Tolerability of Red Yeast Rice (2,400 mg Twice Daily) Versus Pravastatin (20 mg Twice Daily) in Patients With Previous Statin Intolerance

Steven C. Halbert, MD[a,e], Benjamin French, PhD[a,b], Ram Y. Gordon, MD[f], John T. Farrar, MD[a], Kathryn Schmitz, PhD[a], Patti B. Morris, RD[f], Paul D. Thompson, MD[g], Daniel J. Rader, MD[c,d], and David J. Becker, MD[f,*]

Currently, no consensus has been reached regarding the management of hyperlipidemia in patients who develop statin-associated myalgia (SAM). Many statin-intolerant patients use alternative lipid-lowering therapies, including red yeast rice. The present trial evaluated the tolerability of red yeast rice versus pravastatin in patients unable to tolerate other statins because of myalgia. The study was conducted in a community-based setting in Philadelphia, Pennsylvania. A total of 43 adults with dyslipidemia and a history of statin discontinuation because of myalgia were randomly assigned to red yeast rice 2,400 mg twice daily or pravastatin 20 mg twice daily for 12 weeks. All subjects were concomitantly enrolled in a 12-week therapeutic lifestyle change program. The primary outcomes included the incidence of treatment discontinuation because of myalgia and a daily pain severity score. The secondary outcomes were muscle strength and plasma lipids. The incidence of withdrawal from medication owing to myalgia was 5% (1 of 21) in the red yeast rice group and 9% (2 of 22) in the pravastatin group ($p = 0.99$). The mean pain severity did not differ significantly between the 2 groups. No difference was found in muscle strength between the 2 groups at week 4 ($p = 0.61$), week 8 ($p = 0.81$), or week 12 ($p = 0.82$). The low-density lipoprotein cholesterol level decreased 30% in the red yeast rice group and 27% in the pravastatin group. In conclusion, red yeast rice was tolerated as well as pravastatin and achieved a comparable reduction of low-density lipoprotein cholesterol in a population previously intolerant to statins. **(Am J Cardiol 2010;105:198–204)**

In patients with a history of statin-associated myalgia (SAM), muscle symptoms often recur when another statin drug is initiated.[1] Because no definitive approach has been determined for treating patients with recurrent SAM, many patients seek complementary or alternative therapies to manage their dyslipidemia. One such treatment is red yeast rice, a popular lipid-lowering dietary supplement that contains low levels of statin-like metabolites, including monacolin K (lovastatin).[2,3] Consumer spending on red yeast rice grew nearly 80% from 2005 to 2008 in the United States, with sales of $20 million in 2008.[4] Studies in the United States and China have documented the lipid-lowering efficacy of red yeast rice.[5–8] In a previous placebo-controlled study, we demonstrated that 93% of subjects with a history of SAM were able to tolerate red yeast rice for 24 weeks without a recurrence of myalgia.[8] However, no trials have addressed whether red yeast rice is associated with a reduced incidence of myalgia compared to statin therapy. The primary goal of the present study was to compare the effect of red yeast rice versus pravastatin on the rate of myalgia recurrence in subjects with a history of SAM.

Methods

This study was conducted from January to September 2008 in a community-based setting in the Philadelphia, PA area (trial registration at clinicaltrials.gov, identifier NCT00639223). The institutional review boards at the University of Pennsylvania and Chestnut Hill Hospitals approved the study. All participants provided written informed consent. The subjects were recruited from preventive cardiology clinics at University of Pennsylvania and Thomas Jefferson University Hospitals, and 2 suburban Philadelphia cardiology practices. The subjects were eligible if they had had previous, documented SAM leading to discontinuation of at least one statin other than pravastatin, with resolution of myalgia after discontinuation. The exclusion criteria in-

[a]Center for Clinical Epidemiology and Biostatistics, Departments of [b]Biostatistics and Epidemiology and [c]Medicine, and [d]Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [e]Jefferson-Myrna Brind Center for Integrative Medicine, Philadelphia, Pennsylvania; [f]Division of Cardiology, Chestnut Hill Hospital, University of Pennsylvania Health System, Philadelphia, Pennsylvania; and [g]Division of Cardiology, Hartford Hospital, Hartford, Connecticut. Manuscript received June 18, 2009; revised manuscript received and accepted August 25, 2009.

This study was supported by an unrestricted grant from the Commonwealth of Pennsylvania, and Chestnut Hill Health System, Philadelphia, Pennsylvania. Dr. Halbert was supported by grant T32AT000600 from the National Center for Complementary and Alternative Medicine, Bethesda, Maryland, and grant T32AG000253 from the National Institute on Aging, Bethesda, Maryland.

*Corresponding author: Tel: (215) 233-9700; fax: (215) 233-9710.
E-mail address: dbeckerchcardiology@hotmail.com (D.J. Becker).

0002-9149/10/$ – see front matter
doi:10.1016/j.amjcard.2009.08.672

Table 1
Chemical analysis of red yeast rice (600 mg/capsule)*†

Component	Quantity
Active monacolins	
Monacolin K (lovastatin) (mg/capsule)	1.245
Monacolin KA (mg/capsule)	0.54
Potential contaminants‡	
Citrinin (ppb)	<10
Arsenic (mg/kg)	0.21
Lead (mg/kg)	0.06
Cadmium (mg/kg)	0.03
Mercury (mg/kg)	<0.01

* Performed by Eurofins Scientific, Inc., Petaluma, California.
† Two bottles of 120 capsules/bottle (600 mg/capsule) were sent for analysis; manufactured by Sylvan Bioproducts, Inc., Kittanning, Pennsylvania.
‡ All microbial counts were less than the detectable levels.

cluded statin or red yeast rice use during the month before randomization, a history of statin-associated myositis or rhabdomyolysis, a history of generalized chronic pain, the use of medications that inhibit cytochrome P450 CYP3A4, the use of dietary supplements that could mitigate SAM or lower lipids, abnormal baseline laboratory values (creatine phosphokinase >500 U/L, triglycerides ≥400 mg/dl, aspartate aminotransferase or alanine aminotransferase >2.5 times normal, serum creatinine >2 mg/dl, thyroid-stimulating hormone >4.5 μU/ml), and pregnancy.

Eligible participants were randomized to receive red yeast rice 4,800 mg daily (four 600-mg capsules twice daily; Sylvan Bioproducts, Kittanning, Pennsylvania) or pravastatin 40 mg/day (1 overencapsulated 20-mg tablet to appear identical to the red yeast rice capsules and 3 identical-appearing placebo capsules twice daily) for 12 weeks. A sample of red yeast rice was independently analyzed for chemical composition (Eurofins Scientific, Petaluma, California; Table 1). An investigational new drug application for using red yeast rice in the present trial was approved by the Food and Drug Administration. Adherence to the study medication was determined by pill counts of the returned study medication every 4 weeks. The mean adherence to pravastatin and red yeast rice (excluding dropouts and subjects who withdrew from medication) was 97% and 93%, respectively ($p = 0.10$). To ensure that both groups received identical lifestyle education, all participants attended weekly 3.5-hour sessions of a therapeutic lifestyle change program[5] (see Appendix [on-line only]). Attendance at these meetings averaged 83%, with no significant difference in attendance between the 2 groups.

The primary outcome of the present study was the rate of withdrawal from treatment because of intolerable muscle symptoms. The co-primary outcome was the daily pain severity score measured using one question adapted from the Brief Pain Inventory[9] regarding the average pain during the past 24 hours (on a 0 to 10 scale). Participants rated both nonmyalgic and myalgic pain using this scale. The same blinded physician reviewed these pain scales weekly. If the subjects reported intolerable myalgia, their study treatment was discontinued, but all planned measurements were obtained. Isometric hip flexor muscle strength was determined by the same blinded physical therapist at baseline and every

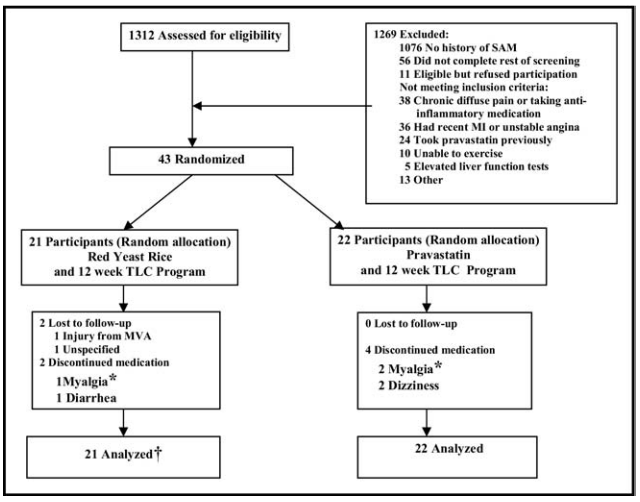

Figure 1. Participant flow through study. *Primary end point. †Those with missing data were included in analysis of primary outcome. MI = myocardial infarction; MVA = motor vehicle accident; SAM = statin-associated myalgia; TLC = therapeutic lifestyle program.

4 weeks using a standard protocol with a hand-held dynamometer (model 01163, Lafayette Industries, Lafayette, Indiana). The hand-held dynamometer has a high correlation (0.91) with isokinetic muscle testing and is useful in comparing serial muscle strength tests.[10]

A fasting blood sample was obtained at baseline and week 12 to determine the low-density lipoprotein (LDL) cholesterol, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, and thyroid-stimulating hormone (baseline only) levels. Analyses were performed by the Hospital of the University of Pennsylvania.

Adherence to the dietary recommendations was assessed by collecting two 24-hour diet recalls[11] (1 weekend day and 1 weekday) at baseline and week 12. Blinded, trained staff collected the dietary survey by telephone interview, with data collection centralized at the Penn State Department of Nutritional Sciences (University Park, Pennsylvania). The dietary intake data were analyzed using Nutrition Data System, version 2007 (Nutrition Coordinating Center, Minneapolis, Minnesota). Physical activity was assessed using the Paffenbarger Physical Activity Questionnaire at baseline and week 12. This validated, reliable, self-administered questionnaire quantifies the number of kilocalories subjects expend per week in sports, leisure, and recreational activities.[12]

The subjects were randomized to the study medication in blocks of 4. Although all participants had a history of myalgia with at least one statin drug, many had previously been challenged with other statins. Therefore, the randomization was stratified into 3 groups: those who had not developed myalgia on challenge with a different statin, those who had developed intolerable myalgia with all previous statin challenges, and those who had never been challenged with another statin drug. The randomization sequence was computer-generated using a randomization program available on the Internet (www.randomization.com)[13] with the fixed block option. All subjects and study team members were kept unaware of treatment allocation

Table 2
Baseline characteristics of study participants

Characteristic	Red Yeast Rice (n = 21)	Pravastatin (n = 22)	p Value
Mean age (years)	62.4 ± 8.9	62.9 ± 6.6	0.87
Women	16 (76%)	16 (73%)	0.80
Mean No. of statins not tolerated	1.3 ± 0.5	1.5 ± 0.6	0.27
Statin drug not tolerated			
Atorvastatin	16 (76%)*	15 (68%)*	0.57
Simvastatin	9 (43%)	14 (64%)	0.17
Rosuvastatin	2 (10%)	4 (18%)	0.41
Lovastatin	1 (5%)	2 (9%)	0.58
Interval to onset of statin-related myalgia <12 weeks[†]	15 (79%)[‡]	18 (90%)[§]	0.34
Family history of statin-related myalgia			0.19
Yes	5 (24%)	1 (5%)	
Unknown	1 (5%)	1 (5%)	
Education			0.27
High school or less	2 (10%)	7 (32%)	
Some college	5 (25%)	5 (23%)	
College graduate	9 (45%)	5 (23%)	
Postgraduate	4 (20%)	5 (23%)	
Medical history			
Essential hypertension	8 (38%)	14 (64%)	0.09
Coronary artery disease	3 (14%)	3 (14%)	0.95
Diabetes mellitus	2 (10%)	5 (23%)	0.24
Hypothyroid	6 (29%)	3 (14%)	0.23
Local arthritis	5 (24%)	6 (27%)	0.80
Low back pain	5 (24%)	5 (23%)	0.93
Mean body mass index (kg/m^2)			0.21
18.5–24.8	2 (10%)	2 (9%)	
25–29.9	10 (48%)	5 (23%)	
>30	9 (43%)	15 (68%)	
Mean blood pressure (mm Hg)			
Systolic	127.9 ± 11.5	133 ± 17.7	0.27
Diastolic	77.8 ± 6.1	79.5 ± 8.9	0.46
Mean fasting glucose (mg/dl)	98.1 ± 26.2	96.8 ± 26.6	0.87
Mean creatine phosphokinase (U/L)	124.3 ± 61.7	125.1 ± 72.5	0.97
Mean thyroid-stimulating hormone (μU/ml)	1.32 ± 0.7	1.33 ± 0.9	0.99
Mean baseline energy expenditure (kcal/wk)	1,368.2 ± 1,536.5	1,074.5 ± 1,034.4	0.77
Mean weight (kg)	81.9 ± 21.2	96.3 ± 30.4	0.15
Mean Brief Pain Inventory score[¶]	1.4 ± 1.9	1.1 ± 1.5	0.82

Data are presented as mean ± SD or numbers (%).

* Numbers in each column may not sum to the total number of subjects because some subjects received >1 statin.

[†] Subject had a history of the development of myalgias within 12 weeks of any previous statin challenge.

[‡] Of 19 patients total.

[§] Of 20 patients total.

[¶] Scores on Brief Pain Inventory range from 0 (no pain) to 10 (worst pain imaginable); score represents average pain during previous 24 hours reported at baseline.

throughout the 12-week study. To assess blinding, the participants guessed their treatment allocation at the end of the study; 37% of those taking pravastatin and 67% of those taking red yeast rice guessed their treatment assignment correctly.

Sample size calculations were performed on the basis of the 7% rate of intolerable myalgias seen with red yeast rice in our previous study[8] and rates of approximately 50% reported in the published data[14] with a statin rechallenge, assuming a 20% dropout rate. According to these rates, a sample size of 20 to 22 subjects per group would provide 80% power to detect a difference of 40% between the 2 groups for intolerable myalgic symptoms, with $\alpha = 0.05$. All primary analyses were conducted using the intention-to-treat approach. We compared the incidence of withdrawal from the study medication because of intolerable myalgia between the 2 groups using Fisher's exact test. A linear regression model was used to compare the difference between the treatment groups in the mean Brief Pain Inventory pain severity score, defined as the maximum reported score for myalgic and nonmyalgic pain during each day. The robust variance estimator was used to adjust the standard error estimates for correlation due to repeated measurements.[15] Missing pain scores were treated as missing, because only 2 subjects (dropouts) had missing data (<5%). A linear mixed-effects model was used to analyze hip flexor strength at baseline and weeks 4, 8, and 12. The covariates in the models for pain and muscle strength included strati-

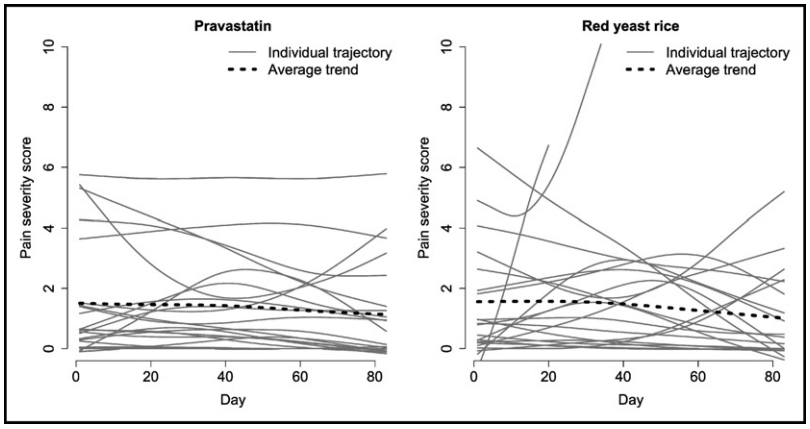

Figure 2. Individual maximum pain severity scores *(solid lines)* and average trend *(dashed line)* during study period for each treatment group. Individual trajectories and average trend plots were obtained using scatterplot smoother.

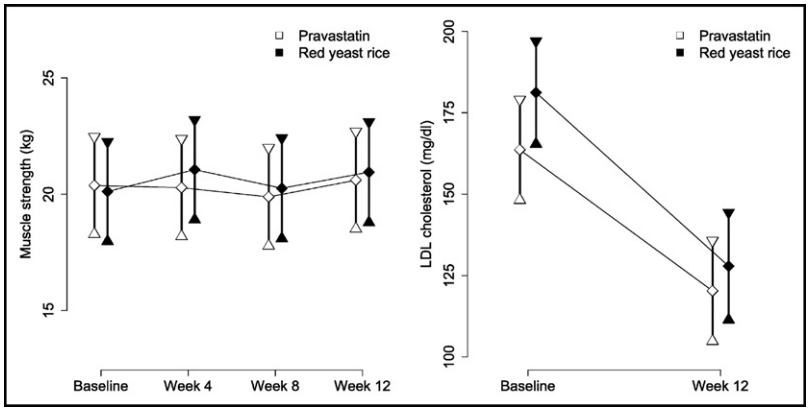

Figure 3. Point estimates and 95% CIs for mean muscle strength and mean LDL cholesterol for pravastatin group *(white)* and red yeast rice group *(black)*.

fication assignment,[16] age, baseline thyroid-stimulating hormone level, and baseline physical activity. A secondary analysis was performed to assess the differences between groups in the occurrence of myalgic pain during the intervention period. For participants who reported myalgic pain, we created dichotomous outcomes, defined a priori, indicating whether the subjects had persistent myalgia starting after >2 weeks of study treatment and of ≥1 week's duration. Comparisons between treatment groups were made using Fisher's exact tests.

To evaluate treatment efficacy, descriptive statistics were computed for LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides at baseline and week 12. Linear regression models quantified the differences in the mean LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides at week 12 across the treatment groups. Each model was adjusted for its respective baseline lipoprotein measure and baseline body mass index. To assess the adherence to the therapeutic lifestyle change program, we compared the mean percentage of change from baseline to week 12 across the treatment groups for the following outcomes using 2-sample t tests: total energy intake, total fat, saturated fat, percentage of energy from fat, fiber, weight, and total kilocalories expended per week. Safety parameters, including liver-associated enzymes and creatine phosphokinase, were analyzed for differences between the 2 groups using 2-sample *t* tests. The differences in the adverse event rates were compared between treatment groups using Fisher's exact tests. Statistical analyses were performed using Stata version 9.2 (StataCorp, College Station, Texas). All comparisons were 2-tailed, and the level of significance was set at $p = 0.05$.

Results

During a 3-month period, 180 patients with a history of SAM completed the screening. Of those, 54 met the eligibility criteria and 43 agreed to participate (Figure 1). The red yeast rice and pravastatin groups had similar baseline characteristics (Table 2). The incidence of treatment discontinuation because of myalgia was 5% (1 of 21) in the red yeast rice group and 9% (2 of 22) in the pravastatin group ($p = 0.99$). Of the 21 subjects in the red yeast rice group and 22 in the pravastatin group, 14 (67%) and 15 (68%) reported pain at some point during the study period. Figure 2 displays the maximum pain severity scores for each subject and the average trend for each treatment group during the study period. In the linear regression analysis that was controlled for stratification assignment, age, and baseline thyroid-stimulating hormone level, no significant difference was found between the 2 treatment groups in the mean pain severity score. The estimated difference in the mean pain severity

Table 3
Descriptive analysis of myalgic pain from Brief Pain Inventory scores

Outcome Measure	Red Yeast Rice (n = 21)		Pravastatin (n = 22)		p Value
	n (%)	95% CI	n (%)	95% CI	
Persistent myalgia only*					
Generalized myalgia†	0		3 (13.6%)	0–7	0.23
Local myalgia‡	2 (9.5%)	1–9	1 (4.6%)	0–6	0.60
Combined local and generalized myalgia	2 (9.5%)	0–5	4 (18.1%)	0–8	0.66
Persistent and intermittent myalgia§					
Generalized myalgia	1 (4.8%)	0–3	6 (27.3%)	2–10	0.10
Local myalgia	4 (19.1%)	1–8	3 (13.6%)	0–6	0.70
Combined local and generalized myalgia	5 (23.8%)	1–9	8 (36.4%)¶	4–12	0.51

* Persistent myalgia defined as persistent myalgia starting after ≥2 weeks of study treatment and of ≥1 week's duration.
† Bilateral myalgia in major muscle groups.
‡ Unilateral myalgia in a major muscle group.
§ Persistent and intermittent myalgia includes any myalgia reported during the study regardless of duration.
¶ Total did not sum to total number in column because 1 subject reported both local and generalized myalgia.

Table 4
Descriptive analysis of secondary outcome measures between groups at baseline and week 12

Outcome Measure	Red Yeast Rice		Pravastatin	
	Patients (n)	Mean ± SD	Patients (n)	Mean ± SD
Low-density lipoprotein cholesterol (mg/dl)				
Baseline	21	181.2 ± 38.9	22	163.6 ± 32.7
12 weeks	17	126.1 ± 37.6	22	120.3 ± 38.7
Mean percentage of change		−30.2 ± 10.5		−27.0 ± 15.4
Total cholesterol (mg/dl)				
Baseline	21	260.7 ± 41.5	22	253.4 ± 40.4
12 weeks	17	200.9 ± 41.7	22	198.6 ± 44.9
Mean percentage of change		−23.0 ± 7.3		−19.6 ± 11.0
High-density lipoprotein cholesterol (mg/dl)				
Baseline	21	51.1 ± 16.6	22	53.1 ± 16.7
12 weeks	17	50.8 ± 14.7	22	53.0 ± 16.9
Mean percentage change		−3.8 ± 9.0		0.2 ± 8.7
Triglyceride (mg/dl)				
Baseline	21	142.2 ± 78.9	22	148.4 ± 65.0
12 weeks	17	120.9 ± 68.4	22	126.1 ± 45.4
Mean percentage change		−7.8 ± 30.5		−7.0 ± 32.2
Hip flexor strength (kg)				
Baseline	21	20.1 ± 4.3	22	20.4 ± 5.2
4 weeks	20	20.8 ± 6.3	21	20.5 ± 4.9
8 weeks	18	19.7 ± 5.3	19	20.3 ± 4.4
12 weeks	18	20.7 ± 5.4	22	20.6 ± 5.2

score between the 2 groups was 0.02 (95% confidence interval [CI] −0.12 to 0.15; p = 0.81). Also, in the linear mixed-effects model for hip flexor strength, adjusted for stratification assignment and age, no difference was found in the mean strength scores between the 2 groups at week 4 (p = 0.61), week 8 (p = 0.81), or week 12 (p = 0.82). Figure 3 displays the mean and 95% CIs for muscle strength at baseline and weeks 4, 8, and 12 for the red yeast rice and pravastatin groups. In a secondary analysis of myalgic pain (Table 3), the reports of myalgia were fewer in the red yeast rice group.

The descriptive statistics for the lipid outcome measurements are listed in Table 4. Figure 3 displays the mean and 95% CIs for LDL cholesterol at baseline and week 12 for both treatment groups. In the linear regression models adjusted for baseline lipoprotein measure and body mass index, no significant differences were found between the 2 groups in the mean LDL cholesterol (−10.7 mg/dl, 95% CI −27.2 to 5.7; p = 0.194) total cholesterol (−9.6 mg/dl, 95% CI −25.9 to 6.6; p = 0.23), triglycerides (0.5 mg/dl, 95% CI −21.2 to 22.3; p = 0.96), or HDL cholesterol (−2.5 mg/dl, 95% CI −5.7 to 0.63; p = 0.114).

No significant differences were found between the red rice yeast group and the pravastatin group in the percentage of change from baseline to week 12 in any measure of adherence to the lifestyle change program (Table 5). The incidence of treatment discontinuation owing to all adverse events (including myalgia) was 10% (2 of 21) in the red yeast rice group and 18% (4 of 22) in the pravastatin group (p = 0.66). No statistically significant differences were

Table 5
Changes in selected dietary measures and physical activity between groups at baseline and week 12

	Red Yeast Rice			Pravastatin			p Value*
	Baseline	Week 12	Mean Change (%)	Baseline	Week 12	Mean Change (%)	
Energy (kcal/day)	1,650.1 ± 671.8	1,310.6 ± 474.4	−10.3	1,727.5 ± 630.5	1,564.4 ± 693.0	−7.4	0.76
Fat (g/d)	54.3 ± 30.5	36.7 ± 18.8	−17.5	68.5 ± 33.8	52.0 ± 30.5	−21.1	0.73
Calories from fat (%)	28.0 ± 7.2	24.0 ± 6.3	−9.6	34.7 ± 7.0	28.8 ± 7.5	−16.5	0.30
Saturated fat (g/day)	18.5 ± 14.1	10.6 ± 5.8)	−23.5	22.0 ± 10.4	15.3 ± 13.2	−30.1	0.57
Fiber (g/day)	18.5 ± 9.8	21.7 ± 10.3)	23.4	17.0 ± 6.9	19.7 ± 8.1	37.7	0.55
Weight (kg)	81.9 ± 21.2	76.9 ± 19.0)	−2.2	96.3 ± 30.4	95.0 ± 30.4	−1.4	0.45
Energy expenditure (kcal/wk)	1,368.2 ± 1,536.4	2,009.5 ± 1,596.4	237.9	1,074.5 ± 1,034.4	1,510.1 ± 1,015.3	171.7	0.49

* From 2-sample *t* tests for mean percentage of change in each outcome from baseline to week 12; no statistically significant differences found in baseline variables between the 2 groups.

Table 6
Nonmyalgic adverse events

Symptom	Red Yeast Rice (n = 21)	Pravastatin (n = 22)
Muscular weakness	1	1
Abdominal gas, bloating	2	0
Alopecia	2	0
Arthralgia	1	1
Back pain	5	6
Diarrhea	2	0
Dizziness	0	2
Dyspepsia	1	0
Fatigue	0	3
Fracture, extremity	1	0
Headache	2	2
Motor coordination decreased, L hand	0	1

found between the 2 groups in the incidence of adverse events (Table 6) or in mean values of safety measures at week 12.

Discussion

This is the first randomized, double-blind trial comparing the tolerability of red yeast rice to a statin drug in a population with SAM. Our results showed that red yeast rice was as well tolerated as pravastatin in patients with a history of SAM. Both treatments were associated with a low incidence of treatment discontinuation because of myalgia, no evidence of muscle weakness, and a similar level of LDL cholesterol reduction.

Few studies have evaluated the rates of myalgia on statin rechallenge in patients with statin intolerance. Depending on the definition of myopathic events used in these studies, the reported incidence of myalgia recurrence has varied from 0% to 57%.[14,17–23] The lack of a well-defined and consistently applied outcome measure for SAM has contributed to the conflicting results. Our trial used a validated measure of pain severity and a specific definition of recurrent myalgia to address this methodologic issue.

Our results have shown that both the red yeast rice and the pravastatin groups had very low rates of recurrent myalgia. The 12-week therapeutic lifestyle program intervention, which emphasized improved nutrition (increasing dietary omega-3 fatty acids and plant-based antioxidants), regular exercise, and relaxation methods, might have had positive effects on muscle function and pain perception in both groups. The 5% rate of recurrent intolerable myalgia from red yeast rice is consistent with the results from our earlier study showing a 7% incidence of this end point.[8] Because the risk of SAM is known to increase with higher doses of statins,[1,24] this low rate might have been due to the reduced quantities of monacolin K (lovastatin <10 mg/day in this study) in red yeast rice.[25] In addition, red yeast rice contains 13 other monacolins[2] that might act synergistically to lower LDL cholesterol but have less myotoxicity.

Although both groups reported low rates of recurrent myalgia, we were unable to demonstrate a significantly reduced incidence with red yeast rice compared to pravastatin. Possible explanations for this include that the published 50% myalgia recurrence rate for statins used in our power calculation was overestimated; the true recurrence rates for both treatments were not detected in our small, short-term study; pravastatin might have a lower recurrence rate compared to other statins owing to its hydrophilic properties[26]; and the 40 mg/day dose of pravastatin used in the present study might have been low enough to be well-tolerated.

Although the comparison of our primary outcome of drug discontinuation owing to intolerable myalgia showed no between-group differences, we also conducted an exploratory analysis of the rates of recurrent myalgia reported as persistent and generalized. This pattern of myalgic pain is most consistent with the clinical descriptions of SAM.[14,27] In the latter analysis, an absolute risk reduction of 14% was found in favor of red yeast rice compared to pravastatin that we believe deserves additional investigation.

The limitations of our study included the small sample size and short duration. Although recurrent SAM typically occurs soon after the initiation of statin therapy, ~30% of patients can report the onset of myalgias later than 12 weeks.[14] Also, one should not generalize our results using a rigorously analyzed red yeast rice product to other widely available red yeast rice formulations sold as food supplements. The potency differs among various products and contamination with citrinin (a potential nephrotoxin) has

been reported.[28] Finally, no inferences could be made about the long-term effects of red yeast rice on cardiovascular morbidity or mortality from the present trial, which was limited to the tolerability of therapy and lipid-lowering effects.

Statin-associated myalgia is an important clinical problem that will likely become more prevalent owing to the ever-expanding indications for statin use. Although no definitive conclusions could be drawn, our data showed that the red yeast rice was as well tolerated as pravastatin and achieved similar and clinically significant levels of LDL cholesterol reduction in a population with previous statin intolerance.

Acknowledgment: We thank Greg Fromell, MD, Executive Director of the Office of Human Research at the University of Pennsylvania School of Medicine for his help with critical revisions of the Investigational New Drug application. We are grateful to David Margolis, MD, PhD, for his participation on the Data Safety Monitoring Committee, and to Kenneth Rockwell, PharmD, MS, for technical support.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.amjcard.2009.08.672.

1. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–1690.
2. Li YG, Zhang F, Wang ZT, Hu ZB. Identification and chemical profiling of monacolins in red yeast rice using high-performance liquid chromatography with photodiode array detector and mass spectrometry. *J Pharm Biomed Anal* 2004;35:1101–1112.
3. Ma J, Li Y, Ye Q, Li J, Hua Y, Ju D, Zhang D, Cooper R, Chang M. Constituents of red yeast rice, a traditional Chinese food and medicine. *J Agric Food Chem* 2000;48:5220–5225.
4. Supplement Business Report 2009. Boulder, CO: Nutrition Business Journal; 2009:44.
5. Becker DJ, Gordon RY, Morris PB, Yorko J, Gordon YJ, Li M, Iqbal N. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. *Mayo Clin Proc* 2008;83:758–764.
6. Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VL. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. *Am J Clin Nutr* 1999;69:231–236.
7. Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol* 2008;101:1689–1693.
8. Becker DJ, Gordon J, Halbert SC, French B, Morris PB, Rader DJ. Red yeast rice versus placebo in dyslipidemic, statin-intolerant patients enrolled in a therapeutic lifestyle program: a randomized, controlled trial. *Ann Intern Med* 2009;150:830–839.
9. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004;20:309–318.
10. Martin HJ, Yule V, Syddall HE, Dennison EM, Cooper C, Aihie SA. Is hand-held dynamometry useful for the measurement of quadriceps strength in older people? A comparison with the gold standard Bodex dynamometry. *Gerontology* 2006;52:154–159.
11. Thomson CA, Giuliano A, Rock CL, Ritenbaugh CK, Flatt SW, Faerber S, Newman V, Caan B, Graver E, Hartz V, Whitacre R, Parker F, Piece JP, Marshall JR. Measuring dietary change in a diet intervention trial: comparing food frequency questionnaire and dietary recalls. *Am J Epidemiol* 2003;157:754–762.
12. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;314:605–613.
13. Dallal G. Randomization.com. Available from: www.randomization.com. Accessed May 2, 2008.
14. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403–414.
15. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22.
16. Simon R. Patient subsets and variation in therapeutic efficacy. *Br J Clin Pharmacol* 1982;14:473–482.
17. Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* 2005;165:2671–2676.
18. Backes JM, Moriarty PM, Ruisinger JF, Gibson CA. Effects of once weekly rosuvastatin among patients with a prior statin intolerance. *Am J Cardiol* 2007;100:554–555.
19. Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. *Am J Cardiol* 2008;101:1747–1748.
20. Backes JM, Venero CV, Gibson CA, Ruisinger JF, Howard PA, Thompson PD, Moriarty PM. Effectiveness and tolerability of every-other-day rosuvastatin dosing in patients with prior statin intolerance. *Ann Pharmacother* 2008;42:341–346.
21. Glueck CJ, Aregawi D, Agloria M, Khalil Q, Winiarska M, Munjal J, Gogineni S, Wang P. Rosuvastatin 5 and 10 mg/d: a pilot study of the effects in hypercholesterolemic adults unable to tolerate other statins and reach LDL cholesterol goals with nonstatin lipid-lowering therapies. *Clin Ther* 2006;28:933–942.
22. Stein EA, Ballantyne CM, Windler E, Simes PA, Sussekov A, Yigit Z, Seper C, Gimpelewicz CR. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. *Am J Cardiol* 2008;101:490–496.
23. Mackie BD, Satija S, Nell C, Miller J, Sperling LS. Monday, Wednesday and Friday dosing of rosuvastatin in patients previously intolerant to statin therapy. *Am J Cardiol* 2007;99:291.
24. Jacobson TA. Statin safety: lessons from new drug applications for marketed statins. *Am J Cardiol* 2006;97:44C–51C.
25. Li Z, Seeram NP, Lee R, Thames G, Minutti C, Wang HJ, Heber D. Plasma clearance of lovastatin versus Chinese red yeast rice in healthy volunteers. *J Altern Complement Med* 2005;11:1031–1038.
26. Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol* 2006;97:69C–76C.
27. Franc S, Dejager S, Bruckert E, Chauvenet M, Giral P, Turpin G. A comprehensive description of muscle symptoms associated with lipid-lowering drugs. *Cardiovasc Drugs Ther* 2003;17:459–465.
28. Heber D, Lembertas A, Lu QY, Bowerman S, Go VL. An analysis of nine proprietary Chinese red yeast rice dietary supplements: implications of variability in chemical profile and contents. *J Altern Complement Med* 2001;7:133–139.