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Результаты исследования мнения родителей детей с ахондроплазией о роли Возоритида в лечении заболевания

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The results of the survey among the parents of patients with achondroplasia on the role of vosoritide therapy

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Introduction Achondroplasia (ACP) is a common skeletal dysplasia. Vozoritide is the first drug that has an effect on the pathogenesis of impaired enchondral growth in achondroplasia. Clinical trials of the second and third phases have shown its effectiveness according to the latest literature data presented. After providing scientifically grounded information, a questionnaire was completed by parents of children with ACP to have their opinion before the introduction of the drug into medical practice. **Materials and methods** The survey was conducted on June 21-24, 2021 at the Ilizarov Center supported by the patient's organization Small People Support Center for Patients with Achondroplasia and Other Bone Dysplasias and Their Families. The questionnaire included 5 questions, compiled by the first author of this study. 65 completed questionnaires were received for the analysis. **Results and discussion** The overwhelming majority of parents have confidence in the use of vozoritide as a means of achieving targeted growth which may allow to avoid surgical treatment. However, the parallel use of this drug and surgical treatment for incomplete growth of a child is not excluded if the growth graphs show that the required parameters have not been achieved by the time the growth zones are closed. Despite the fact that at present only the influence of vozoritide on the growth of a child with ACP has been reliably proven, parents feel confident with the information about the possible effect of the drug on other problems associated with impaired enchondral growth, and are ready to start therapy at an earlier age and for a longer period. Parents do not oppose the pharmacological treatment to surgical treatment. Vozoritide is seen as the main component of treatment, and surgery as a complementary one that follows (if necessary). This reasonable combination increases the parents' confidence in the predicted favorable treatment outcome.
Keywords: achondroplasia, Vosoritide, survey

INTRODUCTION

Achondroplasia is the most common skeletal dysplasia, characterized by a disproportionate and pathologically short stature. The incidence of the disease is 1:25.000 newborns [1–5]. This disease is caused by a dominant mutation of the gene encoding the fibroblast growth factor receptor (FGFR3) that results in permanent pathological activation of mitogen-activated protein kinase (MAPK), which, in turn, leads to inhibition of enchondral ossification [6]. Disturbance of enchondral ossification is manifested by pathologically short stature, rhizomelic type of limb shortening, macrocephaly, angular and torsional deformities of the extremities, stenosis of the lumbar spine, and impaired development of the facial bones of the skull [7–9]. Stenosis of the foramen magnum and the associated compression of the cervical spine may cause apnea of the central genesis and a 6-fold increased risk of sudden death in early childhood compared to the rest of the population [7–9]. Other problems in children with achondroplasia (ACP) include obstructive apnea associated with relative tonsillar hypertrophy, hydrocephalus, respiratory failure, hypotension, lumbar pain syndrome, hearing loss [7–9]. The above disorders cause functional disorders that impair the quality of life and cause psycho-social problems [10-13]. A 2-fold increase in mortality in people with ACP compared with the rest of the population is observed in the period from birth to the age of 4 years and in the fourth and fifth decades of life. Life expectancy is shorter by 10 years on average [14].

The administration of growth hormone has had a very limited success in the pharmacological correction of ACP problems. Growth stimulation with the hormone was observed only during the first two years of treatment [15]. On average, the increase in height was 2.5 cm in men and 2.8 cm in women at a follow-up period of 10 years [16]. Moreover, there was no decrease in disproportionality. Surgical interventions for limb

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lengthening and deformity correction are a rather effective but very aggressive method of treatment. It does not have an effect on other manifestations of ACP, except short stature and limb deformities [17–19].

Type C natriuretic peptide is a natural stimulant of enchondral growth and ossification. Long-term intravenous injections of exogenous natriuretic peptide corrected the impaired growth of long bones in mice with ACP, interrupting the inhibitory effect of the pathologically activated FGFR3 receptor [20].

Vozoritide (BioMarin) is a recombinant C-type natriuretic peptide with a longer half-life than endogenous, what provides its stable pharmacological activity [21].

Preclinical and clinical trials of this drug in the second and third phases have shown the following effects [22, 23]:

– in the second phase of trials, an annual increase in the growth rate of 1.5–2 cm was obtained with daily subcutaneous administration of a dose of 15 mg/kg for more than 42 months;

– administration of the drug for 60 months provided a cumulative significant increase in height by 9.08 cm (a significant difference from the cohort, identical in age and sex) with an average annual additional increase in height by 1.34 cm;

– in the third phase of clinical trials, an additional annual increase in height of 1.57 cm was noted, an increase in the standard deviation of growth values, on average, by 0, 28 (Z-score) after 52 weeks of daily subcutaneous injection of vozoritide at a dose of 15 mg/kg in children aged 5-15 years (significant difference from the placebo group);

– after 52 weeks of clinical trials, there was a tendency (statistically insignificant) in the decrease of disproportionality in the length of the trunk and limbs;

– it is important to note that the stimulation of growth by vozoritide occurred along with a natural gradual decrease in the growth rate, characteristic of both children with normal growth and children with ACP;

– the placebo group, that began to receive vozoritide after 52 weeks, showed later the same shifts in the growth rate as the group that received the drug from the first day;

– no acceleration of bone age was observed due to vozoritide effect;

– among the adverse and side effects, only minor and weak ones were detected (reactions at the injection sites, asymptomatic hypotension), with a follow-up period of 5 years, no bone anomalies and developmental disorders caused by the action of the drug were found. However, the long-term impact vozoritide is unknown;

– it is assumed that a longer use of vozoritide, begun at an early age, may positively influence the correction of other manifestations of ACP: disproportionality of body parameters, stenosis of the lumbar spine, deformities of the extremities, impaired development of the facial part of the skull, stenosis of the foramen magnum, etc.

Vozoritide is the first drug capable to influence the pathogenesis of achondroplasia and that changes the strategy of providing medical care to children with ACP. Understanding the role of such pharmacological intervention into the problems due to ACP requires that the medical community know the opinion of parents of children with ACP regarding this type of treatment, as well as participation in the formation of structured and scientifically based knowledge about the possibilities of the drug, including its effectiveness, features of use, adverse effects, probable unknown effects, as well as potential combination (sequential or parallel) with other methods of correction.

In our opinion, a simple informative communication about a new pharmacological effect on the pathogenesis of ACP, which is mandatory in any case, requires a feedback opinion before starting the introduction of the drug into medical practice, since we are talking about the formation of a strategy for correcting problems associated with ACP, which refers to almost all aspects of the life of children with this pathology. Therefore, after presentation of the information at a webinar and posting on the website of the patient organization ANO "Small People Support Center for Patients with Achondroplasia and Other Bone Dysplasias and Their Families" on the use of vozoritide and its effects found in the clinical trials, we considered it important conducting a survey for parents of children with ACP in the form of a questionnaire developed by doctors who are experts in the problems of achondroplasia.

MATERIAL AND METHODS

This anonymous voluntary survey was conducted on June 21–24, 2021. The questionnaire was developed by prof. D.A. Popkov, a member of the Vosoritide (BMN111) Steering Committee EMEA. The questionnaire was available printed for parents of children undergoing orthopedic surgical treatment at the Federal State Budgetary Institution “Ilizarov National Medical Research Center (Kurgan), and in an electronic form, posted on the site www.achondroplasia.ru.

A questionnaire of five questions is presented below. Parents had to choose one of the answers to questions 1–4 and to question 5 – to arrange their opinions in decreasing order of importance on the significance of ACP manifestations. It was also required to indicate the age of their child.

Descriptive statistics were used to process quantitative data using the AtteStat 12.0.5 program (I.P. Gaidyshev).

Question 1 Vozoritide is the first drug that corrects the pathophysiology of enchondral ossification disorders and, according to clinical trials, reliably stimulates the annual growth of a child. Consider theoretically: vozoritide use provided the targeted (planned) stature (usually 140–150 cm) achieved by the time the zones of long bone growth are closed, is it still necessary to increase the stature surgically?

1. Yes

2. No, only residual deformity correction is necessary

Question 2 If it becomes obvious that vozoritide administration even during the growth process (for example, at the age of 7–9 years) (according to the growth curves) cannot provide that the required final growth is not achieved, then should vozoritide and surgical lengthening of the limbs be practically simultaneously used?

1. Yes

2. No. One should wait for growth completion and then perform surgical treatment

Question 3 The positive effects of vozoritide on the formation of normal sizes and proportions of the lumbar spine (the problem of stenosis of the lumbar spine), foramen magnum, middle face are not obvious, which may be due to the short period of vozoritide administration. Does the use of this drug should be started at an earlier age in order to have a longer time period for its effect?

1. Yes

2. No

Question 4 Vozoritide is a fundamentally new drug with a short history of its application. We may not know all the side and negative effects. Surgical lengthening, which is known and understood, should be preferred despite its possible complications and application problems. Do you agree?

1. Yes

2. No, the surgery is too aggressive. Pharmacological correction of growth may avoid surgical intervention or decrease its role

Question 5 What problems in children with achondroplasia do you consider the most significant? Please rank the manifestations below in descending order of importance (NB! The list is incomplete, but do not add anything).

1. Pathologically short stature

2. Angular and torsional deformities of the lower extremities

3. Disproportion between the length of the trunk and the length of the limbs

4. Restrictions of movement in the joints

*5. Problems of the axial skeleton (lumbar stenosis) and associate*d neurological complications

Your order of problems (descending order of importance): ……

RESULTS

A total of 65 questionnaires were completed. Answers to questions 1–4 were given correctly for processing in all 65 cases. It was possible to analyze answers given in 37 questionnaires to question 5 on the order of arranging problems according to the parents' choice.

Table 1 shows the distribution of children by age periods.

Table 1

Age periods

Child's age	0 – 4.99 years old	5 – 9.99 years old	10.1 – 17 years old
Number of completed questionnaires	39	22	4

In most cases (60 %), the opinion of parents whose child was younger than the age accepted for the initiation of surgical treatment in our country is presented.

The results of the survey are presented in the following diagrams (Fig. 1–4).

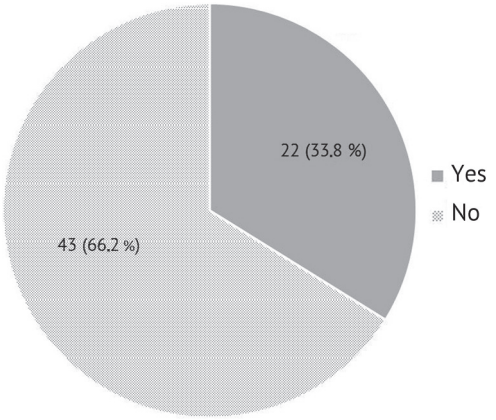

Fig. 1 Answers to question 1(percent)

Obviously, most parents do not consider increasing stature with surgical interventions if the

targeted growth of the child has been achieved with pharmacological treatment.

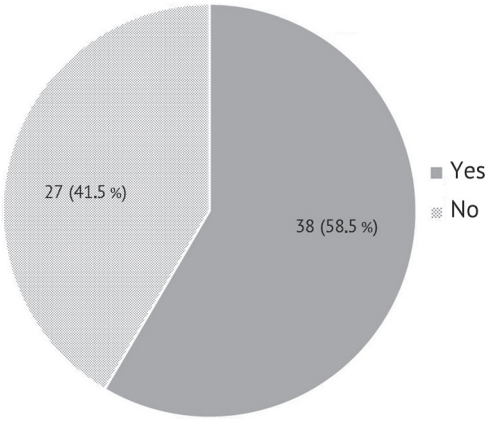

Fig. 2 Answers to question 2 (percent)

However, in the case when the insufficient effectiveness of pharmacological treatment becomes evident before the completion of natural growth, many parents (58.5 %) would prefer to combine drug therapy and surgical orthopedic intervention at the same time.

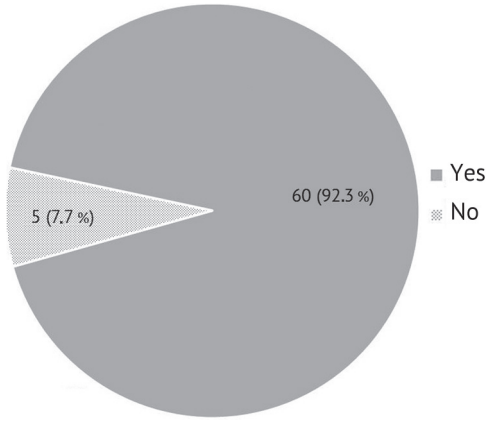

Fig. 3 Answers to question 3 (percent)

An unambiguous positive fact is the opinion of parents about the early start and long-term treatment with vozoritide in order to manifest its positive effects for the correction of other problems of ACP, and not just short stature.

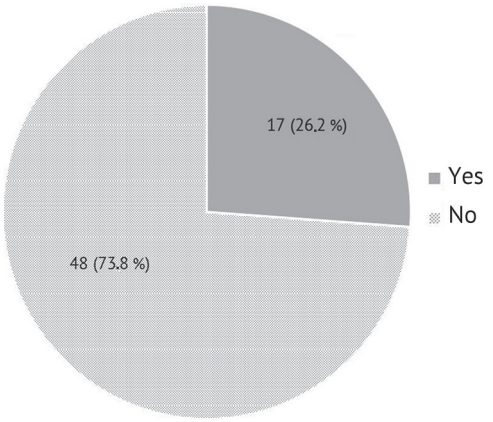

Fig. 4 Answers to question 4 (percent)

Interesting, especially regarding previous responses, is the opinion that surgical treatment remains preferable over pharmacological treatment for 26.2 % of parents. We believe that it reflects certain concerns about the drug, the long-term effects and full spectrum of action of which are unknown.

Variations of parents' answers depending on the child's age did not show a significant difference between the groups (Table 2).

It is obvious that regardless of the child's age, the preferences of the parents are on the side of drug therapy. The tendency that the proportion of parents who trust surgical treatment slightly increases as the child grows up what is probably associated with a decreasing expectation of the effect of pharmacological treatment, on the one hand, and with obtaining a specific result from surgical treatment.

Table 3 allows us to identify two groups of parents. One of them ranks the orthopedic manifestations of ACP in the first place, highlighting pathologically low growth and deformities of the limbs and disproportionality. The second, on the contrary, does not consider low stature as the leading problem but determines the impaired quality of life caused by the restriction of self-service and potential neurological problems as the primary one, assigning the last rank to low height.

Table 2

Percentage of parents' positive answers to questions 1–4 according to age

Age (years)	Answer 1	Answer 2	Answer 3	Answer 4
0–4.99	33.3 %	53.8 %	97.4 %	25.6 %
5–17	34.6 %	65.4 %	84.6 %	26.9 %

Table 3

Ranking of descending order of ACP manifestation importance

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Pathologically low stature	**15**	1	5	1	**15**
Limb deformities	5	**11**	11	7	3
Trunk to limb disproportion	6	**14**	8	4	5
Joint contracture	2	9	7	**13**	**6**
Problems of axial skeleton formation	9	2	6	**12**	**8**

DISCUSSION

The overwhelming majority of parents have confidence in the use of vozoritide as a means of achieving targeted growth and avoiding surgical treatment. However, the parallel use of this drug and surgical treatment even in the period of the child's growth is not rejected if the growth graphs reflect that the required parameters could not be achieved with the pharmacological agent by the time the growth zones are closed. Despite the fact that at present only the impact of vozoritide on the growth of a child with ACP is reliably proven, parents are confident in the information about the possible effect of the drug on other problems associated with impaired enchondral growth, and are ready to start therapy at an earlier age and for a longer period. Only 26.1 % of parents prefer surgical correction of short stature and limb deformities to the use of vozoritide. We also note the heterogeneity of parents' opinions about the importance of various ACP manifestations in their children, which should be taken into account for determining the treatment strategy.

In general, the attitude of the parents who took part in the survey is highly positive regarding the trust in this drug. According to the survey results, parents do not oppose pharmacological and surgical treatments. Vozoritide is seen as the main component of treatment, and surgery as a complementary one to follow if necessary. This reasonable combination increases the parents' confidence in the predicted favorable outcome of the treatment.

CONCLUSION

This study contributed to several objectives. Parents of children with ACP were informed on the most scientifically substantiated data on the possibility of pathogenetic treatment with recombinant C-type natriuretic peptide. The parents' answers to the questionnaire helped to structure the information and determine the place of this drug in the arsenal of modern means of both pharmacological and surgical treatment of children with ACP. We conclude that this way of cooperation between patient organizations and expert doctors is scientifically grounded, open, and effective in achieving research goals to enable mutual efforts in rendering help for children with systemic diseases.

***Conflict of interest**: Popkov Dmitry Arnoldovich is a member of Vosoritide (BMN111) Steering Committee EMEA*

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