Chapter

Statins for Children with Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH) is the most common genetic disorder in the world. It is characterized by increased level of total cholesterol (TC), low-density lipoproteins (LDL-C) since childhood. The diagnosis and initiation of therapy are optimal in childhood before complications (aortic stenosis, atherosclerotic changes in the arterial walls) appear. The initiation of lipid-lowering therapy in FH since childhood is important to reduce the cumulative effect of LDL-C, to increase patient's life expectancy. Statins are recommended as first-line drugs for treatment with monitoring of the recommended clinical, biochemical markers under the supervision of a physician. However, due to limited experience, there are differing opinions among clinicians regarding the age of initiation of lipid-lowering therapy. This review is an attempt to critically study the available data from the world literature concerning the use of statins in children with FH, their effectiveness, safety. It is important to determine the endpoints for determining the effectiveness of statins, such as lowering LDL-C, assessing the thickness of the intima-media complex. The frequency of occurrence of possible side effects in children is considered - diabetes mellitus, hepatotoxicity, muscle pain and others. There is a need to continue randomized trials to prove the lifelong benefit of low LDL-C in patients with FH.

Keywords: children, familial hypercholesterolemia, total cholesterol, low density lipoprotein efficacy, treatment, statins, side effects

1. Introduction

Hypercholesterolemia occupies an important place among the factors of cardiovascular mortality [1]. It is known that the level of lipids in 40–60% of cases is due to genetic reasons [2]. Familial hypercholesterolemia is one of the most common hereditary diseases: its prevalence is 1: 200–1: 500 in the general population [3]. The estimated number of people with a heterozygous form of the disease in Russia should be about 1 million [4]. Despite the high urgency of early detection of the disease, in our country it is diagnosed in less than 1% of the expected number of patients. Diagnosis and initiation of therapy for the disease in childhood are considered optimal before complications such as aortic stenosis, atherosclerotic changes in the arterial walls appear. Statins are recommended for treatment as first-line drugs, but experience with their use in children is limited and requires special analysis.

Statins are 3-hydroxy-3-methyl coenzyme A reductase inhibitors that limit the rate of endogenous cholesterol synthesis. This leads to a decrease in the content of

intracellular cholesterol and the level of circulating LDL-C in the blood. In addition to the lipid-lowering effect, statins affect atherosclerotic plaque (reduce its size, stabilize the surface, thereby reducing the risk of rupture and ulceration), as well as inflammatory factors and endothelial function (pleiotropic effects) [5]. The main goal of prescribing statins in familial hypercholesterolemia is to reduce the risk and rate of development of atherosclerosis and coronary heart disease in order to delay the onset of cardiovascular accidents as much as possible. It should be noted that the use of statins among the adult population, as a rule, is not in doubt, while the pharmacotherapy of hypercholesterolemia in pediatrics raises questions from doctors and parents regarding its effectiveness, long-term prospects and possible complications.

2. Use of statins in world wild practice

The effectiveness of statins in familial hypercholesterolemia can be judged primarily by the degree of decrease in serum LDL cholesterol levels. The European and International Atherosclerosis Societies stated that, based on the available data, the hypothesis of atherogenesis associated with high LDL-C levels is no longer a hypothesis and can be considered a proven fact [6]. Randomized studies show that the effect of LDL-C on the development of atherosclerotic vascular disease is determined not only by the absolute level of LDL cholesterol, but also by its cumulative effect on the arterial wall [6–8]. It is known that the cumulative effect of LDL-C increases with age and is 160 mmol in a healthy person by the age of 55. In the absence of treatment, patients with familial hypercholesterolemia reach this value from the age of 35. It has been shown that starting statin therapy from 18 years of age allows this cumulative load to be postponed to 48 years of age. When statins are taken from the age of 10, the accumulation of LDL-C of 160 mmol is achieved only by the age of 53, which is close to the indicators of healthy people [9].

Demonstrated clinically significant reduction in LDL cholesterol levels in children with familial hypercholesterolemia taking statins compared with children receiving placebo. Moreover, the degree of reduction varied depending on the dose and the drug used. In the work of S.B. Clauss et al. (2005) [10] described the experience of using lovastatin in girls with familial hypercholesterolemia at a dose of 20–40 mg/day for 24 weeks. The authors concluded that in the lovastatin group there was a significant decrease in LDL cholesterol from baseline by 23–27%, total cholesterol by 17–22%, and apolipoprotein B by 20–23%. In another study, pravastatin versus placebo in children with familial hypercholesterolemia younger than 14 years old at a dose of 20 mg/day and over 14 years old - at a dose of 40 mg/day with a duration of therapy of 104 weeks, the decrease in LDL cholesterol levels reached 24.1% [11]. A number of works have been devoted to the experience of using atorvastatin in childhood. It was shown that the appointment of atorvastatin at a dose of 20–40 mg/day compared with placebo for 6–48 months led to a significant decrease in LDL cholesterol by an average of 32–39%, total cholesterol by 32%, triglycerides by 12% and apolipoprotein B by 34% [12–14]. It should be noted that in one of the studies, a statistically significant increase in the level of HDL cholesterol by 2.8% was stated [12]. In a study by H.J. Avis et al. (2010) [15], who studied the efficacy of rosuvastatin in children with familial hypercholesterolemia compared with placebo, showed a decrease in LDL cholesterol, total cholesterol and apolipoprotein B levels for all three doses (5 mg, 10 mg and 20 mg) with a duration of 12 week Thus, in general, the results of studies evaluating the effects of statins in familial hypercholesterolemia demonstrate the effectiveness of statins in lowering LDL cholesterol and total cholesterol levels in children.

3. Effect of statins on the thickness of the intima-media complex

Another important endpoint for determining the effectiveness of statins is the thickness of the intima-media complex, a clinically significant marker of cardiovascular disease. It is noted that the thickness of the intima-media complex in children depends on age, gender and LDL cholesterol level [16]. In children with familial hypercholesterolemia, a much faster increase in this parameter with age was found than in healthy brothers and sisters [17]. Currently, there is a number of studies demonstrating the effect of statins on reducing the thickness of the intima-media complex. M.J. Braamskamp et al. [18] found that in the case of initiation of statin therapy in familial hypercholesterolemia from the age of 12 years, the thickening of the intima-media complex in children occurs more slowly than in peers with familial hypercholesterolemia who do not take statins. The authors concluded that early initiation of statin treatment can delay atherosclerotic changes in the vessels in adolescents and young adults [18]. Statin therapy also has a positive effect on markers of atherosclerosis such as flow-dependent vasodilation. In a study by S. De Jongh et al. (2002) [19], it was found that against the background of 28-week treatment with simvastatin, the flow-dependent vasodilation significantly improved by an average of 4% in children with heterozygous familial hypercholesterolemia compared with that in healthy peers who received placebo.

4. Long-term studies of the effectiveness of statins in childhood

The need for long-term studies to assess the effectiveness of statins in childhood has been repeatedly emphasized. In October 2019, a group of scientists published the results of the longest to date follow-up of children with familial hypercholesterolemia taking statins [8]. 214 patients with this disease and their 95 healthy brothers and sisters were under observation for 20 years. It was found that patients taking statins did not significantly differ from their healthy siblings in terms of an increase in the thickness of the intima-media complex. At the same time, the incidence of cardiovascular diseases and mortality from them at the age of 39 years among patients with familial hypercholesterolemia was lower than among their parents suffering from this disease, and amounted to 1% versus 26% and 0 versus 7%, respectively. These studies make it possible to substantiate the need for the use of statins for the primary prevention of complications and increase life expectancy in children with familial hypercholesterolemia. The effectiveness of treatment depends on the dose of drugs and the age of initiation of therapy. The authors of these and a number of other clinical studies emphasize the need to start statin therapy at the age of 8–10 years [9, 20–23].

5. Features of statins usage in children with FH in clinical practice

In clinical practice, along with an increase in the frequency of statin use, their side effects are increasingly the subject of research. In adults, statin-related side effects include elevated liver transaminases, creatine kinase, and rhabdomyolysis [24]. The main concerns in the pediatric population are the risk of developing myalgias, as well as the possible effect of statins on liver function [13, 19], cholesterol-dependent production of steroid hormones in the gonads and adrenal glands [24] and energy metabolism [25], as well as the child's growth [26].

In a number of studies, when using statins in children with familial hypercholesterolemia, it is noted the occurrence of muscle pain: when taking pitavastatin, they

developed within 3 months in 9.3% cases [18], and when taking pravastatin and atorvasttin - for 48 months in 12.2% of cases [12]. This prevalence of side effects in the form of muscle damage is higher than in adults, who experience myalgia in only 1.5–5% of cases [27]. In this regard, the authors concluded that most of the presented cases of side effects of statins on skeletal muscles in children may not be myalgias directly related to taking statins, but "growing pains" and subjective feelings of the child. A meta-analysis of 6 studies evaluating the efficacy and safety of statins in children with familial hypercholesterolemia with a total of 798 study participants with statin treatment durations from 12 to 104 weeks did not reveal a statistically significant increase in the number of side effects, including myalgias, when prescribing statins compared with placebo [28]. The European Society of Atherosclerosis recommends measuring the level of creatine phosphokinase (CPK) before treatment and 1–3 months after the start of statin therapy [29] in order to control the possible occurrence of myalgias.

The studied side effects, in respect of which remain alert, is hepatotoxicity. Several studies with a total of 943 children with familial hypercholesterolemia taking statins have examined the effect of statins on liver function [30, 31]. The authors emphasize the absence of significant differences in the incidence of violations of the activity of hepatic transaminases in treatment with statins and taking placebo. This confirms the good tolerability of the drugs. The European Society of Atherosclerosis recommends measuring the levels of alanine and aspartate aminotransferases (ALT and AST) before starting statin therapy, and then every 3 months during treatment if there is a history of liver disease or an increase in the level of hepatic transaminases by more than 3 times from the upper limit of normal [32].

Other discussed potential side effects of statins include puberty disorders. Randomized studies evaluating the efficacy and safety of statins in children with familial hypercholesterolemia found no signs of impaired puberty when pravastatin was used at a dose of 20–40 mg/day for 104 weeks [9] and pitavastatin at a dose of 1 mg/2 mg/4 mg/days for 12 weeks [18]. S.B. Clauss (2005) [10] in his article expressed theoretical concerns regarding the use of statins in adolescent girls with potential effects on pituitary hormones (luteinizing hormone and follicle-stimulating hormone), menstrual cycle and physical development. However, in a 24-week study in which adolescent girls with familial hypercholesterolemia took lovastatin 20–40 mg/day, these side effects were not reported [33]. A number of researchers have also demonstrated the safety of using drugs (pravastatin, atorvastatin, rosuvastatin) in children over a similar 2-year period [10, 19, 34].

In recent years, the likelihood of an increase in the risk of developing type 2 diabetes mellitus with prolonged use of statins in adults in the general population has been actively discussed. In a study by J. Besseling et al. (2015), including more than 63 thousand patients with familial hypercholesterolemia taking statins, showed that the prevalence of type 2 diabetes in this group was significantly lower than that of their relatives (1.75% versus 2.93%; $p < 0.05$) [35]. A 10-year prospective follow-up of 194 children with familial hypercholesterolemia receiving statins revealed one new case of type 2 diabetes mellitus without significant differences in morbidity in their 83 siblings without familial hypercholesterolemia [36]. N. Joyce et al. (2017) [37] also showed no significant differences in the incidence of type 2 diabetes mellitus among children taking statins compared with children not receiving drugs in this group.

Thus, it should be noted that the occurrence of side effects when using statins in children cannot be completely ruled out. However, the analysis of studies carried out in this direction emphasizes the low probability of their occurrence. The key when prescribing statins to a child with familial hypercholesterolemia is careful

monitoring of complaints, clinical condition, and a number of biochemical markers in the blood (ALT, AST, CPK). It is also necessary to monitor the patient's condition with prompt correction of the drug and the dose received by the child.

Separate sections devoted to the use of statins in childhood are presented in the most frequently cited clinical guidelines for the diagnosis and treatment of dyslipidemia: American [38], Japanese [20] and Australian [21]. In 2019, the results of a study conducted in 8 European countries (Norway, Great Britain, Czech Republic, Portugal, Greece, Austria, the Netherlands, Belgium) were published, which compared the tactics and results of treatment of familial hypercholesterolemia in a total sample of 3064 children. It has been shown that the proportion of children taking statins increases with age and by the age of 15, already 79% of patients in these countries are taking statins [39]. The goals for children over 10 years of age are to achieve LDL cholesterol <3.5 mmol/L (<135 mg/dL), at a younger age - to reduce this indicator by ≥50%. In the United States and Europe, simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin are approved for use in children with familial hypercholesterolemia. In the United States, all of these statins are approved from the age of 10, with the exception of pravastatin, which is recommended from the age of 8. In Europe, rosuvastatin is approved from 6 years old, in Australia atorvastatin is approved in children from 6 years old. It is recommended to start statin therapy with low doses and increase it until the set goals are achieved [29] with a possible increase to the maximum admissible dose in childhood established for each of the drugs. This dose is 20 mg for pravastatin for children under 13 years of age and 40 mg for children under 18; for rosuvastatin - 10 mg up to 9 years and 20 mg - up to 18 years; for atorvastatin - 40 mg regardless of age [12].

The results of recent randomized studies on the efficacy and safety of statins in children with familial hypercholesterolemia formed the basis for the joint recommendations of the European Society of Cardiology and the European Society of Atherosclerosis [29]. In 2018, Russian guidelines for the diagnosis and treatment of familial hypercholesterolemia were published [40]. These recommendations serve as the main document in the work of a pediatric cardiologist and pediatrician when monitoring children with familial hypercholesterolemia. According to these recommendations, statin therapy should be considered in children aged 8–10 years with heterozygous disease.

Particular vigilance should be shown in relation to children with a homozygous form of familial hypercholesterolemia, in which lipid-lowering therapy should be started as early as possible, immediately after the diagnosis. It is recommended to prescribe therapy with maximum tolerated doses of statins in combination with other lipid-lowering drugs in order to maximize the reduction of LDL cholesterol [40].

6. Conclusions

Thus, the initiation of lipid-lowering therapy in familial hypercholesterolemia from childhood is of great importance for reducing the cumulative effect of LDL cholesterol and increasing the patient's life expectancy. When answering questions regarding the treatment of children with dyslipidemia, one should take into account the compelling reasons to follow international recommendations and use statins for familial hypercholesterolemia from the age of 8–10 years, with monitoring of the recommended clinical and biochemical markers under the supervision of a physician. There is currently a need to continue randomized trials to prove the lifelong benefit of low LDL cholesterol in patients with familial hypercholesterolemia.

Acknowledgements

We want to thank the Head of Tatarstan Republic's Ministry of Health, the Rector of Kazan State medical University, Kazan, Russian Federation, the Head of the Children's Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan, Russian Federation and for the help in the organization of Children's Lipid Center, where we run our observation of children with Familial Hypercholesterolemia.

Conflict of interest

The authors declare no conflict of interest.

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