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Mini Review

Second Line and Exceptional Treatments for Hypercholesterolemic Patients

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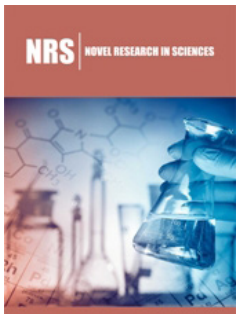

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Abstract

Apart from statins, fibrates and PCSK9 inhibitors there are the so called second line treatments in hyperlipidemia. Starting with the ones acting in cholesterol absorption, there are as well ezetimibe, nicotinic acid and in familial hypercholesterolemia the possible choice of LDL apheresis. Cholestyramine-resin sequestering bile acids are effective drugs for LDL-C reduction, useful in patients who are contraindication to the use of vastatins, in the treatment of family hypercholesterolemia in children and as an association with other lipid-lowering agents. Unlike resins, ezetimibe is a selective inhibitor of intestinal cholesterol absorption. Ezetimibe inhibits intestinal absorption of cholesterol by inhibiting the Niemann Pick C1 Like1 protein on the surface of the enterocyte. This protein is responsible for the absorption of cholesterol, but not of other fats in the intestine. Its greatest advantage, however, is in the association with a vastatin, in a treatment strategy called double inhibition (inhibition of cholesterol synthesis by vastatin and its intestinal absorption by ezetimibe). Phytosterols compete in intestinal absorption of cholesterol, leading to a slight decrease in LDL-C. To act efficiently, they must be ingested before three meals. Nicotinic acid, which has been used as a lipid-lowering agent since 1955, is suitable for the treatment of all types of dyslipidemia except familial sistosterolemia. It can be used alone or associated with any lipid-lowering agent. The main mechanism of action of nicotinic acid is by inhibiting peripheral lipolysis, inhibiting the mobilization of fatty acids to the liver. Omega 3 fatty acids, eicosapentanoic and docosaexanoic acids have been used to treat severe hypertriglyceridemia at doses of 3 to 10g/day. The LDL-C apheresis method can be considered a type of selective hemodialysis, in which only LDL particles are removed from plasma.

Keywords: Phytosterol; Ezetimibe; Nicotinic acid; Omega 3; LDL apheresis; Cholestyramine

Abbreviations: ALT: Alanine Aminotransferase, Aminopeptidase N: CD 13, Apo A-1: Apoprotein A-1, AST: Aminotransferase, CK: Creatinoquinase, CYP3A4: Cytochrome P450 3A4 protein, HDL-C: High Density Lipoprotein Cholesterol, HMG-CoA Reductase: 3-Hidroxi-3-Methyl-Glutaril-CoA Reductase, LDL-C: Low Density Lipoprotein Cholesterol, VLDL: Very Low-Density Lipoprotein

Introduction

Cholesterol absorption inhibitors

Inhibitors of cholesterol absorption in the intestine play an important role in the treatment of hypercholesterolemia, as these drugs not only inhibit the absorption of cholesterol from the diet, but also prevent the absorption of bile cholesterol, which has been excreted in bile by the liver and which will return to the body by the enterohepatic circulation. Bile acid sequestering resins - in Brazil, only cholestyramine is available for clinical use. These are effective drugs for the reduction of low-density lipoprotein cholesterol (LDL-C), useful in patients who are contraindicated to the use of vastatins, in the treatment of family hypercholesterolemia in children and as an association with other lipid-lowering agents.

Mechanism of action: This ionic resin binds in the intestine to bile acids that are high in cholesterol, increasing fecal excretion from those and disrupting the enterohepatic circulation. This decrease in absorption leads to a deviation in the hepatic flow of cholesterol to the production of bile acids due to a growth in the activity of the enzyme 7a-hydroxylase, which

is responsible for catalyzing the limiting reaction in the synthesis of these acids. The decrease in intrahepatic cholesterol increases the expression of LDL receptors, responsible for the absorption of LDL particles from plasma. There is also a growth in intracellular cholesterol synthesis by increased activity of 3-hydroxy-3-methyl-glutaril-CoA reductase (HMG-CoA reductase), attenuating the effect on LDL reduction. At the same time, there is an increase in the hepatic synthesis of Very Low-Density Lipoprotein (VLDL), with an increase in the rate of triglycerides.

Effectiveness: Resins decrease LDL-C by approximately 15 to 30% and increase High Density Lipoprotein Cholesterol (HDL-C) by about 2 to 5%. They are very efficient when associated with vastatins. As mentioned earlier, doubling the dose of a vastatin, there is on average an additional reduction of LDL-C of only 6%. However, with the addition of a resin, this additional reduction will be 12 to 15%.

Safety and tolerability: Resins are very safe drugs because, not being absorbed, they do not present systemic toxicity and can be used even in children. They are excreted entirely by the digestive system. However, there are two problems with them: tolerability and interference in intestinal absorption of other substances. Resins have low tolerability because, in addition to not being palatable, they cause unpleasant digestive symptoms, such as dyspepsia, intestinal constipation, flatulence, nausea and bloating. Consequently, there is low treatment adhering. Resins also lead to malabsorption of other drugs, such as digitoxin, warfarin, thyroxin, thiazoid diuretics, beta-blockers, and also diet substances such as fat-soluble vitamins and folic acid.

Dosage: The dose of cholestyramine is 4 to 16g/day, taken at meals. Other medicines used by patients should be administered 1 to 2h before or 4h after resins. Generally, pediatric patients require vitamin supplementation and folic acid.

Contraindications: Resins are absolutely contraindicated in biliary obstruction and in cases of hypertriglyceridemia with triglycerides above 400mg/dl. With triglycerides between 200 and 400mg/dl, contraindication is relative, and these levels should be monitored. In patients with diabetes and intestinal autonomic neuropathy, there is a risk of the occurrence of severe intestinal constipation with possible fecaloma formation.

Ezetimibe

Unlike resins, ezetimibe is a selective inhibitor of intestinal cholesterol absorption, not inhibiting the absorption of bile acids and other fats.

Mechanism of action: Ezetimibe inhibits intestinal absorption of cholesterol by inhibiting the Niemann-Pick C1 Like1 protein on the enterocyte surface. This protein is responsible for the absorption of cholesterol, but not of other fats in the intestine. Kramer et al. [1] described another possible mechanism of action of ezetimibe: interference with another membrane protein, aminopeptidase N (CD 13), leading to endocytosis blockage of cholesterol-rich membrane microdomains.

Effectiveness: Ezetimibe, at a daily dose of 10mg, alone, leads to a decrease in LDL-C by an average of 20%. Its greatest advantage, however, is in the association with a vastatin, in a treatment strategy called double inhibition (inhibition of cholesterol synthesis by vastatin and its intestinal absorption by ezetimibe). In this case, when 10mg of ezetimibe is added to a vastatin, the LDL-C reducing power of the combination increases by 18% compared to vastatin alone. Just for comparison, as discussed earlier, doubling the dose of vastatin, the increase would be only 6%.

However, the Enhance [2], study compared, in patients with heterozygous family hypercholesterolemia, the use of 80mg in simvastatin with the combination of 80mg/ezetimibe 10mg and showed no statistically significant difference in the primary endpoint, which was the non-progression of the intima-media of carotid strains between the two groups, although the LDL-C achieved with the medication was significantly lower than that achieved with isolated simvastatin (141.3mg/dl and 192.7mg/dl, respectively).

The latest SHARP study, which allocated 9,270 patients with chronic kidney disease, during a mean follow-up of 4.9 years, comparing the use of the combination of simvastatin plus ezetimibe with placebo, led to a decrease of about 32.86mg/dl of LDL-C and a 17% reduction in the incidence of atherosclerotic events, including ischemic stroke, vascular death, acute myocardial infarction, or revascularization procedures; this difference is maintained in patients undergoing dialysis procedures or not. The authors concluded that the decrease in LDL-C by combining 20mg with ezetimibe 10mg/day safely reduced the incidence of atherosclerotic events in patients with advanced chronic renal failure [3].

Safety and tolerability: Side effects of ezetimibe include diarrhea, abdominal pain, low back pain, arthralgia and sinusitis. Hypersensitivity reactions such as angioedema and rash, pancreatitis, hepatitis, and myopathy rarely occur. Ezetimibe, despite being absorbed and its effect is systemic, is not metabolized by cytochrome P450 3A4 (CYP3A4), with no interference with most drugs. However, when used with cyclosporine, there is an important increase in its plasma concentration, which may lead to an increase in the incidence of its side effects. Unlike resins, it is very well tolerated. Another advantage is the non-interference with the absorption of bile acids, fat-soluble vitamins, folic acid and other drugs.

Dosage: Ezetimibe is used in a single dose of 10mg/day in a single take and can be given together with vastatins. Its use with fibrates seems to be safe, but there are ongoing studies for this evaluation.

Contraindications: It should not be used in case of active liver disease and in women during pregnancy and lactation.

Orlistat

Although used as an anti-obesity drug, orlistat, a pancreatic lipase inhibitor, besides being able to lead to a reduction of up to 10% in weight, can act by decreasing triglycerides and LDL-C.

Phytosterols

Compete in intestinal cholesterol absorption, leading to a slight decrease in LDL-C. To act efficiently, they must be ingested before three meals.

Nicotinic acid

Nicotinic acid, which has been used as a lipid-lowering agent since 1955, is suitable for the treatment of all types of dyslipidemia except family chylomicronemia. It can be used alone or associated with any lipid-lowering agent.

Mechanism of action: the main mechanism of action of nicotinic acid is by inhibiting peripheral lipolysis, inhibiting the mobilization of fatty acids to the liver. In addition, it decreases liver synthesis and secretion of lipoproteins rich in apolipoprotein-B.

Effectiveness: nicotinic acid at doses of 2 to 3g/day reduces LDL-C by about 10 to 25%, triglycerides from 20 to 50%, and increases HDL-C by 15 to 35%, further reducing postprandial lipemia, lipoprotein(a), small and dense LDL, and fibrinogenemy [4]. It is the most effective substance available so far for the elevation of HDL-C in clinical use. Since 1975, the year of publication of the Coronary Drug Project [5], it is known that nicotinic acid reduces cardiovascular risk. This secondary prevention study showed that, in 5 years, nicotinic acid decreased total cholesterol by 10% and the risk of a new coronary event by 12.2% (compared with placebo, which decreased 8.9%). In the follow-up of the patients, 9 years after the end of the study, mortality in the nicotinic acid group was 11% lower than in the placebo group, a highly significant result.

Safety and tolerability: Nicotinic acid has serious tolerability problems, although the new formulations type extended release or "intermediate release", which distribute the absorption for a period of 8 to 12h, have decreased the intensity of side effects and improved the treatment of patients (not to be confused with the preparations "controlled release", "long-acting" and time released, which release the drug in more than 12h and have greater hepatotoxicity. Among these side effects are flushing, feeling of generalized itching, and symptoms of gastrointestinal irritation such as heartburn, epigastric pain, abdominal pain, nausea, vomiting, and diarrhea.

Flushing and the feeling of itching are due to the release of prostaglandin D2. Laropiprant, the antagonistic substance of this prostaglandin, was then developed, which associated with nicotinic acid decreases these side effects by about 50%. In addition to these symptoms, nicotinic acid can also cause increased hepatic transaminases, increased blood glucose and uric acid, effects that are reversible with the suspension of the drug. Rarely, more severe liver injury can occur, which is characterized by increased transaminases, jaundice, centrolobular cholestase and parenchyma necrosis, which may lead to liver failure, appearing these changes mainly with the use of "long action" preparations. The extend-ed release preparation seems to reduce this risk. Rarely, myopathy and cystic maculopathy, both reversible, may rarely occur. Cases of angina worsening are also reported in patients with unstable angina.

Dosage: The daily dose of nicotinic acid to be reached is 2 to 3g/day, in crystalline form, and 1.5 to 2g/day, in the extended-release form (Niaspan®). In the case of crystalline preparation, which in our environment is only available by manipulation, it should be started with the dose of 100mg, 3 times/day, after three meals, gradually increasing every 15 days. However, with the introduction of the extended-release form, with a much better tolerability profile, preference should be given to it. Its administration should be done after dinner, about 30 minutes after ingestion of 100mg of acetylsalicylic acid, as this decreases the side effects of flushing and itching, starting with 500mg and increasing 500mg every 15 days until the desired dose is reached (maximum of 2g per day).

Contraindications: The main contraindications to the use of nicotinic acid are hypersensitivity, active liver disease or jaundice, gout, peptic ulcer, hypotension, biliary lithiasis, and inflammatory bowel disease. Relative contraindications are hyperglycemia and diabetes mellitus.

Omega 3 fatty acids

Eicosapentanoic acids and docosaexanoic acids have been used to treat severe hypertriglyceridemia at doses of 3 to 10g/day, depending on tolerability, and may be considered as an alternative to the use of fibrates and nicotinic acid. Its benefit in primary prevention has not yet been confirmed in large studies.

However, its benefit has already been demonstrated in secondary prevention, and in the GISSI-Prevenzione study [6], there was a reduction in total mortality and incidence of myocardial infarction and stroke. Other smaller studies confirmed these findings. It is interesting to note that the greatest reduction occurred in cases of sudden death and it is considered that these products, considered drugs in the dose used, would have action on the membrane of myocardial cells, leading to a stabilization of these with a lower incidence of arrhythmias.

Probucol

Used in the 1970s and 1980s as a lipid-lowering and antioxidant agent, it was withdrawn from the Brazilian market and other countries for reducing HDL-C. However, it continues to be used in Japan and Canada, where it has shown benefit when used in the prevention of post-coronary angioplasty backenose. It is possible that its HDL-C reducing effect is actually ore to a more efficient uptake of the probucol by the hepatocyte SRB1 receptor, increasing reverse transport and improving the dynamics of lipid metabolism [7]. Further studies are necessary for a complete evaluation of this substance in the atherogenic process.

Other Types of Treatment

LDL-C apheresis - this method can be considered a type of selective hemodialysis, in which only LDL particles are removed from plasma, and this can be performed by various methods, such as plasmapheresis by double filtration, thermo filtration, immunoadsorption, chemo adsorption on dextran sulfate cellulose, etc. This method is used by patients with homozygous family hypercholesterolemia, who have very high LDL-C levels and when

dietary and drug treatment is not enough to lower them to an adequate level.

Apoprotein A-1 (apoA-1) Milano - variant of apoA-1 that presents high reverse transport capacity, and its benefit has been demonstrated in several studies to reduce atheroma's.

Laboratory follow-up - current guidelines recommend a reassessment of lipid levels after the start of therapy to verify their efficacy, treatment adhering and whether desired levels are being achieved and recommended by these guidelines. These evaluations should be performed according to the clinical picture of the patient.

After 1, 3, 6, 9 and 12 months, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), CK Creatine Kinase (CK) tests should be performed, as lipid-lowering substances, especially vastatins, fibrates and niacin, may cause elevations in these enzymes due to liver and muscle damage [8]. These tests should also be performed whenever there is a dose increase and periodically after 1 year. In the case of niacin use, blood glucose and uricemia should also be monitored.

However, a task force of the National Lipid Association and the International Atherosclerosis Society on the safety of vastatins has reached the following conclusions [9]:

Routine monitoring of liver function tests is not supported by available evidence, and current monitoring recommendations should be reviewed by the Food and Drug Administration (FDA) and drug manufacturers

Cases of jaundice, malaise, fatigue and lethargy may be signs of hepatotoxicity, and the doctor should perform fractional bilirubin tests and prothrombin time, as well as look for other signs of liver failure, rather than performing only AST and ALT scans

A. If significant liver damage is proven, the medicine should be discontinued.

B. In cases of asymptomatic increase of 1 to 3 times the normal rate of AST or ALT level, the medicinal product should be continued.

C. In cases of asymptomatic increase of more than 3 times the normal level of AST or ALT, the test should be repeated, other causes for such increase should be sought and clinical considerations should be made for continuation, dose reduction or discontinuation of the drug.

D. It is not necessary to control CK in asymptomatic patients using vastatin.

CK control tests should be performed only in symptomatic patients to assess the severity of muscle injury and decide whether to continue use, decrease dose or discontinue the drug

Conclusion

Vastatins should be discontinued in patients who develop rhabdomyolysis, with CK 10,000 IU/L or about 10 times the normal method with creatinine elevation. These conclusions of the International Atherosclerosis Society and the National Lipid Association, recently published, are not yet part of the Brazilian guidelines on the safety of lipid-lowering substances.

Acknowledgment

None.

Conflicts of Interest

No conflict of interest.

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