Statin Clinical Trial (REALITY) for Prostate Cancer: an Over 15-Year Wait is Finally Over Thanks to a Dietary Supplement

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KEYWORDS: Prostate cancer, Red yeast rice, Statins, REALITY trial

The authors believe the time has come to formally evaluate this relationship in a prospective randomized trial.

RED YEAST RICE

The field of dietary supplements has evolved, and offers new opportunities for clinical trials. One such area is lipid-lowering treatment. Most lipid-lowering dietary supplements are ineffective, particularly compared with pharmacologic statins. The field of dietary supplements has evolved, and offers new opportunities for clinical trials. One such area is lipid-lowering treatment. Most lipid-lowering dietary supplements are ineffective, particularly compared with pharmacologic statins.

RYR has demonstrated a significant reduction in cardiovascular events (primary end point) in a randomized controlled trial of almost 5000 participants followed for a median of 4.5 years.55 RYR is a traditional Chinese herbal medicine first mentioned in 800 AD in the Tang Dynasty for blood circulation.18,26,27 It is produced by the fermentation of the fungal strain Monascus purpureus Went (red yeast) over moist and sterile rice. RYR is also called a common dietary compound and food colorant utilized in numerous Asian countries. In China, Japan, and several other countries it is used as an additive and preservative for fish and meat. It has a vibrant red color, flavor, and aroma, thus it is also used as a flavoring agent in several Chinese recipes and dishes, and is even used for brewing red rice wine. RYR is also known by several synonyms as a food product, including HongGou, Hung-Chu, Angkak, Ankak rice, red mold rice, and Beni-Koji. In the late 1970s, Akira Endo47 found that a Monascus yeast strain naturally produced a substance that inhibits cholesterol synthesis. He named it "monacolin K." This compound was later isolated and is now known to be of the same structure as lovastatin, the first marketed statin. Thus, RYR is the first statin used in medical history. Like RYR, a fungus, 3 of the first prescribed statins utilized in the United States were derived from fungi (lovastatin, pravastatin, and simvastatin).18,29 Certain fungi use statin-like compounds to block the synthesis of cholesterol required by intruders (bacteria) for their cell wall synthesis, thus in part deactivating or eliminating the intruder. The analysis of this fascinating protective mechanism led to the isolation of a class of medications (statins) that have benefitted patients substantially. RYR contains 10 different compounds known as "monacolins" (statin-like compounds) that block the rate-limiting enzyme for cholesterol synthesis,22,30 and these are listed in Box 1. Of these, Monacolin K is likely most responsible for the low-density lipoprotein (LDL) cholesterol reduction associated with RYR.

CLINICAL EFFICACY OF RYR

A meta-analysis of 9625 patients in 93 randomized trials involving 3 different commercial variants of RYR has summarized this large experience.31 The mean reduction in total cholesterol, LDL cholesterol, triglyceride, and increase in high-density lipoprotein (HDL) cholesterol was respectively the following: -35 mg/dL (-0.91 mmol/L), -28 mg/dL (-0.73 mmol/L), -36 mg/dL (-0.41 mmol/L), and 16 mg/dL (0.10 mmol/L).

Box 1

Monacolin compounds that can be detected in red yeast rice (RYR)

<table>
<thead>
<tr>
<th>Monacolin</th>
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<tbody>
<tr>
<td>Dihydroxyacetic acid</td>
</tr>
<tr>
<td>Monacolin K</td>
</tr>
<tr>
<td>Monacolin JA</td>
</tr>
<tr>
<td>Monacolin K (lovastatin equivalent)</td>
</tr>
<tr>
<td>Monacolin KA</td>
</tr>
<tr>
<td>Monacolin L</td>
</tr>
<tr>
<td>Monacolin LA</td>
</tr>
<tr>
<td>Monacolin M</td>
</tr>
<tr>
<td>Monacolin X</td>
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<tr>
<td>Monacolin XA</td>
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</tbody>
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Total monacolin content (sum of the 10 detectable monacolins)

Xuezhikang is a commercial RYR product evaluated in a large, randomized, placebo-controlled clinical trial with robust end points.25,52 The China Coronary Secondary Prevention Study (CCSPS) enrolled 4870 participants (3986 men, 884 women) with pre-existing myocardial infarction (MI), and baseline mean total cholesterol, LDL cholesterol, triglyceride, and HDL cholesterol of approximately 206 mg/dL (5.38 mmol/L), 129 mg/dL (3.34 mmol/L), 165 mg/dL (1.85 mmol/L), and 46 mg/dL (1.19 mmol/L). Participants received RYR, 600 mg twice daily (1200 mg total, monacolin K 2.5–3.2 mg/capsule) or matching placebo and were followed for 4.5 years. The trial was conducted from May 1996 to December 2003 in 65 hospitals in China. The primary end point was nonfatal MI or death from coronary or cardiac causes. Secondary end points included total mortality from cardiovascular disease, total all-cause mortality, need for coronary revascularization procedure, and change in lipid levels. Fasting blood samples were drawn at baseline, 6 to 8 weeks after randomization, and at 6-month intervals.

There were 2 interim analyses, and the second one demonstrated a significant difference for the primary end point. The study was stopped in June 2003. A total of 98% of the participants completed the study. Synopses of the results are found in Tables 1 and 2. It is of interest that a plethora of clinical end points were significantly reduced with the exception of a nonsignificant reduction in fatal MI. Cancer mortality and all cause mortality were reduced. Lipids were also modestly and significantly reduced. No serious adverse events were observed during this trial.

Table 1

Multiple clinical end-point observations in the largest randomized trial (CCSPS) of RYR
Total adverse events and treatment cessation rates were similar for RYR and placebo. The number needed to treat (NNT) to prevent a primary end point over the 4.5-year duration of the trial was 21, which favorably compares with the NNT range (19–56) observed in previous secondary prevention trials.20 Subsequent subgroup evaluations from the CCSPS trial have found equivalent benefits with RYR among diabetic, elderly (mean age 69 years),23 and hypertensive participants.24 Potential anticancer benefits found in the overall trial with RYR were also found among the elderly (significant reduction in cancer deaths)25,36 and included a 51% reduction in cancer incidence.35 Thus, the data have been consistent in that RYR reduces lipid parameters, especially LDL,37–39 and appears to have a favorable impact on clinical end points.25

A randomized trial of 74 dyslipidemia patients comparing 40 mg of simvastatin to a high potency RYR (2.53 mg monacolin K per capsule, total monacolins, 3.3 mg) resulted in significantly lower LDL levels for RYR compared with simvastatin. The study population included patients with a broad range of lipid profiles. At 12 weeks, total cholesterol levels were significantly lower with RYR compared with simvastatin (101 mg/dL vs 114 mg/dL, respectively).21 A similar reduction was seen in LDL levels (61 mg/dL vs 72 mg/dL, respectively).21 Mean HDL levels were higher in the simvastatin group compared with the RYR group (51 mg/dL vs 47 mg/dL, respectively).21 There were no significant differences in triglyceride levels between the two treatment groups.21 

The REALITY trial will include a monacolin K content similar to that used in the largest randomized trial of RYR, and be confirmed to be void of citrinin and other contaminants.30–33 The contraindications for RYR should be similar to lovastatin, including hepatic or renal impairment, and allergies to yeast or fungus. RYR should be taken with or especially after meals, because lovastatin absorption is significantly improved under these circumstances, but only as long as pectin or oat bran (high fiber) is not consumed with it because these products specifically reduce absorption.77–79 There has been no consistent mention of this potentially positive and negative interaction with RYR and food in the medical literature or data relating to RYR specifically (only lovastatin).

The authors believe that the active surveillance population is ideal for an initial clinical trial of RYR.74 Repeat biopsy and prostate-specific antigen kinetic data can be gleaned from the surveillance of these low-risk patients, and can prevent the progression of a minimal volume low-grade tumor to a more clinically significant disease would be of enormous value in this population of men. Heart disease is the number one cause of mortality in men with prostate cancer, so an agent that simultaneously improved heart and prostate health in active surveillance patients is a rational choice.76 The observational data suggest that statins provide benefit, they do so by preventing progression or transformation to an aggressive disease state. One literature review stated

**LIMITATIONS OF RYR**

Quality control with this over-the-counter product is an issue.56–59 Different commercial products of RYR have different concentrations of monacolins. Some contain a potentially harmful by-product of yeast fermentation known as “citrin.”64 The REALITY trial will contain a monacolin K content similar to that used in the largest randomized trial of RYR, and be confirmed to be void of citrin and other contaminants.

RYR has been promoted as a safe and effective alternative to statins.56–63 Myopathy on statins is not a contraindication to RYR.20–24,60–63 However, RYR requires medical oversight. Case reports of hepatotoxicity,64,65 myopathy,66–67 and rhabdomyolysis have been reported.24 The contraindications for RYR should be similar to lovastatin, including hepatic or renal impairment, and allergies to yeast or fungus. RYR should be taken with or especially after meals, because lovastatin absorption is significantly improved under these circumstances, but only as long as pectin or oat bran (high fiber) is not consumed with it because these products specifically reduce absorption.77–79 There has been no consistent mention of this potentially positive and negative interaction with RYR and food in the medical literature or data relating to RYR specifically (only lovastatin).

**SUMMARY**

RYR is a safe, inexpensive, widely used natural compound, which acts as an effective statin and appears to inhibit prostate cancer proliferation in preclinical studies. It is very compelling as a preventive agent for both heart disease and prostate cancer. The active surveillance population is ideally suited for evaluating the effect of this agent on prostate cancer progression.

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**References**

Statin Clinical Trial (REALITY) for Prostate Cancer:

http://www.farrlabs.com/study-statinity-alliprol/