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Original Research

Efficacy and Tolerability of a Nutraceutical Combination (Red Yeast Rice, Policosanols, and Berberine) in Patients with Low-Moderate Risk Hypercholesterolemia: A Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: Statins are at the forefront of strategies to manage hypercholesterolemia. However 10% to 15% of patients are intolerant to any statin drugs, even at low daily doses and almost one-third of statin users discontinue therapy within 1 year. Some nutraceuticals are prescribed as lipid-lowering substances, but doubts remain about their efficacy and tolerability.

Objectives: We aimed to investigate the efficacy and the safety of a nutraceutical combination consisting mainly of 200 mg red yeast rice extract (equivalent to 3 mg monacolins), 500 mg berberine, and 10 mg policosanols (MBP-NC) in patients with low-moderate risk hypercholesterolemia.

Methods: In this single centre, randomized, double-blind, placebo-controlled study 60 consecutive outpatients (29 men and 31 women; age range = 18–60 years), with newly diagnosed primary hypercholesterolemia not previously treated, after a run-in period of 3 weeks on a stable hypolipidic diet, were randomized to receive a pill of MBP-NC (n = 30) or placebo (n = 30) once a day after dinner, in addition to the hypolipidic diet. The efficacy and the tolerability of the proposed nutraceutical treatment were fully assessed after 4, 12, and 24 weeks of treatment.

Results: In the MBP-NC group both total cholesterol and LDL-C already showed a significant reduction at Week 4 (–30.3% ± 33.9% and –29.4% ± 35.3%, respectively) that remained substantially unchanged at Week 12 (–26.7% ± 33.1% and –25.6% ± 31.5%, respectively) and at Week 24 (–24.6% ± 32.1% and –23.7% ± 32.6%, respectively). The between-groups differences were significant at all time points for both total cholesterol and LDL-C. There were no significant changes in HDL-C, fasting glucose, and triglyceride serum levels in either group. MBP-NC was also safe and well tolerated.

Conclusions: In patients with low- to moderate-risk hypercholesterolemia a nutraceutical combination in association with a hypolipidic diet significantly reduced total cholesterol and LDL-C levels and may favor the reaching the recommended cholesterol targets. ClinicalTrials.gov identifier: NCT02078167.

Introduction

Many epidemiologic studies have shown that serum cholesterol levels are strongly related to cardiovascular risk.[1,2] Consequently lowering cholesterol levels is a fundamental prognostic goal in the primary and secondary prevention of cardiovascular events. The 3-hydroxy-3-methylglutaryl-coenzime A reductase inhibitors, commonly known as statin drugs, are the drugs of first choice to lower serum cholesterol levels, especially in patients at high or very-high risk of cardiovascular diseases, in view of their established efficacy in reducing cardiovascular mortality and morbidity in both primary and secondary prevention.[3,4] Statin drugs are generally well tolerated and in controlled trials the adverse events were similar in patients treated with statins and those treated with placebo.[4] However, in clinical practice, 10% to 15% of patients are found to be intolerant to any statin drugs, even at low daily doses and almost one-third of statin users discontinue therapy within 1 year.[5] Furthermore some other patients, especially in primary prevention, refuse statin drugs because of the fear of possible side effects. Some nutraceutical products may represent an alternative treatment to be considered for the above-mentioned cases, above all in patients with marginally high hypercholesterolemia.[4,6] Because the use of the full dose of

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nutraceuticals entail some tolerability concerns, a combination of nutraceuticals with different but synergic mechanisms of action at lower and safer dosages could be preferable. In particular, in recent years there has been growing interest in a nutraceutical combination containing monacolin (the biologically active component of red yeast rice), berberine, and policosanols (MBP-NC). The cholesterol-lowering effect of MBP-NC consumed in conjunction with a standard Mediterranean healthy diet has been observed in a large Italian study carried out by general practitioners[7] in patients intolerant to >1 statin,[8] in patients with metabolic syndrome or who are overweight,[9,10] and in elderly patients with hypercholesterolemia.[11] Moreover, the MBP-NC mixture has been reported to have some direct protective vascular effects, similar to pharmacologic lipid-lowering agents, such as improvement in endothelial dysfunction[12] and improvement in aortic stiffness.[13] Another recent study reported that a 2-month treatment with MBP-NC improved insulin sensitivity in patients with metabolic syndrome.[14]

Hitherto the cholesterol-lowering effect of MBP-NC has not been evaluated in long-term double-blind, placebo-controlled studies. The aim of our single-center, randomized, double-blind, placebo-controlled study was to evaluate the efficacy and the safety of a 24-week treatment with a MBP-NC mixture in patients with low-moderate risk hypercholesterolemia.

Materials and Methods

Population

A cohort of 66 consecutive outpatients with newly diagnosed primary hypercholesterolemia not previously treated who applied to the lipid clinic of the Department of Internal Medicine at the University of Siena, Italy, were considered for enrolment in our study. The inclusion criteria were age between 18 and 60 years, body mass index between 18.5 and 29.9, serum LDL-C >150 mg/dL (3.88 mmol/L), and an estimated 10-year cardiovascular risk <20% according to Framingham risk scoring. The exclusion criteria were history of cardiovascular disease or coronary risk equivalents; secondary hyperlipidemia caused by diabetes mellitus, renal, liver, or thyroid diseases; alcohol consumption >40 g/d; estimated 10-year cardiovascular risk >20% according to Framingham risk scoring; and muscular diseases or abnormally elevated creatine phosphokinase (CPK) levels or drug treatment with antiplatelet, anti-inflammatory, or hypolipidemic agents, or hormone replacement therapy either ongoing or any time during the previous 2 months. Instead, the patients stable while taking antihypertensive treatment for at least 3 months were included. All patients were instructed to maintain their habitual physical activity during the study period.

At the screening visit, all patients were instructed to follow a hypolipidic diet (ie, low-cholesterol/low-saturated fat diet approximately consisting of 55% carbohydrates, 20% proteins, and 25% lipids) during a run-in period of 3 weeks, after which all patients who met the inclusion criteria (29 men and 31 women), were randomized to receive a pill of MBP-NC (n=30) or placebo (n=30) once a day after dinner, in addition to the hypolipidic diet. The placebo pills, identical in taste and appearance to the MBP-NC pills, consisted of inactive compound. Randomization and blinding were provided by Rottapharm Madaus SpA (Monza, Italy). The composition of the patented proprietary combination of nutraceuticals investigated was 200 mg red yeast rice extract (equivalent to 3 mg monacolins), 500 mg berberine, 10 mg policosanol, 0.2 mg folic acid, 2 mg coenzyme Q10, and 0.5 mg asthaxantin (Armolipid Plus, Rottapharm Madaus SpA).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki, as revised in 2000 and 2008, and the study protocol was approved by the Ethics Committee of the University Hospital of Siena. Written informed consent was obtained from each patient.

Clinical and anthropometric evaluation

All patients underwent physical examination at baseline and after 4, 12, and 24 weeks of treatment. All the determinations were made at the lipid clinic at 9:00 AM, after an overnight fast of 12 hours. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index was calculated as weight in kilograms divided by height meters[2]. Brachial blood pressure was measured by a physician with a mercury sphygmomanometer after patient had been seated for at least 10 minutes and the average of 3 measurements was considered for the analysis. Waist circumference was also measured at each visit midway between the lowest rib and the iliac crest using an anthropometric tape.

In all patients, body composition (fat mass percentage, fat-free mass, and fat-free mass to fat mass ratio) was assessed by anthropometry and bioelectrical impedance analysis using a single-frequency 50 kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Florence, Italy). All bioelectrical impedance analysis measurements were carried out by the same operator according to the standard tetrapolar technique, with patients in a supine position for at least 20 minutes. The electrodes were placed on the dorsal surface of the right foot and ankle and the right wrist and hand.

Biochemical measurements

In all patients fasting venous blood samples were drawn at baseline and after 4, 12, and 24 weeks to assess serum levels of total cholesterol, triglycerides (TG), HDL-C, and LDL-C. All lipid parameters were measured using a colorimetric method (Autoanalyzer, Menarini, Florence, Italy). In our institution the intra- and interassay coefficients of variation were, respectively, 1.8% and 3.8% for total cholesterol, 2.0% and 3.0% for HDL-C, 1.7% and 2.9% for TG, and 1.5% and 2.3% for LDL-C assessment. To monitor the safety of the MBP-NC in all patients at the same time points serum levels of glucose, uric acid, creatine phospho kinase (CPKw), gamma-glutamiltranferase, and transaminases were also assessed. Tolerability was monitored by recording symptoms. Medication compliance was assessed by counting the number of pills returned at the clinic visits.

Statistical analysis

All values were expressed as mean (SD). Clinical data and initial values of the variables measured in the study groups were compared using Student *t* test for unpaired data. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of the outcome variables. For all parameters the absolute changes over time for each patient were expressed as a percentage of the baseline values. Paired *t* test and Wilcoxon matched-pairs signed-rank test were used, where appropriate, to compare the changes with baseline values. Two-way ANOVA for repeated measures was used to compare the response of the study variables to the 2 different treatments. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. All tests were performed using the SPSS statistical package for Windows version 16.0 (IBM-SPSS Inc, Armonk, New York).