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Novel Agents for Treatment of Hyperlipidemia

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Abstract

Those with abnormal lipid profile are at increased chance of developing heart diseases. The high levels of total cholesterol and serum triglycerides in the blood increases the risk for atherosclerosis and the high levels of LDL-C are toxic as well as atherogenic. Likewise the elevated ranges of HDL-C are protective. Management strategies include various antihyperlipidemic medicines, diet and therapeutic lifestyle changesFirst line agent for hyperlipidemia is statins. The lipid lowering potential may differ from one another. In other words, it varies with different agents belongs to this class. Rosuvastatin is superior to other statins. If target levels of LDL-C are not achieved with statin monotherapy, combination therapy may be beneficial. The core of the combination therapy is statins. Several nonstatin therapies are available as adjunctive treatment for patients who do not respond adequately to statins or for those who are intolerant of statins. These include Bile Acid Sequestrants, fibric acid derivatives, niacin, cholesterol absorption and synthesis inhibitors, as well as the recently approved class, PCSK9 inhibitors. In this, we are discussing about several newer antihyperlipidemic drugs such as PCSK9 inhibitors, MTP inhibitors, Squalene synthase inhibitors, thyroid mimetics, ACAT Inhibitors, antisense oligonucleotides, omega 3 fatty acids and DGAT inhibitors and their clinical significance.

Keywords: Antihyperlipidemic, HMGCoA reductase, PCSK9 inhibitors, MTP inhibitors, Squalene synthase inhibitors.

INTRODUCTION

Cardiovascular diseases are the major cause of morbidity and mortality in most of the developing and developed countries. The major cause of cardiovascular diseases is due to higher amounts of of LDL-C and lower amounts of HDL-C. Atherosclerosis is the main manifestation of hyperlipidemia and it is one of the main cause of cardiovascular diseases. So controlling of plasma lipid is essential. [1]

Management strategies should include both lifestyle changes and therapeutic agents. Lifestyle changes include diet, weight control, exercise, cessation of antisocial activities like alcohol, smoking and pan chewing and smoking.[4] LDL lowering therapy must be essential for those who are at increased risk of coronary artery diseases .[2] Antidyslipidemic agents include HMGCoA reductase inhibitors, fibrates, bile acid sequestering agents, nicotinic acid etc.[4]Several newer agents were developed such as MTP inhibitors, PCSK9 inhibitors, Antisense oligonucleotide against Apolipoprotein B, Apolipoprotein A1 mimetics.[9]

The current therapy for hyperlipidemia includes HMGCoA reductase inhibitors, fibrates, bile acid sequestering agents, nicotinic acid, ezetimibe etc. The superior one is statins and its superiority is due to its safety and efficacy in lowering LDL-C and coronary heart disease risk. Among statins, Rosuvastatin is the superior one because it shows significant larger reductions in LDL-C and it is highly effective to raise HDL-C than other agents belong to this class. Other lipid lowering agents are much less effective and less tolerated than statins, but gives better results when combined with statins. Among all lipid lowering agents, Statins are the most safe and effective.[10,6]

CONVENTIONAL TREATMENT

1. STATINS

Statins are the first line agents for hyperlipidemia due to their safety and efficacy. Statins are HMGCoA reductase inhibitors is the most commonly prescribed drug more than 20 years ago.

First generation agents– Lovastatin, Pravastatin, Fluvastatin.

Second generation agents – Atorvastatin, Simvastatin.

Third generation agents – Rosuvastatin.[7]

MECHANISM OF ACTION

These drugs inhibit HMGCoA reductase, rate limiting enzyme in biosynthesis of cholesterol. It is effective in lowering 20-50 % cholesterol and these are the most potent agents for reducing LDL-C and its response can be predicted with agent to agent and dose to dose. An additional 5-7 % decrease in LDL-C can be provided with every doubling of dose after starting the dose. If the goal is not achieved, aggressive dose titration is warranted.[8]

2. FIBRATES

Fibrates or fibric acid derivatives were introduced in to the market more than 35 years ago. The first approved fibric acid derivative was fenofibrate for treatment of severe hypertriglyceridemia. It reduces LDL cholesterol, Triglycerides, Total Cholesterol, Apo lipoprotein B levels and increase in HDL cholesterol. For patients with mixed dyslipidemia and cardiovascular disease, fenofibrate can be used in combination with statins for reducing triglyceride level and to raise HDL Cholesterol.[8,3]

MECHANISM OF ACTION

Fibrates are agonists of the PPAR-α receptor in muscle, liver, and other tissues.

Activation of PPARα signaling results in:

- β-oxidation in the liver is increased
- Hepatic triglyceride secretion is decreased

- Lipoprotein lipase activity is increased, thus increased VLDL clearance is also increased
- Increased HDL
- Clearance of remnant particles is also increased.[8,3]

3. BILE ACID SEQUESTRANTS

They are hypolipidemic agents. Cholestyramine, Colesevelam, and Colestipol are the drugs belong to bile acid sequestering agents. The newer agent Colesevelam has more affinity towards bile acids than older drugs

MECHANISM OF ACTION

In the GIT, these agents binds with certain components of the bile juice and it interrupts the enterohepatic circulation of bile acids. Due to their low concentration, cholesterol gets converted back to bile and concentration of cholesterol in the liver reduced. As a result, increases the LDL receptor activity of liver increases and it results in increased clearance of LDL. Because of their large polymeric structure, they are not get absorbed in to bloodstream and excreted in faeces.[8]

4. EZETIMIBE

These agents are lipid lowering agents. They are selective inhibitors of intestinal absorption of cholesterol. It is prescribed alone or in combination with statins. Ezetimibe alone gives 17% decrease in LDL-C and 25.1% decrease when used with statin.[12]

MECHANISM OF ACTION

It has localized action in the small intestine. The absorption of cholesterol in the intestine gets inhibited and it leads to reduced input of cholesterol in to the liver, thus hepatic cholesterol gets reduced and clearance of cholesterol from the blood also increased.[12]

5. NIACIN & NICOTINIC ACID

Niacin in the form of nicotinic acid reduces cholesterol. It reduces the production of TG, VLDL, LDL and increase in HDL. It is better to raise HDL cholesterol than other antidyslipidemic drugs.[8]

MECHANISM OF ACTION

- Inhibits the synthesis of VLDL
- Inhibits the secretion of free fatty acids from adipose tissue,
- Lipoprotein lipase activity gets increased
- Hepatic synthesis of VLDL-C and LDL-C are diminished.[8]

COMBINATION THERAPY

If target levels of LDL-C are not achieved with statin monotherapy, combination therapy may be beneficial. Core of the therapy is statins. For those patients with satisfactory levels of triglycerides, bile acid sequestrants in small doses need to be added and for patients with reduced amounts of HDL-C and with mild hypertriglyceridemia, have to add niacin in their regimen. For those who are at greater risk, these three drugs have to be considered in combination. The tolerability for combination therapy is much lower than statin alone and chances of more adverse events. Combination therapy of ezetimibe and statin therapy shows significant reductions in LDL-C and ezetimibe when combined with fibric acid derivative also reduce LDL-C than when fibric acid used alone.[14,15]

NEWER AGENTS

1. PCSK9 INHIIBITORS

PCSK9 is a serine protease, the major enzyme in the metabolism of cholesterol. It can reduce LDL-C amounts by increasing the expression of LDL receptors by diminishing the degradation of LDL receptor. Activating mutations in PCSK-9 results in FH whereas inactivating mutations results in 0.3–0.5 mmol/l reductions in plasma LDL-C and 70–80% reduced risk of cardiovascular diseases. The activity of PCSK9 is associated with fasting, postprandial lipid metabolism and hormonal control of lipids. Thus inhibitors of PCSK-9 increase LDL-R expression and reduce plasma LDL-C by 20%.[8]

MECHANISM OF ACTION

Normally PCSK9 binds with LDL receptors and it degrades inside lysosomes, thus plasma levels of LDL-C increased. Thus PCSK9 inhibitors inhibits binding with LDL-R, allows its recycling on the surface of hepatocytes, thus increases the clearance of LDL-C and Apolipoprotein B.[20,18]

ALIROCUMAB

Second line agent for lowering LDL-C approved by FDA on 2015. It is an IgG1 type of human monoclonal antibody administered as subcutaneous injection. It is used for those patients who need additional lowering of LDL-C and not responsive to high dose statin.[17]

EVOLOCUMAB

Second PCSK9 inhibitor approved by FDA for the treatment of lipid disorders. It is an IgG2 type of human monoclonal antibody administered as subcutaneous injection. . It is used for those patients who need additional lowering of LDL-C and not responsive to high dose statin.[17]

2. MTP INHIBITORS

Microsomal triglyceride transport proteins play the major role in the transport of triglycerides, cholesteryl esters, phosphatidyl choline and assembly of VLDL and chylomicrons. Thus inhibition of the proteins decreases the secretion of intestinal chylomicrons and hepatic VLDL and also results in reduction of plasma levels of LDL, VLDL and triglyceride.[12]

LOMITAPIDE

Lomitapide has approved for treatment of homozygous familial hypercholesterolemia. It is an orally active MTP inhibitor approved by FDA as an orphan drug. It shows dose dependant reductions in VLDL and LDL, decline in HDL-C at higher doses and normalize ApoB containing lipoprotein. Single dose administration reduces triglycerides and a considerable decrement has seen with multiple doses. In clinical trials, it results in reduced levels of TC, LDL-C, TG and ApoB and it results in elevated levels of HDL-C & ApoA when used in combination with Ezetimibe. There were hepatic side effects, but the potential benefits outweigh risks.[12]

IMPLITAPIDE
It shows significant effect in reducing plasma levels of TC, LDL-C, TG and VLDL but the effect on HDL-C is not satisfying.[12]
CP-346086
In hepatic G2 cells, CP-346086 inhibits apolioprotein B and triglyceride secretion, but has no effect on apolipoprotein A-1 secretion and lipid synthesis. It reduces both triglycerides and cholesterol (LDL, VLDL, and TC).[12]

3. SQUALENE SYNTHASE INHIBITORS
Squalene synthase is an enzyme in the biosynthesis of cholesterol so; inhibition of Squalene synthase ultimately results in decrease of circulating levels of LDL.12]
This enzyme catalyze the biotransformation of farnesyl pyrophosphate to lanosterol, thus the ultimate cholesterol synthesis gets inhibited while other byproducts of cholesterol biosynthesis like geranyl geranyl pyrophosphate and ubiquinone are not inhibited.

- BMS-187745 & BM-188494 :- plasma cholesterol levels were reduced following oral administration
- YM-53601 :- reduces plasma triglycerides and cholesterol
- ER-27856 & TAK-475 :- circulating LDL levels were reduced and it donot possess hepatotoxicity
- EP-2306 & EP-2302 :- dose dependant cholesterol biosynthesis and efficacy similar to simvastatin.10]

4. ACYL CHOLESTEROL ACYL TRANSFERASE INHIBITORS
Acyl cholesterol acyl transferase (ACAT) is a membrane bound enzyme which is found in RER of several tissues which are responsible for cholesterol homeostasis.[11,12]
Functions:

- Cholesterol and long fatty acids gets re-esterified into intracellular cholesterol esters
- Free acids re-esterified and its transport as chylomicrons(intestine)
- Secretion of VLDL in the liver
- Storage of cholesterol esters mediated by macrophages and further formation of plaque.[12]

Inhibition of this enzyme results in;

- Prevent accumulation of cholesterol esters and formation of atherosclerotic plaque
- It lowers the cholesterol absorption from intestine.[12]

AVASIMIBE
First orally available ACAT inhibitor is avasimibe. The drug is now under clinical trial. Animal studies results in reduced levels of various lipids but a significant reduction is seen with higher doses of drug.[9,11]
CL-277082
The effect of this agent on cholesterol absorption, sterol excretion and lipoproteins are not satisfying.[11]
DuP-182
It shows 14 % reduction of cholesterol and 5% reduction in LDL.[11]
CS-505 & F-1394 under preclinical studies.[11]

5. ANTISENSE OLIGONUCLEOTIDE THERAPIES
Infusion of a short complementary antisense oligonuceotide sequence to mRNA can reduce or silence gene expression. These interfering mRNAs are unstable and a number of methods are available to make it stable.[13]
MIPOMERSEN
First ASO therapy approved by FDA in 2013. It is indicated for homozygous familial hypercholesterolemia together with fat free diet and other hypolipidemic drugs. It is given as subcutaneous injection and it decrease apoB and LDL-C respective to the dose and it reduces lipoprotein A by 25% by affecting its synthesis. It is not indicated for homozygous familial hypercholesterolemia.[13]

6. THYROID MIMETICS
It acts through increased expression of LDL-C receptors. It also has effects on lipoprotein synthesis like niacin. These drugs are thyroid β-receptor agonists.[18]
EPROTIROME
Thyroid hormone analogue that possess lipid lowering properties. It is a hepatoselective thyroid hormone analogue that reduces LDL cholesterol by 7-32 %. It is indicated for heterozygous familial hypercholesterolemia and to those people who were not achieved target LDL-C concentration with statins and ezetimibe.[18]
SOBETIROME
Beta-1 hepatoselective thyroid hormone analogue that possess both antilipidemic and antiatherosclerotic properties. It reduces both plasma LDL-C and triglycerides.[18]
T-0681
Hepatoselective thyromimetic effectively reduce plasma cholesterol by inducing the metabolism of bile acids and the secretion of biliary sterol. On prolonged treatment with T-0681, the hepatic expression of both LDL receptor and scavenger receptor class B, type 1 gets increased.[18]

7. OMEGA 3 FATTY ACIDS
It lowers triglycerides and it shows dose dependant reduction of triglyceride by docosahexanoic acid and eicosapentanoic acid. In patients with hypertriglyceridemia, it shows 33-45% decrease in triglyceride.[18]
8. DGAT INHIBITORS
DGAT is an important enzyme in the biosynthesis of triglyceride. There are two forms of DGAT-1 and DGAT-2. Inhibition of DGAT-1 is found to have more effects than DGAT-2 on hyperlipidemia. Inhibitors of DGAT bind with acylcoA binding site of DGAT and inhibit DGAT-1 mediated triglyceride synthesis.[12,18]
T 863
Orally active potent DGAT inhibitor binds with acyl-coA binding site of DGAT and inhibits triglycerol synthesis. It decrease both serum and hepatic triglycerides and decrease serum cholesterol.[12]

CONCLUSION

The current therapy for hyperlipidemia is statins. Among statins, the superior one is rosuvastatin. Various newer antihyperlipidemic agents were developed, which are targeted to various proteins, receptors etc. Most of the newer drugs are under preclinical and clinical trials. PCSK9 inhibitors acts on LDL receptors facilitate the LDL-C reuptake. It is safe and it gives better results when added to statins. MTP inhibitors (Lomitapide) and Antisense oligonucleotide (Mipomersen) acts against ApoB (atherogenic lipoprotein) are approved for treatment of homozygous familial hypercholesterolemia. Squalene synthase inhibitors act on the biosynthetic pathway of cholesterol and it reduces LDL-C concentration. Acyl Cholesterol Acyl Transferase inhibitors alters the cholesterol homeostasis, under clinical trial. The development of these drugs will be a milestone in the treatment of coronary artery diseases to a great extent.

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