NEW HORIZONS

New Horizons in Management of Dyslipidemia

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The coronary artery disease (CAD) is the leading cause of death worldwide and dyslipidemia has emerged as the major risk factor for CAD. In the 1980s, clinical trial evidence first established the protective effect of pharmacological cholesterol reduction on coronary morbidity. The Lipid Research Clinic study showed that bile acid binding resins could lower cholesterol levels in individuals with high baseline levels, and a decrease in coronary morbidity accompanied the drop in the serum cholesterol levels. The current therapies to treat dyslipidemia revolve around life style modification and cholesterol lowering medication, mainly the HMG-Co reductase inhibitors (statins). Although statins have been successful in reducing the cardiovascular events in a large patient population as evidenced by primary and secondary clinical intervention studies;there still remains a large burden of residual cardiovascular risk as many patients fail to attain desirable benefits from statins or combination therapies.(1-9) Thus, there continues to be a search for additional safe and effective lipid lowering drugs to modify atherosclerotic disease and reduce cardiovascular risk. It has been estimated that global market for drugs to treat dyslipidemia will grow by an average of around 2% a year in next ten years and by which time it will be worth just over 31 billion dollars. (1,2)

The majority of new compounds are in various stages of development and in initial phases of clinical testing, with limited information about their safety and efficacy in human population. As of now, two new compounds ,,mipomersen and MTP inhibitor lomitapide have received recommendations for use in patients of homozygous familial hypercholesterolemia by the drug advisory committee of United States Food and Drug Administration (USFDA) in Oct 2012 and both drugs are currently under FDA review.

A. Potential therapies to lower serum LDL-C (2-4)

1.*Apolipoprotein B Antisense (mipomersen):* It is a second generation antisense oligonucleotide causing inhibition of Apo B 100 production resulting in decrease in apo B, LDL-C and lipoprotein (a) in humans. The drug was approved by USFDA for the treatment of familial hypercholesterolemia with the boxed warning of liver toxicity. It is available for clinical use and is administered once weekly by subcutaneous injections. It has been shown to lower LDL-c by about 25% from the baseline and side effects are raised liver enzymes and increase in liver fat.

2.*Microsomal triglyceride transfer protein (MTP) inhibitors* (1,3,4): MTP is lipid transfer protein necessary for formation of chylomicrons, VLDL and downstream remnants. Lomitapide which inhibits MTP was approved for the treatment of homozygous familial hypercholesterolemia and is available as oral formulation for clinical use .The increase in transaminases and liver fat accumulation is also seen with this compound.

3.*Proprotein convertase subtilisin/kexin type-93*, (4): Also known as PCSK9,is an enzyme that in humans is encoded by the PCSK9 gene. This gene encodes a proprotein convertase which leads to synthesis of a protein, which plays a major regulatory role in cholesterol homeostasis.PCSK9 binds to the epidermal growth factor (EGF-A),a domain of the low density lipoprotein receptor

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(LDLR) inducing LDLR degradation. LDL-c is removed from the blood when it binds to an LDLR on the surface of liver cells and is taken inside the cells.When PCSK9 binds to an LDLR,the receptor is destroyed along with LDL-c particle. But if PCSK9 doesnot bind it ,the receptor can return to the surface of the cell and remove more cholesterol.Thus reduced LDLR levels result in decrease metabolism of LDL-C, which could lead to hypercholesterolemia. Drugs can inhibit PCSK9 ,leading to lower circulating levels of cholesterol. A num ber of monoclonal antibodies that bind to PCSK9 near the catalytic domain , that interact with the LDLR and hence inhibit the function of PCSK9, are in clinical trials. These include Evolocumab, bocoizumav and alirocumab. In a study, involving 2000 patients with elevated LDL-c , presented to American College of Cardiology on march 2014, it was reported that Evolocumab lowered LDL-c by 55% to 66% as compared to placebo.Even though FDA has accepted it for review, more evidence is needed that the way these drugs lower cholesterol also lead to decrease in cardiovascular event rate.

4.*Squalene synthease inhibitors:* Squalene synthease is a enzyme localized to the membrane of endoplasmic reticulum .Catalysis by squalene synthase is the first commited step in sterol synthesis,since the squalene produced is converted exclusively into various sterols,such as cholesterol, via a complex, multistep pathway.Squalene inhibitors have been shown to decrease the cholesterol as well as plasma triglycerides levels and may provide an alternative to HMG-CoA reductase inhibitors in some statin -intolerant patients. However after some promising initial trials with squalene synthase inhibitors like TAG-475, Zoragozic acid and RPR-107393, further progress has been extremely slow.

5. *Thyroid hormone analogue*: The thyroid hormone lowers LDL-c by increasing expression of LDL receptor gene in the liver, but it cannot be used in dyslipidemia because of its undesirable effects on the heart and other tissues. Eprotirome was developed to circumvent those problems. It is selective for the beta from of the thyroid hormone receptor, which is expressed in liver tissues, over the alpha form which is expressed in the heart. However clinical trials with eprotirome in patients with heterozygous familial hypercholesterolemia, were discontinued after animal studies indicated that long term exposure could result in cartilage damage. The safety issues need to be addressed after analysis of data available from animal studies, before more clinical trials can be undertaken with this compound. The cholesterol vaccination to induce anti-LDL antibodies and hasten LDL clearance from serum and gene transfer are conceptually appealing therapies that are under study but years away from being available for use.(7)

B. Investigational Therapies for Modulating HDL-C (4,5,6,8) The patients who are treated with high doses of statins, especially for secondary CAD prevention, regardless of their resulting LDL -c level , are still at very high risk of recurrent cardiovascular events. Therefore there has been in growing interest in HDL -c directed therapies. Novel approaches are ongoing in developing and assessing the agents that closely mimic the structure of HDL-c or replicate its function for example reverse cholesterol transport, vasodilation, anti-inflammation or inhibition of platelet aggregation.

1. *Cholesterolester transfer protein (CETP) inhibitor:* This class of drugs inhibits CETP which normally transfers cholesterol from HDL-c to very low density or low density lipoprotein. Inhibition of this process results in higher HDL levels and reduced LDL levels. Clinical trials with to earlier CETP inhibitors Torcetrapib and Dalcetrapib were discontinued because of lack of clear clinical efficacy in lowering cardiovasculars event rates as compared to placebo. Two other compounds Antcetrapib and evacetrapib are presently undergoing clinical trials, the result of which will be known in 2017.

2. *ApoA-1 mimetics: Apolipoprotein A- 1 Milano (ETC-216, MDCO- 216)* is a naturally occurring mutated variant of the apolipoprotein A1 protein found in HDL-

C. In 1990s , researchers at the Cedars- Sinai medical center showed that injection of synthetic version of the mutant apoA- 1 into rabbits and mice could reverse vascular plaque build up. Currently no drug based on apoA-1 minano is available for clinical use. The progress with production and clinical trials is slow as it is a complex protein, which is very expensive to produce and also intravenous administration makes it less desirable for routine use.

3. *Liver X Receptor Agonists:* The liver x receptor is a member of the nuclear receptor family of transcription factors and is closely related to nuclear receptors such as PPAR, FXR and RXR. Liver x receptors are important regulators of cholesterol, fatty acids and glucose hemostasis. The importance of LXRs in physiological lipid and cholesterol metabolism suggests that they may influence the development of metabolic disorders, such as hyperlipidemia and atherosclerosis. The treatment with LXR agonists lowers the cholesterol level in serum and liver and inhibits the development of atherosclerosis in murine disease models. LXR agonists which are currently undergoing clinical trials are GW3965 and hypocholomide.

4. *Novel Peroxisome Proliferator-Activated Receptor Agonists (PPAR-a):* Fibrates, which are PPAR-alpha activators are well recognized for increasing HDL-c and lowering triglycerides. PPAR alpha is a nuclear receptor involved in the regulation of lipid metabolism. However, as they are only weak agonists of PPAR-a, the selective agonists are in phase of development, which are more potent then fibrates like dual PPAR-a/d agonists GFT50,which has been shown to decrease the triglycerides by 21% and increase HDL-c by 9 % as compared to placebo. (8)

Thus after the very important observation from the new guidelines released by the American College of Cardiology-American Heart Association (ACC-AHA) task force, for management of dyslipidemia, released on November 12, 2013, that the extensive review of clinical trials involving non- statin drugs (like nicotinic acid,fibrates and bile acid sequestering agents) in clinical use uptil now[such as FIELD and ACCORD], no evidence was found to support the use of these drugs, either combined with statin therapy or in statin-intolerant patients; the need for new effective therapies ,in addition to statins for management of dyslipidemia, will only gain momentum.(9)

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