1.1. Red yeast rice – an overview of the reported ADRs

Introduction

Statins are effective agents for improving lipid spectrum in order to reduce the risk of atherosclerotic disease. However, not all patients use statins to lower their cholesterol level. Some patients use alternative products to influence their lipid levels. Also, consumers without dyslipidemia or increased cardiovascular risk use alternative products to lower their cholesterol. One of these alternative products is red yeast rice extract (RYR) [1]. Red yeast rice is a Chinese herbal supplement produced by fermenting white rice with the yeast Monascus purpureus. RYR contains a variety of monacolins, which inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. In the USA consumption of RYR has increased recently specially among patients who might be intolerant to standardized therapy due to statin-associated myalgia [2]. Because the Netherlands Pharmacovigilance Centre Lareb sees an increase in the number of reports on RYR, and this product has the status of a food supplement although it contains pharmacologically active substances, this overview gives insight in the reported ADRs for RYR.

Reports

In the period from December 2007 till June 2017, the Netherlands Pharmacovigilance Centre Lareb received sixteen reports of the adverse drug reactions related to the use of the RYR containing supplements. Two of the reports were reported by the specialist doctor, two by the pharmacist, one by the physician and 11 by the consumers themselves. Musculoskeletal complaints (consumers A,C,H,J and K) and mild gastrointestinal complaints (consumers A,B,C, and F) are the most often reported adverse reactions.

Tabel 1: Reports of the ADRs on fermented yeast rice supplements

Number, Sex, Age, Reporter	Suspect drug, Dose, Indication	Concomitant medication	Reaction MedDra term	Time to onset, Action with drug, Outcome
A 73756 F, 51-60 Years Consumer	Red yeast rice with 2,4 mg Monachol 2dd1 Hypercholesterolaemia	Zink gluconate, Wild yam Re-Cal-B Manga-Vita	Lip swelling Eye swelling Appetite decreased NOS Weight loss Rash Myalgia Palpitations Hyperhidrosis Nausea	8 Weeks Drug withdrawn Recovering
B 169611 M, 61-70 Years Consumer	Arkosterol Arkopharma® 2dd1 Hypercholesterolaemia		Abdominal discomfort	1 day Drug withdrawn Recovered/resolved with sequel
C* 182222 F, 51-60 Years Consumer	Red yeast rice capsules		Myalgia Regurgitation of food Appetite absent Fatigue Upper abdominal pain	4 Months Drug withdrawn Recovered/resolved
D 183981 F, 61-70 Years Consumer	Red yeast rice capsules Hypercholesterolaemia Botox Osta k2& d3 algae Macrogol		Urinary incontinence	2 Weeks Not applicable Dose increased Not recovered/not resolved

E 189210 F, 61-70 Years Physician	Red yeast rice capsules Hypercholesterolaemia Codeine Cough	omeprazole amitriptyline levothyroxine sodium perindopril atorvastatin calcium carbonate/colecalciferol acetylsalicylic acid dipyridamole levothyroxine sodium	Pancreatitis acute Cholecystitis	1 Day Drug withdrawn Recovering/resolving
F* 189654 M, 71 Years and older Consumer	Red yeast rice capsules 1dd1 Hypercholesterolaemia	Soft Multi 65+ en D10 A.Vogel ProstaforceMed®	Vomiting Diarrhoea	50 Minutes Drug withdrawn Recovering/resolving
G 215976 F, 61-70 Years Pharmacist	Red yeast rice capsules	valsartan hydrochlorothiazide metoprolol acetylsalicylic acid flecainide	Blood pressure increased	17 Days Drug withdrawn Recovered/resolved
H 221937 M, 41-50 Years Consumer	Arkosterol® 2dd1 Prophylaxis		Fatigue Malaise Myalgia	3 Days Drug withdrawn Recovered/resolved
I 224019 M, 61-70 Years Pharmacist	Arcokaps rode rijst gist® Hypercholesterolaemia	acenocoumarole	INR decreased	4 Weeks Dose not changed Recovering/resolving
J 233126 M, 61-70 Years Consumer	Red yeast rice capsules Hypercholesterolaemia		Chest pain	2 Days Drug withdrawn Recovered/resolved
K 233127 M, 61-70 Years Consumer	Red yeast rice tablets Hypercholesterolaemia	pantoprazole olanzapine zolpidem clopidogrel hydrochlorothiazide oxazepam	Pain in hip	2 Days Drug withdrawn Recovered/resolved
L 233873 F, 61-70 Years Specialist doctor	Red yeast rice capsules Hypercholesterolaemia	amitriptyline colecalciferol metoprolol pantoprazole oxazepam paracetamol morphine nadroparin calcium metoclopramide carbasalate calcium	Pancreatitis	4 years Drug withdrawn Recovered/resolved
M 237752 F, 61-70 Years Consumer	Rode gistrijst Kruidvat® 1dd1 Hypercholesterolaemia	acetylsalicylic acid isosorbide mononitrate	Flank pain Urine color abnormal Myalgia Urine odour abnormal Muscle cramps	Unknown Drug withdrawn Recovered/resolved
N 239411 M, 71 Years and older Specialist doctor	Bio Active Rode Gist® extract 315mg 1dd1 Hypercholesterolaemia	diclofenac sodium hydrochlorothiazide telmisartan omeprazole	Malaise Urine discoloration Rhabdomyolysis Abdominal pain Nausea	Few months Drug withdrawn Recovered/resolved

O 239870 M, 71 years and older Consumer	Red yeast rice tablets with 10mg monacoline K Hypercholesterolaemia Acenocoumarole	INR decreased Drug interaction inhibition	3 months Dose not changed Recovered/resolved after adjustment (dosage increasing) acenocoumarol
P 242505 M, 51-60 years consumer	Red yeast rice 1dd1 Hypercholesterolaemia	Insomnia	Hours Dose not changed, Intake schedule changed Recovered

***The samples of the RYR products used by the consumer C and F were analyzed by The National Institute for Public Health and Environment (RIVM).**

In the sample C, beside monacoline K at least two other monacolines with a similar pharmacologic effect were found. The recommended daily intake of 4 capsules provides 8mg lovastatin or total 16mg on total monacolines.

In the sample F also two other monacolines beside monacoline K were found (hydrolovastatin and lovastatin hydroxyl acid). The content of lovastatin in two analyzed capsules differ from each other for a factor 2. The recommended intake of 2 capsules daily provides a dosage between 6-14mg lovastatin.

Consumer E and L developed pancreatitis. Consumer E used also codeine for which pancreatitis is labelled in the SmPC [3].
Consumer L concerns a 61-70 years old female who was hospitalized due to developing pancreatitis after she had used a red yeast rice product for 4 years. A differential diagnosis excluded other causes for the condition. The RYR supplement was withdrawn. She was treated with pantoprazole and pain killers. She had a history of pancreatitis with an unknown/not reported etiology.

Consumer M was intolerant to statins and therefor she switched to a red yeast rice supplement brand Kruidvat®, containing 10mg monacoline K. She reported flank pain, muscle pain, cramps and darkly orange colored urine. She consulted a rheumatologist. She was admitted to the hospital and was treated with morphine and muscle relaxants. The diagnosis polymyalgia rheumatica was postulated. Polymyalgia rheumatica is mentioned in the product information of simvastatin as a possible hypersensitivity syndrome related to statins [4] but is it not a known adverse drug reaction of RYR.

Consumer N had been using a red yeast rice supplement already for a few months. Four days after she accidentally fell down she was admitted to the hospital due to the malaise, red brown discoloration of urine and nausea. The diagnosis rhabdomyolysis was confirmed, based on the lab tests: CK was 2550U/l and her eGRF was 14ml/min. She was treated with i.v saline infusion and paracetamol. The RYR supplement and also her other medication, consisting of hydrochlorothiazide, diclofenac, telmisartan and omeprazole, were withdrawn. She recovered after 4 days, her CK normalized to 372 u/l and the eGRF raised above 60ml/min.

Consumers I and O are using acenocoumarol. Both reported the INR decreasing after starting with a RYR supplement. A possible mechanism for this effect is unknown. Decreasing of the INR is contradictory to the information found in the literature for the effect of lovastatin on the coumarins: bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin based anticoagulants concomitantly with lovastatin [5]. The INR in consumer O normalized after dose adjustment of acenocoumarol.

Other sources of information

Literature

The Panel of the European Food Safety Authority (EFSA) concludes that a cause and effect relationship has been established between the daily consumption of about 10mg of monacolin K from red yeast rice and maintenance of normal blood LDL- cholesterol concentrations. The target population is assumed to be adults in the general population [6].

Red yeast rice contains a fungus (Monascus purpureus), which was utilized in the original production of lovastatin (Mevacor®), the first marketed pharmaceutical statin, and is chemically identical to this product. Their identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin. The red yeast rice ingredient that blocks cholesterol production is monacolin K. Since red yeast rice preparations have large variability in monacolin K content, predicting or understanding dose-related efficacy and side-effect risks of red yeast rice is practically impossible. The lipid-regulating potency of red yeast rice in commercial preparations was found extensively different according to the number and/or concentration of monacolin K they possess. Furthermore, more than one type of monacolins were found in different preparations (or batches) of red yeast rice. Other ingredients found in red yeast rice are also known to be potentially toxic [7]. Red yeast rice can contain the mycotoxin citrinin and several other substances that are not yet toxicologically evaluated [8]. Citrinin is a mycotoxin that produces the Monascus fungus as antibiotic for defense against bacteria. However, it is a nephro- and hepatotoxic component that should be avoided at all times in finished dietary supplements. Unfortunately, a study (Gordon et al., 2010) found that citrinin levels were observed in four of the twelve analyzed products. This is probably because production without citrine production is not possible [9]. The consumption of such yeast preparations in the amount required to obtain the claimed effect would result in an exposure significantly higher than the concentration with no reason for concern regarding the nephrotoxicity of citrinin. A maximum content of 2 mg / kg for citrinin in red-rice rice preparations has been established to ensure that the potential exposure to citrinin from red-rice rice preparations remains considerably lower than the nephrotoxicity level of 0.2 µg / kg body weight for an adult. Therefore, a maximum content of citrinin in red-rice rice preparations should be established [10].

One meta-analysis on 36 publications from 20 studies, involving 6663 subjects in which RYR with a known content of Monacoline K was tested against placebo or an active control group for at least 4 weeks, revealed no different in the risk for myalgia, risk of liver abnormalities or kidney injury between RYR and control groups. Rhabdomyolysis or myopathy with increased CK > 10 times upper limit of normal was not observed in any of the studies. Patients mainly complained of gastro-intestinal and musculoskeletal symptoms [1].

As with synthetic statins, RGR products can expect drug interactions with CYP3A4 inhibitors, especially if the daily dose is equivalent to contains 10 mg or more monacoline K. Even with the simultaneous use of certain foods or herbs such as grapefruit and St. John's wort, hazardous interactions may occur. However, the RGR product vouchers do not provide or provide insufficient information about interactions [11]. In the Italian study of the spontaneous reporting of adverse effects of RGR, myopathy occurred much more frequently in women than in men [12].This male-female difference is not specific to RGR and has also been shown for lovastatin and other statins. The fact that side effects during statin use are reported more frequently for women than men can be explained by the 15-20% higher plasma concentration achieved with statins in women and due to the increased risk of adverse drug- drug interactions via CYP3A4 [13]. Lovastatin has been considered by the FDA as a means absolutely contraindicated in pregnancy [14]. The same warning should therefore apply to RGR. However, the enclosed texts of some RYR products in the Netherlands are not unambiguous at this point [11].

Mechanism

Red yeast rice contains several structurally related substances called monacolins. The most abundant is monacolin K, which is pharmaceutically known as lovastatin [15]. Their identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin [7]. Lovastatin causes dose independent myopathy which sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, In the Expanded Clinical Evaluation of Lovastatin (EXCEL) study also pancreatitis, hepatitis, cirrhosis and fatal and non-fatal hepatic failure were observed [5]. Potent inhibitors of CYP3A4 and grapefruit juice increase the risk of adverse drug reactions by reducing the elimination of lovastatin [15].

Discussion and conclusion

In various non-medical publications, red yeast rice (red fermented rice, RYR) is recommended as a cholesterol-lowering substance. This supplement contains a naturally occurring statin, namely monacolin K. Users of RYR should aware of the potential drug interactions and serious risks associated with its use [2]. The European Food Safety Authority (EFSA) approves health claims for RYR dietary supplements that (intend to) give pharmacotherapeutic effects. They identify consumers

rather than patients as the intended user group. Patients and consumers in Netherlands may freely purchase these RYR dietary supplements. It is left to national authorities to regulate such products as medicines but they are confronted with the burden of evidence for each single product. As authorities cannot embark on clinically evaluating dietary supplements, they much rely on signals of harm [15]. The FDA issued warnings to consumers in 2007 and in 2013 against taking red yeast rice products due to the lack of assurance regarding its efficacy, safety, and lack of standardized preparation methods [7].

The presented cases showed that RYR may cause typical statin-related adverse drug reactions. Based on the lovastatin content alone, the RYR products that were tested by the RIVM could be considered an unregistered medicine. Also additive pharmacological effects may be expected for other monacolins present [15]. On the other hand due to the lack of the quality control and standardization, also the presence of the toxic metabolite citrinin could not be excluded.

At present, pharmacologically active dietary supplements may enter and remain on the market because here is no premarket screening. Without active post marketing surveillance for adverse drug reactions valuable signals of product safety are lost. If the current regulatory status for pharmacologically effective RYR dietary supplements does not permit adequate warnings and active monitoring of adverse drug reactions, then their regulatory status may not be appropriate [15].

It should be considered if the current status of RYR as a dietary supplements is appropriate.

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This overview was published on July 11, 2017. It is possible that in the meantime other information became available.