



Adverse events of replacement therapy in children with growth hormone deficiency

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Abstract. Background. The purpose was to analyze and summarize the accumulated short-term and long-term safety data in children with growth hormone deficiency (GHD) treated using recombinant human growth hormone (rhGH) based on the results of a physical examination, assessment of vital signs, laboratory parameters, and follow-up. **Materials and methods.** The study was conducted at the Odessa Regional Children's Clinical Hospital from 2012 to 2022, with 92 children treated for GHD using rhGH at an average dose of 0.033 mg/kg/day. The evaluation of the safety of this therapy was based on assessing the incidence of adverse events (AEs) as a negative consequence of medical care. We analyzed both short-term and long-term outcomes. **Results.** When studying the short-term safety of rhGH therapy according to physical examination data, AEs were found in 18 (19.57 %) children, including intracranial hypertension (1), arthralgia (1), prepubertal gynecomastia (1), anemia (3), manifestation of latent adrenal insufficiency (3), latent thyroid insufficiency (2), impaired glucose tolerance (7). 20.6 (7.0 ÷ 34.2) % of patients with unacceptable adherence to rhGH therapy reported painful injections compared to 4.3 (–1.6 ÷ 10.2) % of children with acceptable compliance ($\chi^2 = 5.15$; $p = 0.02$). None of the children experienced serious adverse events such as scoliosis progression, slipped capital femoral epiphysis, edema, and impaired vital functions. AEs in terms of hematological and biochemical parameters were usually transient, often in combination with intercurrent diseases, and were not associated with rhGH. In long-term safety, there was no association between rhGH therapy and the risk of cancer, cardiac, and cerebrovascular diseases. Still, three children (3.26 %) had type 2 diabetes, with overweight in one case and obesity in two. **Conclusions.** In general, in the short-term context, rhGH therapy for children with GHD is safe. The pain at the injection site is a clinically significant AE as a cognitive emotional barrier to the adherence to rhGH therapy. From the point of view of the long-term safety of rhGH therapy, the fact that type 2 diabetes was detected in 3 (3.26 %) children with increased body weight and obesity is essential.

Keywords: children; recombinant human growth hormone; safety

Introduction

The Pediatric Endocrine Society has recently updated its guidelines for recombinant human growth hormone (rhGH) therapy in children with growth hormone deficiency (GHD) [1]. The new policies are more conservative than their predecessors and recommend short-term safety monitoring for potential issues like intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression. It is also recommended to reassess adrenal and thyroid axes after initiating GH therapy and monitor the GH recipient's glucose homeostasis. Long-term safety control includes monitoring cancer incidence and cardiovascular pathology [2]. Research has shown that GH therapy is safe for children with no known risk factors for can-

cer [3, 4]. When combined with environmental, genetic, and ethnic risk factors and comorbidities, rhGH therapy increases the risk of cardiac and cerebrovascular diseases in the long term [5]. Relevant studies have also examined the short-term and long-term safety of prolonged rhGH preparations administered once a week, once every two weeks, or monthly [6, 7]. Antibody production risk is also assessed in clinical research [8]. Overall, ensuring the safety of rhGH treatment is a top priority, and it has been found that therapy does not increase overall mortality in childhood rhGH recipients [9]. However, many observational studies that report on rhGH safety are short-term and not conducted independently of pharmaceutical companies [2].

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The purpose was to analyze and summarize the accumulated short-term and long-term safety data on rhGH-treated children with GHD based on the results of a physical examination, assessment of vital signs, laboratory parameters, and follow-up.

Materials and methods

A prospective observational cohort study was conducted in 2012–2022 at the Odesa Regional Children's Clinical Hospital (Odesa, Ukraine) with the permanent inclusion of new patients. Ninety-two children with GHD (69 boys and 23 girls) who were treated with rhGH were enrolled. The diagnosis of GHD was based on an integrated evaluation of clinical signs, auxological data, bone age, cranial magnetic resonance imaging, and growth hormone release < 10 ng/ml in provocative testing. Essential therapy was performed with rhGH at an average dose of 0.033 mg/kg/day. At the beginning of treatment, the children's chronological age was 7.20 ± 0.36 years, they had a pronounced short stature ($SDS = -3.4 \pm 0.1$). The evaluation of the short-term and long-term safety of rhGH therapy in children with GHD was based on identifying the overall incidence of adverse events (AE), defined as any untoward medical occurrence in a patient. Recording the symptoms or disorders reported by the patient or identified during the interview, physical examination, laboratory tests, or other methods are recommended [10]. Children's adherence to rhGH therapy was assessed using the Morisky Medication Adherence Scale. The study has been approved by the local ethics committee and carried out following the WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. Written informed consent was obtained from participants and their parents before study entry.

The categorical variables were expressed as frequency (percentage) and analyzed by χ^2 -test. A $p < 0.05$ was considered statistically significant.

Results and discussion

Short-term safety monitoring included the detection of AEs based on physical examination, vital signs, and hematological and biochemical parameters outside the normal laboratory range in children with GHD (Table 1).

According to a complete physical examination, AEs were found in 18 (19.57 %) GH recipients. Intracranial hypertension was diagnosed in 1 (1.09 %) child, arthralgia in 1 (1.09 %), prepubertal gynecomastia in 1 (1.09 %), anemia in 3 (3.26 %), manifestation of latent adrenal insufficiency

— in 3 (3.26 %), manifestation of latent thyroid insufficiency — in 2 (2.17 %), impaired glucose tolerance — in 7 (7.61 %) children with GHD. None of the observed children had serious adverse events, such as progression of scoliosis, slipped capital femoral epiphysis, and edema.

One of the methods for assessing the short-term safety of therapy was the evaluation of the site of rhGH injection (Table 2). Pathological signs at the injection site were detected in 22 (27.5 %) GH recipients, including redness in 3 (3.7 %), bruising in 4 (5.0 %), edema in 4 (5.0 %), itching in 2 (2.5 %) and pain in 9 (11.2 %) cases. The clinical significance of the pain at the injection site as a cognitive emotional barrier in the formation of acceptable adherence of patients with GHD to rhGH therapy has been detected. Among children with unacceptable adherence to rhGH therapy, painful injections were noted in 20.6 (7.0 ÷ 34.2) % of cases compared to 4.3 (–1.6 ÷ 10.2) % in those with acceptable adherence ($\chi^2 = 5.15$; $p = 0.02$).

In a cohort of children with GHD, rhGH therapy was not accompanied by impaired vital signs — blood pressure, respiratory rate, heart rate, and temperature. All GH recipients did not show any clinically significant abnormalities in visual assessment and heart rate measurements, PR interval, QRS complex, QT interval, and QTc interval on the standard 12-lead electrocardiogram.

According to the complete blood test panel, AEs were found in 38 (41.3 %) GH recipients. Changes in hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume had clinical significance and were considered manifestations of anemia in 3 (3.3 %) children on rhGH therapy. In some GH recipients, AE manifested itself as a deviation in the number of leukocytes in 6 (6.5 %) cases, neutrophils in 5 (5.4 %), eosinophils in 4 (4.3 %), lymphocytes in 5 (5.4 %), and platelets in 1 (1.1 %). In most cases, the detected AEs were of a short-term transient nature, more often based on intercurrent pathology, and were not associated with rhGH. In the selected cohort of children with GHD, there were no cases of changes in the number of basophils and monocytes during rhGH therapy.

A biochemical blood test revealed AEs in 36 (39.1 %) patients, including deviations from the average level of total protein in 1 (1.1 %), uric acid in 1 (1.1 %), sodium in 1 (1.1 %), serum iron in 3 (3.3 %), transferrin in 3 (3.3 %), albumin in 3 (3.3 %), total cholesterol in 10 (10.9 %) and free fatty acids in 14 (15.2 %) children with GHD. All listed

Table 1. Frequency of adverse events in GH recipients based on physical examination, vital signs, and laboratory parameters, n; % (95% CI)

Adverse events	Age < 7 years (N = 46)	Age > 7 years (N = 46)	Total (N = 92)
Symptoms and disorders	7; 15.2 (4.8 ÷ 25.6)	11; 23.9 (11.6 ÷ 36.2)	18; 19.6 (11.5 ÷ 27.7)
Vital sign disorders	0	0	0
Blood test parameters	22; 47.8 (33.4 ÷ 62.3)	16; 34.8 (21.0 ÷ 48.5)	38; 41.3 (31.2 ÷ 51.4)
Biochemical parameters	8; 17.4 (9.1 ÷ 30.7)	4; 8.7 (3.4 ÷ 20.3)	12; 13.0 (7.6 ÷ 21.4)
Lipidogram parameters	10; 21.7 (12.3 ÷ 35.6)	14; 30.4 (19.1 ÷ 44.8)	24; 26.1 (18.2 ÷ 35.9)
Urinalysis parameters	5; 10.9 (4.7 ÷ 23.0)	4; 8.7 (3.4 ÷ 20.3)	9; 9.8 (5.2 ÷ 17.5)

Table 2. The frequency of adverse events at the site of rhGH injection in children with GHD, n; % (95% CI)

Adverse events	Age < 7 years (N = 42)	Age > 7 years (N = 38)	Total (N = 80)
Redness	2; 4.8 (1.3 ÷ 15.8)	1; 2.6 (0.5 ÷ 13.5)	3; 3.7 (1.3 ÷ 10.4)
Bruise	1; 2.4 (0.4 ÷ 12.3)	3; 7.9 (2.7 ÷ 20.8)	4; 5.0 (2.0 ÷ 12.2)
Edema	2; 4.8 (1.3 ÷ 15.8)	2; 5.3 (1.4 ÷ 17.3)	4; 5.0 (2.0 ÷ 2.2)
Itching	1; 2.4 (0.4 ÷ 12.3)	1; 2.6 (0.5 ÷ 13.5)	2; 2.5 (0.7 ÷ 8.7)
Pain	3; 7.1 (2.5 ÷ 19.0)	6; 15.8 (7.4 ÷ 30.4)	9; 11.2 (6.0 ÷ 20.0)

AEs had no clinical significance, they were sometimes associated with intercurrent diseases, had transient nature, and were not associated with GH therapy. In the GH recipient cohort, there were no cases of changes in the levels of urea, residual nitrogen, creatinine, potassium, chlorine, bicarbonate, calcium, phosphate, total bilirubin, direct bilirubin, indirect bilirubin, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase.

Urinalysis revealed AEs in 9 children (9.78 %), including minor proteinuria in 1 (1.1 %), leukocyturia in 5 (5.4 %), erythrocyturia in 2 (2.2 %) and changes in urine color in 1 (1.1 %) case. The changes were transient and were not associated with rhGH. In the short term, GH recipients did not show bilirubin, glucosuria, ketonuria, pH, and specific gravity changes in urine.

The long-term safety evaluation for children with GHD was conducted over several years, with individual cases lasting up to 11 years. The results did not reveal an association between rhGH therapy and the risk of cancer, cardiac, and cerebrovascular diseases. However, three children (3.26 %) had type 2 diabetes, along with overweight in 1 child (1.09 %) and obesity in 2 (2.17 %).

Thus, assessing the short-term safety of rhGH therapy showed the absence of serious adverse events in the examined children. Among the identified AEs, intracranial hypertension, anemia, manifestations of latent adrenal insufficiency, latent thyroid insufficiency, and impaired glucose tolerance are of the most significant importance. Among AEs at the injection site, the clinical significance of pain as a barrier to the formation of adequate compliance with rhGH therapy was revealed. Overall, these data support the view of Allen D.B. et al. [11] that rhGH therapy can be considered safe in the short term for approved indications for GH use. Data on the long-term safety of rhGH therapy are consistent with the results of the study by Van der Steen M. et al. [12] on the association between rhGH therapy and an increased risk of type 2 diabetes in children with obesity, genetic predisposition, and poor lifestyle. It is known that AE can manifest itself not only as a medication side effect but also as psychological trauma [13]. According to our data, rhGH therapy is not associated with psychological harm in children with GHD. Moreover, according to our previous study, rhGH therapy leads to normalization of the psycho-emotional state and increases self-esteem in children with GHD [14].

Prospects for further research are continued monitoring of GH recipients for the potential development of long-term AE to prevent type 2 diabetes and cerebrovascular diseases.

Conclusions

1. In the short term, rhGH therapy in children with GHD can generally be considered safe based on the assessment of physical examination, vital signs, and laboratory parameters.

2. Painful injections should be regarded as a clinically significant AE, representing a cognitive emotional barrier in the formation of adherence to rhGH therapy in children with GHD.

3. Long-term rhGH therapy in children with GHD was associated with type 2 diabetes in 3 (3.26 %) overweight and obese children.

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Небажані явища замісної терапії в дітей із дефіцитом гормону росту

Резюме. **Мета:** проаналізувати й узагальнити накопичені дані про короткострокову та довгострокову безпеку лікування рекомбінантним гормоном росту людини (рГРл) дітей із дефіцитом гормону росту (ДГР) на основі результатів фізикального обстеження, оцінки життєво важливих функцій, метаболічних параметрів та спостереження. **Матеріали та методи.** Дослідження проводилося на базі Одеської обласної дитячої клінічної лікарні з 2012 по 2022 рік і включало 92 пацієнтів із ДГР, які отримували лікування рГРл у середній дозі 0,033 мг/кг/добу. Оцінка безпеки такої терапії ґрунтувалася на визначенні загальної частоти небажаних подій (НП) як негативного наслідку медичної допомоги. **Результати.** При вивченні короткострокової безпеки терапії рГРл за даними фізикального обстеження у 18 (19,6 %) дітей виявлені НП, у тому числі внутрішньочерепна гіпертензія (1), артралгія (1), препубертатна гінекомастія (1), анемія (3), маніфестація прихованої адреналової недостатності (3), прихованої тиреоїдної недостатності (2), порушення толерантності до глюкози (7). У 20,6 (7,0 ÷ 34,2) % дітей із неприйнятною прихильністю до терапії рГРл виявлено болючість ін'єкцій

порівняно з 4,3 (-1,6 ÷ 10,2) % дітей із прийнятною прихильністю ($\chi^2 = 5,15$; $p = 0,02$). Жодна дитина не мала таких серйозних небажаних явищ, як прогресування сколіозу, епіфізіоліз головки стегна, набряки, порушення життєво важливих функцій. НП за гематологічними та біохімічними параметрами зазвичай були транзиторними, часто на тлі інтеркурентних захворювань, і не мали зв'язку з прийомом рГРл. У контексті довгострокової безпеки не виявлено зв'язку між терапією рГРл та ризиком онкологічних, кардіологічних та цереброваскулярних захворювань, але 3 дітей (3,26 %) мали цукровий діабет 2-го типу з надлишковою вагою в 1 дитини та ожирінням у 2 дітей. **Висновки.** У цілому в короткостроковій перспективі терапія рГРл є безпечною в дітей із ДГР. Біль у місці ін'єкції є клінічно значущою НП як когнітивно-емоційний бар'єр прихильності до терапії рГРл. З точки зору довгострокової безпеки терапії рГРл важливим є факт виявлення діабету 2-го типу в 3 (3,26 %) дітей із підвищеною масою тіла та ожирінням.

Ключові слова: діти; рекомбінантний гормон росту людини; безпека