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

Efforts to initiate a prospective study of cholesterol-lowering agents have been unsuccessful to date. Many designs, including the evaluation of lipid reduction for the prevention of prostate cancer in average and high-risk patients, for men with prostate cancer on active surveillance, or as a neoadjuvant or adjuvant treatment, have been proposed over the last 15 years. Lack of interest in such a trial has been due to multiple barriers, including: perceived lack of a compelling scientific rationale, concerns over unpredictable toxicity, lack of funding, corporate instability, competition from generics, and a perception that other micronutrients (vitamin E, selenium, and so forth) may be of more interest.[1–3]

However, over the last 7 years a great deal of epidemiologic and observational data has renewed interest in the relationship between cholesterol-lowering agents and prostate cancer progression.[4–17] 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.[18] Most lipid-lowering dietary supplements are ineffective, particularly compared with pharmacologic statins.[18–21]

An important exception is red yeast rice (RYR) extract. This compound favorably competes with lovastatin, pravastatin, and simvastatin in terms of potency, and is a realistic alternative for statin-intolerant patients.[18,22–24] 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.[25]

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 actually 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

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a food product, including Hong Qu, Hung-Chu, Angkak, Ankak rice, red mold rice, and Beni-Koji.

In the late 1970s, Akira Endo[28] 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 +6 mg/dL (+0.15 mmol/L).

Box 1
Monacolin compounds that can be detected in red yeast rice (RYR)

- Dihydromonacolin K
- Monacolin J
- Monacolin JA
- Monacolin K (lovastatin equivalent)
- Monacolin KA
- Monacolin L
- Monacolin LA
- Monacolin M
- Monacolin X
- Monacolin XA
- 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.[25,32] The China Coronary Secondary Prevention Study (CCSPS) enrolled 4870 participants (3986 men, 884 women) with a previous myocardial infarction (MI), and a baseline mean total cholesterol, LDL cholesterol, triglyceride, and HDL cholesterol of approximately 208 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

Table 1
Multiple clinical end-point observations in the largest randomized trial (CCSPS) of RYR

Clinical End Points	Risk Reduction (%) with RYR Compared with Placebo	*P* Value
Nonfatal myocardial infarction	−62	<.001
Coronary disease death	−31	.005
Fatal myocardial infarction	−33	.19
Fatal stroke	−9	.85
Revascularization	−36	.004
Death from cardiovascular disease	−30	.005
Death from cancer	−56	.014
Total deaths	−33	.0003