

Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients

A Randomized Trial

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Background: Red yeast rice is an herbal supplement that decreases low-density lipoprotein (LDL) cholesterol level.

Objective: To evaluate the effectiveness and tolerability of red yeast rice and therapeutic lifestyle change to treat dyslipidemia in patients who cannot tolerate statin therapy.

Design: Randomized, controlled trial.

Setting: Community-based cardiology practice.

Patients: 62 patients with dyslipidemia and history of discontinuation of statin therapy due to myalgias.

Intervention: Patients were assigned by random allocation software to receive red yeast rice, 1800 mg (31 patients), or placebo (31 patients) twice daily for 24 weeks. All patients were concomitantly enrolled in a 12-week therapeutic lifestyle change program.

Measurements: Primary outcome was LDL cholesterol level, measured at baseline, week 12, and week 24. Secondary outcomes included total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, liver enzyme, and creatinine phosphokinase (CPK) levels; weight; and Brief Pain Inventory score.

Results: In the red yeast rice group, LDL cholesterol decreased by 1.11 mmol/L (43 mg/dL) from baseline at week 12 and by 0.90

mmol/L (35 mg/dL) at week 24. In the placebo group, LDL cholesterol decreased by 0.28 mmol/L (11 mg/dL) at week 12 and by 0.39 mmol/L (15 mg/dL) at week 24. Low-density lipoprotein cholesterol level was significantly lower in the red yeast rice group than in the placebo group at both weeks 12 ($P < 0.001$) and 24 ($P = 0.011$). Significant treatment effects were also observed for total cholesterol level at weeks 12 ($P < 0.001$) and 24 ($P = 0.016$). Levels of HDL cholesterol, triglyceride, liver enzyme, or CPK; weight loss; and pain severity scores did not significantly differ between groups at either week 12 or week 24.

Limitation: The study was small, was single-site, was of short duration, and focused on laboratory measures.

Conclusion: Red yeast rice and therapeutic lifestyle change decrease LDL cholesterol level without increasing CPK or pain levels and may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.

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Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are the most effective lipid-lowering medications for primary and secondary prevention of coronary artery disease (1–3). Although statins are generally well tolerated, some patients experience adverse effects, including elevated hepatic enzyme levels; gastrointestinal symptoms; and statin-associated myalgias (SAMs), which include muscle pain and weakness. Myositis (elevated creatinine phosphokinase [CPK] level) and rhabdomyolysis are more serious but rare complications of therapy (4).

Statin-associated myalgias are dose related and typically occur in the absence of myositis. Currently, no optimal treatment exists for patients who develop SAM but still require therapy for hyperlipidemia. Because of SAM, patients may seek alternative therapies to manage their hypercholesterolemia, including red yeast rice (*Monascus purpureus*), a widely available dietary supplement that has been used as an herbal medication in China for centuries. Red yeast rice decreases low-density lipoprotein (LDL) cholesterol level (5–7), but no trials have investigated its use in patients with SAM.

Our primary goal was to assess the efficacy and tolerability of red yeast rice for hypercholesterolemia in patients with previous SAM. We enrolled all patients in a therapeutic lifestyle change program and compared the lipid-lowering efficacy of red yeast rice with placebo in patients with a history of intolerance to at least 1 statin.

METHODS

Design Overview

We recruited patients from a cardiology practice in suburban Philadelphia. The institutional review board of Chestnut Hill Healthcare approved the trial, and all patients gave written informed consent. All authors had complete access to the primary data.

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Context

Statin-associated myalgias prevent some patients who would benefit from drug therapy for dyslipidemia from receiving it. Red yeast rice is a dietary supplement that can decrease low-density lipoprotein (LDL) cholesterol level and could be a treatment option for patients with statin-associated myopathy.

Contribution

After 12 and 24 weeks, patients who received red yeast rice, 1800 mg twice daily, had significantly larger improvements in both LDL and total cholesterol levels than did patients who received placebo. Pain, creatinine phosphokinase levels, and liver enzyme levels did not differ between groups.

Implication

Red yeast rice may be a treatment option for dyslipidemic patients who cannot tolerate statins.

—The Editors

Setting and Patients

Patients were eligible if they were 21 to 80 years of age; had known hypercholesterolemia; and had discontinued at least 1 statin because of myalgias, with resolution of muscle pain when the medication was discontinued. We excluded patients if they had received a statin or red yeast rice in the month before random assignment; had a history of statin-associated myositis, rhabdomyolysis, chronic pain, or inability to exercise; had myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting in the previous 6 months; had received weight-loss medications or dietary supplements that might mitigate SAM or decrease lipid levels; or had abnormal baseline laboratory values (LDL cholesterol level <2.6 mmol/L [<100 mg/dL] or >5.5 mmol/L [>210 mg/dL], triglyceride level ≥ 4.4 mmol/L [≥ 400 mg/dL], CPK level >500 U/L, aspartate transferase or alanine transferase level >1.5 times the upper limit of normal, or an abnormal thyroid-stimulating hormone level).

Randomization and Interventions

Figure 1 shows the flow of patients through the trial. We recruited patients between September 2006 and March 2007. We screened 174 patients with SAM; 112 were ineligible for the study or declined to participate. Sixty-two patients were randomly assigned, and baseline laboratory tests were drawn and measurements taken. Table 1 shows baseline characteristics.

We randomly assigned all enrolled patients to receive three 600-mg capsules of red yeast rice (1.8 g by weight) or 3 placebo capsules twice daily for 24 weeks. We randomly assigned patients in blocks of 4 and stratified them into 4 categories to improve power and subgroup analyses: LDL cholesterol level less than 3.9 mmol/L (<150 mg/dL),

LDL cholesterol level of 3.9 mmol/L or greater (≥ 150 mg/dL), body mass index less than 27 kg/m², and body mass index of 27 kg/m² or greater. We generated the random assignment list on a computer by using the blockrand library (8) of the R programming environment with the fixed-block option (9).

We purchased both the red yeast rice and placebo directly from the manufacturer (Sylvan Bioproducts, Kittanning, Pennsylvania); they were identical in size, shape, and color. Participants received a 30-day supply of study product at monthly visits. At the end of the trial, we assessed treatment adherence by self-report of the average number of missed doses per week.

All patients also enrolled in our previously published, multidisciplinary, 12-week therapeutic lifestyle change program (10). Briefly, patients attended weekly 3.5-hour meetings and were taught about cardiovascular disease, nutrition, exercise, and relaxation techniques (Appendix, available at www.annals.org).

After the therapeutic lifestyle change program ended at week 12, we again conducted laboratory tests and took measurements. We then instructed patients to follow the recommendations of the program and continue to take their study medication for an additional 12 weeks. We held meetings each month to review dietary and exercise logs and provide study product. Attendance in the 12-week program and all subsequent monthly meetings was 92%. All patients and study team members were blinded to treatment allocation throughout the 24-week study. At week 24, we conducted the final laboratory tests and took the final measurements.

One patient in the red yeast rice group dropped out at week 10 because he could not attend the program. Two patients in the placebo group dropped out, 1 at week 12 because of newly diagnosed hypothyroidism and 1 at week 16 because of nonadherence to the lifestyle change program. Fifty-nine patients completed the 24-week study: 30 in the red yeast rice group and 29 in the placebo group. We conducted the study between April 2007 and October 2007.

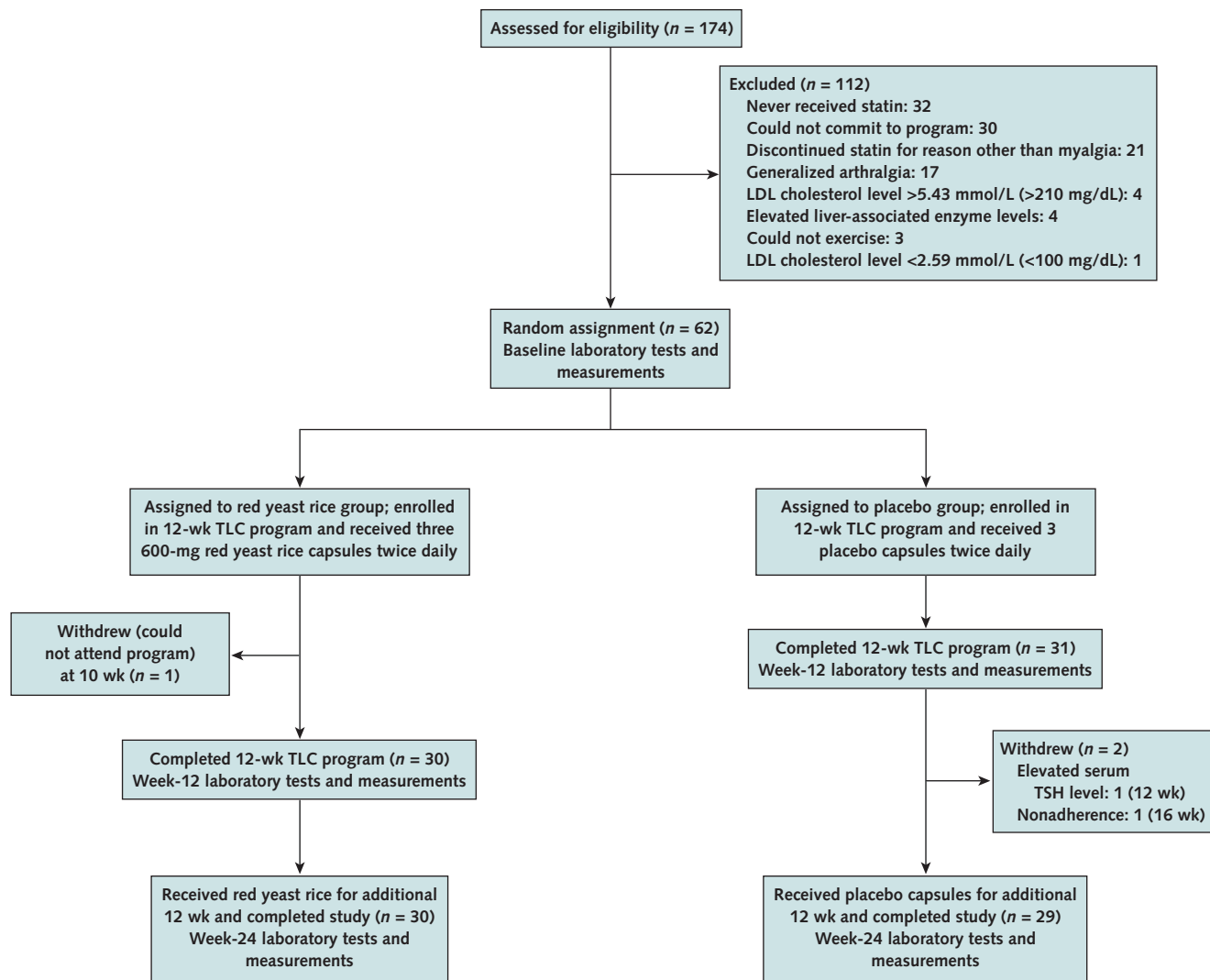
Outcomes and Follow-up

The primary outcome was LDL cholesterol level, measured at baseline, week 12 (end of the therapeutic lifestyle change program), and week 24 (end of the study). Other secondary outcomes included total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and weight.

Safety

All patients completed the Brief Pain Inventory Short Form (BPI-sf) (Appendix Figure, available at www.annals.org) at baseline, week 12, and week 24. The BPI-sf is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and the effect of pain on daily function (11). To assess pain severity, we used a question from the Brief Pain Inventory Pain Severity subscale that asks about average pain severity over the past

Figure 1. Study flow diagram.



LDL = low-density lipoprotein; TLC = therapeutic lifestyle change; TSH = thyroid-stimulating hormone.

week (on a 0- to 10-point scale) rather than calculate a mean score across all items. We used this for the secondary outcome of measuring pain severity score at baseline, week 12, and week 24. We also assessed safety by measuring CPK and liver-associated enzyme levels in all patients at baseline, week 12, and week 24. We reviewed the results of laboratory tests independently at week 12 to monitor safety.

Anthropometry

We measured weight to the nearest 0.1 kg and height to the nearest centimeter at baseline, week 12, and week 24. We calculated body mass index as weight (kg) divided by height (m)². We measured blood pressure in patients in the sitting position by using standard sphygmomanometry.

Laboratory

We obtained a fasting blood sample at baseline, week 12, and week 24 for a lipid panel, complete metabolic

profile, and CPK and thyroid-stimulating hormone levels. The Laboratory Corporation of America (Burlington, North Carolina) performed the analyses.

ConsumerLab.com (White Plains, New York) analyzed the red yeast rice (Table 2). The laboratory tested red yeast rice for individual and total monacolins by using high-performance liquid chromatography. They used thin-layer chromatography to detect citrinin, a potential contaminant. We did not disclose the identity of the products to the laboratory performing the testing.

Statistical Analysis

We used the intention-to-treat principle for all data analysis on the patients at baseline and week 12. We computed descriptive statistics for primary and secondary outcome measures at baseline, week 12, and week 24. We assumed outcomes were normally distributed and fit a lin-

Table 1. Baseline Patient Characteristics

Characteristic	Red Yeast Rice Group (n = 31)	Placebo Group (n = 31)	P Value
Mean age (SD), y	60.5 (9.3)	61.5 (8.2)	0.44
Women, n (%)	19 (61)	21 (68)	0.79
Race, n (%)			0.53
White	26 (84)	22 (71)	
Black	4 (13)	8 (26)	
Hispanic	1 (3)	1 (3)	
Coexisting disease, n (%)			
Essential hypertension	12 (39)	16 (52)	0.44
Coronary artery disease	6 (19)	4 (13)	0.73
Diabetes mellitus	1 (3)	2 (6)	>0.99
Smokers, n (%)	0	1 (3)	>0.99
Mean blood pressure (SD), mm Hg			
Systolic	125.9 (8.6)	127.2 (8.2)	0.127
Diastolic	78.9 (5.8)	79.0 (6.1)	0.85
Mean fasting glucose level (SD)			0.21
mmol/L	93.0 (9.7)*	100.3 (17.3)	
mg/dL	5.17 (0.54)	5.57 (0.96)	
Mean weight (SD), kg	81.0 (12.8)	81.9 (15.7)	0.82
Mean body mass index (SD), kg/m ²	28.8 (4.3)	29.2 (5)	0.84
Mean Brief Pain Inventory score (SD)	1.4 (1.9)	2.6 (2.2)	0.026
Mean creatine phosphokinase level (SD), U/L	122.4 (69.2)	117.5 (87.5)	0.51
Mean aspartate aminotransferase level (SD), U/L	22.9 (5.4)	24.9 (7.5)	0.35
Mean alanine aminotransferase level (SD), U/L	24.4 (10.2)	26.0 (10.0)	0.52
Mean number of statins not tolerated (SD)†	2.0 (1.1)	1.7 (0.87)	0.37

* Available for 30 participants.

† Statin use discontinued before study because of intolerable myalgias.

ear mixed-effects model for each outcome to account for the correlation due to repeated measurements. Each model allowed for patient-specific intercepts. We modeled raw outcomes together (baseline, week 12, and week 24), and the model included an interaction term between treatment indicator and the 3-level categorical variable for week. These models gave an estimate of the treatment effect, which represents the estimated difference in the mean outcome between the red yeast rice and placebo groups at weeks 12 and 24. Specifically, these models provided point estimates and CIs for differences in the mean LDL cholesterol, total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; BPI-sf pain scores; and body mass index between the treatment and placebo groups at weeks 12 and 24. We also used each model to test for a difference between the treatment effect at weeks 12 and 24 to evaluate any change in the treatment effect over this time. The model for BPI-sf pain severity scores included the number of statins previously not tolerated as a categorical covariate. We performed appropriate model diagnostics. We analyzed safety parameters (CPK and liver-associated enzyme levels) for differences between groups by using linear mixed-effects models.

The amount of missing data was small (<4.8%) and we treated these data as missing in the analysis. We completed all statistical analyses by using Stata, version 9.2 (StataCorp, College Station, Texas).

Role of the Funding Source

Our study was funded by an unrestricted grant from the Commonwealth of Pennsylvania, which had no role in

the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

RESULTS

Table 1 shows the baseline characteristics of enrolled patients. The mean age was 60.5 years (SD, 9.3) in the red yeast rice group and 61.5 years (SD, 8.2) in the placebo group. Forty (65%) of the 62 patients were female. Mean baseline weight was 81.0 kg in the red yeast rice group and

Table 2. Chemical Analysis*

Component	Red Yeast Rice	Placebo
Monacolins, mg/capsule		
Total	2.16	0.0933
Monacolin JA	0.0120	Not detected
Monacolin J	0.0186	Not detected
Monacolin XA	0.0080	Not detected
Monacolin KA	0.607	0.0041
Monacolin LA	0.0802	Not detected
Monacolin X	Not detected	Not detected
Monacolin K (lovastatin)	1.02	0.0892
Monacolin L	0.0546	Not detected
Monacolin M	0.0065	Not detected
Dihydromonacolin K	0.212	Not detected
Other components, ppm†		
Citrinin	<5	<5

* Performed by ConsumerLab.com (White Plains, New York). We sent 2 bottles of red yeast rice product (manufactured by Sylvan Bioproducts, Kittanning, Pennsylvania), containing 120 capsules per bottle, for analysis.

† Heavy metals and microbes were undetectable for both red yeast rice and placebo.

81.9 kg in the placebo group. Mean number of statins received before intervention was 2.0 (SD, 1.1) in the red yeast rice group and 1.7 (SD, 0.9) in the placebo group. The groups did not significantly differ at baseline except in BPI-sf score, which was significantly higher in the placebo group ($P = 0.026$).

Effects on Lipids and Lipoproteins

Tables 3 and 4 show descriptive statistics for the primary and secondary outcome measures. In the red yeast rice group, mean LDL cholesterol level was 4.2 mmol/L

(163 mg/dL) at baseline, 3.1 mmol/L (120 mg/dL) at week 12, and 3.3 mmol/L (128 mg/dL) at week 24 (Table 3). In the placebo group, mean LDL cholesterol level was 4.3 mmol/L (165 mg/dL) at baseline, 4.0 mmol/L (154 mg/dL) at week 12, and 3.88 mmol/L (149.8 mg/dL) at week 24. The mean percentage of change in LDL cholesterol level from baseline for the red yeast rice group was -27.3% (SD, 16.4%) at week 12 and -21.3% (SD, 22.7%) at week 24. In the placebo group, the mean percentage of change from baseline was -5.7% (SD, 13.3%)

Table 3. Plasma Lipid Measures at Baseline, Week 12, and Week 24

Outcome Measure	Red Yeast Rice Group		Placebo Group	
	Patients, <i>n</i>	Mean (SD)	Patients, <i>n</i>	Mean (SD)
Low-density lipoprotein cholesterol level				
Baseline	31		31	
mmol/L		4.23 (0.70)		4.28 (0.81)
mg/dL		163.3 (27.0)		165.1 (31.3)
Week 12	29		30	
mmol/L		3.11 (0.95)		3.99 (0.81)
mg/dL		120.0 (36.8)		154.2 (31.4)
Week 24	30		29	
mmol/L		3.32 (1.05)		3.88 (0.85)
mg/dL		128.3 (40.4)		149.8 (32.8)
Change (baseline to week 12), %		-27.3 (16.4)		-5.7 (13.3)
Change (baseline to week 24), %		-21.3 (22.7)		-8.7 (14.1)
Total cholesterol level				
Baseline	31		31	
mmol/L		6.35 (0.79)		6.37 (0.91)
mg/dL		245.2 (30.5)		246 (35.3)
Week 12	29		30	
mmol/L		5.03 (1.05)		6.01 (1.03)
mg/dL		194.1 (40.6)		232.2 (39.6)
Week 24	30		29	
mmol/L		5.41 (1.15)		5.97 (0.99)
mg/dL		208.7 (44.3)		230.4 (38.4)
Change (baseline to week 12), %		-21.4 (12.3)		-4.7 (12.2)
Change (baseline to week 24), %		-14.9 (15.9)		-5.3 (11.4)
High-density lipoprotein cholesterol level				
Baseline	31		31	
mmol/L		1.37 (0.31)		1.33 (0.36)
mg/dL		52.8 (12.1)		51.5 (13.8)
Week 12	29		30	
mmol/L		1.33 (0.28)		1.25 (0.33)
mg/dL		51.4 (10.9)		48.3 (12.6)
Week 24	30		29	
mmol/L		1.46 (0.32)		1.40 (0.38)
mg/dL		56.4 (12.3)		54.0 (14.6)
Change (baseline to week 12), %		-0.6 (13.0)		-3.8 (12.0)
Change (baseline to week 24), %		8.6 (17.0)		7.9 (18.1)
Triglyceride level				
Baseline	31		31	
mmol/L		1.64 (0.93)		1.67 (0.87)
mg/dL		145.5 (82.3)		147.7 (77.0)
Week 12	29		30	
mmol/L		1.28 (0.48)		1.67 (0.90)
mg/dL		113.3 (42.9)		148.1 (79.4)
Week 24	30		29	
mmol/L		1.36 (0.64)		1.51 (0.82)
mg/dL		119.9 (57.0)		133.7 (72.6)
Change (baseline to week 12), %		-11.8 (33.2)		8.2 (39.9)
Change (baseline to week 24), %		-7.2 (43.9)		-1.4 (37.2)

at week 12 and -8.7% (SD, 14.1%) at week 24. **Figure 2** displays the mean and 95% CI for LDL cholesterol level at baseline, week 12, and week 24 for the red yeast rice and placebo groups. Mean LDL cholesterol level differed significantly between the red yeast rice and placebo groups (treatment effect) at week 12 ($P < 0.001$) and week 24 ($P = 0.011$). Treatment effect for LDL cholesterol was also significantly attenuated at week 24 compared with week 12 ($P = 0.041$). At week 24, 9 of 30 patients in the red yeast rice group achieved an LDL cholesterol level less than 2.6 mmol/L (<100 mg/dL), compared with 2 of 29 patients in the placebo group.

Mean total cholesterol level differed significantly between the red yeast rice and placebo groups (treatment effect) at week 12 ($P < 0.001$) and week 24 ($P = 0.016$). Treatment effect for total cholesterol had a marginally significant attenuation at week 24 compared with week 12 ($P = 0.051$). The groups did not significantly differ in mean high-density lipoprotein cholesterol or mean triglyceride level at week 12 or week 24.

Weight

In the red yeast rice group, weight decreased an average of 3.7 kg (3.7%) at 12 weeks and 3.5 kg (4.0%) at 24 weeks from baseline. In the placebo group, weight decreased an average of 3.6 kg (4.2%) at 12 weeks and 3.6 kg (5.0%) at 24 weeks from baseline (**Table 4**). **Figure 2** shows mean and 95% CIs for body mass index at baseline, week 12, and week 24 for both groups. The groups did not significantly differ in mean body mass index at either week 12 or week 24 (**Table 5**).

Safety

Figure 2 displays the mean and 95% CI for BPI-sf scores at baseline, week 12, and week 24 for both groups. Although the BPI-sf score was significantly higher in the placebo group at baseline, the linear mixed-effects model for BPI-sf score, adjusted for the number of statins not tolerated previously, showed no significant differences in pain scores between groups at either week 12 or week 24 (**Table 5**). However, BPI-sf scores were positively skewed, and a linear mixed-effects model may therefore not be appropriate.

Two (7%) of 29 patients in the red yeast rice group developed persistent intolerable myalgias and discontinued treatment. Their CPK levels were within normal limits. Two other patients discontinued red yeast rice, 1 because of dizziness and 1 because of loose stools. All 4 patients remained in the study and completed the study protocol. One of 30 patients in the placebo group developed persistent intolerable myalgias and discontinued treatment but completed the study protocol. The groups did not significantly differ in the development of intolerable myalgias ($P = 0.61$) or CPK or liver-associated enzyme level at week 12 or 24 (**Table 5**).

Table 4. Secondary Outcome Measures

Outcome Measure	Red Yeast Rice Group		Placebo Group	
	Patients, n	Mean (SD)	Patients, n	Mean (SD)
Weight, kg				
Baseline	31	81.0 (12.8)	31	81.9 (15.7)
Week 12	30	77.3 (12.4)	31	78.3 (15.0)
Week 24	29	77.5 (12.5)	29	78.3 (15.1)
Change (baseline to week 12), %		-3.7 (2.9)		-4.2 (3.3)
Change (baseline to week 24), %		-4.0 (3.6)		-5 (4.6)
Brief Pain Inventory score*				
Baseline	31	1.4 (1.9)	31	2.6 (2.2)
Week 12	29	1.4 (1.6)	33	1.9 (2.1)
Week 24	30	1.2 (1.6)	29	2.0 (2.5)
Creatine phosphokinase level, U/L				
Baseline	31	122.4 (69.2)	31	117.5 (87.5)
Week 12	29	135.7 (89.2)	30	101.8 (40.8)
Week 24	30	128.3 (90.2)	29	101.2 (48.1)
Aspartate aminotransferase level, U/L				
Baseline	31	22.9 (5.4)	31	24.9 (7.5)
Week 12	29	24.8 (11.5)	30	24.8 (11.4)
Week 24	30	22.5 (4.4)	29	22.0 (5.6)
Alanine aminotransferase level, U/L				
Baseline	31	24.4 (10.2)	31	26.0 (10.0)
Week 12	29	24.4 (14.3)	30	27.5 (18.0)
Week 24	30	21.8 (8.9)	29	20.1 (6.9)

* Scores range from 0 (no pain) to 10 (worst pain imaginable). Score represents the reported average pain over the past month. A change in score of ≥ 3 points has been cited as a clinically meaningful change.

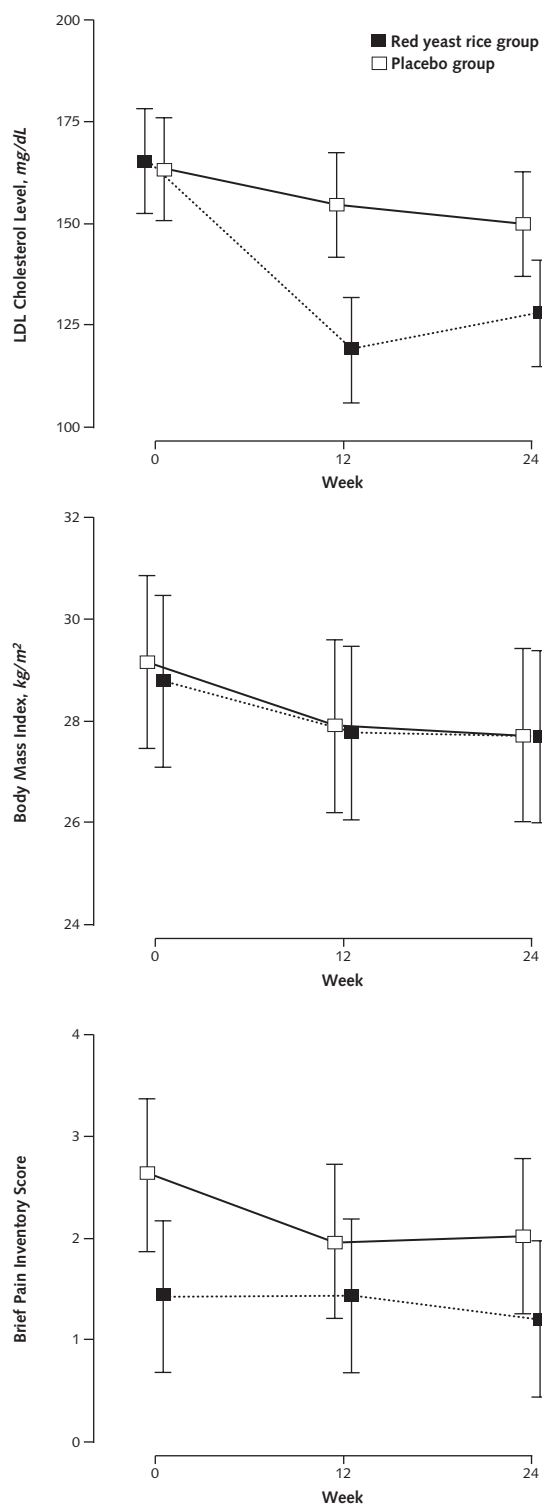
DISCUSSION

To our knowledge, ours is the first randomized, double-blinded, placebo-controlled trial to evaluate red yeast rice in patients with a history of SAM. Red yeast rice significantly decreased LDL and total cholesterol levels compared with placebo and did not increase the incidence of myalgias over a 24-week period. The regimen of red yeast rice and therapeutic lifestyle change may offer a lipid-lowering option for patients with a history of intolerance to statin therapy.

Although the occurrence of myalgias after statin initiation is poorly defined, SAMs are a major clinical issue. An English-language MEDLINE search for *statin myopathy* yielded 1023 articles from July 1983 to April 2009. The incidence of SAM may be as high as 10% (12, 13) and may affect approximately 1.3 million people in the United States (14). The median time of myalgia onset has been reported to be 1 to 6.3 months (12) but it can occur at any time, with a range of 1 week to 48 months (15).

No optimal therapy exists for patients who develop SAM but continue to require therapy for hyperlipidemia. Although alternative or natural therapies have never been tested in this population, several approaches exist for treating hyperlipidemia in patients with SAM (**Table 6**) (16–

Figure 2. Point estimates and 95% CIs for mean LDL cholesterol level, body mass index, and Brief Pain Inventory score.



Estimates shown for weeks 0 (baseline), 12, and 24 for the placebo and red yeast rice groups. Estimated from separate linear mixed-effect models for each outcome. To convert LDL cholesterol to mmol/L, multiply by 0.0259. LDL = low-density lipoprotein.

27). Of note, adding coenzyme Q10 (ubiquinone) to patients with SAM is a popular but controversial practice. Although supplementation with ubiquinone increases serum coenzyme Q10 level, a recent meta-analysis (28) showed no clear-cut benefit in reducing myalgias.

Because no definitive treatment for SAM exists, many patients adopt alternative therapies to manage their hypercholesterolemia, including red yeast rice. In 2006, American consumers spent \$17 million on this dietary supplement, a 55% increase from 2005 (29). Red yeast rice contains naturally occurring lovastatin (monacolin K) and other monacolins that may inhibit HMG-CoA reductase and reduce LDL cholesterol levels compared with placebo (5–7).

It is unclear why red yeast rice may be better tolerated than statins in patients with SAM. The low rate of myalgias in the red yeast rice group was striking because the recurrence rate of myalgias is as high as 57% when patients are challenged with a second statin (15). One clue may be related to the increasing risk for SAM with higher doses of statins (17). The dose of red yeast rice in our study (3.6 g/d) was equivalent to a daily lovastatin dose of only 6 mg (Table 2), far less than the established therapeutic dose (20 to 40 mg/d) (30). A recent study showed that patients with variants in the *SLCO1B1* gene were more likely to develop statin-associated myopathy with higher doses of simvastatin (31). It is therefore possible that the low dose of monacolin K (lovastatin) in our red yeast rice product was below the threshold necessary to cause SAM.

Another possibility is the presence of compounds in red yeast rice, other than monacolin K, that may inhibit HMG-CoA reductase (Table 2). Little is known about their pharmacodynamics, but these monacolins may either have lipid-lowering effects or potentiate the effects of monacolin K. They may also be less likely to deplete mevalonate metabolites distal to HMG-CoA reductase, such as intracellular isoprenoids (for example, ubiquinone) and guanosine triphosphate-binding regulatory proteins, which are believed to mediate statin-induced muscle injury (32).

Our therapeutic lifestyle change program also played an integral role. It incorporated the Mediterranean diet (33–36), an exercise program, and relaxation techniques, which have been collectively shown to favorably affect serum lipid levels and reduce weight, blood pressure, and mortality (37, 38). The excellent adherence rate seen in our study was probably due to intensive follow-up, education, and support, unlike other studies involving diet and exercise, which reported higher rates of recidivism (39–41).

Our study has limitations. Low-density lipoprotein cholesterol level increased slightly in the red yeast rice group between weeks 12 and 24, probably because of decreased adherence to the red yeast rice regimen after the 12-week lifestyle change program ended and patients were expected to continue taking their study medication. In addition, although red yeast rice was effective in decreasing

Table 5. Estimated Difference in Mean Outcomes Between Red Yeast Rice and Placebo Groups at Week 12 and Week 24*

Outcome Measure	Week 12		Week 24	
	Mean (95% CI)	P Value	Mean (95% CI)	P Value
Low-density lipoprotein cholesterol level		<0.001		0.011
mmol/L	−0.92 (−1.36 to −0.48)		−0.56 (−1.0 to −0.13)	
mg/dL	−35.5 (−52.4 to −18.6)		−21.8 (−38.7 to −5.0)	
Total cholesterol level		<0.001		0.016
mmol/L	−1.02 (−1.52 to −0.52)		−0.62 (−1.12 to −0.11)	
mg/dL	−39.4 (−58.6 to −20.2)		−23.8 (−43.2 to −4.4)	
High-density lipoprotein cholesterol level		0.48		0.56
mmol/L	0.06 (−0.11 to 0.23)		0.05 (−0.12 to 0.21)	
mg/dL	2.3 (−4.1 to 8.7)		1.9 (−4.5 to 8.3)	
Triglyceride level		0.078		0.22
mmol/L	−0.35 (−0.75 to 0.04)		−0.24 (−0.65 to 0.15)	
mg/dL	−31.2 (−66.1 to 3.5)		−22.0 (−57.1 to 13.2)	
Weight, kg	−0.2 (−7.17 to 6.77)	0.96	0.11 (−6.86 to 7.09)	0.98
Body mass index, kg/m ²	−0.1 (−2.4 to 2.1)	0.91	−0.04 (−2.3 to 2.3)	0.98
Brief Pain Inventory score†	−0.5 (−1.5 to 0.5)	0.30	−0.8 (−1.8 to 0.2)	0.120
Creatine phosphokinase level, U/L	36.1 (−1.1 to 73.4)	0.057	27.4 (−9.8 to 64.7)	0.149
Aspartate aminotransferase level, U/L	−0.04 (−4.2 to 4.1)	0.98	0.67 (−3.5 to 4.8)	0.75
Alanine aminotransferase level, U/L	−3.3 (−9.3 to 2.8)	0.28	1.6 (−4.5 to 7.7)	0.51

* Based on linear mixed-effects model analyses.

† Scores range from 0 (no pain) to 10 (worst pain imaginable).

LDL cholesterol level, only 30% of patients who received treatment achieved an LDL cholesterol level of 2.6 mmol/L or less (≤ 100 mg/dL). This was probably because of the weak potency of our red yeast rice product (monacolin K, 1.02 mg/capsule; total monacolins, 2.16 mg/capsule). A recent trial (10) showed that a more potent red yeast rice product (monacolin K, 2.53 mg/capsule; total monacolins, 5.3 mg/capsule) reduced LDL cholesterol level by 42% when combined with therapeutic lifestyle change and fish oil. However, more potent red yeast rice products could also increase the incidence of myalgias in patients with previous SAM.

Another limitation of the trial is the current regulatory status of red yeast rice as a dietary supplement. Although the chemical composition of red yeast rice was known and controlled in the current study, the lack of consistency between different manufacturers is a major problem (42, 43). There is an ongoing need for the FDA to regulate the manufacturing of red yeast rice products.

Although our trial showed that red yeast rice was well tolerated over the 24-week trial, receiving red yeast rice without a physician's oversight may be unsafe. Red yeast rice has been reported to cause myopathy (44–48), rhabdomyolysis (49), and hepatotoxicity (50).

It is also possible that our 6-month trial was too short to evaluate the development of SAM in patients receiving red yeast rice. Statin-associated myalgias have been reported as late as 48 months after initiation of statin therapy (15). Future studies are needed to evaluate the risk for SAM in patients receiving red yeast rice for more than 6 months.

Despite the limitations of our small, single-center study, red yeast rice significantly reduced LDL cholesterol

level compared with placebo in a cohort with a history of SAM. This raises important questions that need to be addressed in future studies: Does red yeast rice reduce the incidence of myalgias when directly compared with statin therapy? Is red yeast rice effective in patients with previous SAM who are not enrolled in a lifestyle change program? Finally, did the therapeutic lifestyle change program alone play a positive role in decreasing the risk for recurrent myalgias in our cohort (for example, through improved mood or the role of exercise and weight loss).

A final issue raised by our study concerns the relationship between red yeast rice and cardiovascular outcomes. A

Table 6. Approach to Patients With a History of Statin-Associated Myalgias*

1. Initiate or intensify therapeutic lifestyle changes (National Cholesterol Education Program Adult Treatment Panel III Guidelines) (18)
2. Decrease statin dose
3. Discontinue statin and rechallenge at a later date
4. Reduce dose of statin and add ezetimibe (19)
5. Use a different statin or statin-like supplement
 - a. Fluvastatin, 80 mg/d (20)
 - b. Rosuvastatin at a low dosage (5 or 10 mg/d) (21)
 - c. Rosuvastatin once weekly (22), twice weekly (23), or every other day (24)
 - d. Atorvastatin, 10–40 mg, 3 times weekly (25)
 - e. Red yeast rice, 1800 mg, twice daily
6. Pulse statin therapy (16)
7. Switch class of lipid-lowering agent
 - a. Use ezetimibe alone (19)
 - b. Combine ezetimibe and colesevlam (26)
8. Check vitamin D levels and replenish if low (27)
9. Low-density lipoprotein cholesterol apheresis in qualified patients (16)
10. Add coenzyme Q10 (ubiquinone), 200 mg/d, to statin therapy (28)

* See references 16 and 17.

recent secondary prevention trial (51) showed a decreased incidence of nonfatal myocardial infarction or death from cardiac causes in patients randomly assigned to receive red yeast rice versus placebo. Future trials are needed to confirm this finding and to evaluate cardiovascular outcomes in a primary prevention setting.

Presently, no consensus has been reached on lipid-lowering therapy for patients who develop SAM. In our small, single-center, randomized study, patients with a history of SAM who enrolled in a therapeutic lifestyle change program and received red yeast rice had significantly lower LDL and total cholesterol levels than those who enrolled in the lifestyle program and received placebo over a 6-month period, with no increase in intolerable myalgias. Given our positive results, our approach may provide a therapeutic lipid-lowering option for the large cohort of patients with a history of SAM. A larger, multicenter trial with longer follow-up is needed to determine whether red yeast rice offers a safe and effective solution for this unmet medical need and to evaluate its effects on cardiovascular outcomes.

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APPENDIX: THERAPEUTIC LIFESTYLE CHANGE PROGRAM

All patients enrolled in the trial participated as a group in a 12-week, multidisciplinary therapeutic lifestyle change program. The group consisted solely of patients enrolled in the trial and involved attending weekly 3.5-hour meetings with a board-certified cardiologist, certified dietician, exercise physiologist, and several alternative/relaxation practitioners.

During the first part of the session, the cardiologist taught patients about cardiovascular risk factors, the pathogenesis of coronary plaque formation, the importance of preventive measures, and methods to improve communication with their personal physician.

A dietician taught the group about the basic principles of nutrition and encouraged patients to follow a Mediterranean diet that was modified by reducing saturated fat and limiting total fat to less than 25% of daily caloric intake. Sugars and noncomplex carbohydrates were restricted, and patients learned how to count calories, although no formal caloric restrictions were imposed. Patients were also given dietary advice about shopping for food and eating in restaurants. Individualized advice was given in the form of a question-and-answer session at the end of each teaching period.

An exercise physiologist taught the group about the health benefits of cardiovascular exercise, stretching, and light strength training. Participants were instructed to gradually increase exercise up to 5 to 6 times per week. Aerobic exercise was encouraged and included walking, swimming, or jogging for 30 to 45 minutes at a time. Although the sessions did not involve actual exercise, the exercise physiologist demonstrated proper techniques for various exercises (such as sit-ups, pushups, and using an exercise ball) and patients were encouraged to track their progress by completing weekly exercise logs. The exercise physiologist reviewed the logs and then gave patients individualized advice about improving their exercise regimen and tolerance.

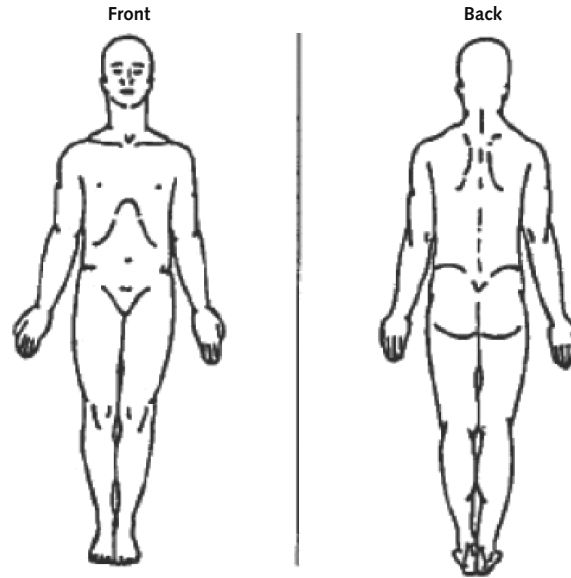
During the 12-week program, various guest practitioners exposed patients to relaxation methods, including yoga, acupuncture, medical massage, meditation, hypnosis, deep breathing, humor, and tai chi.

Appendix Figure. Brief Pain Inventory Short Form questionnaire.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain **over the past week**?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst over the past week**.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least over the past week**.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average over the past week**.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

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