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Alternative Treatment with Red Yeast Rice to Reduce Hyperlipidemia

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Abstract

- First line treatment of cardiovascular disease is lifestyle modification followed by the pharmacologic intervention of HMG-CoA reductase inhibitors or statins
- Statins are commonly associated with intolerable side effects such as myalgia leading to medication non-compliance
- RYR preparations claim to inhibit cholesterol synthesis without causing myalgia
- RYR preparations have naturally occurring monacolins such as monacolin K which is chemically identical to lovastatin
- RYR is not regulated by the FDA leading to questionable manufacturing practices producing varying ingredient composition
- The purpose of this study is to investigate the role RYR in hyperlipidemia treatment compared to statins by evaluating efficacy, side effects, and the potential to reduce medication non-compliance in adults
- Clinicians potentially could recommend RYR as an alternative treatment to hyperlipidemia in patients unable to comply with statin treatment to decrease cholesterol levels and reduce the progression of atherosclerosis

Introduction

- Statins reduce lipid levels when lifestyle modifications are not adequate
- Potential adverse effects of statins include myalgia and rhabdomyolysis
- Non-compliance increases the risk of further atherosclerosis formation potentially leading to cardiovascular disease and related events
- RYR has been utilized in China since the Tang Dynasty in 800 AD
- Over the counter RYR has flourished in popularity with claims of being a natural product formed from cultured *Monascus purpureus* yeast on rice (See Figure 1), conveniently ordered online, and costing less than prescription statins
- Clinicians desire alternative treatment options for patients to reduce non-compliance that are effective and safe to reduce lipid levels and slow the progression of atherosclerosis

Statement of the Problem

- Studies are needed to determine if RYR supplement in the treatment of hyperlipidemia is a comparable treatment option to statins in efficacy, side effects, and safety to potentially reduce medication non-compliance.

Research Question

- In patients with hyperlipidemia does RYR supplement as compared to statin treatment provide efficacious hypolipidemic results?

• Figure 1: Red Yeast Rice

Literature Review

PATHOPHYSIOLOGY OF HYPERLIPIDEMIA

- Excess lipids form plaque in the arteries reducing blood flow (See Figure 4)
- LDL cholesterol transfers cholesterol to cells in tissues and is equal to the risk of atherosclerosis in predicting coronary disease (Papadakis, Tierney, & McPhee, 2011)
- HDL cholesterol transfers cholesterol from the cells in tissues to be eliminated and is inversely equal to the risk of atherosclerosis (Papadakis et al., 2011)
- 11.5 years of life is projected to be lost in consequence to the development of atherosclerosis leading to coronary heart disease (Sikka et al., 2011).

TREATMENT OPTIONS FOR HYPERLIPIDEMIA

- Statin and RYR have similar pathophysiology due to sharing the same active ingredient, monacolin
- MOA: Interfere with the conversion of Acetyl CoA to Mevalonate by inhibiting the enzyme HMG-CoA reductase (See Figure 2) (Verhoeven et al., 2013)
- RYR comes in variations that do not have equal potency due to varying active potentials just as statins do not have equal potency when compared to each other (Musselman, Pettit, & Derenski, 2012)

Acetyl CoA
↓
HMG-CoA
RYR or Statins (Monacolins)→ ↓ ←HMG-CoA Reductase (Inhibited)
Mevalonate
↓
Cholesterol

– Figure 2: Adapted from *Applied Pharmacology* by Bardal, Waechter, & Martin, 2011 reflecting the effects of stains and RYR on cholesterol biosynthesis

EFFICACY OF RYR THERAPY

- RYR was compared to placebos such as the American Heart Step 1 Diet, phytosterol tablets, lifestyle changes, fish oil with all trials resulting in the reduction of total and LDL cholesterol that was superior or equal to placebo
- The meta-analysis conducted by Liu et al. (2006) evaluated 93 randomized trials consisting of 9,625 participants utilizing three different variations of RYR preparations, *Cholestin*, *Xuezhikang*, and *Zhibituo*, with treatment duration ranging from 4 to 24 weeks with all 3 variations of RYR significantly reducing total cholesterol

EFFICACY OF STATINS VS RYR

- Three trials involving prescription statin intervention reflected a reduction in coronary events by 23-34% and coronary heart disease mortality by 20-42% (Yang & Mousa, 2012)
- Becker et al. (2008) compared RYR to simvastatin reflecting significant LDL reduction without significant differentiation between test groups
- Halbert et al. (2010) compared tolerability of pravastatin to RYR without significant difference in LDL reduction between test groups

STATINS VS RYR SIDE EFFECTS

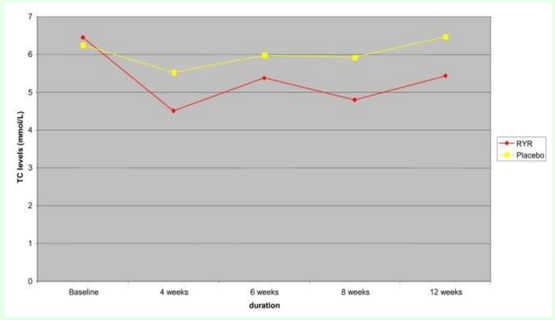
- Statins are generally well tolerated, possible side effects include: myalgia, myositis, rhabdomyolysis, and hepatoxicity with 10-15% of statin users developing myalgias (Bardal et al., 2011)
- 57% statin users experience myalgias when trying a second statin (Abd & Jacobson, 2011)
- RYR side effects include: dizziness, decreased appetite, nausea, abdominal pain, distension, and diarrhea occurring in 1.3-36% of patients (Liu et al., 2006)
- Halbert et al. (2010) compared tolerability of pravastatin to RYR with 67% in RYR group reporting pain and 68% in the pravastatin group therefore similar tolerability

STATINS VS RYR SAFETY

- Heber et al. (2001) analyzed 9 different commercially available RYR products and discovered varying monacolin content from 0-0.58% and toxic citrinin byproduct in 7 out of 9 preparations
- No studies are available regarding long-term cardiovascular prevention with RYR as with statin use
- Statin safety concern addressed by the FDA ten years ago involved Bayer removing the statin, cerivastatin, after 31 patients died from rhabdomyolysis (Bardal et al., 2011)
- Between 1987 and 2001 the FDA recorded 42 deaths or one death per million 30-day supply prescriptions of statins from rhabdomyolysis (Sikka et al., 2011)

Discussion

- Childress et al. (2013) summarized RYR utilization has increased in popularity exponentially due the public's perception of RYR being "natural" compared to prescription medication, perceived less side effects such as myalgia, reduced cost, over the counter availability, and lack of drug-drug interactions
- Verhoeven et al. (2013) proposed less patient non-compliance with RYR due to reduced monthly cost of RYR $20-30 vs statins $120-300
- Becker et al. (2013) reported 40% statin discontinuation within first year due to fear of adverse effects, cost, and reluctance to take medication chronically
- Becker et al. (2009) trial demonstrated RYR had a significant reduction in LDL and total cholesterol when compared to placebo without increased myalgia making RYR a potential treatment option
- Halbert et al. (2010) trial reflected RYR and pravastatin were tolerated equally with both groups experiencing recurrent myalgia and achieving comparable LDL cholesterol values therefore not supporting RYR as an alternative option
- The meta-analysis conducted by Liu et al. (2006) evaluated RYR supplements (*Cholestin, Xuezhikang, and Zhibituo*) vs placebo. reflecting the three RYR variations significantly reducing total cholesterol levels compared when compared to placebo over a 12 week duration (See Figure 3)

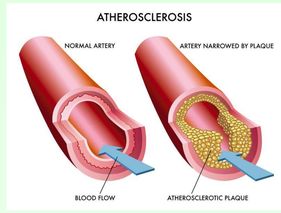


– Figure 3: RYR supplements (*Cholestin, Xuezhikang, and Zhibituo*) vs placebo. Adapted from *"Chinese Medicine"* (2006), Retrieved from: http://www.cmjournal.org/content/1/1/4 reflecting RYR significantly reducing total cholesterol levels

- When 101 products containing RYR were reviewed none could be confirmed as passing any independent laboratory verification testing necessary to promote consistent composition of the active ingredient, monacolin, and no possible toxic byproducts including citrinin (Childress et al., 2013)
- RYR supplements are not strictly regulated by the FDA due to being considered a food not a drug therefore side effects are not documented as systematically as prescription medications such as statins
- Halbert et al. (2010) and Becker et al. (2009) highlight various RYR potency, unsupervised availability, and possible contamination with citrinin due to lack of consistency between different manufacturers supporting RYR is not safe for the general public's consumption
- Liu et al. (2006) assessed the safety concerns of not only the lack of regulation of red yeast rice preparation composition but also what is the recommended dosages and duration
- Randomized trials prove RYR is effective in mild to moderate hyperlipidemia in various populations to lower LDL cholesterol, but it may not be sufficient to treat moderate to severe hyperlipidemia and should not be recommended for hyperlipidemia treatment (Gordon & Becker, 2011)

Applicability to Clinical Practice

- RYR has potential to reduce hyperlipidemia as reflected in short duration trials but at this time can not be recommended due to lack of standardization, long-term side effects, narrow test populations, and secondary cardiovascular prevention
- RYR is not practical in healthcare setting due to lack of FDA regulation allowing for varying amounts of monacolin and potential toxic citrinin byproduct
- Current FDA approved pharmacologic lipid modifying agents include niacin (vitamin B5), bile acid sequestrants, HMG-CoA reductase inhibitors, fibrates, and Ezetimibe with each group of agents having a unique mechanism of action to prevent further atherosclerosis (See Figure 4)



- Figure 4: Atherosclerosis

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