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PCSK9 INHIBITORS: TO SOLVE OUT MANY CVS PROBLEMS

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ABSTRACT

Cardiovascular diseases are mostly due to unhealthy cholesterol rich diet. This becomes one of the most important cause of premature deaths. Cholesterol rich diet results in accumulation of this inside our body. There are HDL and LDL lipoproteins in body in which HDL is good cholesterol and the other is bad. So it is essential to lower the undesirable LDL. From the 1980s the most effective medicament prescribed for treating this dyslipidemic condition were statins. These drugs were most common and effective in lowering the LDL level. Worldwide, physicians still prefer statins as it has a very good and effective role in decreasing the LDL level. However it has some side effects like muscle pain, liver damage, increase in blood glucose level, muscle damage leading to rhabdomylosis, even various neurocognitive side effects etc. Recently a new therapy, PCSK9 inhibitors is brought out which is more efficient in the cholesterol lowering . Considering its safety profile which is more efficient than statins, can treat many cardiovascular patients efficiently.

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INTRODUCTION

Abmormalities of plasma lipids can result in predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease. Cholesterol, triglycerides and phospholipids are transported in the blood stream as complexes of lipids and proteins known as lipoproteins. Elevated total and LDL cholesterol and reduced HDL cholesterol are associated with the development of coronary heart disease.

The response to injury hypothesis states that risk factor such as oxidised LDL, mechanical injury to the endothelium, excessive homocysteine, immunological attack induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. The eventual clinical outcomes include angina, myocardial infarction, arrhythmia, stroke, peripheral arterial disease, abdominal aortic aneurysm and sudden death.

Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of sub othelial space. Once the artery wall, LDL is chemically modified through oxidation and non enzymatic glycation. Midly oxidised LDL then recruits monocytes into the artery wall. These monocytes then become transformed into macrophages that accelerates LDL oxidation.

Oxidised LDL provokes an inflammatory response mediated by a number of chemo attractants and cytokines. Repeated injury and repair within an atherosclerotic plaque eventually lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T-lymphocytes Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis.

The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or rarely a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to the lack of LDL degradation by the cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL being inversely proportional to the deficit in LDL-Rs.

After the discovery of PCSK9 inhibitors during 2003, a new therapy which were most efficient in clearing the LDL level was introduced into the pharmacy sector PCSK9 boned therapy played a vital role in care of treating familial hypercholesterolemia along with reducing the LDL level in the blood. In this article our aim is to emphasize the utility and efficacy of pcsk9 inhibitors and to provide sufficient information about pcsk9 inhibitors.

PCSK9:

PCSK9 is just proprotein convertase subtilisin/kexin type 9 since 2003, belongs to proprotein convertase family of proteins that activate other proteins. PCSK9 is a secretory serine proteinase. PCSK9, found at chromosomeIP32, is 32kb in length , with 12 exons that encode a 692 amino acid protein [1,2], in the 9th member of PCSK family, the first eight, are serine proteins whose major part is processing of precursor proteins to generate functional and bioactive polypeptide peptides and hormones, which has a vial role in regulation of growth and metabolism [1,5,6,7].

The synthesis of PCSK9 is upregulated in transcriptional level by the action of SREBP-2. SREBP2 is sterol regulatory element biniding protein-2. SREBP-2 action is more in very low levels of intracellular cholesterol in the hepatocytes and its main role is to promote the transcription of LDL-R and PCSK9[1,13].

The PCSK protein product is comprised of N-terminal signal peptide, prodomain, catalytic domain, hinge region and cysteine rich c-terminal domain [1,4,8]. Following the removal of signal peptide domain, PCSK9 is synthesised as a ~74kDa zymogen, which undergoes autocatalytic cleavage in the endoplasmic reticulum and golgi bodies, to generate prodomain fragment and ~ 6ekDa nature protein, which remain strongly associated to one another [1,9;10,11].

PCSK9 is mainly produce by hepatocytes and after its production, i.e., after an auto-processing cleavage reaction, it is secreted in the plasma where it binds with LDL-R.

Normally LDL receptor outside the hepatocytes will bind with LDL and form a complex which further comes into the cell and the LDL-C is degraded by lysosome and the LDL receptor is recycled and the number of LDL-R is not reduced. Hence the plasma cholesterol clearance increases. But when this PCSK9 attaches with LDL receptor carrying LDL, results in complete destruction of both, by lysosomes. This results in reduction in the recycling of LDL-R and the receptor are reduced in the surface of hepatocytes. Reduction in clearance of cholesterol from the blood, which leads to many cvs diseases.

PCSK9 – inhibitors:

Proprotein convertase subtilisin/kexin typer9 binds to the LDL receptors and the complex LDL receptor PCSK9 is degraded in the lysosomes. Therefore increased plasma concentration of PCSK9 results in the low levels of LDL-R at the cell surface and increase at the cell surface and increase cholesterol. This is what usually happens. When monoclonal antibody of PCSK9 inhibitors are administered, the antiAb will inhibit the attachment of PCSK9 with the LDL-R. So there cannot be any degradation of LDL-R. So the normal clearance of LDL from the blood occurs.

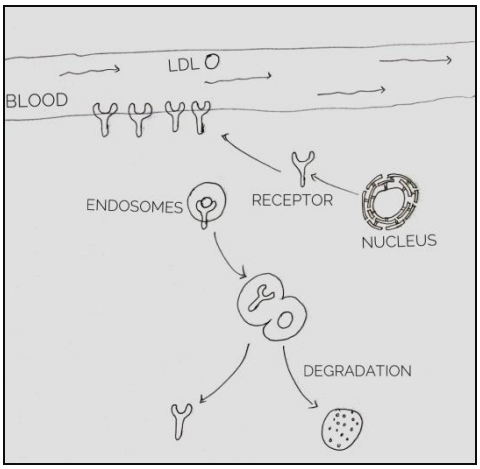

Fig 1: Usually happens when LDL is more.

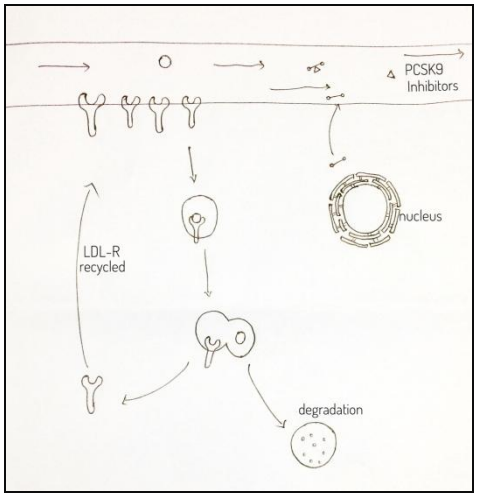

Fig 2: This happens in the presence of PCSK9.

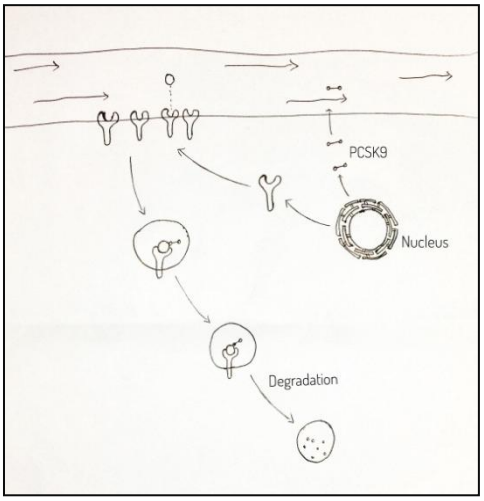

Fig 3: In the presence of PCSK9 inhibitors.

PCSK9 INHIBITORS V/S STATINS:

After the discovery of first statin in the year 1987 it became the most promising medicament that reduced lipid level in different cardiovascular diseases. As its long term use led to statin intolerance in some patients, which were primarily due to muscle symptoms and also liver damage.

Recently after the discovery of PCSK-9 inhibitors which became a fantastic drug to lower the LDL-C level. American college of cardiology recommends that, PCSK9 inhibitors usage only when:

1. Considered high risk for CVS problems and when cholesterol is not controlled with statins or other cholesterol lowering agents.
2. When genetic condition such as hypercholesterolemia, which involves extremely high cholesterol levels.

Clinical high reveals that PCSK9 inhibitors are powerful in reducing LDL-C levels. But there are some side effects and risks arising during clinical trials. Some of the side effects are neurocognitive issue and injection site swelling. Many more advantages resides to PCSK 9 inhibitors while the only thing which makes it undesirable is only its cost. Recent pharmacoeconomic analysis by the US institute for clinical and economic review, calculated the overall price, best representing the potential benefits to patients, would be between $3615 and $4811 a 67% discount on the current list price .

There are two PCSK9 inhibitors currently approved by USFDA. Alirocumab and Evolocumab. They are injected under the skin every 2-4 weeks. Its not available as tablets. It is the most costly drug when compared to the other antihyperlipidemics which limits its use in developing countries .

CONCLUSION

Cardiovascular disease, mainly dyslipidemia related cases are most commonly treated with statins. Recently a group of new drugs, PCSK9 inhibitors were brought out to the public. Considering its safety profile which is more efficient than statins, can treat many cardiovascular patients efficiently. But its high cost tends to lower its usage in common men. After few years PCSK9 inhibitors would be seen in the market and would be the modern physicians choice.

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