Review

GH Therapy in Non–Growth Hormone Deficient Children

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Posted Date: 5 November 2024

doi: 10.20944/preprints202411.0325.v1

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 doi:10.20944/preprints202411.0325.v1

Review

GH Therapy in Non–Growth Hormone Deficient Children

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Abstract: Before 1985 growth hormone (GH) was extracted from human pituitaries, and its therapeutic use was limited to children with severe GH deficiency (GHD). The availability of unlimited amount of recombinant GH (rhGH) allowed to investigate the efficacy of rhGH therapy in a number of conditions other than GHD. Nowadays, patients with Turner syndrome, SHOX deficiency, Noonan syndrome, Prader-Willi syndrome, idiopathic short stature, chronic kidney disease, and children born small for gestational age can be treated with rhGH in order to improve adult height. In patients with Prader-Willi syndrome rhGH therapy also improves body composition and cognitive function. Large post-marketing multinational studies in a huge number of pediatric patients demonstrated a good safety profile for rhGH. Recently, long-acting formulations of rhGH have been approved and licensed for GHD, and clinical trials are ongoing for other conditions. In this paper, we will review the use of rhGH for the treatment of children with conditions other than GHD.

Keywords: children; growth hormone; Turner syndrome; SHOX deficiency; Noonan syndrome; Prader-Willi syndrome; idiopathic short stature; chronic kidney disease; small for gestational age; long acting growth hormone

1. Introduction

Before 1985 growth hormone (GH) was extracted from human pituitaries, and its therapeutic use was limited to children with severe GH deficiency (GHD). The availability of unlimited amount of recombinant GH (rhGH) allowed to investigate its efficacy in a number of conditions other than GHD, including Turner syndrome (TS), SHOX deficiency, Noonan syndrome (NS), Prader-Willi syndrome (PWS), children born small for gestational age (SGA), idiopathic short stature (ISS) and chronic kidney disease. A summary of clinical recommendations for rhGH therapy in these patients is reported in Table 1. Recently, long-acting formulations of rhGH (LAGH) have been approved and licensed for GHD, and clinical trials are ongoing also for other conditions (Table 2). Large post-marketing multinational studies in a huge number of pediatric patients demonstrated, reportedly, a good safety profile for rhGH [1–4]. However, some adverse events are potentially associated with rhGH therapy and need to be monitored. In the short term, the most common adverse event is headache and is usually transient and benign. Intracranial hypertension with pseudotumor cerebri and slipped capital femoral epiphysis have also been described. In the long term, an increased risk of malignancy and insulin resistance are the most feared adverse events. Abnormalities of glucose tolerance and type 2 diabetes mellitus may occur, but the clinical significance appears to be low if any [5]. Conversely, an increased risk of new primary malignancies in pediatric patients treated with rhGH has never been reported [2]. Finally, rhGH therapy affects both thyroxine and cortisol catabolism that should be monitored before starting treatment and throughout [6–8].

Table 1. Recommendations for rhGH therapy in conditions other than GHD.

	rhGH dose	Criteria for rhGH therapy	Approved by
Turner syndrome	0.045–0.068 mg/kg/day	Short stature and/or	FDA and EMA

 doi:10.20944/preprints202411.0325.v1

		growth failure	
SHOX deficiency	0.045-0.050 mg/kg/day	Short stature	FDA and EMA
Noonan syndrome	0.035-0.066 mg/kg/day	Short stature	FDA and EMA
Prader-willi syndrome	0.5-1.4 mg/m²/day	Absence of: severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis	FDA and EMA
Small for gestational age	0.033-0.067 mg/kg/day	Short stature Age>3-4 years	FDA and EMA
Idiopathic short stature	0.24-0.47 mg/kg/week	Short stature	FDA
Chronic kidney disease	0.045-0.05 mg/kg/day	Short stature and/or growth failure Age>6 months Dialysis or stage 3–5 of CKD or kidney transplant or nephropathic cystinosis Absence of severe secondary hyperparathyroidism, diabetic retinopathy, acute critical illness, and active cancer	FDA and EMA

Table 2. Clinical trials on LAGH in conditions other than GHD.

	Published	**Ongoing** [50]
Turner syndrome	Gao et al. 2022 [51] Jintrolong, 75 patients, 2 years of therapy	NCT05690386, Lonapegsomatropin NCT05330325, Somapacitan NCT05723835, Somapacitan NCT05838885, YPEG-rhGH
SHOX deficiency	-	-
Noonan syndrome	-	NCT05330325, Somapacitan NCT05723835, Somapacitan
Prader-willi syndrome	-	-
Small for gestational age	Juul et al. 2023 [60] Somapacitan, 62 patients, 26 weeks of therapy Juul et al. 2024 [61]	NCT05330325, Somapacitan NCT05723835, Somapacitan NCT03878446, Somapacitan NCT05838885, YPEG-rhGH

 doi:10.20944/preprints202411.0325.v1

	Somapacitan, 62 patients, 52 weeks of therapy	
Idiopathic short stature	Choi et al. [62]	NCT05330325, Somapacitan
	EutropinPlus, 10 patients, 12 months of therapy	NCT05723835, Somapacitan
		NCT05838885, YPEG-rhGH
Chronic kidney disease	-	-

In this paper, we will review the use of rhGH for the treatment of children with conditions other than GHD.

2. Turner Syndrome

TS is a sex chromosome disorder caused by the complete or partial absence or by structural abnormalities of one of the X chromosomes. TS is the most common chromosome disorder in females, and has a prevalence of 25-50/100.000 [9]. Patients with TS typically present with short stature, hypergonadotropic hypogonadism and mild skeletal dysplasia, although the clinical presentation is variable. The growth failure usually starts during foetal life and a decline of height standard deviation score (SDS) is progressive and may be evident since the first years of life [9]. The most important cause of short stature in patients with TS is probably the haploinsufficiency of the short stature homeobox-containing (*SHOX*) gene located in the pseudoautosomal region (PAR) of the X chromosome [10]. However, the cause of short stature in these patients is multifactorial. Abnormalities in GH and insulin-like growth factor-1 (IGF-1) function, such as resistance to IGF-1 [11–13], and estrogen deficiency [14] may also contribute to reduce linear growth. Adult height in untreated girls with TS is approximately 15-20 cm below the adult height of healthy women (144.3 ± 6.7 versus 160.2 ± 6.3 cm) [15].

The use of recombinant rhGH to treat short stature in TS patients has been approved almost thirty years ago, and many studies have shown its efficacy in improving height velocity and adult height [16]. The latest international guidelines [9] recommend to start rhGH therapy early to prevent further loss of potential height. Treatment may be proposed from as early as 2 years of age in the presence of short stature or likelihood of short stature and growth failure (growth velocity below normal value or declining). In case of late diagnosis, rhGH treatment may still be started, as long as the epiphyses are open. RhGH treatment should be discontinued when bone age is ≥14 years and/or height velocity is <2 cm/year since there are no reasons for continuing rhGH therapy after epiphyseal closure.

Despite more than fifty studies on rhGH treatment in TS, only few randomized, controlled trials (RCTs) have compared the treated group with untreated or placebo control groups [17–21] and only two of these RCT have followed the untreated control group up to adult height [17,19]. The 2007 Cochrane Center review [16] based on these studies concluded that the growth velocity of patients with TS treated with rhGH is 2-3 cm/year higher than untreated patients. More recently, a meta-analysis [22] based on data from the two RCTs that followed untreated patients with TS up to adult height [17,19], reported a mean adult height gain of 7.2 cm in patients with TS treated with rhGH, with adult height within the normal range for 40%-50% of treated individuals versus 4%-16% of untreated subjects. Other studies reported gains of 15-17 cm in patients with TS treated since young age with high dose of rhGH versus estimated adult height [23–25]. Large observational studies have confirmed the efficacy of rhGH therapy in TS patient, with an adult height gain of about +1 SDS, but with significant individual variability [26]. In summary, if catch-up growth in the first 2 years of treatment brings height within the normal range, and sustained normal height velocity can be achieved, adult height is likely to be in the lower part of the normal range for most GH-treated patients with TS. However, these patients may experience absent or minimal pubertal growth spurt that often results in partial loss of the relative pre-pubertal height SDS gain [27].

The recommended dose of rhGH in patients with TS is 0.045–0.050 mg/kg/day (or 1.3-1.5 mg/m^2/day) [9], (Table 1). According to international guidelines and local authority-approved dose range, if response is suboptimal, the rhGH dose may be increased to a maximum of 0.068 mg/kg/day

 doi:10.20944/preprints202411.0325.v1

(or 2.0 mg/m²/day). The outcome is better in girls with taller target height, younger age at initiation of treatment, and a longer duration between rhGH treatment start and onset of puberty.

Both long-term prospective and observational clinical trials have demonstrated a good safety profile of rhGH treatment in TS [26,28–40]. However, routine monitoring of IGF-1 concentrations and glucose metabolism is recommended. IGF-1 should be maintained within the normal range for age, sex and pubertal stage. If IGF-1 levels are persistently higher than the normal levels for age, rhGH dose reduction is recommended [9]. Girls with TS appear to have an increased risk of intracranial hypertension, slipped capital femoral epiphysis and scoliosis during rhGH treatment compared with patients with idiopathic GHD or ISS [26,41,42]. However, scoliosis is common in girls with TS regardless of rhGH therapy [43]. Likewise, girls with TS have an increased risk of carbohydrate metabolism impairment [44–46] and transient abnormalities of carbohydrate metabolism have been reported during or following rhGH therapy [24,47–49]. Finally, there is no evidence of higher risk of neoplasm in patients with TS treated with rhGH [9].

Recently, LAGH have been approved for the treatment of patient with GHD (Table 2). Several trials with LAGH in children with TS are ongoing [50]. A single 2-year retrospective study [51] showed that pegylated LAGH have a comparable effect to daily rhGH therapy on growth promotion without serious adverse effects. Further studies are required to recommend LAGH formulations for the treatment of short stature in girls with TS.

Other strategies have been investigated to improve stature in TS patients. Addition of oxandrolone to rhGH has been used off-label for decades [52–56] with a positive effect on the adult height of 2-4 cm [57,58]. However, FDA withdrew oxandrolone in 2023 due to adverse events, and accordingly, the latest guidelines no longer recommend its use in TS [9].

Other authors speculated that the use of ultra-low-dose oral ethinyl estradiol during the prepubertal period, combined with rhGH, could increase adult height [18,20,59]. However, further studies are required to confirm long-term growth benefit and establish formulation, route, and dosing of estrogen. Again, the latest guidelines do not recommend the use of prepubertal very-low-dose estrogen replacement as a growth-promoting therapy in patients with TS [9].

Finally, it is recommended to start low dose estrogen replacement between 11 and 12 years of age, if pubertal induction is required (FSH elevated on at least two sequential measurements) [9]. There is no evidence that delaying pubertal induction (at about 14 years old) results in better adult height.

3. SHOX Deficiency

The *SHOX* gene deficiency is the most frequent monogenic cause of growth disorder and may be associated with isolated or syndromic forms of short stature [63]. The *SHOX* gene is located in the pseudoautosomal region 1 (PAR 1) of the short arms of the sex chromosomes. *SHOX* gene function is dose-dependent and both males and females express two active copies of this gene. Thus, haploinsufficiency or complete loss of function of *SHOX* determine atypical proliferation and differentiation of chondrocytes with compromised growth of the long bones. The phenotype varies from mild isolated short stature (loss of function of one allele), to more extreme phenotype such as Langer syndrome osteodysplasia (extreme short stature, mesomelia, and limb deformity) and Leri–Weill syndrome (severe short stature, abnormal craniofacial phenotype, and mesomelia of the upper and lower limbs). Conversely, expressing an extra copy of *SHOX* can cause tall stature, as is seen in Klinefelter syndrome (47, XXY) [60–62].

Children with *SHOX* mutations have been shown to benefit from rhGH therapy (Table 1), with outcomes similar to those observed in girls with TS [66,67].

Data from the multicentric observational “Genetics and Neuroendocrinology of Short Stature International Study” (GeNeSIS) [68] confirm the efficacy and safety of rhGH therapy in these patients. A more recent study [69] reported that adult height of patients with SHOX haploinsufficiency treated with rhGH therapy was 6.3 cm (1 SD) higher than untreated ones. In the same study, the authors reported that the use of GnRH analogues in addition to rhGH in pubertal patients allowed the

 doi:10.20944/preprints202411.0325.v1

attainment of an adult height similar to patients who start rhGH therapy alone in the prepubertal age. Further studies are needed to confirm these data.

4. Noonan Syndrome

NS is an autosomal dominant disorder with an estimated incidence of 1 in 1.000–2.500 live births. The phenotype is variable with 50%–70% of patients presenting short stature. Other features may include early feeding difficulties and mild mental retardation, typical facial features such as hypertelorism, large head and forehead, down slanting eyes, epicanthal fold, heart defects (pulmonary valve stenosis or hypertrophic cardiomyopathy), chest and spinal deformities [70,71].

NS is caused by pathologic variants in genes that encode proteins of the RAS-MAPK signal transduction pathway [71,72]. A number of genes have been described associated to NS. For most genetic mutation the transmission follows a dominant pattern of inheritance (PTPN11, BRAF, KRAS, MAP2K1, MRAS, NRAS, RAF1, RASA2, RIT1, RRAS2, SOS1, or *SOS2* [73]). Both dominant and recessive mutations have been described for *LZTR1* [74,75].

The use of rhGH treatment in patients with NS was first approved by the FDA in 2007, and then almost worldwide. Although some studies have reported reduced response to rhGH treatment in PTPN11 positive patients [76,77], the majority of them have demonstrated an increased growth velocity and an increased mean height SDS [78–83], with a mean height gain of 0.6–2.0 SDS. The outcome is significantly correlated to the dose, age at the start, bone age and the duration of treatment, but not gender [78,80].

The suggested dose varies among studies, ranging from 0.035 and 0.066 mg/kg daily [78,79,84] (Table 1). No severe adverse events have been reported [80]. The RAS-MAPK pathway is important for cellular differentiation and proliferation, and mutations of its components increase the risk of malignancy in patients with NS regardless of the use of rhGH therapy [85–88]. Although it is not known whether rhGH treatment may affect cancer risk, close monitoring of IGF-1 levels and periodic tumor surveillance is highly recommended [89]. A phase III study is ongoing to compare the efficacy and safety of weekly rhGH in children with NS [90] (Table 2).

5. Prader-Willi Syndrome

PWS is a complex rare disease with an incidence of approximately 1 in 16.000 to 1 in 21.000 live births. PWS is an imprinting disorder caused by three main mechanism affecting the genes that are exclusively expressed in the paternal inherited chromosome, specifically in the 15q11.2–q13 region [91]. Most cases (61%) are due to a paternal deletion of the 15q11.2–q13 region, followed by maternal uniparental disomy (UPD in which both chromosome 15 are inherited from the mother) in the 36% of the cases, and an imprinting defect (ID, 3%) [92].

The phenotype differs according to age. Newborns may present severe hypotonia and feeding problems, while children may present developmental delay and hypothalamic hyperphagia which lead to a progressive development of obesity associated with temper tantrums [93,94]. Short stature, adrenal insufficiency [95], hypogonadism [96], hypothyroidism may also be associated.

RhGH therapy has changed the natural history of PWS [97]. Treatment has been shown effective in preventing the complications of PWS patients and increasing their life span [98]. Treatment is effective also on body composition and lipid profile [94,98–100], exercise tolerance [101], psychomotor development [98,102], muscle strength, and bone health [103]. Early treatment is associated with better improvements of psychomotor development [102,104].

RhGH should be started before 1 year of age, or at least as soon as possible before the onset of obesity [105], and continued for as long as benefits overwhelm the risks [106]. Severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis must be ruled out before starting treatment [106].

Current guidelines [106] suggest to start with a daily dose of 0.5 mg/m2/day to a maximum of 1.4 mg/m2 (~0.047 mg/kg) according to the clinical response and IGF-1 levels that should remain always within the normal range (Table 1).

 doi:10.20944/preprints202411.0325.v1

No major adverse events have been reported during rhGH treatment in PWS and no increased risk of diabetes, scoliosis or central and obstructive apnoea have been observed [98,105,107–109]. Patients and families must be informed about the potential association between rhGH therapy and unexpected death, and polysomnography should be obtained before starting therapy for the reported possible association between rhGH therapy and lymphoid tissue growth [110] that may lead to unexpected death. Some authors reported a higher risk of leukaemia and lymphoma not related to rhGH in patients with PWS [111].

6. Small for Gestational Age

Children born SGA have birth weight and/or birth length below −2 SDS for their gestational age. In the first 2–3 years of life most of them catch-up growth (defined as a growth rate higher than 0 SDS, allowing to reach a height into the normal height range, according to the mid-parental height). However, about 10% of SGA children will have persistent short stature and are at risk of becoming short adults [112–114].

Several studies have shown that rhGH therapy is effective to improve adult height in these patients [115–120], with an increase in mean height gain of +1.25 SDS, although variable between different studies. RhGH therapy has been approved since 2001 for children born SGA without catch-up growth. RhGH therapy-induced catch-up growth is characterized by normal body proportions [116,121]. The recent international consensus guidelines [114] recommend to start rhGH therapy in short children born SGA at an age after which catch-up growth is unlikely (3-4 years of age), after having ruled out other causes for short stature.

The recommended rhGH starting dose is 0.033 mg/kg/day, to be increased to a maximum dose of 0.067 mg/kg/day if growth response is unsatisfactory (height gain <0.5 SDS) during the first year of treatment (Table 1). It is recommended to monitor IGF-1 concentrations at least annually.

A number of factors can be associated with growth response to rhGH treatment in children born SGA [119,122–126], and among them duration of treatment, age and height at rhGH start, birth length and birth height are the most important. The variability in response to rhGH therapy is likely to be also associated with possible underlying genetic variants, responsible for intrauterine growth restriction and short stature [127]. RhGH therapy is not recommended in genetic disorders with predisposition to develop cancer (chromosomal breakage syndromes, DNA repair disorders, and others) [114].

RhGH treatment has proven to be safe [4]. SGA children commonly have reduced insulin sensitivity which worsens during rhGH treatment [128]. However, glycated haemoglobin concentrations remain within the normal range, and type 2 diabetes mellitus does not develop [129–131]. This phenomenon is probably due to a compensatory increase in insulin secretion owing to the insulin-antagonistic effects of GH [129,130,132,133]. Insulin sensitivity improves after cessation of rhGH therapy [123,132]. According to recent guidelines [114], during rhGH treatment it is recommended to monitor thyroid function annually. Conversely, routine evaluation of metabolic parameters (fasting serum lipid and glucose/insulin/HbA1c concentrations) is recommended only for SGA children with associated risk factors (overweight, obesity, family history).

Recently, LAGH resulted effective and safe also in SGA patients in the first phase 2 study after 52 weeks of treatment (Table 2). This study has shown that treatment with somapacitan at the dose of 0.24 mg/kg/week was not inferior to daily rhGH at the dose of 0.067 mg/kg/day in children born SGA [61].

7. Idiopathic Short Stature

ISS is defined as a condition with height SDS ≤–2.25 (≤1.2nd percentile) for a given age, sex, and population group, associated with growth rates unlikely permits the attainment of adult height in the normal range, with normal birth height and weight, without evidence of systemic, nutritional, endocrine, or chromosomal abnormalities. This definition includes a heterogeneous group of children with unidentified causes of short stature, and also short children with familial short stature and constitutional delay of growth and puberty [134].

 doi:10.20944/preprints202411.0325.v1

The first short-term trial in children with ISS treated with pituitary derived GH was conducted in 1983. The authors reported an increase of growth rate of 2 cm/year during GH therapy [135]. Since then, a large number of studies have been published [136–138], but only few of them are controlled and/or randomized [139–141]. A recent metanalysis [142] including both the controlled (115 children, 79 cases and 36 controls) [139–141], and the non-controlled studies (477 children, 181 cases and 296 controls) [143–149], showed a mean adult height gain of 0.45-0.65 SD (about 3-4 cm). The authors concluded that no single, high quality evidence trial was conducted up to adult height, that the overall effect of rhGH therapy in ISS patients was lower than that achieved in other conditions for which rhGH was licensed, and that the response to therapy was highly variable among patients and studies [142]. Many factors are involved in the individual variability in the response to rhGH therapy including age at start of therapy, length at birth, dose of GH, difference between height and target height, and difference between age and bone age [150].

In 2003 the FDA approved rhGH therapy for ISS children, while EMA has not authorized this treatment. Indeed, to date the real efficacy of rhGH treatment in patients with ISS is still debated [138].

Thus, current guidelines [151] suggest to take the decision to treat with rhGH on a case-by-case basis, after assessment of physical and psychological burdens, and discussion of risks and benefits with the parents. The recommended initial dose is 0.24 mg/kg/week, to be titrated according to clinical response to a maximum dose of 0.47 mg/kg/week (Table 1). Discontinuation of rhGH therapy is recommended if the response is not after one year of treatment is not adequate (increase in Height SDS >0.3–0.5).

Aromatase inhibitors have been used to delay bone maturation alone or in combination with rhGH [152–155]. However, the use of aromatase inhibitors is still not approved due to potential adverse effects (increased insulin resistance, reduced high-density lipoprotein cholesterol, vertebral deformities, long-term effects on spermatogenesis and infertility, impairment of cognitive function) [156].

Finally, studies are ongoing to evaluate efficacy, safety and tolerability of LAGH formulation in ISS children, with promising results [62] (Table 2).

8. Chronic Kidney Disease

Most patients with chronic kidney disease (CKD) have decreased growth rate with consequent short stature, that is often not normalised by dialysis and results in reduced adult height [157]. A large number of factors are responsible for the growth failure observed in these children. Among them the most important factors are malnutrition, abnormalities of the GH/IGF-1 axis with GH insensitivity, and corticosteroid therapy [157]. A number of trials have shown that rhGH therapy increases growth rate and improves height SDS in children with chronic renal failure [158,159]. Current guidelines recommend that children aged above 6 months on dialysis or with stage 3–5 of CKD should be candidates for rhGH therapy if have persistent growth failure (height <3° percentile for age and sex and height velocity <25° percentile, or height between 3° and 10° percentile and persistent height velocity <25° percentile) once other potentially treatable causes of growth failure have been considered. Children who received a kidney transplant can be treated with rhGH if they have persistent growth failure 1 year after transplantation and if steroid-free immunosuppression is not an option. In children with CKD due to nephropathic cystinosis with persistent growth failure, rhGH therapy is considered at all stages of CKD.

RhGH therapy should not be started in patients with severe secondary hyperparathyroidism (parathyroid hormone >500 pg/ml), diabetic retinopathy, acute critical illness and active malignancy [157].

The recommended dose of rhGH is 0.045-0.05 mg/kg/day [157] (Table 1). The response to rhGH therapy should be regularly assessed, in terms of both efficacy and safety, with adjustements of the rhGH dose or eventual discontinuation in case of adverse events. Poor response to rhGH therapy is common in children with CKD. According to the Summary of Expert Opinion [160], rhGH should be discontinued if height velocity is below 2 cm/year after 1 year of therapy.

 doi:10.20944/preprints202411.0325.v1

The expected height gain after 2-5 years of rhGH treatment is estimated to be about 7 cm in prepubertal children [157,158]. Studies in pubertal children have yielded conflicting results [161,162].

A number of open issues are still in place on the use of hGH in patients with CKD. Among all, the effect on adult height is inconsistent and unpredictable [160], due to the extreme heterogeneity of the patients. In fact, CKD has multiple causes, and its duration is highly variable. Associated steroid therapy, nutrition, hormone resistance, and comorbidities are among other confounding factors. For these reasons a personalized approach to the patient is of paramount importance and the option to start GH treatment should be carefully evaluated for every single patients [163].

9. Conclusions

RhGH treatment is classically indicated in patients with GHD and has proven effective and safe. RhGH treatment produces an increase in growth velocity and normalizes adult height in a great number of SGA children. Although to a lesser extent, rhGH therapy is also effective in increasing adult height in patients with Turner syndrome, SHOX deficiency, Noonan syndrome and in children with chronic kidney disease. RhGH therapy has proven beneficial also in patients with Prader Willi syndrome with positive effects on growth, body composition, muscle function and cognition. RhGH therapy has been approved in many countries also for children with ISS, although its efficacy is still debated.

In all conditions the response to therapy exhibits a large interindividual variability and it is difficult to predict. Therefore, the decision to start GH treatment must be considered on an individual basis taking into account auxological, clinical and psychosocial issues.

In the near future, LAGH formulation will probably be available to treat these patients and improve their adherence to therapy and quality of life.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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