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Is Red Yeast Rice Tolerable in Treating Patients With Dyslipidemia Who Have Statin-Associated Myalgia?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not patients who have statin-associated myalgia have improved tolerability for red yeast rice (RYR) as an alternative treatment.

Study Design: This review consists of three double blinded randomized controlled trials published in English in 2009, 2010, 2013.

Data Sources: Three randomized, controlled, double blinded clinical trials on the tolerability of red yeast rice were found on PubMed and Ebsco Host. Two trials comparing red yeast rice to placebo and the third trial comparing red yeast rice to pravastatin.

Outcomes measured: Each of the three articles analyzed whether patients with statin-associated myalgia could tolerate red yeast rice in lowering serum cholesterol levels without adverse effects of myalgia. The outcomes measured were based on a structured questionnaire form that assessed the presence of myalgia as well as a brief pain inventory short form (BPI-sf) which assessed pain on a scale of 0-10.

Results: In Becker et al, the RYR group and placebo group did not significantly differ at baseline except in BPI-sf scores which was significantly higher in the placebo group P=0.026. In the RYR group, 2 of 29 patients developed persistent intolerable myalgia and discontinued treatment. In Halbert et al, 67% (14 of 21) in the RYR group reported pain whereas 68% (15 of 22) in the pravastatin group reported pain. The incidence of treatment discontinuation due to myalgia was 5% (1 of 21) in the RYR group and 9% (2 of 22) in the pravastatin group (p=0.99). In Verhoeven et al, 4 participants in the RYR group and 2 participants from the placebo group reported myalgia.

Conclusions: Based on the systematic reviews of the three randomized controlled trials, it is inconclusive whether red yeast rice is a tolerable method for statin-intolerant patients. It has been proposed that patients are able to tolerate the lower doses of monacolin K (lovastatin) than in statins. However, it is unclear of the maximum threshold patients are able to tolerate.

Key Words: Red yeast rice, dyslipidemia, myalgia, statin-intolerant, statin-associated myalgia

INTRODUCTION

Dyslipidemia is a disorder of lipid metabolism characterized by elevated plasma cholesterol, triglycerides, and/or low-density lipoprotein (LDL-C), or a deficiency in high-density lipoprotein (HDL-C). Such cases can lead to atherosclerosis, an inflammatory condition caused by plaque buildup inside the arteries.[1] At elevated levels, LDL-C tends to deposit in the walls of the arteries. Macrophages take up the LDL-C, triggering the release of inflammatory mediators that lead to the thickening and/or rupture of plaque lining the arterial walls. HDL-C can mitigate this problem by transporting LDL-C to the liver for processing. Sufficient amount of HDL-C and/or control of LDL-C can substantially reduce cardiovascular morbidity and mortality.[2]

Dyslipidemia is a major cause of coronary heart disease which is the leading cause of death in the United States. An estimated 71 million (33.5%) U.S. adults aged ≥ 20 years had high LDL-C, but only 34 million (48.1%) were treated and 23 million (33.2%) had their LDL-C controlled. Dyslipidemia can be diagnosed in anyone and has no discrimination for any particular race or ethnicity.[3] The majority of patients with dyslipidemia show no signs or symptoms; manifestations of dyslipidemia are usually detected by routine laboratory screening. The causes may be genetic or secondary to diabetes, alcohol use, hypothyroidism, obesity, sedentary lifestyle, renal/liver disease, or drugs.[2] The total cost of dyslipidemia associated with cardiovascular diseases and stroke in the U.S. was estimated to exceed $400 billion in 2006.[4] In 2009, 96 million visits to doctors' offices (9.2% of all visits) involved a cholesterol test.[3] As a physician assistant, it is important to know the common incidence as well as risk factors for dyslipidemia in order to educate patient on healthy diet and exercise habits to prevent dyslipidemia and further complications such as coronary heart disease.

Patients can slow the progression of dyslipidemia by decreasing the intake of saturated fat, trans fats, and dietary cholesterol. Instead, they can increase monounsaturated and polyunsaturated fats, antioxidants, and fiber by eating fruits and vegetables. Alongside diet, patients should do some type of aerobic exercise for at least thirty minutes a day such as running and cycling.[1] It is also important to encourage smoking cessation among patients who smoke because it can exacerbate the decrease of HDL-C.[5] Patients also have pharmacologic options such as statins (HMG-CoA reductase inhibitors), niacin, bile acid sequestrants (cholestyramine, colesevelam, colestipol), fibric acid derivatives (gemfibrozil and clofibrate), and ezetimibe.[2]

Statins are first-line therapy but many patients experience myalgia. However, statin-associated myalgia affects approximately 1.3 million people in the U.S.[6] Therefore patients need to discontinue the statins. Currently, there is no optimal treatment for patients who develop statin-associated myalgia. Red yeast rice may be used as an alternative for patients. It is a herbal supplement that is derived from yeast, *Monascus purpureus* that grows on rice.[7] It can decrease LDL-C levels and has been proposed to have less adverse effects of myalgia than statins.[8] This paper evaluates three double blind, randomized controlled trials which evaluate the tolerability of red yeast rice (RYR) as a treatment for patients with dyslipidemia who have statin-associated myalgia.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is red yeast rice tolerable in treating patients with dyslipidemia who have statin-associated myalgia?"

METHODS

All three randomized, double blind controlled trials utilized for this review were selected because they included patients from the age of 18 to 80 who had statin-associated myalgia.[6,8]

These articles were in English and were found through the search engines, PubMed and EbscoHost. Red yeast rice, dyslipidemia, statin-associated myalgia, statin-intolerant were keywords used in the searches. All the articles are published in peer reviewed journals and were based on patient oriented outcomes. The POEM (Patient Oriented Evidence that Matters) was based on statin-intolerant patients who developed myalgia and their tolerability of red yeast rice as an alternative treatment. A summary of statistics used include p-values, relative risk increase (RRI), absolute risk increase (ARI), and number needed to harm (NNH).

Becker et al and Verhoeven et al compared red yeast rice to an experimental group who received a visually matched placebo. Halbert et al compared red yeast rice to a 40 mg pravastatin. Becker et al randomly assigned 62 patients using the blockrand library of R programming environment with the fixed-block option to receive 600 mg capsules of red yeast rice or 3 placebo capsules twice daily for 24 weeks.[6] Halbert et al randomized eligible participants to receive red yeast rice 4,800 mg daily or an identically appearing pravastatin 40 mg/day for 12 weeks.[9] Verhoeven et al included medical doctors along with their partners as the participants and utilized a commercially available red yeast rice that contains 1.5% Monacolin K.[8] Both Becker et al and Halbert et al included patients who had resolution of myalgia when they discontinued statins. In addition, both studies ordered red yeast rice capsules from Sylvan Bioproducts in Kittanning, Pennsylvania.[6,9]

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/ D	Interventions
Becker, 2009	Double Blind RCT	62	21-88 years old	Patients 21 to 80 y.o. who had known dyslipidemia and discontinued at least 1 statin because of myalgia	If patients received a statin or red yeast rice in the month before random assignment	3	Red yeast rice 1800 mg vs. placebo twice daily for 24 weeks
Halbert, 2010	Double Blind RCT	43	Trial did not include ages of pts.	Previous statin associated myalgia leading to discontinuation of at least one statin other than pravastatin, with resolution of myalgia after discontinuation	Statin or red yeast rice use during the month before randomization; History of statin-associated myositis or rhabdomyolysis, and generalized chronic pain	3	Red yeast rice 4,800 mg daily (Four 600 mg capsules twice daily) vs. pravastatin 20 mg twice daily for 12 weeks
Verhoeven, 2013	Double Blind RCT	52	> 18 years old	Men and women over age 18 with a total fasting cholesterol level above 200 mg/dL	Present treatment with statins and triglyceride values > 400 mg/dL or changes in medication/food supplements which affect lipid levels during study	2	Red yeast rice containing Monacolin K 5,025 mg, Ubiquinone 30 mg, Procyanidins 20 mg, and Lecithin 300 mg vs. placebo for 8 weeks

Table 1 summarizes the demographics and characteristics of the inclusion and exclusion criteria in each study.

OUTCOMES MEASURED

The outcomes measured in Becker et al and Halbert et al were based on the Brief Pain Inventory Short Form (BPI-sf) which is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and effect of pain on daily function from a scale of 0-10. 0 is no pain while 10 is the worst imaginable pain.[6,9] In Becker et al, the score reports an average pain over the past month and a change in scores ≥ 3 points has been cited as a clinically meaningful change. The model for BPI-sf pain severity scores included the number of statins previously not tolerated as a categorical covariate.[6] In Halbert et al, a blinded physician reviewed pain scales weekly on reported intolerable myalgia and whether they discontinued the study.[9] At the end of study for Verhoeven et al, participants filled in a structured questionnaire regarding adverse events for myalgia but the article does not state that it is specifically used the BPI-sf method.[8]

RESULTS

The results were presented in dichotomous data in all three studies analyzed. Becker et al had a study period of 24 weeks, Halbert et al had a study period of 12 weeks, and Verhoeven et al had a study period of 16 weeks. Becker et al and Halbert et al compared red yeast rice to a visually similar placebo while Verhoeven et al compared red yeast rice to pravastatin.[6,8,9]

In Becker et al, treatment adherence was assessed by self-report of average number of missed doses per week. The conducted study resulted with 30 participants in the red yeast rice group and 29 in the placebo group. The mean age in red yeast rice group was 60.5 years and 61.5 years in placebo group. A computer randomization program was used to randomize patients

into three groups as follows: those who had never been challenged with another statin drug, those who developed intolerable myalgia with a previous statin challenge, and those who had not developed myalgia with a different statin. The 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.[6]

Table 2: Becker et al Brief Pain Inventory Score - Baseline, Week 12, Week 24

	RYR Patients	RYR Mean (SD)	Placebo Patients	Placebo Mean (SD)
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)

Table 2 shows that the groups did not significantly differ at baseline except in BPI-sf scores which was significantly higher in the placebo group P=0.026.[6]

Table 3: Estimated Difference in Myalgia between RYR and Placebo at Week 12 and 24

	Week 12		Week 24	
	Mean (95% CI)	P Value	Mean (95% CI)	P Value
BPI-sf	-0.5 (-1.5 to 0.5)	0.30	-0.81 (-1.8 to 0.2)	0.120

Table 3 showed insignificant differences in pain scores between groups at either week 12 or week 24, P=0.61. In the RYR group, 2 of 29 patients developed persistent intolerable myalgia and discontinued treatment.[6]

Table 4: Baseline Characteristics of Halbert et al Mean Brief Pain Inventory Score

	RYR Mean ± SD	Pravastatin Mean ± SD	p Value
Baseline	1.4 ± 1.9	1.1 ± 1.5	0.82

In the Halbert et al. study, 43 patients were eligible and agreed to a three month study. Table 4 shows that the red yeast rice and pravastatin groups had similar baseline characteristics. In the red yeast rice group, 67% (14 of 21) reported pain whereas 68% (15 of 22) in the pravastatin group reported pain. The incidence of treatment discontinuation due 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). Therefore there were slightly but not significantly less participants that reported myalgia in the red yeast rice group than placebo. Fisher's exact tests were used to make comparisons between the treatment groups. 67% participants taking red yeast rice and 37% participants taking pravastatin guessed their treatment allocation correctly as an assessment of blinding.[9]

In the Verhoeven et al study, 54 participants were randomized through the chief investigator by randomly generating even for intervention and uneven for control numbers with no stratification for age, sex or cholesterol level. At the end of the study, participants filled a structured questionnaire regarding cardiovascular risk status and eventual side effects specific to myalgia and other side effects. As a result, 4 participants in the red yeast rice group and 2 participants from the placebo group reported myalgia. No one discontinued the study. However, 1 participant in the red yeast rice group expressed that experiencing myalgia was unacceptable to him since he was seeking for an alternative with no adverse effects of myalgia.[8]

Table 5: CER, EER, RRI, ABI, NNH, P value Comparison Among 3 Studies

Study	CER	EER	Relative Risk Increase	Absolute Risk Increase	Number Needed to Harm	P value
Becker et al	3%	7%	130%	4%	25	0.61
Halbert et al	9%	5%	-44%	-4%	-25	0.99
Verhoeven et al	9%	12%	33%	3%	33	N/A

Table 5 summarizes the CER, EER RRI, ARI, NNH, and p-value among the three studies. In Becker et al and Halbert et al studies, the p value greater than 0.05 demonstrates a statistically insignificant association with a high possibility that the results were due to chance. NNH is the number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. In Becker et al, the positive value for NNH represents for every 25 participant who took red yeast rice, there was 1 more incidence of myalgia than in the group of participants taking the placebo. In the Halbert et al study, analysis of the results showed the opposite, the negative NNH value means that for every 25 participants who took red yeast rice, there was 1 fewer incidence of treatment discontinuation due to myalgia than the group of participants taking pravastatin. In Verhoeven et al study, a positive NNH represents for every 33 participants who took red yeast rice, there was 1 more incidence of myalgia than in the group of participants taking placebo. When red yeast rice was compared to a placebo group, there was a higher incidence of myalgia than when compared to pravastatin.

DISCUSSION

Red yeast rice derives from a fermentation process combining the yeast, *Monascus purpureus* with rice. Red yeast rice has been a food staple for thousands of years in Asia. It has been used for food coloring in Peking duck, red wine, rice cakes, pastries and pickled tofu during celebrations and festivities. It can be grounded into fine powder to use for cooking, baking, and wine making in China and Japan. In 800 AD in China, people started using red yeast rice as an herbal medication to build their immune system against diseases. In addition, it has been used for indigestion, diarrhea, improving blood circulation, spleen and stomach health. *Monascus purpureus* has chemical compounds called monacolin K which is the active ingredient to lower cholesterol.[7] It has the same chemical structure as lovastatin, a HMG-CoA inhibitor which is

first-line therapy for dyslipidemia. Therefore red yeast rice and lovastatin has the same adverse and interaction effects.[8]

Red yeast rice is contraindicated in patients who are taking niacin, macrolides, cyclosporine, ketoconazole, and gemfibrozil because it can increase the risk of muscular problems. Red yeast rice should not be taken by pregnant women because it can cause fetal CNS defects in the 1st trimester. In addition, it should be used cautiously in patients with liver problems because it can increase liver damage. Alcohol consumption should be avoided while on red yeast rice due to same exacerbation of liver disease. Patients should use red yeast rice with caution because they could be at risk for rhabdomyolysis. It has been reported that users have complained about other adverse effects such as GI upset, headaches, and dizziness.[7]

Monacolin K levels per gram of labeled "active product" are not standardized and show substantial variability among marketed products. It is not possible to make a comparison between formulations and information on labels of content may differ. Therefore, consumers need to be warned that the actual content of commercially available preparations is not regulated which can raise issues in effectiveness and safety. FDA considers these supplements as unapproved drugs when they contain a specific standardized amount of lovastatin.[8] Most commercially available products contain other active substances such as coenzyme Q10, isoflavones, probiotics, others and manufacturers commonly do not disclose levels of active substances in their preparations. Doctor's Best is voluntarily recalling lot 3121005 of Red Yeast Rice dietary supplement 600 mg Capsules to retail level.[10]

The median time of myalgia onset has been reported to be 1 to 6 months but can occur at any time with a range of 1 week to 48 months. A 6 month trial in the Becker et al study was too short to evaluate the development of statin-associated myalgia in patients receiving red yeast

rice. The study was small, short-duration, focused on a laboratory measure.[6] Similarly, in Verhoeven et al, the size did not adequately assess the adverse effects of myalgia due to sample size.[8]

CONCLUSION

Based on the systematic reviews of the three randomized controlled trials, it is inconclusive whether red yeast rice is a tolerable method for statin-intolerant patients. Becker et al and Halbert et al state that there was no increase in the incidence of myalgia in the RYR group. According to Becker et al, there are probably lower dosages of monacolin K (lovastatin) in RYR compared to statins. However, the exact dosage of monacolin K is unknown.[6] Halbert et al states that red yeast rice contains 13 other monacolins that might act synergistically and has less myotoxicity. However, this threshold is unclear since the amount of monacolin K contained in different red yeast rice products is unknown.[9] In Verhoeven et al, there is a strong warning in the risk of myalgia due to naturally occurring statins due to its lack of regulation.[8]

These three studies had flaws in their methods which can propose for future research. There are insufficient studies on the pharmacodynamics of monacolins in red yeast rice.[6] Therefore a characterization process is needed to differentiate among fermentation products and valid estimations of monacolin K present in each formulated product. This can help clarify the effects of each fermentation product, ratio of monacolin K, and monacolin threshold limit in which patients can tolerate the red yeast rice product.[8] If future research is done on the characterization process, a universal product can be developed for a possibility of FDA approval. In addition, a longer study should also be performed in order to determine the tolerability in patients because myalgia onset has been reported to be 1 to 6.3 months in statin-intolerant patients but it can occur at any time with a range of 1 week to 48 months.[6] Another study

mentioned in Becker et al stated that patients with variants in SLCO1B1 gene were more likely to develop statin-associated myopathy with higher doses of statin.[6] Therefore, further research in this genetic variant can be proposed in patients using red yeast rice.

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