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(REVIEW ARTICLE)

Lipid lessening drugs overview

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Abstract

Lipid lessening drugs are groups of drugs used to treat the conditions or diseases that associated with elevated blood levels of lipids (cholesterol, triglyceride) and low-density lipoprotein (LDL). These conditions known as dyslipidemias, which is hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia. Many studies found that dyslipidemias inclined and increase the risk of other diseases such as atherosclerosis, diabetes mellitus, and coronary arteries disease.

Keywords: Dyslipidemias; Statin; Fenofibrate; Coronary arteries disease

1. Introduction

Lipids (cholesterol, triglyceride, and their derivatives) are biomolecules presented inside the human body in different ratio. Cholesterol is an important component of the human cell membrane and is a precursor for steroid hormones and bile acids. Moreover, Triglyceride stored inside the adipocyte and has an important role in energy production [1].

Increase blood levels of lipids, hyperlipidemia, is almost the important risk factor for many diseases such as coronary heart diseases, diabetes mellitus and metabolic syndrome. Patients with type 2 diabetes have an atherogenic lipid profile, which greatly increases their risk of coronary heart disease (CHD) compared with people without diabetes [2].

Therefore, the human must treat hyperlipidemia by changing life style and diet control. If he failed to suppress his elevated blood levels of lipids, he must treat with a therapy called lipid-lessening agents. Either mono therapy or combined therapies of drugs with different mechanisms of action can be effectively used in the treatment of patients with severe hypercholesterolemia or combined hyperlipidaemia. The combinations of bile acid sequestrates, HMG CoA reductase inhibitors, and nicotinic acid, are the most effective [3].

2. Classes of lipids de-escalating medications

2.1. Statins

Statins are well absorbed, extracted by the liver and are exposed to massive metabolism by cytochrome enzymes CYP3A4 or CYP2D6. Simvastatin is an inactive lactone prodrug that metabolized in the liver to its active form, the corresponding β-hydroxy fatty acid [4].

Statins inhibit HMG Co A reductase a rate-limiting enzyme in cholesterol biosynthesis, thereby it is lower cytoplasmic cholesterol level and enhancing the synthesis of LDL receptors in hepatocytes to increases the hepatic LDL uptake from the plasma, leading to decreasing the plasma LDL level [3,5].

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Additionally, statin drugs prescribed as potential therapeutic agents against various neuroinflammatory and neurodegenerative disorders. As statin inhibits HMG-CoA reductase, then mevalonate and farnesyl pyrophosphate (FPP) synthesis are inhibited and thereby inhibit other factors like activation of Nuclear factor- κB (NF-κB),expression of inducible nitric oxide synthase (iNOS) and activation of many proinflammatory cytokines such as (tumor necrosis factor-α (TNF-α),interleukines-1b (IL-1b)) [6,7].

As statins inhibit the expression of iNOS, but it can stimulate endothelial nitric oxide synthase eNOS-derived NO production in the vascular walls independently on cholesterol lowering mechanism. Thereafter, the endothelial function can be repaired in those patients with atherosclerosis and hypercholesterolemia who had a declined in endothelium-derived NO synthesis [3, 8].

As statins inhibit geranylgeranylation of G-protein (Rac) and thereby diminish the level of NADPH oxidase-mediated generation of superoxide. Thereby, the production of reactive oxygen species (ROS) by several inflammatory and degenerative stimuli declined [9, 10].

Seven types of statins are available, lovastatin (Mevacor: 1987), pravastatin (Pravachol: 1991), simvastatin (Zocor: 1991), fluvastatin (Lescol: 1993), atorvastatin (Lipitor: 1996), rosuvastatin (Crestor: 2003) and pitavastatin (Levalo: 2009). Many studies found that simvastatin; atorvastatin and pravastatin reduce cardiac events and prolong life, and are safe. Statins have many uses in patients with arteriosclerosis such as; cholesterol-lowering and anti-inflammatory activities, amended endothelial function and plaque stabilization, anti-thrombotic, anti-proliferative, and anti-oxidative effects [2, 3].

Mild side effects include nausea, constipation, diarrhea, flatulence, fatigue, insomnia, and rash. More critical adverse events are rare, but include rhabdomyolysis, hepatitis, and angioedema. Estimation of blood level of creatine kinase is important if the patients developed muscle aches and it may alert to stop the drug due to rhabdomyolysis. Cerivastatin , was withdrawn because of rhabdomyolysis and drug interactions [5].

Liver function tests should be performed before and after starting treatment, because all of the statins have been associated with mild-to-moderate serum aminotransferase elevations during therapy that are typically transient, asymptomatic and may resolve even with continuation. All have also been associated with rare instances of clinically apparent acute liver injury [2].

Statin avoided in alcoholic patients and in patients with other liver disease, and contraindicated during pregnancy. The risk of rhabdomyolysis increased by concomitant use of statin with other drug such as fibrate or drug that inhibit statin metabolism, e.g. macrolides. The potency of statin increased by simultaneous use with drug that hinders cholesterol absorption [8].

2.2. Fibrates

Fibrates like Bezafibrate and gemfibrozil are completely absorbed when given by mouth, highly protein bound, and excreted mainly by the kidneys. Fibrates reduced fatty acid and triglyceride (TG) levels by stimulating the peroxisomal *β*-oxidation pathway by binding to the nuclear receptor (peroxisome proliferator-activated receptor α (PPARα)) which is present in many tissues inside the body including fat. They stimulate lipoprotein lipase, increase LDL uptake by the liver and lower fibrinogen level [11, 12].

PPARs are a group of three nuclear hormone receptor isoforms, PPAR-*α*, PPAR-*γ*, and PPAR-*δ*, encoded by different genes. Many studies found that Fibrate drugs such as clofibrate and fenofibrate activate PPAR-*α* more than PPAR-*γ* [13, 14].

With the presence of fibrate drugs, PPAR-*α* heterodimerizes with retinoid X receptor-*α* (RXR-*α*), and the resultant complex modulates the transcription of genes containing peroxisome proliferator-responsive elements (PPREs) in their promoter sequence. Other activators of PPARs involved a number of natural ligands, such as polyunsaturated fatty acids (PUFAs), leukotriene B4 (LTB4), 8-S-hydroxy eicosatetraenoic acid (8-S-HETE), and prostaglandin J2 (PGJ2) [14-16].

In mitochondria, Fatty acids are *β*-oxidized while very long chain and long-chain fatty acids are *β*-oxidized in peroxisomes, which stimulated with the presence of fibrate drugs. After chain shortening in peroxisomes, fatty acids transported into the mitochondria for complete *β*-oxidation [17].

Additionally, fibrate drugs can stimulate fatty acid ω-oxidation in the liver, and can decline the effects of some inhibitors of fatty acid oxidation, such as 4-pen-tenoate, and decanoyl-carnitine [18, 19].

Fibrates also increase the activity of acyl-CoA synthetase and the CoA content of liver while the level of malonyl-CoA, the precursor of de novo fatty acid synthesis, goes down .Apart from stimulating fatty acid oxidation-associated molecules; fibrates also increase lipolysis via PPAR-α-dependent up-regulation of lipoprotein lipase [20].

Alike to statins, fibrates drugs also can inhibit the production of different proinflammatory molecules. They suppress cytokine-induced IL-6 production in smooth muscle cells (SMCs), iNOS activity in murine macrophages, and VCAM-1 expression in endothelial cells [21].

Three forms of fibrates are presented, gemfibrozil (Lopid: 1981), fenofibrate (Lifibra, Tricor, Antara, Lipofen, Trigilde: 1993), and clofibrate (Abitrate, Atromid-S: withdrawn 2002) and used mainly for the treatment of patients with mixed dyslipidaemia and with type III hyperlipoproteinaemia [16].

Clofibrate used in lesser extent, because it increases the biliary cholesterol secretion and predisposes to gall stones. Furthermore, while it reduced the number of myocardial infarctions in the WHO trial, it increased the number of cancers of various kinds. The meaning of this idea extensively debated, but remains obscure [22].

Fibrates treatment reduced the risk of coronary heart disease (CHD) and amended atherogenic dyslipidemia through many steps such as increases the clearance of very low density lipoprotein-cholesterol, decreases triglycerides level , increases high-density lipoprotein (HDL)-cholesterol by lowering the exchange of triglyceride and HDL-cholesterol through the cholesterol ester transfer protein (CETP), and a reduction of hepatic cholesterol biosynthesis [22].

Fibrate (gemfibrozil) used for treatment of obesity by its direct stimulatory effect on the catabolism of fat ,and restored leptin transport across the blood brain barrier (BBB) thereby reduced leptin resistance and leptin level [23].

Fibrates can cause myositis (in severe cases rhabdomyolysis with acute renal failure), especially in alcoholics and in patients with impaired renal function (in whom elimination is prolonged and protein binding reduced). Therefore, Fibrates used with caution in patients with renal or hepatic impairment, should not be used in patients with gall-bladder disease or with hypoalbuminaemia, and contraindicated in pregnancy and in alcoholics. Fibrates associated with mild-to-moderate serum aminotransferase elevations during therapy that are typically transient, asymptomatic and may resolve even with continuation [24].

Clofibrate withdraws from use because of its fatal side effects with the long-term use in reducing cardiovascular mortality. Gemfibrozil and fenofibrate remain in wide scale use. However, fenofibrate treatment correlated to many cases of clinically apparent liver injury, which can be severe, prolonged, and converted to chronic liver disease and cirrhosis [16, 25, 26].

2.3. Anion-exchange resins (bile acid resins)

The bile acid resins or sequestrates are the oldest and safest lipid lowering agents, but are less potent than other classes and are not almost well tolerated. The bile acid sequestrates are highly positively charged and bind to the negatively charged bile acids in the intestine, inhibiting their lipid solubilizing activity and thus reducing cholesterol absorption [27].

They also inhibit the reabsorption of bile acids (absorption of which is typically 95%) and thus cause a reduction of the bile acid pool, which leads to increased bile acid synthesis that competes with cholesterol synthesis in the liver; this may also contribute to a lowering of cholesterol. Colestyramine or colestipol used for hypercholesterolaemia especially in the treatment of severe disease (e.g. heterozygous familial hypercholesterolaemia (FH)) which was ineffectively responsive to statin monotherapy [27].

Resins administered in doses of several grams, are unpalatable, and commonly cause abdominal bloating and diarrhea. Resins treatments have limited usefulness in children and in breast-feeding women, and were ineffective in patients with complete biliary obstruction, in whom there are no bile salts to bind in the gut lumen. Furthermore, they cause malabsorption of fat-soluble vitamins and restrict the absorption of many drugs [27].

2.4. Proprotein convertase subtilisin / kexin type 9 inhibitors

Proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors are a new class of agents that used to treat hypercholesterolemia, first introduced in 2015. PCSK9 is a circulating serine protease that decreases the activity of the LDL cholesterol receptor in the liver. Blocking this receptor by circulating PCSK9 causes a decrease in the uptake of LDL cholesterol particles, resulting in an increase in LDL cholesterol in the blood. Inhibition of the activity of this protein by anti PCSK9 drugs would thereby cause a decrease in the total and LDL cholesterol [28].

Two types of anti-PCSK9 monoclonal antibodies were developed and approved for use in 2015: alirocumab (Praluent) and evolocumab (Repatha). Treatment with these monoclonal antibodies causes decrease in LDL cholesterol by 50% or more in patients who have familial hypercholesterolemia (homozygotes and heterozygotes) as well as in patients who are resistant or intolerant to standard lipid lowering medications, such as the statins [28].

The anti-PCSK9 monoclonal antibodies typically gave subcutaneously every 2-4 weeks. Recently, they used to decrease the incidence of cardiovascular events. Neither of the monoclonal anti-PCSK9 agents has associated with episodes of clinically apparent liver injury [28].

2.5. Miscellaneous agents

2.5.1. Ezetimibe

Ezetimibe given by mouth then is absorbed into intestinal epithelial cells, where it localizes to the brush border and is selectively inhibits intestinal cholesterol absorption. Ezetimibe inhibit cholesterol absorption, by its binding to the intestinal protein known as Neiman Pick C1 like protein 1 (NPLC1L sterol) transporter in the brush border of enterocytes that is the major cholesterol transport protein in the intestine. Inhibition of cholesterol absorption usually followed by an increase in hepatic cholesterol synthesis, which blocked by HMG-CoA reductase inhibitors [29].

Ezetimibe (Zetia: 1999) is used in combination with statins (Vytorin) for severe hypercholesterolaemia; also in occasional patients who cannot tolerate statins or where statins are contraindicated, and in (rare) cases of homozygous sitosterolaemia. Ezetimibe uses associated with diarrhea, abdominal pain, or headaches. Rash and angioedema also reported. It related to low rate raises of mild-to-moderate serum aminotransferase during therapy, rare instances of clinically acute liver injury, and contraindicated in breast-feeding [29].

2.5.2. Niacin

Niacin is a water-soluble vitamin B (vitamin B3, nicotinic acid). It used in high doses, more than minimum requirements as vitamin, to treat dyslipidemia. Niacin reduced triglyceride synthesis by inhibition of synthesis and esterification of free fatty acids. It used to treat all types of dyslipidemia, hypertriglyceridemia, and increasing HDL- cholesterol levels. Niacin is available in multiple generic forms and as a combination with various statins (lovastatin: Advicor and simvastatin: Simcor). High doses of niacin are associated with a high rate of acute liver injury particularly if taken as slow releasing forms [30].

2.5.3. Omega-3 fatty acids

Omega-3 fatty acids are essential polyunsaturated fatty acids that have several functions in normal metabolism and health and commonly known as "fish oil." Many formulations of omega-3 fatty acids are available over-the-counter as nutritional supplements in support of general health. High doses of omega-3 fatty acids can lower serum triglyceride levels and several formulations prescribed for treatment of severe hypertriglyceridemia including omega-3 acid ethyl esters (Lovaza 2004), icosapent ethyl (Vascepa, 2012) and omega-3 carboxylic acids (Epanova, 2014). These agents are intermittently associated with transient and mild serum enzyme elevations during treatment but are not associated with cases of clinically apparent liver injury [30].

3. Conclusion

In conclusion, hyperlipidemia and obesity are backbone for many disorders and diseases such as atherosclerosis, coronary artery disease, myocardial infarction, diabetes, peripheral vascular disease, cerebrovascular ischemic stroke, and neuro-inflammatory disease. Therefore, in addition to amend life-style and dietary intake, lipid-lessening drugs needed to attenuate the escalated blood levels of different forms of lipids.

Compliance with ethical standards

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Disclosure of conflict of interest

There are no conflicts of interests to declare.

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