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The treatment of hypercholesterolemic children: Efficacy and safety of a combination of red yeast rice extract and policosanols☆

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Red yeast rice extract;
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Abstract *Background and aims:* The prevention of cardiovascular risk, as occurs in lipoprotein disorders, is required since childhood. Aim of the study was to evaluate, in a group of children affected by primary dyslipidemia, the efficacy, tolerability and safety of a short-term treatment with a dietary supplement containing red yeast rice extract and policosanols.
Methods and Results: 40 children affected by heterozygous Familial Hypercholesterolemia (FH) ($n = 24$) and Familial Combined Hyperlipidemia (FCH) ($n = 16$), aged 8–16 years, were enrolled in a double-blind, randomized, placebo-controlled, cross-over trial. After a 4-week run-in period with only dietary advice, children received a dietary supplement containing 200 mg red yeast rice extract, corresponding to 3 mg of monacolins, and 10 mg policosanols once-daily and placebo for 8 weeks, separated by a 4-week washout period. Lipid profile was assessed after each treatment period.

The dietary supplement, compared with the placebo, significantly reduced total cholesterol by 18.5% ($p < 0.001$), LDL-C levels by 25.1% ($p < 0.001$), and apolipoprotein B by 25.3% ($p < 0.001$) when patients were considered as a whole group. Similar results were obtained when FH and FCH were considered separately and no significant difference between groups was detected. No significant differences were observed in HDL-C and apolipoprotein A–I levels. No adverse effects were detected when liver and muscular enzymes (AST, ALT, and CK) were determined.
Conclusions: The treatment with a dietary supplement containing red yeast rice extract and policosanols has been for the first time successfully employed in hypercholesterolemic children. Results indicate this strategy as an effective, safe and well tolerated in a short-term trial.

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Introduction

Primary hyperlipidemias are often complicated by premature cardiovascular disease (CVD) and CVD risk is correlated to increased LDL cholesterol (LDL-C) levels [1]. It is well known that lipoprotein changes that occur in primary hyperlipidemia start in childhood and track to adulthood [2]. A precocious vascular damage has been demonstrated since pediatrics, as evidenced by the carotid intima-media thickness measurement or the endothelial dysfunction [3]. A hot topic is so far represented by CVD prevention through lipid lowering treatment in children affected by lipoprotein disorders [4].

Intervention strategies are mandatory early in life and guidelines underline the management of diet and drugs therapy since childhood. The statement by the American Academy of Pediatrics (AAP), updated July 2008, provides recommendations for treatment [5]. Childhood LDL-C values overcoming 3.36 mmol/L (130 mg/dL) are considered elevated but the dietary intervention not always succeed in satisfying results. Statins have been demonstrated effective and safe in short-term studies, however their long term effects are not fully established [6]. Drugs are allowed to subjects over 8 years when LDL-C levels exceed 4.9 mmol/L (190 mg/dL) or 4.1 mmol/L (160 mg/dL) in the presence of positive familial history of premature CVD or 2 other cardiovascular risk factors (obesity, hypertension or cigarette smoking) or in diabetic children with LDL-C $\geq$ 3.36 mmol/L (130 mg/dL) [5]. Statin therapy is limited to high risk subjects so that pharmacological treatment of dyslipidemia in children is still an open issue.

Nutraceutical is a new class of food that includes any substance, food or a part of it, which provides medical or health benefits (including the prevention and treatment of chronic disease) beyond basic nutritional functions. It comprises a series of products effective in reducing cholesterol levels, such as phytosterols [7], soluble fibers [8], policosanols [9] and red yeast rice [10]. The latter is obtained by rice fermentation with the mycete *Monascus purpureus*. The red rice has been largely employed as a food additive to flavour and colour food for many centuries in China [10]. Its recognized lipid lowering effect is known to be related to the lovastatin content. It was tested successfully in studies performed in adulthood [11–14], but no trials have been conducted in childhood so far.

The aim of this study was to evaluate the short-term efficacy, tolerability and safety of a combined red yeast rice extract and policosanols dietary supplement in children and adolescents affected by inherited lipoprotein metabolism disorders.

Methods

Patients

We recruited 40 pediatric outpatients affected by primary hypercholesterolemia affering to our Lipid Clinic. Twenty-four resulted affected by heterozygous Familial Hypercholesterolemia (FH) (M/F, 11/13) and 16 by Familial Combined Hyperlipidemia (FCH) (M/F, 8/8). The diagnosis of FH was made according to the standard clinical criteria including a careful reconstruction of a two-generation family tree [15]. FCH was diagnosed in subjects with total cholesterol (TC) and/or triglyceride (TG) serum levels greater than 90th percentile of the reference population, with hypercholesterolemia and/or hypertriglyceridemia in at least one first-degree relative and intra-familial variability.

Entry criteria included children aged 8–16 years, showing serum levels of TC higher than 5.17 mmol/L and/or LDL-C levels higher than 3.36 mmol/L after a Step 1 and Step 2 dietary intervention for at least 6 and 3 months respectively, as suggested by the National Cholesterol Education Program [16]. Exclusion criteria were represented by secondary dyslipidemias, including renal, endocrine and liver disorders, as well as patients affected by chronic diseases and submitted to drug therapies. Short treatment for intercurrent illness (antipyretics, anti-histaminics, antibiotics except macrolides) was not an exclusion criteria. All the study participants were no smokers and none of them was on a lipid lowering treatment for the last 3 months.

Study design

This was a double-blind, randomized, placebo-controlled, cross-over trial. Subjects started with a 4-week diet run-in period. They were instructed, as well as their parents, by a trained dietician to continue a low-saturated fat, low-cholesterol diet according to Step 2, and not to pursue any change in food selection or physical activity that could modify their lipid concentrations. Children were then randomly assigned to consume either the dietary supplement or the placebo for 8 weeks each. Twenty children started with the dietary supplement and twenty with the placebo. After a 4-week washout period, children switched the treatment for another 8 weeks. They were asked to provide a dietary weekly diary to control any deviation from the indicated diet. The diary was completed by children and their parents and at each visit the dietician checked the records for accuracy. Moreover children's physical activity was evaluated at any control.

The dietary supplement was formulated as a tablet (Armolipid™, Rottapharm S.p.A., Monza, Italia) and administered once-daily 1 h after dinner. Its composition was: 200 mg red yeast rice extract (equivalent to 3 mg of monacolins, particularly monakolin K or lovastatin), 10 mg policosanols, 0.2 mg folic acid, 2 mg coenzyme Q10 and 0.5 mg astaxanthin. The product employed was citrinin and aflatoxins-free. The rice-powder placebo mimicked the colour and the appearance of the active product. The dietary supplement and the placebo were purchased directly from the manufacturer. The compliance was checked on the basis of the number of tablets returned by the same physician who performed the physical evaluation.

Patients were submitted to laboratory measurements at baseline and at the end of each treatment period. At the same time they were also submitted to physical evaluation (including measures of weight, height, BMI and Tanner Stage) by a physician who had no prior knowledge of the patient clinical presentation and lipid profile. They were asked to list any symptom, intercurrent illness or drug assumption which underwent along the trial.