EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
115-123
Year: 2018

HYPERCHOLESTEROLEMIA

Jisha Vijayan*, Sruthy S. A., Neethu J., Nithin Manohar R., Babitha M. and Soumya R. V.

Asst. Professor, Department of Pharmacy Practice Sreekrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram.

***Corresponding Author: Jisha Vijayan**
Asst. Professor, Department of Pharmacy Practice Sreekrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram.

Article Received on 26/06/2018 **Article Revised on 16/07/2018** **Article Accepted on 05/08/2018**

INTRODUCTION

Although the incidence of atherosclerosis related vascular disease events is declining in the united state, coronary heart disease ischemic cerebrovascular disease and peripheral disease still account for the majority of morbidity and mortality among middle aged and older adult. Hypercholesterolemia is the major cause of increased atherogenic risk, and both genetic disorder and diet enriched in saturated fat and cholesterol contribute to the elevated level of our population and many other developed countries in world. Recognition of hypercholesterolemia as a risk factor had lead to the development of drugs that reduce cholesterol level. These drugs have been used in well controlled studies of patients with high cholesterol level caused primarily by elevated of low density lipoproteins and these trials indicates CHD mortality reduced by as much as 30% to 40% and the nonfatal events are reduced when patients are treated with moderate dose of hypolipidemic drugs. Hypercholesterolemia is the presence of high level of cholesterol in the blood. It is the form of hyperlipidemia and hyperlipoprotenemia. Cholesterol is a sterol, a sort of fat. It is one of three major classes of lipids which all animal cells utilize to construct their membranes and is thus manufactured by all animal cells. Plant cells do not manufacture cholesterol. it is also precursor of the all steroid hormones, bile acid and vitamin D. cholesterol circulate in the blood stream. It is an essential molecule for the human body. Cholesterol is a molecule from which hormone and steroids are made. it is also used to maintain nerve cells between 75% and 80% of the cholesterol that circulate in a person blood stream is made in that precursor liver. cholesterol is found in animal source of blood. It is not found in animal. Normal blood cholesterol level is a number derived by laboratory analysis. A normal or desirable cholesterol level is defined as less than 200mg of cholesterol per deciliter of blood. Blood cholesterol is considered to be border line when it in the range of 200 to 239mg/dl. Elevated cholesterol is level is 240mg/dl or above. Elevated level cholesterol is considered to be hypercholesterolemia. Since cholesterol is insoluble in water, is transported in the blood plasma within protein particles (lipoprotein). Lipoprotein are classified by their density very low density lipoprotein (VLDL), Intermediate density lipoprotein (IDL), Low density lipoprotein (LDL), High density lipoprotein. All the lipoprotein carry cholesterol, but elevated level of lipoprotein other than HDL(termed non HDL cholesterol), particularly LDL-cholesterol are associated with an increased risk of atherosclerosis and coronary heart disease. In contrast higher levels of HDL cholesterol are protective. Elevated level of non HDL cholesterol and LDL in the blood may be a consequence of diet, obesity inherited (genetic) disease or the presence of other disease such a diabetes under active thyroid. Reducing dietary for recommended to reduce total blood cholesterol and HDL in adults.

In people with very high cholesterol diet is often insufficient to achieve the desired lowering of HDL and lipid lowering medications or absorption are usually required. If necessary other treatment, including LDL apheresis or even surgery are performed. Hypertriglyceridemia, if severe(>1000mg/dl) requires therapy to prevent pancreatitis. Moderately elevated triglycerides level(150 to 400mg/dl) also are concern because they often occur as part of a syndrome distinguished by insulin resistance, obesity, hypertension and substantially increased CHD risk. The atherogenic dyslipidemia in patients with this insulin resistance or metabolic syndrome is characterized by moderately elevated triglycerides, low HDL-C levels and lipid depleted LDL. Metabolic syndrome is common in CHD patients, hence identification of moderate hypertriglyceridemia in a patient, even if the total cholesterol level is normal should trigger an evaluation to identify to disorder. Hyperlipidemia and reduce HDL-C level occur as a consequence of several factors that effects the concentration of various plasma lipoproteins.[1] The study reveals the prevalence of hypercholesterolemia, hypertriglyceridemia and abnormally high LDL-C and low HDL-C levels which are well-known risk factors for cardiovascular diseases in all age groups increased prevalence of dyslipidemia in

young adults was found to be one of the major contributors of CVD.[2] The high prevalence of hypercholesterolemia, hypertriglyceridemia and low HDL, in our 31-40 years age group is a major cause of concern. It has been observed that in comparison with western population, a relatively lower level of cholesterol appears to predispose Indians to CAD. Also in a Chennai based hospital study, it was shown that around 75% of patients with myocardial infarction (MI) had TC levels <200mg/dl indicating that the threshold for the TC levels above which it posses a risk for CAD is low in Indians. The crude prevalence of hypertriglyceridemia differs between the age groups and it was higher in men than in women. The contributing factor for hypertriglyceridemia in our population could be our diet rich in carbohydrates. High TG levels have been associated with increased levels of small dense LDL which are considered to be highly atherogenic Low HDL-C levels are stronger predictor of occurrence and reoccurrence of MI and stroke and are also associated with premature and severe CAD. Oxidative modification of LDL-C is a key process of atherosclerosis and elevated LDL-C has been recognized as primary risk factor for CAD by NCEP – ATP. Increased LDL-C has been found to be contributing majorly to dyslipidemia irrespective of age and gender. On comparing the prevalence of dyslipidemia and impaired blood glucose (IBG) levels between males and females, it to be higher in males suggesting this group at higher risk of dyslipidemia, which in turn can lead to increased risk of developing CAD.[3]

Scope and Objectives

To reveals the prevalence of hypercholesterolemia in our population and to get information regarding the treatment and management of hypercholesterolemia. Cardiovascular disease (CVD) is the leading cause of death in India, accounting for 28% of mortality. Deaths from CVD have increased from 2,266,000 in 1990 to 2,669,100 in 2004, which is a 17.8% increase in less than two decades. Prevalence of CVD in the urban Indian population is between 6.5 to 13.2% and in the rural population between 1.6 to 7.4%. The prevalence in the rural areas is growing rapidly possibly due to changing life styles. Special efforts are required to identify individuals with hypercholesterolemia in india, as they are at high risk of CHD. The condition is seriously under diagnosed and the diagnosis is often made too late, restricting the benefits of the treatment available. Combination life style therapies, enhanced physical activity and dietary modification and therapeutic intervention would help in treatment and management of hypercholesterolemia.[4]

Hypercholesterolemia

Hypercholesterolemia is the major cause of atherosclerosis and atherosclerosis associated condition such as coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease. This study covers the normal metabolism of lipoproteins, pathophysiology of hypercholesterolemia, and drug used to treat hypercholesterolemia. Drugs covered includes HMG-COA reductase inhibitors-the statins –which are the most effective and best tolerated drugs currently in use, bile acid binding resins, nicotinic acid and fibric acid derivatives. The study includes a brief discussion of potential new classes of drugs that are undergoing clinical and preclinical evaluation.[5]

Epidemiological Studies

Despite a continuing delain in the incidence of atherosclerosis related death the part 35 years, deaths from CHD, cerebrovascular disease and peripheral vascular disease accounted for 30% of the 2.3 million death in the united states during 1997. Two –thirds of atherosclerosis deaths were due to CHD. About 85% of CHD deaths occurred in individuals over 65 years of age. Among the 15% dying prematurely, 80% died during their first CHD events. Among those dying of sudden cardiac death in 1997, 50% of the men and the 63% of women had been previously asymptomatic. This statistics illustrate the important of identifying and managing risk factor for CHD. The major known risk factors are elevated LDL-C, reduced HDL-C, cigarette smoking, hypertension, type 2 diabetes mellitus, advancing age family history premature (men<55;women<65 years) CHD events in a first degree relative. Control of the modifiable risk factor account for 85% of excess risk for premature CHD. Further more, these studies indicate that when total cholesterol levels are below 160mg/dl, CHD risk is markedly attenuated, even in the presence of additional risk factor. This pivotal role of hypercholesterolemia in atherogenesis give rise to the almost universally accepted cholesterol diet CHD hypothesis. The cholesterol diet-CHD hypothesis state that elevated plasma level cause CHD, that diet rich in saturated fat (animal fat) and cholesterol raise cholesterol level, and that the lowering of cholesterol level reduce CHD risk. Although the relationship between cholesterol, diet, CHD was recognized nearly 50 years ago, proof that cholesterol lowering was safe and prevented CHD death required extensive epidemiological studies and preclinical trials. Cardiovascular disease (CVD) is the leading cause of death in India, accounting for 28% of mortality. The average age of onset of CVD is younger (below 55 years) among Indians than in other populations. This may be due to bad lifestyle, genetic factors, or both. Hypertension, smoking, diabetes, and physical inactivity have been identified as modifiable risk factors for heart disease. Hypercholesterolemia is the most common and treatable cause of heart disease. Genetic factors that lead to hypercholesterolemia have not been fully studied in India. Familial Hypercholesterolemia results from mutations in the LDL receptor, ApoB, PCSK9, and ApoE genes. There is an urgent need to screen subjects with premature CAD and their relatives in India for the presence of FH, identify the mutations that lead to high cholesterol, and carry out cascade screening in the at-risk relatives. Those harbouring mutations in the above genes

can be treated to lower the cholesterol levels, prevent early CVD, and avoid death.[6]

Causes

Primary cause

- Environmental factors: obesity and dietary choice.
- Genetic factors: due to the additive effects of multiple gene.

Secondary cause

- Diabetes mellitus and metabolic syndrome.
- Kidney disease(nephritic syndrome)
- Hypothyroidism
- Cushing syndrome
- Anorexia nervosa
- Sleep deprivation
- Zieves syndrome
- Family history
- Antiretroviral drugs, like protease inhibitors and nucleoside reverse transcriptase inhibitors.
- Physical activity

Risk factors

- Being overweight or obese
- Eating a diet high in saturated fat and trans fatty acid
- Not getting enough exercise
- Family history of heart disease
- High blood pressure
- Smoking
- Diabetes[7]

Pathophysiology

Hypercholesterolemia is a disorder absent or grossly malfunctioning low density lipoprotein (LDL) receptors. The LDL receptor gene is located on the short arm of chromosome 19, and the protein is composed of 860 amino acid. It is the primary determinant of hepatic LDL uptake, which normally processes approximately 70% of circulating LDL. Two ligands on LDL bind to the receptors, apolipoproteinB-100(apo-B-100) and apo E. The LDL receptors also binds another ligand, apo-E, and is therefore, more accurately termed the B,E receptors. Apo-E is found on most lipoproteins other than LDL, including very low density lipoprotein and chylomicrons and their remants, intermediate density lipoprotein (IDL), and a subclass of high density lipoprotein (HDL). The LDL receptors binds apo-E with higher affinity than apo-B-100, and some mutation in the receptors may spare uptake of LDL by allowing binding to apoE.[8]

Signs and Symptoms

Homozygous familial hypercholesterolemia

Signs and symptoms of homozygous familial hypercholesterolemia in children include the following:

- Symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis.
- Articular symptoms such as tendonitis or arthralgias.
- Unusual skin lesion, such as cutaneous xanthomas at birth or by early childhood.
- Corneal arcus may be present and is some times circumferential.
- Murmur of aortic stenosis may be present.

Most patients with homozygous familial hypercholesterolemia do not survive adulthood beyond age 30 years unless treated with unusual methods, such as liver transplantation, LDL apheresis or lower their LDLc levels.

Heterozygous familial hypercholesterolemia

Children with heterozygous familial hypercholesterolemia do not have symptoms related to CHD, and most do not develop tendons xanthomas or corneal arcus. However, one parent will have severe hypercholesterolemia and will also probably have either a personal or family history for premature CAD.

Sign and symptoms of heterozygous familial hypercholesterolemia in adults include the following:

- Long standing history of severe hypercholesterolemia dating back to child hood.
- If no previous acute coronary events, symptoms consistent with IHD, especially in the presence of other cardiovascular risk factors.
- Past or present symptoms of recurrent Achilles tendonitis or arthritic complaints.
- If heterozygous hypercholesterolemia is left untreated, tendon xanthomas will occur by third decade of life in more than 60% of patients.[9]

Diagnosis

- Dysbetahypercholesterolemia (type 3 hypercholesterolemia)
- Familial ligand defective apoB-100, familial defective apoB-100.
- Homozygous autosomal recessive hypercholesterolemia.
- Sitosterolemia.

Laboratory Studies

- The diagnosis of both homozygous and heterozygous hypercholesterolemia is based primarily on the finding of severe LDLc elevations in the absence of secondary causes of hypercholesterolemia with triglycerides levels that are within the reference range or mildly elevated and HDL cholesterol levels that are within the reference range or slightly low. A probable diagnosis of heterozygous hypercholesterolemia can be made if the LDLc level is greater than 330mg/dl or if tendon xanthomas are present in a patients with an LDLc level above the 95th percentile. Definitive diagnosis can be made only with gene or receptor analysis.
- Substantial increase in serum triglyceride levels should raise the possibility of another lipid disorder.

Lipid Analysis

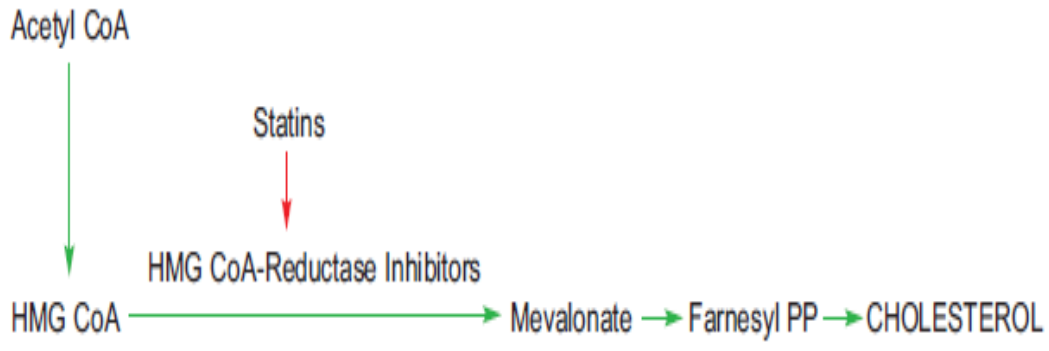
- Cholesterol levels are severely elevated in children and adults with homozygous hypercholesterolemia, with total cholesterol and LDLc levels greater than 600mg/dl and triglyceride levels within the reference range.
- In patients with heterozygous hypercholesterolemia, LDLc levels are commonly higher than 250mg/dl and usually increase with age. An LDLc level higher than 200mg/dl in a patient younger than 20 years is highly suggestive of heterozygous hypercholesterolemia possibly, ligand defective apoB-100. In adults, LDLc levels higher than 290-300mg/dl suggest heterozygous hypercholesterolemia.
- Lipoprotein (a) may be measured because patients with both heterozygous hypercholesterolemia and high levels of lipoprotein (a)(>30mg/dl) have a worse prognosis than those with normal levels of lipoprotein(a). however all patients with hypercholesterolemia are at very high risk for CAD and because no data are available to suggest that lipoprotein (a) should be specifically targeted for treatment.

Test To Rule Out Secondary Hypercholesterolemia

- Other laboratory testing may be suggestive of a findings discerned through history and physical examination.
- In the absence of symptoms or signs suggestive of a particular disorder, a limited work up should be performed to rule out secondary hypercholesterolemia.
- Basic tests to rule out diabetes, hypothyroidism hepatic disease, and renal disease are usually sufficient.[10]

HMG-CoA Reductase Inhibitors

Mechanism of action



Adverse effects

- Head ache Bowel upset
- Vomiting Myopathy
- Hepatotoxicity Nausea

Management

Classification

1. HMG-COA Reductase inhibitors [statin]

Lovastatin
Simvastatin
Pravastatin
Atorvastatin
Rosavastatin
Fluvastatin

2. Bile acid sequestrants[resins]

Cholestryamine
Colestipole
Colesevalam

3. Activate lipoprotein lipase[fibric acid derivatives]

Clofibrate
Gemfibrozil
Benzafibrate
Fenofibrate

4. Inhibit lipolysis and triglyceride synthesis[nicotinic acid derivatives]

Niacin

5. Cholesterol absorption inhibitor

Ezetimibe

6. New lipid lowering agent

MTP inhibitors: Lomitapide
ACAT inhibitors: Avasimibe
CETP inhibitors: Torcetrapibe, Dalcetrapib, Anacetrapib, Evacetrapib

Bile Acid Sequestrants

Mechanism of action

Related to first generation resins but improve patient tolerance. Sequester bile acids and prevent reabsorption. Reduce LDL cholesterol while HDL cholesterol and triglycerides may increase or unchanged.

Adverse effect
- Constipation
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Weight loss

Inhibit Lipolysis and Triglyceride Synthesis[Nicotinic Acid Derivatives]
Mechanism of action
The mechanism involve partial inhibition of release of free fatty acids from adipose tissue and increased lipoprotein lipase tissue and activity which may increase the rate of chylomicron triglycerides removal from plasma.

Adverse effect
- GI upset(nausea, dyspepsia, diarrohea)
- Skin rashes
- Hyperpigmentation
- Sweating
- Hepatotoxicity
- Tachycardia

Activate Lipoprotein Lipase [Fibric Acid Derivatives]
Mechanism of action
Activate lipoprotein lipase is responsible for VLDL cholesterol catabolism with subsequent loss of triglycerides and increase in HDL cholesterol. Protects against atherosclerosis.

Adverse effect
- Abdominal pain
- Constipation
- Diarrhea
- Nausea
- Head ache
- Gall stones
- Epigastric distress
- Myopathy

Cholesterol Absorption Inhibitors
Mechanism of action
Inhibit absorption of cholesterol from diet and bile. Reduce LDL cholesterol, increase HDL cholesterol, no effect on triglycerides. Mechanism similar to plant sterols found in lipid lowering spreads but more potent.

Adverse effects
- Diarrhea
- Cough
- Myalgia
- Fatigue
- Influenza[11]

Newer Drugs Therapy of Hyperlipidemia
MTP Inhibitors
MTP plays a key role in the assembly and release of apoB containing lipoprotein, including LDLc, and inhibition of this protein significantly lowers associated plasma lipid levels. MTP is an intracellular lipid transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Normal concentration and function of MTP in the liver and intestine are necessary for the proper assembly and secrection of apoB containing lipoproteins including very low density lipoprotein from the liver and chylomicrones from the intestine. Inhibition of MTP activity has been shown to prevent both hepatic VLDLc and intestinal chylomicrones secrection, and consequently lowers plasma lipids. Thus, it was initially considered likely that compounds that inhibit MTP should have the ability to profoundly reduce serum levels of both cholesterol and triglycerides. Both invitro and invivo animal studies with MTP inhibitors support the concept that inhibition of MTP results in decreased secrection of apoB containing lipoproteins and consequent reduction of plasma cholesterol level.[15]

Lomitapide
Lomitapide inhibits lipid transfer by directly binding to MTP in the liver and intestine. In vitro experiments using uni lamellar vesicles, lomitapide inhibited rat, hamster and human MTP with an inhibitory concentration 50% of 5 to 7nM. Kinetics studies performed as part of the phase-2 lomitapide study in subjects with HoFH confirmed that the mechanism of the reductions seen in LDLc was associated with a reduction in apoB output, thus providing supportive evidence for the mechanism of action in humans.[16]

Mechanism of action
Lomitapide directly inhibits production of LDLc in the liver and chylomicrons formation in the intestine, it is expected to results in greater enhanced efficacy in reducing LDLc in patient with HoFH than existing therapies that require a functional LDL receptors as they target the LDL receptor pathway, or only act to address cholesterol absorption in the intestine.[17]

Clinical efficacy
- In atherosclerotic cardiovascular disease.

Lomitapide directly inhibit production of LDLc in the liver and chylomicron formation in the intestine, it is expected to result in greater enhanced efficacy in reducing LDLc in patients with HoFH with existing therapies that require a functional LDL receptor as they target the LDL receptor pathway, or only act to address cholesterol absorption in the intestine.

History
Clinical trials of lomitapide were initiated by Bristol-Myers Sqibb(BMS) in 1996. Clinical of trials phase-2 started in 2003. Clinical trials of phase-3 study of

lomitapide in December 2007. The NDA for lomitapide for the treatment of subjects with HoFH was submitted to the division of metabolism and endocrinology drug products of the FDA on February, 29, 2012. The 4-months safety update report was submitted on June 27, 2012.

Advantage

1). Combination therapy with statin.

- Co-administration of 60mg lomitapide with 40mg simvastatin increased exposure to simvastatin acid approximately 1.7-fold compared to simvastatin alone.
- Co-administration of 60mg lomitapide with 20mg atorvastatin led to a 52% and 49% increase in the AUC of atorvastatin.

Disadvantage

- Lomitapide therapy will cause GI disturbance.
- Lomitapide has bioavilability of 7%,because of high first pass metabolism.[18]

Acat Inhibitors

Acyl-coenzyme A: cholesteryl acyl transferase (ACAT) is an intracellular enzyme that catalyzes the formation of cholesteryl esters from cholesterol and long chain fatty acyl-coenzyme A. ACAT activity has been implicated in several physiological processes. First ACAT is involved in the storage of cholesteryl esters as cytoplasmic lipid droplets. The excess accumulation of cholesteryl esters droplet in cell of the arterial wall, such as macrophages and smooth muscle cells, leads to foam cell formation, a hallmark of atherosclerosis. Secondly, cholesteryl ester formation by ACAT is involved in the assembly and secrection of apolipoproteinB containing lipoprotein. Third, in the small intestine, ACAT plays a role in cholesterol absorption, as a formation of intracellular cholesteryl esters creates a free cholesterol diffusion gradient across the enterocyte membrane.[19]

Avasimibe

Avasimibe is a novel orally bioavilable ACAT inhibitors that has been proven to be highly efficacious as a hypolipidemic compound in several cholesterol fed and non cholesterol fed animal models. In vitro studies in humans macrophages demonstrated that avasimibe reduce foam cell formation not only by enhancing free cholesterol efflux, but also by inhibiting the uptake of modified LDL. The concentration depended reduction in cellular cholesteryl ester content in these cell was not accompanied by an increase in intracellular free cholesterol which is in agreement with a good safety profile for avasimibe. In the liver, avasimibe caused a significant reduction in the secrection of apoB and apoB containing lipoproteins in the plasma. Plasma cholesterol levels were reduced, mainly due to the decrease in the non-HDL cholesterol fraction. Avasimibe treatment can also contribute to increase plaque stability, as it reduce the accumulation of lipids in the arterial wall inhibitors macrophages infilteration in to the media and reduce matrix metalloproteinase expression and activity. Moreover, avasimibe and statins have been shown to have synergistic effects, and the combination therapy may not only inhibit atherosclerotic lesion progression but also increase lesion regression, independently of changes in plasma cholesterol. Finally, avasimibe especially when combined with an hydroxyl methyl glutaryl coA reductase inhibitor, may even promote lesion regression.[20]

Mechanism of action

Avasimibe reduce foam cell formation by enhancing free cholesterol efflux and by inhibiting the uptake of modified LDL.[21]

Clinical efficacy

- The ability to modify the enzymatic processes involved in promoting atherosclerotic plaque disruption and to serially monitor atherosclerotic evolution could provide novel information in the management of patient with atherosclerosis.
- The role of ACAT in the esterfication and accumulation of cholesterol in macrophages suggest that ACAT inhibitors may prevent foam cell formation and the development of fatty streaks. The antiatherosclerotic activity of the ACAT inhibitors can be regarded as indirect, as it was associated to the cholesterol lowering properties of the compound.
- Avasimibe induce cholesterol 7α-hydroxylase and increase bile acid synthesis in cultured rat hepatocytes its administration to rat does not produce and increase of bile in lithogenecity index. Avasimibe may posses direct anti atherosclerotic activity in addition in cholesterol lowering effect. Avasimibe treatment may also contribute to increase plaque stability and prevent the progress of atherosclerosis.
- Avasimibe and statin have shown to synergetic effect and combination not only inhibit atherosclerotic lesion progression. But also induce lesion regression.
- Statin plus avasimibe on atherosclerotic regression and plaque stability as measured by matrix metalloproteinase 1&3 levels.
- The combination of atorvastatin and avasimibe induced a significant regression of the previously established atherosclerotic lesion.
- Atorvastatin alone induced a non significant reduction in the percent staining MMP-1 in atherosclerotic lesion, but the combination treatment with avasimibe led to a significant reduction versus controls.
- The addition of avasimibe to atorvastatin has beneficial effects on both atherosclerotic plaque regression and stabilization.[18]

History

- Avasimibe is a selective ACAT inhibitory lipid regulating agent and development by Pfizer for the potential treatment of hyperlipidemia and

atherosclerosis. The compound currently undergoing phase III clinical trials.

- Avasimibe is an ACAT inhibitor that could receive approval in 2004.[22]

Cetp Inhibitors

Humans and rabbit plasma contain a cholesteryl ester transfer protein(CETP) that promote net mass transfer of cholesteryl esters from high density lipoprotein to other plasma lipoprotein fraction. As predicted, inhibition of CETP in both humans and rabbit increase the concentration of cholesterolin the potentially protective HDL fractions, while decreasing it in potentially pro-atherogenic non HDL fraction. The use of the CETP inhibitors, torcetrapibe, in humans did not reduce atheroma in three imaging trials and caused an excess of deaths and cardiovascular events in a larger clinical out come trials.[23]

Torcetrapib

Torcetrapibe acts by increasing the affinity of CETP for HDLs. This generates a light complex that reduce the amount of CETP available to promote transfer of cholesteryl esters and triglycerides between different lipoprotein particles. In patients taking effective dose of atorvastatin to reduce the level of LDL-c to below 100mg/dL, treatment with tocetrapibe at daily dose of 60mg increased the concentration of HDL cholesterol and apoA-1 by 70% and 25% respectively, and decreased levels of LDL cholesterol and apoB, respectively, 25% and 12.5%.

Mechanism of action

Thus, inhibit CETP in humans affects the concentration and composition of all lipoprotein fractions in ways that are potentially anti-atherogenic. The increased concentration of HDLs that occurs with CETP inhibition promote the efflux of cholesterol from macrophages in the artery wall. Also include an ability to inhibit oxidation of LDLs, as well as the inhibition of vascular inflammation and thrombosis.[24]

Clinical efficacy

❖ **Atherosclerosis**

- **Relationship between CETP activity and atherosclerosis in animals.**

CETP exists in the plasma of a small number of species, including humans and rabbits but not rodents. Mice lack CETP and are resistant to the development of atherosclerosis. In contrast to mice, rabbits have a high levels of CETP activity and are extremely susceptible to the development of diet induced atherosclerosis. Further more inhibiting CETP in rabbits by the use of antisense oligo deoxy nucleotides, an anti-CETP vaccine or by administration of small molecule CETP inhibitors markedly reduce their susceptibility to atherosclerosis.

- **CETP and atherosclerosis in humans**

Inhibiting CETP in humans will be anti-atherosclerosis and thus reduce the risk of having an atherogenic cardiovascular events. CETP include an ability to inhibit oxidation of LDLs, as well as the inhibition of vascular inflammation and thrombosis. HDLs also enhance endothelial function, promote both endothelial repairs and angiogenesis and improve diabetic control.

- **Effects of torcetrapibe on diabetic control**

Evidence of a significant improvement in diabetic control in patients with diabetes. Torcetrapibe also lowered both glucose and insulin levels in the participants without diabetes although the effects were not as great as in those with diabetes.

History

Clinical development of torcetrapibe phase-1 starts on 2004 and torcetrapibe is suspented in phase-3 trials. On 2006 by drug safety monitoring board (DSMB) due to its high mortality rate. Increased mortality rate of torcetrapib is due to hyperaldosteronism, responsible for the electrolyte difference and the blood pressure elevation.

Advantage

Treatment with torcetrapibe at a dose of 60mg per day increased concentration of HDL cholesterol by approximately 60% in all three of these imaging trials. In addition the HDL cholesterol levels was reduced by approximately 20% over.

Disadvantage

1). Increased rate of mortality receiving the combination [torcetrapibe/atorvastatin]. Than those receiving atorvastatin alone.

2). Increased levels of aldosterone a hormones that can increase BP.

Dalcetrapib

Mechanism of action

Inhibit enzyme CETP that involved in transforming particles of good cholesterol in to bad cholesterol.

History

Clinical development of dalcetrapib phase-III starts on January 2008. But atlast DSMB has stoped the phase-III trials of dalcetrapib due to lack of clinically meaningful efficacy.

Anacetrapib

Mechanism of action

Inhibit enzyme CETP that involved in transforming particles of good cholesterol in to bad cholesterol.

Clinical efficacy

Anacetrapib given at a daily dose of 100mg reduce the risk of a composite endpoint (coronary death, myocardial infraction or coronary revascularization) in patients with circulatory problems who have their LDL cholesterol optimally treated with a statin.

History
Clinical development of anacetrapib phse-III announced on December. 2007. The first study program began in April 2008 and was designed to evaluate the long term safety and efficacy of anacetrapib in patients with CHD and is planned to complete in January 2017.

Advantage
1). No increase effects in blood pressure, aldosterone or serum electrolytes in human and does not stimulate the synthesis of aldosterine.
2). Increase HDL and lowers LDL.

Evacetrapib
Mechanism of action
Inhibit enzyme CETP that involved in transforming particles of good cholesterol in to bed cholesterol.

Clinical efficacy
- Cardiovascular disease
- ❖ Evacetrapib given either as monotherapy or in combination with statin.
- ❖ Increase HDL cholesterol and decrease LDL cholesterol more effectively than that with statin monotherapy.

History
Entered clinical development on October 2008, phase-III studies starts on October 2012 and is planned to complete in January 2016.

Advantage
1). Evacetrapib was given either as monotherapy or in combination with statin.
2). Increase HDL and lowers LDL.

CONCLUSION
Hypercholesterolemia is a condition with increased level of cholesterol in the body. The cholesterol are two types, high density and low density classes. Hypercholesterolemia is one of the common risk for many heart disease. Treatment involves using drugs such as HMG-COA reductase inhibitors, Bile acids sequestarants, Activate lipoprotein lipase, Inhibit lipolysis and triglyceride synthesis, cholesterol absorption inhibitors, and newer drugs etc. New drug play an important role in the treatment. New direction for therapy include the using MTP inhibitors, ACAT inhibitors, and CETP inhibitors to the key player in hypercholesterolemia. To minimize the side effects of the older drugs, the newer drugs are invented.

REFERENCE

1. Biggerstaff KD, Wooten JS. "Understanding lipoproteins as transporters of cholesterol and other lipids". Adv physiol Educ., 2003; 28(1-4): 105-106.
2. Reddy KS, Prabhakaran D, Chaturvedi V, Jeemon P, Thankappan KR, Ramakrishnan L, Mohan BVM, Pandav CS, Ahmed FU, Meera R, Joshi PP, Amin RB, Ahuja RC, Das MS, and Jaison TM. Methods for establishing a surveillance system for cardiovascular disease in Indian industrial populations. *Bulletin of the World Health Organization*, 2006; 84: 461-69.
3. Enas EA, Senthilkumar A, Chennikkara H, and Bjurlin MA. Prudent Diet and Preventive nutrition from Pediatrics to Geriatrics: Current Knowledge and Practical recommendations. *Indian Heart J.*, 2003; 55: 310-38.
4. S. Yusuf, S. Reddy, S. Ôunpuu, and S. Anand, "Global burden of cardiovascular diseases. Part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization," Circulation, 2001; 104(22): 2746–2753.
5. Goodman, Gilmans. The pharmacological basis of therapeutics, 10th ed. New York. Mc Graw Hill: 2001, chapter 36; drug therapy for hypercholesterolemia: pg 977-995.
6. R. Gupta, P. Joshi, V. Mohan, K. S. Reddy, and S. Yusuf, "Epidemiology and causation of coronary heart disease and stroke in India," Heart, 2008; 94(1): 16–26.
7. http:// www. Umm. ed/altmed/ articles/ hypercholesterolemia-000084.htm.
8. Bjokhem I, Boberg KM. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Scriver CR, Beceudet AL Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. 8th ed. New York, NY: Mc Graw-Hill, 2001: 2073-2099.
9. Garcia CK, Wiland K, Arca M, Zaliani G, Fellin R, Maioli M, et. Autosomal recessive hypercholesterolemia caused by mutations in putative LDL receptor adapter protein science, May 18 2001; 292(5520): 13494-8.
10. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. 8th ed. New York, NY: Mc Graw-Hill, 2001; 2863-2913.
11. Tripathy KD. The essential of medical pharmacology. 6th ed New delhi: Jaypee Brothers Medical publication (p) LTD, 2006 chap 45, hypolipidemic Drugs and Plasma Expanders.pg. 612-524.
12. Sibley C, Stone NJ. Familial hypercholesterolemia challenge of diagnosis and therapy. Vleve Clin J med., Jan. 2006; 73(1): 57-54.
13. Marks D, thorogood M, Neil HA, Hampheries SE.A review on the diagnosis, natural history, and treatment of familial hypercholesterolemia. Atherosclerosis, May 2003; 168(1): 1-4.
14. Witzum JL. Drugs used in the treatment of hypercholesterolemia In: Hardman JG, limpard LE, et al, eds. Goodman and Gilmans The pharmacology basis of therapeutics. 9th ed. New York, NY-Hill, 1996: 875-897.
15. Hussain, M. M, J Shi, et al. Microsomal triglyceride transfer protein and its role in apo B-lipoprotein

assembly. "Journal of lipid research, 2003; 44(1): 22-32.
16. Wetterau,J. R,R. E.Gregg, et al. An MTP inhibitor that normalizes atherogenic lipoprotein levels in WHHL rabbits. Science, 1998; 282(5389): 751-754.
17. Liao, W, TY, Hai et al." Blocking microsomal triglyceride transfer protein interfere with apo B secretion without causing retension or stress in the ER. "Journal of lipid research, 2003; 44(5): 978-985.
18. Cuchel, M. L. T. Bloedon, et al. "Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia" The new England journal of medicine, 2007; 356(2): 148-156.
19. Bahman KF, Accud M, Farese RV Jr. Mammalian acyl co-enzyme A:cholesterol acyl transferases. Biochhim Biophys Acta., 2000; 1529: 142-154.
20. Burnett JR, Wilcox LJ, Haff MW. Acyl co-enzyme A; cholesterol acyl transferase inhibition and hepatic apo lipoprotein B secretion. Clin Chim Acta., 1999; 286: 231-242.
21. Bocan TM, Krause BR, Rosebary WS, et al. The ACAT inhibitor, avasimibe reduce macrophages and matrix metalloproteinase expression in atherosclerosis lesion regression of hypercholesterolemic rabbits. Arterioscler Thromb Vasc Biol., 2000; 20: 70-79.
22. Delsing DJ, Offerman EH, Van Duyven-voorde W et al. acyl co-enzyme A: cholesterol acyl transferase inhibitor avasimibe reduce atherosclerosis in addition to its cholesterol-lowering effects in Apo E 3-leiden mice. circulation, 2001; 103: 1778-1786.
23. Swenson TL, R.W. Brocia and A.R. Tall. plasma cholesteryl ester transfer protein has binding sites for neutral lipid and phospholipids. J Biol Chem., 263: 5150-5157.
24. Tall A.R. Plasma cholesteryl ester transfer protein. J Lipid Res., 1993; 34: 1255-1274.