Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Dragana Nikolic, Andreea Corina, Peter. P. Toth, Lubna Hammad & Manfredi Rizzo (2019) Choosing an ideal pharmacotherapeutic strategy for dyslipidemia in children, Expert Opinion on Pharmacotherapy, 20:3, 241-244, DOI: 10.1080/14656566.2018.1552942

To link to this article: https://doi.org/10.1080/14656566.2018.1552942

Published online: 06 Dec 2018.

EXPERT OPINION ON PHARMACOTHERAPY
2019, VOL. 20, NO. 3, 241–244
https://doi.org/10.1080/14656566.2018.1552942

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EDITORIAL

Choosing an ideal pharmacotherapeutic strategy for dyslipidemia in children

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ARTICLE HISTORY Received 21 September 2018; Accepted 23 November 2018

KEYWORDS Adolescents; children; dyslipidemia; ezetimibe; familial hypercholesterolemia; statins

1. Introduction

Dyslipdiemia can manifest at a young age, and it is a risk factor for atherosclerotic cardiovascular disease (ASCVD), the principal cause of mortality in developed nations. Therefore, treating it as soon as it is diagnosed is an urgent need. There is much information regarding therapeutic interventions in adults with dyslipidemia, but much less so regarding the interventions needed in paediatric dyslipidemias. To this end, when medication is needed, it must be carefully chosen, weighing the benefits of lipid-lowering therapy against the risks associated with various treatment options.

It is important to determine the cause of dyslipidemia in children, as there are four principal aetiologies: genetic dyslipdiemia, medication-related dyslipidemia, dyslipidemia related to lifestyle factors, and dyslipidemia secondary to a medical condition. The most important cause of dyslipdiemia in children is familial hypercholesterolemia (FH), which is among the most common monogenic autosomal dominant inherited disorders [1]. Consequently, the majority of the available data are related to FH. However, secondary dyslipidemias in children can be due to excess alcohol consumption, drug therapy (corticosteroids, isotretinoin, beta-blockers, oral contraceptives, some chemotherapeutic, and antiretroviral agents), and medical conditions such as hypothyroidism, hypopituitarism, diabetes mellitus types 1 and 2, pregnancy, polycystic ovary syndrome, lipodystrophy, acute intermittent porphyria as well as other renal, hepatic, infectious, inflammatory, and storage diseases [2].

In children, pharmacotherapy is restricted to patients with genetic dyslipidemias after complete assessment of all ASCVD factors. There are different regulatory authorities that control the availability of drugs in different countries, and this should be taken into consideration.

2. The guidelines and expert panel on dyslipidemia management in children and adolescent

Selective screening based on family history of premature ASCVD or cholesterol disorders as the primary factor misses a considerable number (30 to 60 percent) of children with dyslipidemias [3]. In the absence of a clinical or historical marker, identification of children with lipid disorders requires universal lipid screening. Using a combined approach of universal and selective screening based on the indications and age intervals is recommended [2,4].

As normal lipid and lipoprotein values in children vary by age and sex, the recommended universal serum lipid screening for children is between ages 9 and 11 years and again when they reach the ages 17 to 21. Selective screening is recommended for children ages 2 to 8 years and 12 to 16 years who have CV risk factors. Non-high-density lipoprotein (HDL) cholesterol levels have been identified as a significant predictor of persistent dyslipidemia and, therefore, atherosclerosis and future events [3], although it is not clear if postprandial lipemia should be evaluated in children and adolescents [5].

The approach to managing dyslipidemias in children is still staged, with the institution of lifestyle changes at its core. This includes physical activity for 60 min daily, screen time ≤ 2hours daily, attainment of ideal body weight (body mass index [BMI] ≤ 85th percentile for age and gender) and dietary therapy with the Cardiovascular Health Integrated Lifestyle Diet [6].

If low-density lipoprotein (LDL) cholesterol remains ≥ 130 mg/dl after 3–6 months with lifestyle modifications in an individual with additional risk factors, medication may be considered. Persistent elevation of LDL cholesterol ≥ 190 mg/dl is consistent with the diagnosis of familial hypercholesterolemia, and statin therapy is advised. Medication treatment decisions should be based on the average of results from at least 2 fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart and according to the cut points from the pediatric guidelines [3].

There is evidence supporting early treatment of children with dyslipidemia, as the concept of cumulative or life-long LDL cholesterol burden is well established including its link with atherosclerotic CVD [7]. Briefly, subjects with homozygous FH, if untreated, will reach a burden sufficient to develop coronary heart disease (160 mmol) at age 12.5, while those with heterozygous FH (HeFH) by age 35. On the other hand, other CVD risk factors such sex, smoking, hypertension,

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diabetes, high triglycerides/low HDL cholesterol, and lipoprotein (a) [Lp(a)] should be considered when statins or other drugs are initiated.

The goal of lipid lowering therapy in childhood and adolescence is to decrease the LDL cholesterol level to the <95th percentile (≤130 mg/dl). Children younger than 10 years should not be treated with any medication unless they have FH, a severe primary hyperlipidaemia, or a high-risk condition that is associated with serious medical morbidity [3].

3. Current pharmacological approaches for dyslipidemia in children and adolescent

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the medications recommended for first-line treatment of pediatric patients with severe dyslipidemias failing adequate response to diet and lifestyle modification [8].

Statins have been shown to reduce LDL cholesterol by 20%-40% in children and adolescents with marked LDL cholesterol elevation or FH, having a positive effect on other atherogenic lipids such as apoB and very low density lipoprotein (VLDL) cholesterol. The statins also increase apoA1 and HDL cholesterol [9].

Statin use should begin with the lowest available dose given once daily. Target LDL cholesterol is typically below 130 mg/dl or by 50% from pre-treatment levels, but it is ideally under 100 mg/dl in high-risk populations such as FH patients. If target levels are not achieved within 3 months, the dose can be incrementally increased to the maximum as tolerated [3].

The statins are safe. Adverse effects are rare at standard doses and include myalgia, myopathy, and hepatic enzyme elevation, while adverse effects on growth, development, or sexual maturation are not seen [10]. Statins may be teratogenic, so women should be counselled as indicated.

Cholesterol-absorption inhibition with ezetimibe is another good treatment option for children with HeFH or clinically important nonfamilial hypercholesterolemia (nonFH). After 12 months, ezetimibe monotherapy resulted in clinically relevant reductions in LDL cholesterol and other key lipid variables in young children with primary HeFH or primary dyslipidemia, with a favorable safety/tolerability profile [11]. Adverse effects associated with ezetimibe use are rare and mild without having been associated with serious clinical outcomes, whether used alone or in combination with statins. Some cases of myopathy and elevations of liver transaminases were attributed to this agent. It should be noted, however, there are no long-term safety data or outcome studies for ezetimibe treatment in children as of yet [12].

Niacin, or B3 Vitamin, is a water soluble vitamin that participates in oxidation-reduction reactions; decreases hepatic LDL and VLDL production; inhibits adipose tissue lipolysis; decreases hepatic triglyceride biosynthesis; and increases lipoprotein lipase activity [13]. Therefore, it was proposed as a lipid lowering treatment and its efficacy was demonstrated even in children. However, adverse effects such as flushing, abdominal pain, vomiting, headache, or elevated serum aminotransferase levels, is relatively common [14], hence, niacin treatment should be avoided in children.

Fibrates are regarded as broad-spectrum lipid lowering drugs. Fibrates activate a protein called peroxisome proliferator-activated receptor alpha (PPAR-alpha) that regulates transcription of a number of genes involved in lipid and lipoprotein metabolism. PPAR-alpha activation reduces hepatic VLDL production and secretion, increases VLDL lipolysis in serum by activating lipoprotein lipase, and increases hepatic HDL biogenesis [13]. Fibric acid derivatives are not approved and not widely recommended for use in children.

Bile acid sequestrants (BAS) are another treatment option. These drugs act as lipid lowering agents by binding bile acids within the gastrointestinal tract. This induces activation of 7-alpha-hydroxylase, which diverts hepatic intracellular cholesterol toward bile acid biosynthesis. Because intracellular cholesterol levels decrease, hepatocytes respond by upregulating the LDL-receptor, which leads to increased clearance of LDL-cholesterol and reduced serum levels of this lipoprotein. These agents are not systemically absorbed [15], so they are considered safe for children. However, the classical BAS (cholestyramine and colestipol) can lead to gastrointestinal side effects such as constipation, influencing long-term compliance. It should be highlighted that BAS interfere with the absorption of folate and fat-soluble vitamins.

There are inadequate data to support the use of supplements such as psyllium-enriched cereal, garlic extract, omega-3 fatty acids, rapeseed oil and soy protein in children and adolescents with hypercholesterolemia [16]. Non-pharmacologic treatment of hypercholesterolemia as adjuncts to a healthy diet includes functional foods supplemented with plant sterols and stanols (PS). Data remain scarce on the efficacy of PS as add-on therapy to ezetimibe, fibrates, omega-3 fatty acids, or bile acid binding resins and there is even less evidence on the use of it in children [17].

Recently, a new group of drugs, monoclonal antibodies directed against proprotein convertase subtilisin kexin type 9 (PCSK9; evolocumab and alirocumab), has emerged as a promising approach for treating severe hypercholesterolaemia, including HoFH. These agents reduce LDL cholesterol by up to 65% and are safe and well tolerated.

PCSK9 regulates expression of the LDL receptor plays a key role in determining plasma LDL cholesterol levels. In Europe, evolocumab is approved in adolescents (≥12 years old) with homozygous FH. In the United States, alirocumab is approved only for use in adult patients. The use of these agents in pediatric patients is limited to individuals with homozygous FH and/or those with drug-resistant hypercholesterolemia [18]. Long-term clinical trials are needed to evaluate if treatment with PCSK9 inhibitors are cost-effective to start during childhood [16].

4. Expert opinion

Current guidelines recommend initiating statin treatment at equal ages in girls and boys. The excellent tolerability of statins in children and adolescents may be explained by the usage of lower doses compared with adults. The importance of diet in lipid management in children has been emphasized, and a decrease in lipid levels during growth and puberty can occur [19]. Some expert panels recommend pharmacotherapy not be started before the age of 8–10 years in children with

HeFH out of concern that statins may have adverse effects on brain development and steroid hormone production, though this is unlikely [11]. Due to ethical and economic reasons, but also several limitations (bias in the selection of patients, the lack of randomization), large long-term placebo-controlled studies with the use of statin in children are limited [19]. Such studies are urgently needed [20].

Screening in conjunction with routine health visits such as at the time of immunization and cascade screening of first-degree family members are recommended and leads to earlier identification of subjects with severely elevated LDL cholesterol [21].

It should be highlighted that in childhood FH may co-exist with other disorders associated with the development of atherosclerosis, such as type 1 diabetes mellitus, chronic kidney disease, connective tissue disorders, and HIV infection. Consequently, other cardiovascular risk factors should be monitored during annual or bi-annual monitoring and treated, if needed. Cigarette smoking should be strongly discouraged. Physical exercise and a heart healthy diet should be encouraged. There is not enough evidence regarding the use of dietary supplementation with functional foods in children and further investigations are awaited [21]. For instance, food enriched with plant sterols/stanols is not recommended for children under 6 years of age.

Paediatric dyslipidemic subjects should be monitored by experienced primary care practitioners, but also by specialists (cardiologists and lipidologists), especially if several cardiovascular risk factors or complications of pharmacologic treatment are present [21].

In coming years, the use of a combination of case-finding, universal screening, increased public and health professional awareness of the prevalence of dyslipidemia, as well as better education, treatment knowledge and team work between general practitioners and specialists will improve patient identification and treatment approaches. Randomized, placebo-controlled trials are also needed to resolve currently unanswered questions related to the treatment of secondary dyslipidemias in children. Novel analytical methods in research should be developed. Country/region adjustments for LDL cholesterol cut-off levels will also be important to identify.

There is an urgent need for diagnosing pediatric dyslipidemia. It is important to increase awareness and to offer better education of young FH subjects and their parents. In secondary dyslipidemia, first line treatment must be changes in lifestyle. If despite 6 months of lifestyle intervention LDL cholesterol levels do not improve in children over 8–10 years of age, pharmacologic treatment should be considered. Statins and ezetimibe are well tolerated in children and adolescents. Bile acid sequestrants can also be considered. A new class of drugs, PCSK9 inhibitors, is the most promising therapy in children with homozygous FH. The biggest challenge is to institute adequate treatment for children with HeFH and nonFH and to evaluate the cost-effectiveness of treatment. To this end, long-term, well-design, randomized clinical trials are needed.

Funding

This manuscript has not been funded.

Declaration of interest

D Nikolic has participated in clinical trials sponsored by AstraZeneca, Eli Lilly and Company and Novo Nordisk. M Rizzo has given lectures, received honoraria and research support, as well as having participated in conferences, advisory boards and clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Kowa, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Novartis, Roche Diagnostics and Servier. PP Toth has served as a speaker for Amarin, Amgen Inc, Kowa, Merck & Co., Novo Nordisk, Regeneron and Sanofi as well having acted as a consultant for Amarin, Amgen Inc, Kowa, Merck & Co., Novo Nordisk, Regeneron, Resverlogix, Sanofi and Theravance. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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