SUMMARY

Tytuł: Ocena odpowiedzi na leczenie ludzkim rekombinowanym hormonem wzrostu (rhGH) niskorosłych dzieci urodzonych jako zbyt małe do czasu trwania ciąży (SGA) w populacji z sześciu ośrodków uniwersyteckich w Polsce.

Title: Evaluation of the response to treatment with human recombinant growth hormone (rhGH) of short-statured children born small for gestational age (SGA) in a population from six university centres in Poland.

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Introduction

Short stature resulting from SGA has been a mandatory indication for rhGH treatment in Poland since 2015. The population of patients born small for gestational age is heterogeneous, which influences the treatment outcomes as well as the final growth. The safety and benefits of rhGH treatment have been repeatedly confirmed. Assessment of IGF-1 level is one of the parameters that are included in the assessment of response to treatment during mandatory follow-up visits. An increase in IGF-1 correlates with good response to rhGH treatment, but persistent elevated IGF-1 level above reference range may increase the risk of side effects.

Aims of the study

Two main aims of the study were:

1. Assessment of the response to rhGH treatment in patients treated in 2016–2020 in six clinical centers in Poland.
2. To evaluate the IGF-1 local reference ranges for the rhGH treatment centers concerned and to compare these values with the population reference ranges.

Materials and Methods

The study was retrospective in nature and encompassed data from patients treated between 2016 and 2020 at six university centers in Poland. Medical and auxological data of patients were analyzed during the qualification for rhGH treatment and during routine follow-up visits within the first two years of therapy. Visits occurred every 3 months during the first year of treatment and then every 6 months (±3 months). All patients included in the study

underwent the qualification process for rhGH treatment in accordance with the standardized guidelines of the Drug Program and received a positive opinion from the Coordination Team for Growth Hormone Use. The serum IGF-1 concentration was assessed for each patient in a fasting state using the immunological method and compared to the reference ranges used by the local laboratory for measurement, as well as to population norms based on the Italian children population presented by Bedogni et al.

In the first publication, the study group consisted of 235 children (137 boys) with a mean age of 9.08 years at the start of therapy. 190 patients were evaluated at Tanner stage I. Patients were divided into groups based on their additional diagnosis: (1) Patients with non-specific dysmorphic features, (2) Patients with fetal alcohol syndrome (FAS), and (3) Patients with Silver-Russell syndrome (SRS). Poor response to treatment was defined as ΔHt SDS<0.3 and/or ΔHV <3 cm/year.

In the second publication, the study group included 229 children (134 boys) with a mean age of 9 years at the start of therapy, and 186 patients had not yet reached Tanner stage I. Poor response to treatment was defined as ΔHt SDS<0.3 and/or ΔHV<3 cm/year.

Results from the first publication

Seventeen percent of all patients after the first year and 44% after the second year met the criteria of ΔHt SDS < 0.3, while 56% in the first year and 73% in the second year met the criteria of ΔHV < 3 cm/year. Patients with SRS showed the best response to treatment, which was sustained throughout the entire observation period.

Results from the second publication

After 12 months, 56 patients (24%) had IGF-1 values >97th percentile for the local reference range, while only 8 patients (3.5%) did so using population reference ranges; p<0.001. After 24 months of treatment, these values were 47 (33%)>97th percentile according to local norms vs. 6 (4.2%) according to population norms; p<0.001. The dosage of rhGH was reduced in 39 patients after 12 months, of whom twelve (25%) had IGF-1>97th percentile according to local reference ranges, and five (13%)>97th percentile for the population.

Conclusions

Based on the course of the study, the following conclusions were formulated:

1. Despite careful and detailed patient qualification for the therapeutic program, 17% of them did not benefit from the first year of therapy, and 44% from the second year, considering the parameter ΔHt SDS<0.3. The ΔHV<3 cm/year criterion shows a higher percentage of

patients with a poor response to treatment (56% in the first year and 73% in the second year, respectively).

2. Despite high rates of poor response to treatment, both Ht SDS and HV improved significantly in the entire study group and in all subgroups. Patients with SRS were significantly younger at the beginning of the study and exhibited the best response to treatment, which was sustained throughout the entire observation period.
3. Patients responded better to treatment before the onset of puberty compared to the entire study group. Regardless of the stage of puberty at the start of treatment, the best response was observed after the first 12 months of therapy.
4. Patients with fetal alcohol syndrome had the slowest growth rate before treatment and were the latest to qualify for the Drug Program.
5. The study showed that depending on the chosen criterion for assessing treatment response, different percentages of patients are obtained. Assessment of growth rate showed a higher percentage of patients with a poor response to treatment.
6. Accurate monitoring of therapy, an individualized approach to the patient, dosage verification, treatment method, and the decision to continue after a year are essential for optimizing treatment outcomes.
7. To maintain good HV, individualization of GH dosage is recommended for children with SGA.
8. Depending on the chosen norm, a significant percentage of children have elevated IGF-1 levels above the upper limit of the norm, leading to a reduction in rhGH dosage, which can negatively affect growth rate and the final treatment outcome.