Research protocol – Systematic review

Safety and efficacy of Red Yeast Rice in dyslipidemia and cardiovascular risk reduction

Protocol information
Authors: Maaike Gerards, Kees Koks, Victor Gerdes, Ruben Terlou
Contact person: Maaike Gerards
1. Background
Statins are the most effective agents for improving lipid spectrum in order to reduce the risk of cardiovascular morbidity and mortality. However, statin intolerance diminishes therapy adherence and limits the full potential of risk reduction. Several patients with a proven or perceived intolerance to statins, and other established lipid lowering agents, use alternative products to influence their lipid levels. It is a common belief that these ‘natural’ agents do not have side effects. Of these agents, the traditional Chinese red yeast rice extract (RYR), has been studied in more detail. In this article we systematically review the existing evidence on the potential benefits and risks of RYR in order to determine its suitability in clinical practice.

Myopathy is the major reason for statin intolerance. However, also non-specific symptoms such as fatigue, headache or gastrointestinal symptoms do contribute. The prevalence of statin intolerance may be up to 10% in clinical practice. Risk factors for statin intolerance are numerous and include older age, female sex, renal disease, history of myopathy and high statin dose. As these risk factors tend to be exclusion criteria for clinical trials, prevalence of statin intolerance in trials is lower compared to clinical practice.

RYR is well-known in traditional Chinese medicine for its beneficial effects in cardiovascular disease. RYR consists of powdered Monascus purpureus fermented rice. Its cholesterol lowering effect is supported by empirical evidence and a plausible mechanism. Depending on the fermentation conditions of the rice and the Monascus strains used, monacolins may be produced as metabolites during fermentation. Monacolins inhibit HMG-CoA reductase, and the chemical structure of the monacolin K subtype is identical to Lovastatin. In clinical trials, RYR doses varying from 200 to 4800 mg daily have been studied, but monacolin content is not always reported. Although RYR is claimed to be a safer alternative to regular statins, structural similarity with Lovastatin implies that similar adverse events can be expected. Indeed anaphylaxis, toxic hepatitis and rhabdomyolysis have been associated with the use of RYR.

Another RYR specific side effect that may occur is related to accumulation of citrinin in RYR during the fermentation process. Citrinin can lead to nephrotoxicity.

2. Objectives
‘To assess to what extend RYR is an effective and safe agent for improving lipid spectrum in treatment of dyslipidemia or in the need for lipid lowering therapy in prevention of arterial disease’.

- To assess the effect of extract on the lipid spectrum (LDL cholesterol, triglycerides)
- To assess a dose effect relationship between on the one hand, and safety and effectiveness on the other side.
- To assess the safety of RYR defined as:
  o Occurrence of myopathy
  o Occurrence of nephrotoxicity
  o Occurrence of any adverse event
3. Methods

1. Study selection

Types of studies: randomized controlled trials in which ≥1 group is treated with RYR with a known content of Monacolin K.

Patients: patients with an indication for lipid lowering therapy either because of dyslipidemia or for cardiovascular risk reduction. For the analysis of the safety of RYR, there are no restrictions for the indication for RYR.

Interventions: ≥1 group must be treated with RYR with a known content of Monacolin K. Mode of delivery: oral. No lower or upper limit on total daily dose or frequency. Studies with co-interventions such as lifestyle therapy or concomitant (herbal) medication are included, as long as the co-interventions are available for intervention as well as control group.

Comparison: either inactive (placebo) or active control treatment.

Outcome:

1) Effectiveness:

a. Primary: Change in LDL-cholesterol

b. Secondary: Change in Total cholesterol, HDL-cholesterol, Triglycerides

Preferred outcome measure is relative (%) change of the above mentioned lipid parameters compared to baseline (placebo-subtracted). If change score is not mentioned in a specific study and cannot be computed, we will try to retrieve it from authors or impute it from other lipid parameters.

2) Safety outcomes:

- (Statin associated) Myalgia or myopathy (Canadian Working Group Consensus Conference).
- Hepatotoxicity: elevated liver transaminases.
- Citrinin related toxicity: number of subjects with nephrotoxicity (either acute renal failure or 10% increase of creatinin after baseline)
- Any adverse event. Including gastro-intestinal symptoms (diarrea, constipation), development of allergic reaction, other adverse events.

Preferred outcome measure is the incidence (risk) of myopathy, hepatotoxicity and citrinin related toxicity. For any adverse event, we calculated the rate relative to person-time (person-weeks, assuming that in case a patient develops an adverse event, the patient stays at risk for subsequent adverse events).

Time Frame:

Since monacolin K is a statin-like substance, we assume that the timing of the effect on lipid metabolism is the same as in regular statin therapy, and is likely to have a lipid lowering effect within a few weeks. Therefore, we

---

1 Myopathy = general term referring to any disease of muscles, Myalgia = Muscle ache or weakness without creatine kinase (CK) elevation. Myositis = Muscle symptoms with CK elevation Rhabdomyolysis = Muscle symptoms with significant CK elevation (typically 10 x ULN) and creatinin elevation (usually with brown urine and urinary myoglobin)
included studies with a treatment duration of at least 4 weeks. We collect the first series of lipid outcomes after 4 weeks treatment from each study.

For safety analysis, we collect data on all adverse events from baseline to end of follow-up.

2. Search methods for identification of studies

Strategy:
- Search Embase, Pubmed, Cochrane library, references
- Search terms based on intervention and type of studies. As we are interested in RYR for various indications and lipid outcomes as well as safety outcomes, ‘Patients’ and ‘Outcome’ will not be included in the search.
- Language restriction: none

Search terms:
- Search on intervention
  o cholestin
  o ‘red yeast rice’
  o Mold rice
  o Mould rice
  o Red rice
  o Fermented rice
  o Went rice
  o Xuezhikang
  o Hong qu
  o Hon-chi
  o Ang-kak
  o Beni Koji
  o Red koji
  o Monascus purpureus
  o Monacolin
- Search for randomized controlled trials with humans:
  o Embase: (random*.tw. or clinical trial*.mp. or exp health care quality/) not (animal/ not human/), sensitive therapy filter for Embase, advice from AMC librarian

Search pubmed:
Plan van aanpak systematische review RYR_24mrt201416 April 2014

(((clinical[tiab] AND trial[tiab]) OR clinical trials[mh] OR clinical trial[pt] OR random*[tiab] OR random allocation[mh] OR therapeutic use[sh] OR "Drug Evaluation"[mh]) NOT (animals[mh] NOT humans[mh])) AND ((((red yeast rice"[NM]) OR "red yeast rice"[tiab]) OR cholestin[tiab]) OR mold rice[tiab]) OR "red rice"[tiab]) OR "fermented rice"[tiab]) OR went rice[tiab]) OR Xuezhikang[tiab]) OR "hong qu"[tiab]) OR hon-chi[tiab]) OR ang-kak[tiab]) OR "beni koji"[tiab]) OR "red koji"[tiab]) OR "monascus purpureus"[tiab]) OR monacolin[tiab])

Search Embase: 176 results (date ...-2012??)

<table>
<thead>
<tr>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cholestin/</td>
<td>187</td>
</tr>
<tr>
<td>2 'red koji'.ti,ab.</td>
<td>35</td>
</tr>
<tr>
<td>3 'red yeast rice'.ti,ab.</td>
<td>187</td>
</tr>
<tr>
<td>4 xuezhikang.ti,ab.</td>
<td>91</td>
</tr>
<tr>
<td>5 hong qu.ti,ab.</td>
<td>3</td>
</tr>
<tr>
<td>6 hon-chi.ti,ab.</td>
<td>3</td>
</tr>
<tr>
<td>7 ang-kak.ti,ab.</td>
<td>3</td>
</tr>
<tr>
<td>8 mo?ld rice.ti,ab.</td>
<td>54</td>
</tr>
<tr>
<td>9 red rice.ti,ab.</td>
<td>85</td>
</tr>
<tr>
<td>10 fermented rice.ti,ab.</td>
<td>101</td>
</tr>
<tr>
<td>11 'went rice'.ti,ab.</td>
<td>5</td>
</tr>
<tr>
<td>12 'beni koji'.ti,ab.</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 'red koji'.ti,ab.</td>
<td>8</td>
</tr>
<tr>
<td>14 'monascus purpureus'.ti,ab.</td>
<td>177</td>
</tr>
<tr>
<td>15 monacolin.ti,ab.</td>
<td>122</td>
</tr>
<tr>
<td>16 or/1-15</td>
<td>717</td>
</tr>
<tr>
<td>17 random*.tw.</td>
<td>763997</td>
</tr>
<tr>
<td>18 clinical trial*.mp.</td>
<td>1041986</td>
</tr>
<tr>
<td>19 exp health care quality/</td>
<td>1751886</td>
</tr>
<tr>
<td>20 17 or 18 or 19</td>
<td>2920965</td>
</tr>
<tr>
<td>21 animal/ not human/</td>
<td>1345636</td>
</tr>
<tr>
<td>22 20 not 21</td>
<td>2881721</td>
</tr>
<tr>
<td>23 16 and 22</td>
<td>176</td>
</tr>
</tbody>
</table>

From these results, eligibility will be determined from the search results by Kees Koks, Maaike Gerards and Ruben Terlou based on guiding questions in appendix 1. If reviewers have conflicting opinions on the eligibility of a report or study, these discrepancies will be discussed and a compromise will be made. If needed, the 4th reviewer will be asked for help.

3. Data collection

The data mentioned subsequently will be extracted from the studies based on data extraction forms

General characteristics of the studies
- Report ID (by author + year)
- Year of publication
- Country and period of study conduction
- Acknowledgements

Design
Design: participants
- Amounts: Total no. of participants in the study, no. of groups, no. of study centres (country)
- Participant criteria
Plan van aanpak systematische review RYR_24mrt201416 April 2014

- Age limits
- History of myopathy or statin intolerance
- Co-morbidity: Dyslipidemia / metabolic syndrome / hypertension / diabetes, heart failure, coronary heart disease, liver dysfunction, chronic kidney disease, other.
- Run-in phase
- Limitations regarding use of other lipid modifying Rx

Design: general (risk of bias)
- Sequence generation.
- Allocation sequence concealment.
- Blinding (during study conduct)
- Other concerns on bias*.

Design: intervention
- Dose RYR
- Dose monacolins (monacolin K, total monacolins, if available other subtypes)
- Toxins: citrinin and heavy metal components
- Duration of treatment
- Product characteristics reported: manufacturer, tested dose, contents

Design: control group
- Treatment control group: placebo or active

Design: co-intervention
- Lifestyle: diet / lifestyle therapy / combination
- Concomitant therapy

Design: outcomes
- Duration of follow-up
- Predefined primary outcome (specific: biological, statistical and timing)
  - Adverse event measurement: routine monitoring / patient checklist / questionnaire
- Blinding for outcome assessment (safety and effectiveness)

Outcomes

1) General
- LTFU and drop-outs and its reasons in both groups

2) Lipid values
- Timing: first available series of lipid measurements from 4 weeks after start of study treatment (RYR)
- Unit of measurement: % change of (total / HDL / LDL / TG) cholesterol compared to baseline.

3) Adverse events
- Incident cases of myopathy, hepatotoxicity and declining kidney function (denominator = patients randomized)
- Incidence of any adverse event (rate, divided by person-time in weeks)

4. Analysis
If our systematic search results in enough eligible data, we will perform a meta-analysis. In the meta-analysis, we will compare the effectiveness of RYR with the control group (see Ch 3 Primary outcome, % change in intervention, placebo subtracted). We compare the incidence and rate of specified adverse events and any adverse events between intervention and control group.

If meta-analysis is not possible due to lack of data or heterogeneity in design, we will perform a narrative analysis.
Appendix: Checklist study selection

Selection on title:
1. Does the title imply that the study has nothing to do with the effect of RYR in humans?
   a. Yes → exclusion
   b. No → next question
2. Does the title imply that the study is a review, editorial or case report?
   a. Yes → exclusion
   b. No → next question
3. Does the title imply that in vitro processes, pharmacological agent characteristics, has animals as experimental subjects or other preclinical situations are studied?
   a. Yes → exclusion
   b. No → next question
4. Does the title imply that the studied agent is a combination pill instead of RYR alone?
   a. Yes → exclusion
   b. No → next question

Abstract
1. Does the abstract mention that RYR is not studied (as a separate agent)?
   a. Yes → exclusion_agent (combination / other agent)
   b. No → next question
   c. Possibly → next question
2. Study type: Is the study a randomized clinical trial?
   a. No → exclusion_study type (review / in vitro / pharmacology / regulation / opinion / other)
   b. Yes → next question
   c. Possibly → next question
3. Subjects: Is it done in human adults?
   a. No → exclusion_subject (children / animals)
   b. Yes → next question
   c. Possibly → next question

Full text
1. Is the study a clinical trial?
   a. No → exclusion
   b. Yes → next question
2. Are the subjects in the study randomized?
   a. No → exclusion
   b. Yes → next question
3. Is the agent studied red yeast rice as a separate treatment?
   a. No → exclusion
   b. Yes → next question
4. Are the studied subjects human adults?
   a. No → exclusion
   b. Yes → next question
5. Do the inclusion / exclusion criteria result in a population consisting of subjects that are treated with red yeast rice either because of dyslipidemia or for cardiovascular prevention?
   a. No → include only in safety analysis → next question
   b. Yes → next question
6. Is the dose of red yeast rice, and monacolins reported?
   a. Yes → include
   b. No → contact authors