers published from January 2010 to November 2022. The systematic search was conducted according to the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network statement.[7] Using the MEDLINE (PubMed), Cochrane Library, and Web of Sciences databases, the authors identified studies about AH in the setting of TS after only GH treatment. To generate a wide search, the research was based on the combinations of 3 or more of the following key words: ("Turner syndrome") AND ("Adult Height or Final Height") AND ("GH therapy or GH treatment"). In addition to the automated search, a manual search for other relevant publications was conducted of the bibliographies of papers identified automatically. The assessment of eligibility was guided by a flow diagram as reported in the Figure.

Inclusion criteria were as follows: articles written in English, which belonged to the categories of clinical study, clinical trial, clinical trial protocol, multicenter study, randomized controlled trial, or observational study; and a study population consisting of patients with a genetic diagnosis for TS, belonging to a multi-ethnic or monoethnic population. In the selected papers, the following data were sought: TS sample size, number of patients who achieved AH, karyotype, age at the start of GH therapy, stature at the start of GH therapy, body mass index, bone age, target height (TH) or delta taget height-height (delta TH-H), initial and during treatment GH dose, duration of GH treatment, age of GH withdrawal, body proportions (sitting height/height) at the start and end of GH therapy, puberty (induced or not, age onset, duration, age of spontaneous or induced menarche, stature at onset and end of growth), AH (age of attainment, delta adult height-target height (delta AH-TH)), adherence to GH therapy, monitoring, and safety of GH treatment. Exclusion criteria were as follows: studies with a small study population comprising <19 individuals with TS, duration of GH therapy <3 years, receipt of oxandrolone therapy, and ethnic minorities.

The following outcomes were considered: AH of girls with TS and its relationship to the genetic target and parameters of GH treatment (auxologic and laboratory valuation [insulin-like growth factor 1 (IGF-1)]).

Quality Analysis

Quality analysis for each study included was conducted by 3 independent investigators (T.A., G.P., and D.C.) using the Critical Appraisal Checklist for Studies Reporting the Checklist for Text and Opinion Papers developed by the Joanna Briggs Institute.[8,9]

Results

Publications Included

Using the search strategy described earlier (Figure), a total of 391 publications were found (MEDLINE, PubMed, Cochrane Library and Web of Science). A manual search considering the bibliographies of the review articles retrieved no additional papers. A total of 132 papers were found to be duplicated and were therefore excluded. Following assessment of the titles and abstracts, 230 papers were excluded because they were not related to the subject. The analyses of the remaining 29 articles by reading the full texts resulted in the exclusion of 16 papers for the following reasons: wrong comparator (n = 4), wrong outcome (6), wrong study design (n=4), wrong objective (n=4), and insufficient data (n = 1). Subsequently, 4 other studies were excluded due to small numbers of study populations achieving AH (<19 cases). Finally, 9 studies were considered for the final evaluation (Table).[10–18]

Description of the Studies and Demographic Analysis

Nine papers published from 2010 to 2021 were included in this review.[10–18] The main features of these studies are presented in the Table. The population of TS patients with the achievement of final height after treatment with GH was 1122. The number of patients with TS who reached AH after GH treatment analyzed in each study varied from 19 to 527.

Three of these studies evaluated international populations, and nine of the populations were from a single country. Moreover, 3 of them were retrospective, and 9 were prospective. Only 7 studies evaluated the karyotype, although often without considering the relationship between karyotype and growth failure or GH response. The French study conducted by Fiot et al[14] found that karyotype may influence not only spontaneous growth of TS but also response to GH treatment, especially in patients with haploinsufficiency for an unknown Xp gene such as XrX and IsoXq.

Only 1 of the 9 studies considered a very early start of GH therapy (before the age of 6 years). The age range of onset was wide in the remaining 8 studies; only in a few patients with TS was GH therapy started early. Moreover, only one study[17] considered body proportion (sitting height/height) as an auxologic parameter at the end of GH therapy. In addition, many of the studies (5 of 9) did not evaluate bone age at the beginning of GH therapy, and 2 studies did not consider mean TH, which can influence final height at the end of treatment. Considering the importance of the correlation between statural growth and puberty, it is worth noting that the study by Bettendorf et al[15] is the only one that collected data about stature at the beginning and at the end of pubertal development. If the possibility of a coexisting condition of being overweight at the beginning of GH treatment is instead considered, only 6 studies evaluated patients' body mass index; the results, however, were in the normal range. Only one study has the limit of not describing chronological age at the end of treatment,[9] and all selected studies indicate the duration of GH treatment.

No studies considered adherence to GH therapy, a key variable for treatment response, and no studies evaluated the influence of eventual comorbidities on the growth and AH during GH treatment in TS subjects (eg, Hashimoto thyroiditis, celiac disease). Studies show that patients undergoing GH therapy do not develop comorbidities and have regular follow-up; thus, GH therapy is safe.

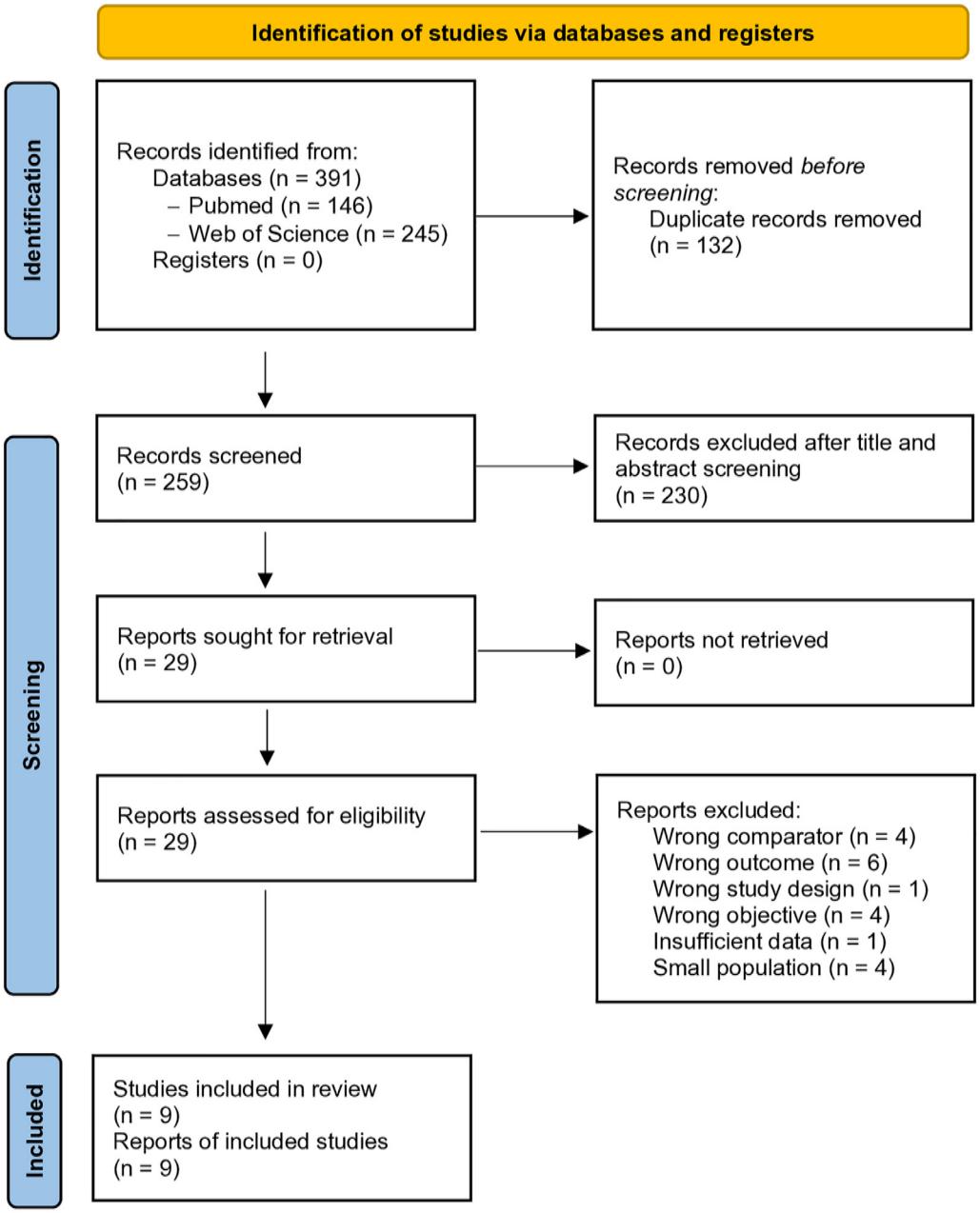

Figure. Study flow diagram.

Discussion

We provide here, based on the literature search, answers to the 5 questions as presented in the Introduction.

What Is the Efficacy of GH on the AH of Girls With TS?

Average AHs of large groups of untreated women with TS from various countries are ~143 to 146 cm, making them ~20 cm below their mid-parental (target) heights and 20 cm below the average heights of their unaffected countrywomen.[19] Thus, prevention of growth failure and maintenance of height within the population normal range throughout childhood and into adulthood may be considered quintessential goals of care in girls with TS.

AH deficits seen in individuals with TS originate, in part, from growth retardation in utero and throughout the first 3 years of life. For this reason, earlier diagnosis enables earlier therapeutic intervention with GH, which may help prevent growth retardation. In addition to maximizing AH, the current goals of GH treatment include normalizing stature during the prepubertal years to mitigate early physical and psychosocial barriers and to allow puberty to begin at a similar age to peers.

The guidelines of the Turner Syndrome Study Group recommend that GH should be administered at the U.S. Food and Drug Administration–approved dose of 1.125 IU/kg per week (0.375 mg/kg per week); this dose can be adapted according to the growth response and IGF-1 levels. It is also recommended that GH treatment should be considered as soon as growth failure is evident, possibly around 4 to 6 years of age.[2]

Table
Data on growth hormone (GH) therapy, target height (TH) and adult height (AH) from the 9 papers considered.

Paper	No. of Patients With TS at AH After GH	AH (cm)	AH (SDS*)	Δ TH-AH (cm)	Duration of GH Treatment (y)	Chronological Age at GH Start (y)	GH Dose† (mg/kg/d)
Backeljauw et al, 2021[10]	35	–	−2.02 (0.9)	11.8 (6.4)	3.21 (2.23)	9.0 (0.7 to 18.5)	0.038 at start of GH treatment, then 0.044
Quigley et al, 2021[11]	51	151.3 (7.3)	−1.56 (1.07)	13.2 (6.15)	6.72 (2.01)	8.29 (1.22)	0.050
Pfäffle et al, 2020[12]	62	–	−2.07 (range, −5.8 to −0.3)	-1.94 SDS (range, 0 to 4.9)	3.01 (0 to 11.14)	8.7 (0.7 to 17.9)	0.033
Cleemann Wang et al, 2020[13]	63	153.7 (5.54)	-2.35 (-2.99 to -2.12)	–	6.7 (3.4 to 9.7)	7.59 (5.36 to 11.97)	0.033
Fiot et al, 2016[14]	527	152 (147 to 156)	−2.05 (−2.95 to −1.20)	9.5 (5.5 to 14.2)	5.8 (3.6 to 8.5)	8.8 (5.3 to 11.8)	0.048
Bettendorf et al, 2013[15]	313 (early, <12 years, 259; late, >12 years, 54)	Early <12 years: 152.5 (5.9) Late >12 years: 151.1 (5.4)	Early <12 years: -2.8 (1.2) Late >12 years: -3.1 (1.1)	Early, <12 years: 11.7 (5.7) Late, >12 years: 11.5 (5.3)	Early, <12 years: 7.5 (2.12) Late, >12 years: 5.2 (1.2)	Early, <12 years: 8.5 (2.2) Late, >12 years: 13.2 (1.1)	0.042 (0.014)
Blum et al, 2013[16]	19	–	-2.35 (1.17)	–	7.4 (1.4)	7.8 (2.0)	0.052 (0.01)
Wasniewska et al, 2013[17]	25	149.1 (5.9)	-2.1 (1.0)	9.3 (5.4)	10.0 (1.7)	4.4 (1.0)	0.047
Ross et al, 2011[18]	27	147.9 (7.4)	-2.29 (1.10)	– (−2.06 (1.01 SDS)	7.4 (2.8)	8.4 (2.7)	0.042

TS = Turner syndrome. SDS = Standard Deviation Score. TH-AH = Target Height - Adult Height.
* For normal population.
† Media or medium.

Some studies have shown only small gains in height, while others claim significant improvement in height. This discrepancy is likely due to several factors such as ethnic and genetic differences, age at which GH is started,[14] dose of GH, age of sex steroid replacement, use of anabolic steroids, sample size of the study, and use of historical or randomized untreated control subjects, all of which may account for the variations in AH when treated with GH.

GH treatment increases growth in girls with TS, with a final AH gain of ~6 cm.[20] There is a negative association between age at the onset of treatment and AH, whereas a positive association has been reported between duration of treatment and AH, raising the question of earlier intervention with GH in this patient population.[21]

Therefore, it may be possible to realize the maximal therapeutic benefits of GH in girls with TS by initiating treatment during the first few years of life. Past studies that investigated GH treatment in TS have not included girls aged <4 years, perhaps, in part, because of delayed diagnosis of TS. Fortunately, in the last decade, guidance on the diagnosis of TS has improved, leading to a rise in the number of girls being diagnosed with TS at an earlier age and promptly treated.

Recent studies have shown that early treatment with GH of infants and toddlers with TS improves growth. Linglart et al[22] reported that in a group of 61 young girls with TS, >4 years of treatment with GH during the first years of childhood, when growth retardation is greatest, leads to large and significant increases in height, with a gain in mean H-SDS of 1 SD. The authors hypothesized that GH treatment in the pre-school years could prevent the progressive growth failure that typically begins in infancy in girls with TS.

In a previous study of our research group,[17] we investigated the growth evolution under GH therapy and AH outcome of 25 girls with TS who began GH therapy before 6 years of age and were treated for a mean period of 10 years, before achieving AH. After an initial acceleration, height velocity declined after the first 4 years of therapy. At the end of the sixth year of therapy, H-SDS gain was 1.9. Thereafter, H-SDS gain from baseline decreased, becoming 0.9 SDS at AH achievement. We hypothesized that the therapeutic regimen adopted in our study was sufficient to induce a significant growth acceleration during the first year, but the response waned after 6 years of treatment.

Ross et al[18] observed that treatment with GH and low-dose estrogens in TS at an average age of 9 years increases AH. The authors' observation of modest growth benefit with the combination of ultra-low-dose childhood estrogen replacement and growth hormone should suggest the clinicians reconsider the practice of delaying estrogen. They propose that a regimen combining early childhood estrogen replacement with growth hormone in girls with TS could optimize AH but also provide the neurocognitive and behavioral benefits of early estrogen administration. However, there is no clinical evidence to suggest starting early childhood estrogen.

Based on data from several placebo-controlled studies, use of oxandrolone in recombinant human growth hormone–treated girls with TS led to a modest increase in the final AH of girls aged up to 18 years with TS.[23] In a large single-center study,[24] the effects on AH after long-term GH treatment with dose titration according to IGF-1 levels were evaluated in 63 girls with TS. The authors reported an AH gain of 3.2 cm in TS, suggesting that this treatment resulted in a lower AH gain compared with previous studies of weight-based GH dosing, in which improvement of AH usually ranges between 5 and 8 cm at GH doses ranging from 42 to 50 μg/kg per day. A Dutch study further reported of gain in AH of 11 to 16 cm using much higher GH doses (45–90 μg/kg per day).[5] An observational, postmarketing surveillance study[25] reported that biosimilar GH is well tolerated and effective in patients with TS managed in real-life clinical practice.

In accordance with literature data, we can infer that optimization of GH dose may contribute to a higher AH in patients with TS. The combination of GH treatment and early estradiol supplementation can be further improved to help individuals with TS attain an AH closer to the population mean.

Is AH Influenced by the Age at Initiation of GH Treatment?

Growth failure is the main clinical auxologic characteristic in TS and results primarily from haploinsufficiency of the short stature homeobox–containing gene (SHOX gene) located on the short arm of the X (and Y) chromosome.[26–28] Patients with mutations or deletion within the coding or enhancer regions of the SHOX gene have variable degrees of growth impairment.[29]

Growth delay in TS is progressive from infancy to adulthood, and it occurs because of growth retardation before birth, throughout childhood, and during adolescence.[30] The average length of full-term TS infants is ∼0.7 standard deviation (SDS) below the mean for the healthy neonatal population. Moreover, length progressively decelerates, and stature falls below –2.0 SDS by 4 years of age,[31] and in adulthood is below –3.0 SDS.[32,33] In untreated adult women with TS, height varies from 143 cm to 146 cm according to the different ethnic group but is ∼20 cm below the average height of healthy women and their TH.[34,35]

GH treatment has shown a beneficial effect, improving the final height in short girls with TS.[4,36,37] GH treatment determines a final height gain of ∼6 cm,[38] but the response to GH is variable, and many factors have been identified as influencing treatment response. The most important factors associated with a good response and a better height gain are age at onset of treatment (negative correlation) and the duration of treatment (positive correlation).[21,39]

The current goal of GH treatment is to maximize AH but also to normalize height during prepubertal years and mitigate early physical and psychosocial barriers and to allow puberty to begin at a physiological age.[40,41] The actual therapeutic guidelines recommend early initiation of GH treatment to prevent the progressive deceleration that typically occurs in the first years of life in girls with TS.[31,20] Because most of the height deficit in girls with TS occurs within the first 3 to 4 years of life, and height SDS continues to decline with age, it is strongly suggested to start treatment as soon as possible.[42] The early initiation of GH in girls with TS prevents ongoing growth failure and leads to normalization of height during childhood and favorable height at pubertal age; this approach thus allows timely estrogen replacement when needed, avoiding the discomfort of hypogonadal aspects of TS in adolescence.

However, the question remained whether the early gains would be maintained throughout the growth period to AH. Linglart et al[22] showed that GH treatment initiated before 4 years of age significantly increased growth in girls with TS compared with the historical control group; 80% of this study population were able to attain a normal height by a mean age of 6.6 years. After 4 years of GH treatment, girls were 1.09 SDS higher than untreated girls. Other studies in which treatment was started at an older age (8–12 years) have shown a gain in height ranging from 0.8 to 2.1 SDS.[43,44]

In the KIGS (Kabi International Growth Study) database, patients who reached final height were analyzed to evaluate the efficacy of late start of GH treatment in adolescence and to assess the utility of a predicted model in selecting GH-responsive patients at early and late treatment start.[11,45] In fact, we emphasize that >20% of girls with TS are diagnosed beyond the age of 11 years with a severe height deficit and pubertal delay.[46,47] These patients have suffered with short stature during school-age and have missed the opportunity to receive a GH treatment to normalize height and prevent psychological discomfort compared with their peers. Although timely initiation of GH treatment, not all patients with a late diagnosis of TS will be able to reach the expected AH. However, a different study[48] emphasized that late initiation of GH therapy determines significant height improvement.

A very recent study[49] enrolled patients with TS divided into 4 different groups depending on the age of start of therapy and of the GH dose: $GH_{33young}$ (started treatment with GH 33 μg/kg per day at age 3–9 years); GH_{33old} (started treatment with GH 33 μg/kg per day at age >9 years); $GH_{67young}$ (started treatment with GH 67 μg/kg per day at age 3–9 years); and GH_{67old} (started treatment with GH 67 μg/kg per day at age >9 years). Belonging to the high-dose group was associated with a greater AH, regardless of age at start of therapy. In addition, being young at the start of GH was associated with a greater growth response. Together, these data suggest that the growth deficit associated with a late GH start can, at least partly, be compensated for by a higher GH dose during the remaining or extended prepubertal growth period.

We thus assert that GH treatment is a great therapeutic opportunity to ameliorate auxologic destiny in patients with TS. It should also be initiated in patients with delayed diagnosis but, whenever possible, GH treatment should be offered within the first 6 years of life.[17,48,49] In addition, it is important to emphasize that early start of GH treatment should be uninterrupted during childhood because treatment discontinuation could contribute to catch-down growth and reduce the efficacy of early treatment.

What Is the Optimal Dose of GH to Improve AH?

The growth response to GH in patients with TS depends on many variables, including TH, age at start of GH treatment, duration of GH treatment, GH dosage, modality of adjusting the dose for body size, age at initiation, and dose of estrogen.

The ideal dose of GH to improve the auxologic outcome of patients with TS remains a topic of debate. The current recommended GH dose for girls with TS is 45 to 50 μg/kg per day, which can be increased to 68 μg/kg per day in cases of significantly impaired AH prediction.[2] In some of the studies selected for this systematic review, it was possible to extrapolate information regarding the dose of GH administered in patients with TS, although the primary objective of these studies was not to assess what the optimal dose of GH was to improve final stature.

Schrier et al[50] retrospectively evaluated efficacy, in terms of AH, and cost-effectiveness of GH therapy by comparing the GH dosage calculated in square meters of body surface area (BSA) (ranging from 1.33–2.67 mg/m^2 per day, corresponding to ∼0.0475–0.095 mg/kg per day) with the dose per kilogram of body weight (ranging from 0.033–0.067 mg/kg per day) in girls with TS by examining several studies. These authors showed that AH gain was greater on a BSA-based regimen than on a body weight–based regimen in patients who start GH treatment before 8 years of age and that the cumulative dose and cost are lower with a BSA-based regimen. Given these findings, they concluded that BSA-based dosing, characterized by a relatively high dose in young patients and relatively low in adolescents, was more cost-effective than that based on body weight.

In the study by Wasniewska et al,[17] published before the 2016 guidelines, it was documented that the fixed GH dose of 33 μg/kg per week, initiated before 6 years of age, resulted in significant growth acceleration during the first year of treatment in patients with TS. However, in subsequent years, particularly after the fourth year of therapy, there was evidence of a decreased response to therapy with an average height gain of 0.9 (0.9) SDS at AH achievement and a final stature below TH.

Wang et al[24] showed that titration of GH dose (average GH dose of 33 μg/kg per day) to maintain IGF-1 levels within the normal range (less than or equal to +2 SDS) leads to lower doses of GH than recommended by guidelines and results in lower height gain and AH than cases evaluated in other studies in which a fixed dose of GH was used.

Backeljauw et al,[25] in an observational study with data from the PATRO Children Study, which included treatment-naive and pretreated patients, documented that the dose of GH treatment used in these patients was lower than the recommended dose. This was true both at the start of treatment (from 10 to 67 μg/kg per day [mean, 38.5 μg/kg per day] in treatment-naive patients; from 10 to 67 μg/kg per day [mean 43.2 μg/kg per day] in pretreated patients) and during the 1 to 1.5 years of treatment follow-up (mean dose, 44.1 μg/kg per day). Among patients (both treatment-naive and pretreated) who achieved AH (51%), this was on average –2 SDS with an improvement of ∼1 SDS over the height documented at the start of GH therapy. The mean difference between AH and

TH was about –1.8 SDS and –2 SDS in pretreated and treatment-naive patients, likely due to late initiation of therapy.

In conclusion, GH dose is only one of the factors affecting the growth and AH in patients with TS and probably not the most affected. The GH dose to be used in patients with TS should be that recommended by the International Turner Syndrome Consensus Group guidelines.[2] Some of the studies reviewed suggest the possibility of considering BSA-based rather than body weight–based GH dose or that a fixed GH dose, lower than that currently recommended, would lead to the achievement of a comparable final stature. However, these are single studies in which the evidence is not strong enough to replace the current recommendations.

Can the Timing of Either Spontaneous or Induced Puberty Influence AH?

TS is usually characterized by hypergonadotropic hypogonadism and primary or secondary amenorrhea. Because of ovarian dysgenesis, only ~20% of girls with TS will spontaneously develop puberty and menstruation, which occurs most frequently in patients with mosaic karyotypes (~54% vs 6% in case of monosomy 45X,0).[51–53] Induction of puberty with hormonal replacement therapy is therefore required in most girls with TS to enable the onset of the physiological pubertal process. This maintains secondary sex characteristics, ensuring growth spurt in adolescence, attaining peak bone mass, and normalizing uterine growth in case of future pregnancies.[2,54,55]

However, estrogens have been shown to be involved in the epiphyseal fusion and may represent a limiting factor for longitudinal bone growth, resulting in a decreased height gain with reduced AH.[55,56] This has raised questions about the timing and means of sex steroid treatment in adolescents with TS, with some authors advocating late puberty induction as a strategy for optimizing growth.[57–59] However, low-dose estrogen regimens do not seem to interfere with growth response to GH therapy when started between 11 and 12 years of age, increasing to adult dosing over 2 to 3 years, as recommended by current therapeutic guidelines.[2,18,60–62]

In contrast, postponing the introduction of estrogens too long can have adverse psychological consequences and may result in decreased bone mineralization.[55,63,64] Therefore, the decision to start hormonal replacement therapy should be balanced by the potential benefit in terms of height outcome and the psychological issues related to feminization. A longer period of GH treatment before induction of puberty is considered among the predictive factors of taller final height, as reported by several authors.[5,43,44,48,65–68] Thus, relatively early initiation of GH is recommended to ensure a longer period of estrogen-free GH treatment that could bring the patients' height into the normal range at the time of pubertal induction, and consequently allow initiation of estrogen therapy at an age-appropriate time.

Accordingly, 2 studies clearly showed that timing of puberty onset (the later, the better) may play a crucial role in determining near-AH or AH.[21,39] Conversely, Massa et al[69] observed no relationship between the age at onset of puberty and final height in a population of 186 patients with TS. More recently, Lanes et al[70] analyzed the KIGS data set to evaluate whether spontaneous versus induced puberty can influence AH in 772 girls with TS. Although girls in the spontaneous puberty group tended to grow slightly more during puberty than those with induced puberty, it was not enough to produce a significant difference in height SDs at near-AH. Puberty began ~1 year earlier in girls with spontaneous puberty, resulting in a shorter length of time taking GH therapy, compared with girls with induced puberty. However, the duration of puberty (from the onset until near-AH) was similar in both groups (3.5 years). Importantly, the authors found that Height-Standard Deviation Score (H-SDS) before and after puberty did not change significantly. Similarly, many authors reported no significant influence in terms of AH between either spontaneous or induced puberty.[17,39,69] These findings support the evidence that the major height gain during GH therapy for TS occurs in the prepubertal years, and the effect is maintained but generally not further improved by continuing therapy until near-AH.[15,70]

In contrast with these data, Quigley et al[11] reported a better AH outcome in girls with TS who had entered spontaneous puberty, and this result was confirmed both in the subgroup of GH early treated patients and early untreated patients. Notably, the early treated/spontaneous puberty subgroup attained the best height outcomes overall.

Can the Karyotype Influence AH in Patients With TS?

The effect of karyotype on growth in patients with TS is still a matter of debate.[14]

Some authors highlighted a more severe growth failure in patients with monosomy of the short arm of the X chromosome rather than in case of mosaicism.[71–76] In addition, 45,X karyotype is reportedly more frequent in girls with TS who require induction of puberty than in those with spontaneous puberty.[70] Therefore, the presence of the second X chromosome seems to influence the appearance of spontaneous puberty. This may suggest that the girls with spontaneous puberty are likely to have a milder phenotype and intrinsically better growth potential. However, this is not a constant finding.[10,39]

AH after GH treatment has been evaluated as a function of karyotype in the study performed by Ranke et al[21] on 987 children with TS in the KIGS database. They found that the height outcomes in the study cohort were not affected by the individual karyotypes. Most of the authors confirmed that karyotype did not show a predictive value on height prognosis and did not affect the outcome of GH administration or the height gain in girls with TS.[5,13,20,22,77] These reports may suggest that the growth disorder in TS is not strictly associated with the karyotype but instead could be related to the genetic predisposition that patients with TS have in common.[21,78]

Conclusions

In analyzing the literature data, even if they show great variability, we can draw several conclusions. First, prolonged GH therapy may enable patients with TS to achieve an AH close to the normal range for height within the general female population and higher than pretreatment height SDS prevision. Second, given the large variation in potential outcome, GH pretreatment- and treatment-related variables associated with higher AH were defined. These variables are: early initiation of treatment, normal height and prepuberal stage at the start of therapy, adequate GH dose, and absence of concomitant diseases. Third, adequate GH dose, according to the most recent international guidelines, is only one of the factors affecting the growth and AH in patients with TS and probably not the most impactful. Fourth, major height gain during GH therapy for TS occurs in the prepubertal years, and the effect is maintained but generally not further improved by continuing therapy until near AH. Finally, karyotype did not show a predictive value on height prognosis and did not affect the outcome of GH administration or the height gain in girls with TS.

Considering recent data from the scientific literature, the authors suggest the following recommendations: (1) start GH therapy as soon as possible (early); (2) use adequate GH doses, according to the last international guidelines, and evaluate possible dose increases in case of late start of therapy or if AH prediction is significantly impaired; (3) perform therapy until reaching AH and check the effectiveness of therapy with periodic auxologic evaluations, IGF-1 measures, and research of possible adverse effects; and (4) do not delay puberty induction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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