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Mini Review

Statin Intolerance: Physiology and Treatment Alternatives

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Abstract

Despite its proven effect on primary and secondary preventions of atherosclerotic disease, statins, which revolutionized the treatment of cardiovascular diseases, are still underutilized. One of the causes of this underuse lies in the fact that some patients have some kind of intolerance to this class of medications, and this intolerance may be related to clinical symptoms of myalgia and sometimes, in a small percentage, reaching severe cases of rhabdomyolysis. The therapeutic alternatives are discussed, highlighting the use of Oriza sativa fermented by Monascus purpureus. The use of Oryza extract fermented by Monascus purpureus is an appropriate alternative for the treatment of hypercholesterolemia in patients intolerant to statins.

Keywords: Intolerance to statins; Cholesterol treatment; Monascus purpureus; Myalgia; Myositis; Myopathy; Rhabdomyolysis

Introduction

Despite its proven effect on primary and secondary preventions of atherosclerotic disease, statins, which revolutionized the treatment of cardiovascular diseases, are still underutilized in this context, with a large percentage of patients who would benefit from their use and do not receive these drugs, with this estimated to occur in approximately 40% of patients eligible for this intervention [1]. One of the causes of this underuse lies in the fact that some patients have some kind of intolerance to this class of medications, and this intolerance may be related to clinical symptoms of myalgia and sometimes, in a small percentage, coming to severe cases of rhabdomyolysis, digestive symptoms such as epigastric pain, heartburn, constipation, flatulence, nausea or vomiting, dyspepsia, headache, rinitis, sinusitis and sometimes raising the level of liver enzymes. Because hypercholesterolemia is an asymptomatic condition, the unpleasant side effects of the drugs used for its treatment end up greatly decreasing adherence to this. In addition, patients generally do not have a very real view of how hypercholesterolemia increases cardiovascular risk, especially in cases of primary prevention. It is noteworthy that these symptoms and signs are much more frequent when there is an association with other drugs used in the treatment of dyslipidemias, such as niacin and fibrates. It is noteworthy here that, of fibrates, genfibrozil is the one that presents the most drug interaction with statins, this occurring by two of its pharmacokinetic characteristics: first ly because it competes with the same glucoronil transferase that metabolizes most statins; secondly because it inhibits an important hepatocyte membrane conveyor, oatp2 (organic anion transporter protein) which is the carrier responsible for internalizing statins in the oxytor (with difficulty in statins entering in hepatocytes, their serum level increases) [2]. Also these undesirable effects are more frequent in real clinical practice than the incidence presented in large clinical studies, where there is a pre-selection of patients.

Statin vs. Myalgia

Of all the side effects mentioned above the most common and greatest responsible for suspending the use of statins is myalgia. The occurrence of this is related to the dose of the drug used and characteristically occurs in the absence of myositis. It is also very common to occur myalgia at the beginning of treatment, when patients are instructed to start a physical exercise program and concomitantly prescribes a statin. For this reason it is our conduct to start first recommending the practice of exercises and only a few days after the beginning of this is that we prescribe statin. Before

entering the pathophysiology of myalgias it is useful to establish diagnostic criteria of the various conditions known as statin-related myopathy. We adopted the criteria of the American Heart Association/American College of Cardiology/National Heart, Lung and Blood Institute [3].

Myopathy: general term referring to any muscle disease.

Myalgia: muscle pain or weakness without elevation of creatinokinase.

Myositis: muscle symptoms with elevation of creatinokinase.

Rhabdomyolysis: muscle symptoms with increased creatinokinase above 10 times the upper normal level, elevation of creatinine, usually with dark urine with urinary myoglobin.

Pathophysiology of Myalgia

The basic mechanism of myopathy is also discussed, and the following are proposed: instability of the membrane of myocytes by decreasing its cholesterol content, depletion of isoprenoids or Coenzyme Q10 and mitochondrial dysfunction. The first mechanism does not seem to be correct, because decreased cholesterol synthesis by scalen sintetase inhibitors does not result in myopathy. As for the depletion of coenzyme Q10 and mitochondrial dysfunction, the various studies are still contradictory [4]. Some recent pharmacogenetic studies suggest that myopathy associated with statin use is genetically determined and is related to polymorphisms in genes responsible for coenzyme Q10 synthesis, especially the COQ2 gene [5-8].

Risk Factors for Myalgia

The risk factors for the onset of myopathy are: patients with complex clinical situations, using polypharmacy, hypothyroidism, women with low weight, intense physical activity, hospitalization for large surgeries, patients geriatric drugs, use of high doses of statins and drug interaction with CYP 3A4 inhibitordrugs, mainly with azole alour antigens (ketoconazole and itraconazole – alternatively use fluconazole), macroliteic antibiotics (erythromycin and clarithromycin), protease inhibitors, cyclosporine, amiodarone and, as already described above, with genfibrozil.

Therapeutic Suggestion for Statin Intolerant

Several treatment strategies have been suggested for use in case of statin intolerance:

Coenzyme Supplementation Q10: as it has been suggested that one of the causes of myopathy would be coenzyme Q10 deficiency in the myocyte membrane, some studies evaluated their supplementation in these cases. The results were contradictory and a systematic review was inconclusive [9]. Coenzyme Q10 per day concomitantly with statin has been used 100 to 200 mg per day, with a reasonable improvement in tolerance.

Statin change: use of other statins, such as rosuvastatin that is minimally metabolized, pravastatin that is not metabolized by cytochrome P450 and fluvastatin that is metabolized by the passage of 2C9. However this change would only be indicated in cases of drug associations. Also with the use of fluvastatin alone, about 17% of patients had recurrence of myopathy [10]. It is also recommended the use of atorvastatin or rosuvastatin in low doses and in non-daily treatment schemes: the use of these 2 potent statins, of longer effect, in low doses and in 2 to 3 weekly doses, proved to be efficient in reducing the LDL-cholesterol from 13 to 25%, with good tolerance; but studies are lacking that show the improvement of clinical outcomes with these regimens.

Use of ezethyiba: although ezethycitis can, when used in isolation, reduce LDL-cholesterol levels by up to 20%, its efficacy in reducing clinical outcomes has not yet been demonstrated. Ezethyiba is useful when used together with statins.

Use of bile acid sequeblant resins: the use of these resins is efficient in reducing LDL-cholesterol by about 20%, but there is a difficulty in adherence to treatment due to its unpleasant side effects, such as impalatability, intestinal constipation and also interference in the absorption of other drugs. In addition, the use of these medicines may raise the serum level of VLDL.

Use of fermented red yeast rice extract (red yeast rice-extract of Oryza sativa fermented by Monascus purpureus): such extract is a herbal plant that has been used in China since the 800s AD, for various purposes, among them the treatment of diseases of the circulatory system. Currently this product is already produced in a standardized way, registered as a medicine by the National Health Surveillance Agency and contains, in capsules of 600 mg, monacolin K (lovastatin) and 8 other monacolins, in addition to unsaturated fats and other Substances. This product was clinically tested in a large clinical secondary prevention study involving 4,870 patients who had already suffered a myocardial infarction, with an average of 60.5 years (18 to 70 years), with a follow-up of 4.5 years and a dose of 600 mg of the extract , tested against placebo. This study showed a favorable outcome, with statistical significance, in the following parameters: total mortality, cardiovascular mortality, coronary mortality, cancer mortality, non-fatal myocardial infarction and revascularization coronary artery, and such events are also favorable in the subgroups of diabetics and the elderly [11].

Due to these clinical findings, this product has been tested against placebo in a study involving statin-intolerant patients. The patients were randomized and allocated into two groups (placebo and treatment) and both received dietary guidance and for physical exercise. Additionally, patients in the treated group received 1800 mg/day of the extract. The treatment group showed a statistically significant reduction in LDL-C (-21.3% vs. -8.7%), total cholesterol (-14.9% vs. -5.3%) triglycerides (-7.2% vs. -1.4%) compared to the placebo group. The appearance of myalgias and alteration of CPK and liver enzymes was not different between groups [12-15]. A recent systematic review showed that this extract presented a good regulatory effect of lipidemia and was also safe and effective in reducing cardiovascular events in patients with coronary disease complicated with dyslipidemia16. In addition to this effect on lipids, this extract showed a favorable effect on several parameters related to metabolic syndrome and obesity, such as decreased

insulin resistance, serum level of this and also adiponectin and improvement of non-alcoholic steatohepatitis [17,18]. Therefore, the use of Oryza extract fermented by Monascus purpureus is an excellent alternative for the treatment of hypercholesterolemia in patients intolerant to statins.

Conclusion

Despite all this discussion on pharmacological agents, let us not forget that in the treatment of dyslipidemias is fundamental and should always come first the implementation of hygiene measures, with the performance of regular physical exercises and a diet with low saturated fats, sugar and sweets, aiming at improving lipid levels and correcting excess weight when present. It is also worth remembering that phytosterolis, both in pharmaceutical formulation or in the form of functional foods, if ingested at a minimum dose of two daily outlets, can reduce LDL levels from 7 to 10%.

Acknowledgments

None.

Conflicts of Interest

No conflict of interest.

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