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Clinical Study

Growth Hormone Utilization Review in a Pediatric Primary Care Setting

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Abstract

Objective: One of the main problems facing public health providers and administrators in many countries is ensuring the rational use of high-cost drugs. In this regard, on-going process of medication use evaluation can be considered as a useful tool. In this study, we evaluated certain usage aspects of a highly-cost medication, that is, recombinant growth hormone (GH).

Methods: This cross-sectional study conducted from August 2012 to August 2014. Children receiving GH ± gonadotropin releasing hormone (GnRH) analogs were included in the study. A researcher-designed checklist was developed to evaluate the GH utilization in these patients. Baseline demographic characteristics and background clinical and growth data, as well as any aspects of drug therapy including indications, dosing, monitoring, and discontinuation were collected from the patients' medical records.

Findings: Seventy children receiving GH entered the study, of which 23 patients (32.85%) received GH and GnRH analogs simultaneously. At the baseline, 67 children (95.7%) had GH stimulation test, whereas serum insulin-like growth factor-1 (IGF-1) levels were measured in 63 (90%) patients. Sixty-seven patients (95.71%) had thyroid function test, whereas bone age was determined in 68 children (97.14%). The mean ± standard deviation of GH dose for idiopathic short stature, GH deficiency, Turner's syndrome and born small for gestational age in our study was 0.22 ± 0.025 mg/kg/week, 0.23 ± 0.04 mg/kg/week, 0.22 ± 0.015 mg/kg/week, and 0.23 ± 0.02 mg/kg/week, respectively. Height and weight of all patients were followed every 3–6 months, regularly. Thirty patients were treated with GH for at least 1 year, of which thyroid hormones and IGF-1 levels were measured annually in 25 (83.33%) and 26 (86.66%) patients, respectively; while bone age was evaluated in 13 (43.33%) children, annually. GH treatment was discontinued in 15 patients (21.42%), while financial problem was the major reason.

Conclusion: Diagnostic tests and monitoring of height, weight, IGF-1 level and thyroid function was properly performed in this setting. However, a number of patients with ISS and Turner's syndrome were under-dosed.

Key Words: *Growth hormone, medication use evaluation, monitoring, pediatrics*

Introduction

Growth hormone (GH) is a necessary factor for normal constitutional and pubertal growth in children. Growth is increased by direct effect of GH on the growth plates and by its stimulating effect on the production of insulin-like growth factor (IGF). GH deficiency, Turner's syndrome, chronic renal insufficiency, born small for gestational age (SGA), idiopathic short stature (ISS), and Prader–Willi syndrome are among the Food and Drug Administration (FDA) approved indications for recombinant human GH (somatropin).[1] However, treatment with the recombinant human GH has not immediate therapeutic advantages,[2] and to achieve therapeutic benefits, the medication should be given 6–7 injections per week for several years.[3]

Administration of gonadotropin releasing hormone (GnRH) analog is the treatment of choice for central precocious puberty, which can improve adult height by suppressing pubertal development and reducing bone maturation. Monotherapy with GnRH analogs in both sexes has small and variable effect on adult height and is usually not recommended, while combination therapy with a GnRH analog and GH may have potential effect on final adult height.[4,5] Although, it should be noted that GH treatment can have variable treatment efficacies in different patients.[6,7]

Patients should be evaluated every 3–6 months. Increases in height and height velocity are the most important markers of response to GH treatment. Monitoring of serum IGF-1 levels

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is recommended for assurance of compliance, dosing, and safety considerations. Hypothyroidism may occur during the GH treatment; hence, thyroid function assessment should be considered periodically.[8,9]

Postmarketing studies have shown the efficacy and safety of GH when used in FDA-approved indications.[10] Although not prevalent, headache, visual problems, nausea and vomiting, peripheral edema, arthralgia, myalgia, paresthesia, antibody formation, hypothyroidism, and injection site reactions are the reported side effects of GH therapy.[11]

One of the problems facing public health providers and administrators in many countries is ensuring the rational use of drugs.[12] One strategy to ascertain the appropriate use of drugs is the ongoing process of medication use evaluation (MUE). MUE is a tool for monitoring the prescribing patterns of health-care providers to ensure appropriate pharmacotherapy.[13] MUE findings may help health-care systems to improve prescribing patterns and optimize use of scarce resources. Appropriate prescribing can be recognized at three levels: (a) indication for drug therapy, (b) choice of the drug, and (c) duration of treatment, route of administration, frequency of monitoring, and drug interactions.[14] MUE can recognize inappropriate and/or unnecessary high-cost drug therapies by comparing the actual status of medication use with predetermined standards or guidelines.[15]

There are approved protocols for the appropriate use of recombinant GH in different indications;[16] however in Iran because of high treatment expenses and limitations in drug availability, they may not be followed thoroughly. While any incorrect use of the drug (including dosage and duration of treatment) involve the wastage of such highly-cost medication. Since there are sparse data in this regard in our population, the current study was designed to investigate the certain aspects of GH utilization such as indication, dosing, monitoring and discontinuation, in Iranian pediatric population.

Methods

This cross-sectional study conducted from August 2012 to August 2014 at Endocrine clinic, Children's Medical Center, affiliated to Tehran University of Medical Sciences (TUMS). The study protocol was approved by TUMS Ethics Committee. Children receiving GH (somatropin) ± GnRH analog (Triptorelin) were included. A researcher-designed checklist was developed to evaluate the usage pattern of GH and GnRH analogs in these patients. The checklist had four sections: (a) demographic, clinical and laboratory data; (b) GH and GnRH analog indications and dosing schedule; (c) follow-up data such as patient's height, weight, pubertal stage, laboratory tests, drug compliance and side effects; (d) reasons for discontinuation of GH treatment. Data were collected from the patients' medical records.

The baseline variables included: patient's sex, age, birth weight, gestational age and delivery status, current height, weight, bone age, puberty stage, and parents' height.

To measure drug compliance, parents of study subjects were interviewed and asked about the number of missing injections during the last month. Patients were categorized as high compliance if they received more than 80% of injections, moderate compliance if they received 60%–80% of injections and low compliance if they received <60% of injections.

The collected data were analyzed using SPSS software (IBM company, Chicago, IL, USA), version 16.0. Distribution of continuous variables was determined using Kolmogorov–Smirnov test. Continuous variables are shown as mean ± standard deviation (SD), whereas categorical data are shown as number (percentage).

Results

Seventy children receiving GH entered the study, of which 23 patients (32.85%) received GH and GnRH analogue simultaneously. Baseline characteristics and background data of children are shown in Table 1. Duration of GH treatment was 9.27 ± 6.02 months. Twenty-two patients (31.42%) had family history of constitutional delay of growth and puberty, whereas there were no reports of family history of GH deficiency among all patients. One patient was receiving letrozole, 2 were receiving hydrocortisone, 6 were receiving levothyroxine and as mentioned previously, 23 patients were on triptoreline. Among patients who were receiving combination of GH and GnRH analog, 21 (91.3%) were female.

At baseline, GH stimulation test was carried out in 67 children (95.71%) and serum IGF-1 levels were measured in

Table 1: Baseline demographic characteristics and background clinical and growth data of the study patients (*n*=70)

Variable (unit)	Value
Baseline demographic characteristics	
Age (years)	9.05±3.33
Height (cm)	121.21±20.90
Weight (kg)	27.08±11.86
Sex, female	44 (62.85)
Background clinical and growth data	
Height SDS	−2.05±1.50
Delayed bone age	26 (37.14)
Delayed puberty	1 (1.42)
Birth weight under 2.5 kg	26 (37.14)
Normal gestational age	52 (74.3)
Vaginal delivery	33 (47.1)
Traumatic delivery	2 (2.8)
Prolonged jaundice at birth	3 (4.3)
Hypoglycemia at birth	2 (2.8)
Father height under 160 cm	12 (17.1)
Mother height under 150 cm	18 (25.7)
Indications of growth hormone treatment	
Idiopathic short stature	45 (64.2)
Growth hormone deficiency	15 (21.4)
Small born for gestational age	3 (4.3)
Turner's syndrome	3 (4.3)
Others	4 (5.8)

Data are presented as mean±SD or *n* (%), where applicable. SD=Standard deviation, SDS=Standard deviation score

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63 patients (90%). Sixty-seven patients (95.71%) had thyroid function tests, whereas 22 patients (31.42%) had luteinizing hormone (LH) and follicle-stimulating hormone (FSH) measurements. Blood glucose was measured in 11 patients and bone age was determined by X-ray in 68 children (97.14%) at the beginning of treatment.

GH was administrated as nightly subcutaneous injection once a day in almost all children except for seven, which had 6 days a week injections. In four patients with ISS, after 6 months of therapy, GH dose was reduced to 6 days a week, due to increased IGF-1 levels. GH dosing was initiated based on body weight for all patients at the beginning of the treatment and was adjusted according to serum IGF-1 levels after 6 months.

The mean dose of somatropin for children with ISS, GH deficiency, Turner's syndrome and SGA in our study was 0.22 ± 0.03 mg/kg/week, 0.23 ± 0.04 mg/kg/week, 0.22 ± 0.02 mg/kg/week and 0.23 ± 0.02 mg/kg/week, respectively. All patients used pen devices for GH injection. Dosing regimen for triptorelin was 3.75 mg every 28 days and 11.25 mg every 90 days for 17 and 6 patients, respectively.

Height and weight of all patients were followed every 3–6 months. There were thirty patients who were treated with GH for at least 1 year. Thyroid function tests and IGF-1 levels were measured every 6 months in 25 (83.33%) and 26 (86.66%) patients, respectively. Bone age was evaluated in 13 (43.33%) children at least annually. During GH treatment, IGF-1 levels met the therapeutic goal (slightly higher than average) except in four patients in whom IGF-1 increased to higher than normal range and GH dose was adjusted accordingly.

Sixteen patients were treated with the combination of GH and triptorelin for more than 6 months, of which ten patients (62.50%) had measurements of LH and FSH levels, every 6 months during their follow-up. The mean height increment was 4.21 ± 1.91 cm in children who were treated with GH alone, and 3.55 ± 1.61 cm in those who were treated with GH in combination with GnRH analog ($P = 0.16$).

In the current study, three children had leg pain, one had headache and one had experienced injection site reaction. GH treatment was discontinued in 15 patients (21.42%) because of financial problems ($n = 11$), fears of side effects ($n = 2$), orthopedic problems ($n = 1$), and achievement of the final height ($n = 1$).

After 6 months of therapy, height development was 4.59 ± 1.78 cm and 4.82 ± 2.03 cm in girls and boys, respectively. Fifty-three patients (75.71%) had high compliance, while 5 (7.14%) had moderate and 12 (17.14%) had poor compliance to GH injections.

Discussion

GH has been used in various growth disorders for more than five decades. It is usually administered as daily subcutaneous injections. Diagnosis and body weight of the patient are determinants of GH dose.[16] GnRH agonists and GH combination therapy have been used to improve adult height in precocious puberty.[17] GH treatment is costly, and stopping the treatment at a "normal" rather than "maximum" height is a strategy to limit costs. Justifying the cost of treatment by considering the morbidity of short stature and benefits of GH treatment is an issue that those who prescribe and pay for GH treatment are encountered.[18]

Evaluation of GH utilization in our study demonstrated that initiating GH therapy was according to the literature. More than 95% of our patients had GH stimulation test and in 90% of subjects, IGF-1 level was measured. Majority of our patients had ISS and more than half of the patients ($n = 44$) were girls.

In our study, there was no significant difference between males and females growth response. While in a study by Cohen *et al*., prepubertal males had a linear GH dose-response curve for growth which differed from prepubertal females.[19]

Pasquino *et al*. concluded in their study that the growth response obtained with the combination therapy of GH and GnRH analogs is more significant. However, they also recommended that the cost-effectiveness of such invasive treatment must be considered.[17]

In our study, there was no significant difference in growth response between patients treated with GH alone and children treated with combination of GH and GnRH analog. In line with our study, van Gool *et al*. showed that there was no significant difference in height gain among patients who used GH and GnRH agonist combination or GH alone.[20]

In the current study, 48 subjects were treated with lower than recommended GH dose, including 2 patients with Turner's syndrome and 45 patients with ISS. However, despite the insufficient dose, all patients had appropriate growth response to GH treatment. All children with GH deficiency were receiving the adequate dose which can be due to the fact that doses tend to be lower in GH deficiency.[16]

Cohen *et al*. study on prepubertal GH-deficient children showed that individual sensitivity to GH treatment, as manifested by achieved serum IGF-I levels, plays a key role in growth response.[19] In our study, most of the patients' IGF-1 levels met the therapeutic goal during follow up. Based on the data presented here, IGF-1 and thyroid function monitoring were done properly in the studied clinic.

While according to Kaufman and Sy study it seems that bone age monitoring is useful in evaluation of growth response to GH treatment, bone age was only evaluated in 43.33% of our patients.[21] It seems that bone age is a better predictor of response compared with chronological age, because of the relationship between growth potential and bone maturity.[22]

General safety of recombinant human GH for treatment of various pediatric growth disorders has been demonstrated. It has been demonstrated that adverse effects of GH therapy is less frequent in children (3%) than adults (10%).[9] There were few reported adverse effects in our study.

Implementing strategies to improve compliance with GH injection might be of particular clinical benefit.[6] Despite

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the availability of GH vials in our country, all patients used pen devices in our study which can be related to ease of administration.

The main factors which influenced compliance in this study were financial problems and fear of GH adverse effects. Although insurance companies cover 90% of GH costs in Iran, financial problems is still the major barrier to patient compliance and needs to be considered by policymakers. Furthermore, patients should be assured about overall safety of GH therapy by health care professionals.

Diagnostic tests and monitoring of height, weight, IGF-1 level, and thyroid function were properly conducted in the study setting. But GH dosing was not within the recommended dosage range for patients with ISS and Turner's syndrome. Drug compliance was acceptable, although it can be improved by addressing the barriers.

Authors' Contribution

Fatemeh Sayarifard designed the study and interpreted the data, Fereshteh Bakhshi Imcheh selected the patients, obtained and interpreted the data and drafted the manuscript, Toktam Faghihi designed the study, Shirinsadat Badri designed the study and revised the manuscript, Mostfa Qorbani carried out statistical analysis and interpreted the data, Mania Radfar designed and supervised the study, interpreted the data and revised the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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