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Research Article

Red Yeast Rice in the Long-Term Treatment of Hypercholesterolemia. A Single-Center Experience

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Abstract

Red yeast rice (RYR) is an effective and relatively safe treatment for dyslipidemia. However, long-term effectiveness and safety of RYR have not yet been evaluated in western populations. We report a single-center experience in 122 hypercholesterolemic Italian subjects treated for 24-month with a dietary supplement containing a RYR extract.

After 24 months of treatment we observed a significant reduction in total cholesterol levels by 14.0% ($p < 0.001$) and in low density lipoprotein cholesterol levels by 18.7% ($p < 0.001$). No significant differences were observed in body mass index, liver function, triglycerides, low density lipoprotein cholesterol and creatine kinase plasma levels. Myalgia and increased CK occurred in one subject. No other serious adverse events were reported.

Keywords: Red yeast rice; Hypercholesterolemia; Monacolins

Introduction

Red yeast rice (RYR) is the product of rice fermented with *Monascus purpureus* yeast, used in China and other Asian countries for centuries as a traditional medicine [1]. RYR has gained popularity because of its properties as a natural statin and herbal supplements containing RYR have been worldwide marketed to help lower blood cholesterol. RYR contains several compounds including polyketides, unsaturated fatty acids, phytosterols, pigments, and monacolins [2].

Monacolins lower cholesterol by inhibiting HMG-CoA (5-hydroxy-3-methylglutaryl-coenzyme A) reductase, the rate-limiting step for cholesterol synthesis in the liver. At least 13 monacolins have been isolated from RYR, of which the primary is monacolin K, substance chemically similar to lovastatin, a cholesterol-lowering drug [3].

Although RYR is claimed to be a safer alternative to statins, structural similarity with lovastatin implies that similar adverse reactions are possible. Adverse effects of RYR include gastrointestinal effects and may cause myopathy, hepatotoxicity, rhabdomyolysis, and anaphylaxis similar to the use of statins [4-6]. The mycotoxin citrinin, found in poorly produced RYR products, is mutagenic in animal models, genotoxic to human lymphocytes, and can cause kidney failure in animals, although acute toxicity is a rare event [7].

The European Food Safety Authority (EFSA) considers that in order to obtain the claimed effect, 10 mg of monacolin K from fermented red yeast rice preparations should be consumed daily [8]. Because of monacolin K has the same chemical structure as lovastatin, RYR is considered an unapproved drug by the U.S. Food and Drug Administration, and as such all RYR products that contain monacolin K are prohibited [9].

Several clinical trials have been conducted to evaluate the efficacy and safety of RYR. A recent meta-analysis examined 20 randomized trials consisting of 6663 patients and showed a reduction in low density lipoprotein (LDL) cholesterol when comparing RYR to placebo groups (-1.02 mmol/L) [10]. There was no difference in LDL between RYR and statin therapy (0.03 mmol/L, with an incidence of kidney injury and liver abnormalities of less than 5% in both the RYR and control groups.

In the largest randomized controlled trial examining RYR in secondary cardiovascular prevention, 4870 Chinese patients were treated for an average of 4,5 years. RYR reduced nonfatal myocardial infarction, coronary disease mortality, coronary revascularization, and total mortality in patients with a history of myocardial infarction and moderate hypercholesterolemia [11].

The trials conducted in western countries had a follow-up of few weeks and then the long-term effectiveness and safety of RYR in these populations are not well assessable. In this study, we report our experience in a 24-month treatment of hypercholesterolemia Italian subjects with a dietary supplement containing a RYR extract.

Materials and Methods

We evaluated 145 adult outpatients (104 males, 41 females) with primary, mild to moderate hypercholesterolemia, observed in the Clinical Nutrition Unit of Azienda Ospedaliera of Padua-Italy, from January 2013 to June 2015. Mild hypercholesterolemia was defined as an LDL-cholesterol level of 3.4 ± 5.2 mmol/l. The mean age at the first observation was 58 ± 9 years.

Patients were treated with dietary and lifestyle modifications, according to the National Cholesterol Education Program Adult Treatment Panel III (2001) [12] and with one pill once daily of

a commercial dietary supplement (Reductive, Frama S.R.L., Padua-Italy) containing a blend of two RYR dried-extracts (0,4% and 1,5% monacolins by weight, 262 and 130 grams of extract per pill, respectively). Total daily monacolins dose was 3 mg. The RYR extract was tested for its amount of monacolin K using a high performance liquid chromatography method, while citrinin was detected with indirect competitive enzyme-linked immunosorbent assay.

Patients who met the following criteria at the start of treatment were excluded: age below 20 years, previous cardiovascular disease, triglyceride level above 4,5 mmol/l, serum liver transaminase level above the upper normal range, nephrotic syndrome, uncontrolled hypothyroidism, obesity (body mass index ≥ 30 kg/m^2), insulin dependent diabetes or insulin treatment, pregnancy, lactation, history of alcoholism or psychiatric disturbances, malignancy diagnosed during the previous 3 years, and concomitant therapy with any drug that may affect the lipid profile.

Body weight, total serum cholesterol (TC), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(HDL-C), serum triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and creatine kinase (CK) were evaluated before the treatment and after 12 and 24 months. In case of severe side effects or poor effectiveness (LDL-C reduction lower than 5%), RYR treatment was discontinued.

Before the treatment each subject provided written informed consent.

Continuous variables were described as means plus or minus one standard deviation. Student's t test was used to measure the statistical significance of the mean differences. A value of $p < 0.05$ was considered statistically significant.

Results

The level of total monacolin K in the RYR supplement was 0.58 % while citrinin was below detection limits. After 24 months 122 patients (84%) were still using RYR. Twenty-six patients discontinued treatment before 24 months due to personal reasons (14 subjects), lacking effectiveness (8 subjects) and myalgia with increased CK (one subject).

After 12 months of treatment the mean TC level decreased from 7.1 ± 1.2 to 6.0 ± 1.1 mmol/l (-15.5%; $p < 0.001$) and the mean LDL-C decreased from 4.8 ± 0.9 to 3.8 mmol/l ± 0.9 (-20.8%; $p < 0.001$). After 24 months mean TC plasma level was 6.1 ± 1.1 mmol/l (-14.0%; $p < 0.001$) and the mean LDL-C was 3.9 mmol/l ± 0.8 (-18.7%; $p < 0.001$) (Table 1).

No significant differences were observed in BMI, TG, HDL-C, AST, ALT, GGT and CK variations (Table 1). No serious adverse events were reported.

	T0	T1	T2
BMI kg/m^2	25.7 ± 4.1	25.4 ± 4.0 n.s.	25.5 ± 4.1 n.s.
TC mmol/l (reference range: 2.0 - 6.19)	7.1 ± 1.2	6.0 ± 1.1 *p < 0.001*	6.1 ± 1.1 *p < 0.001*
LDL-C mmol/l (reference range: 1.0 - 4.12)	4.8 ± 0.9	3.9 ± 0.8 *p < 0.001*	4.0 ± 0.8 *p < 0.001*
HDL-C mmol/l (reference range: 0.80 - 3.00)	1.94 ± 1.08	1.78 ± 0.98	1.76 ± 1.01
TG mmol/l (reference range: < 1.7)	1.8 ± 1.2	1.6 ± 1.1 *n.s.*	1.7 ± 1.2 *n.s.*
ALT U/l (reference range: 10 - 50)	26.7 ± 7.7	23.3 ± 7.2 *n.s.*	23.0 ± 7.2 *n.s.*
AST U/l (reference range: 10 - 45)	32.8 ± 8.6	29.2 ± 8.0 *n.s.*	29.6 ± 8.3 *n.s.*
GGT U/l (reference range: 3 - 65)	33.7 ± 12.4	31.9 ± 11.9 *n.s.*	32.2 ± 12.1 *n.s.*
CK U/l (reference range: 30 - 200)	83 ± 39	94 ± 43 *n.s.*	91 ± 45 *n.s.*

Table 1: Body Mass Index and biochemical data before (T0), after 12 months (T1) and after 24 months (T2) the treatment (mean ± DS). BMI: Body Mass Index; TC: Total Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; HDL: High-Density Lipoprotein Cholesterol; AST: Aspartate Transaminase; ALT: Alanine Transaminase; GGT: Gamma-Glutamyl Transpeptidase; CK: Creatine Kinase

Discussion

The statins are the first line lipid-lowering therapy due to their efficacy for reducing cardiovascular morbidity and mortality [13]. However, the side effects of statins including myalgias and muscle weakness reduced energy, increased fatigue, liver enzyme elevations may reduce adherence to therapy [14]. Therefore, a safe and effective alternative treatment for dyslipidemia therapy is needed. A recent meta-analysis suggests that red yeast rice is an effective and relatively safe treatment for dyslipidemia [15].

All studies using RYR in Caucasian subjects have followed-up treatment only for few weeks. In this study, we evaluated the long-term effectiveness and safety of a RYR extract in a Italian population. The treatment with RYR was stopped within the first six months in 8 patients (5%) because non-responders and 14 patients (10%) did not complete the treatment even if effective. In the remaining subjects (84%), the RYR extract was able to reduce LDL-C by roughly 20% after 24 months of treatment despite its small content in monacolin (3 mg per day, of which 2,3 mg as monacolin K). A trial in a Asiatic population with a daily intake of 10.0 to 12.8 mg monacolin K evidenced similar data on lipid profile over a period of 4.5 year [11].

As expected, no effect was observed in BMI, TG and HDL-C. The RYR extract was well-tolerated, without induced hepatotoxicity. Mialgya and a rise of CK were observed only in one subject. How-

ever, in patients who completed the treatment mean values of AST, ALT and CK did not rise significantly at the end of the observation.

RYR is effective in cholesterol levels as a low-dose statin so that RYR was tolerated well in patients who were previously intolerant to statins [16].

This observation has not yet been explained. The lipid lowering properties of red yeast rice does appear to be multifactorial. One of the first and more obvious mechanisms to be supported is red yeast rice's ability to inhibit the activity of the rate limiting step of hepatic cholesterol biosynthesis in a dose-dependent manner.

Additionally, animal data in hamsters suggested that red yeast rice also increases the hepatic excretion of bile acids, thereby increasing need for the availability of intrahepatic cholesterol to be used for the synthesis of additional bile [17].

A recent study found dramatic variability of monacolin levels in commercial products and the presence of CN in one third of formulations [18], thereby posing serious doubts about their safety and effectiveness. In the supplement used in our study we found that the contaminant citrinin was virtually absent and the concentration of monacolin K corresponded to the expected, considering that in RYR monacolin K accounts for about 70% of total monacolins [19].

Conclusion

In conclusion, our data showed the effectiveness and safety of RYR in the long-term treatment of a group of Italian hypercholesterolemia subjects. Future trials with larger samples size are needed to confirm our preliminary findings.

Conflict of Interest

The author declare that there are no financial interest and conflict of interest.

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Volume 1 Issue 3 August 2017