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Editorial

Ezetimibe: Is it the answer to statin intolerance?

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The statin hypothesis has ruled the world of cardiology practice for nearly two decades. It states "It is not enough just to lower the Low density lipo-protein (LDL); it should be lowered with a statin*"*. For many years the patients have faced the cumbersome and painful side effects of statins, more appropriately termed as statin intolerance. Statin intolerance is defined as when a patient is unable to continue a statin because of the development of side effects (joint pains, myopathy) or evidence in blood tests revealing elevated enzyme levels (CK, creatine kinase) as a marker of liver or muscle injury. The statin intolerance can be partial (to some selected statins) or total (all statins). The most common presenting features of statin intolerance is muscle aches, pains, weakness, or cramps manifesting in 15% of the statin treated patients. Both statin induced elevation of CK levels (defined as > 10 times the upper limit of normal (ULN) and hepatic transaminases (defined as > 3 times the ULN) have been designated as predictors of statin intolerance [1] or statin induced serious adverse effects.

Overview of Cholesterol Metabolism:
Cholesterol levels are regulated by a delicate balance between intestinal cholesterol absorption and hepatic cholesterol production. Dietary cholesterol contributes less than 25% of the cholesterol entering the intestinal lumen and the rest is derived from biliary cholesterol excretion. From the intestinal lumen cholesterol mixes with bile to form biliary micelles, which are deprived of their lipid content and then transported across the enterocyte membrane by steroid influx transporters. A particular steroid transporter called Niemann-Pick C1-Like 1(NPC1L1) are found in the luminal surface of the enterocyte whose function is to absorb intestinal cholesterol. NPC1L1 is also found at the canalicular interface of the hepatocytes and thereby free cholesterol from the bile can re-enter the hepatocytes through NPC1L1. This NPCIL1 functions in close collaboration with an adaptor protein (AP2) and a Clathrin molecule.[2] The free cholesterol in the enterocyte and hepatocytes can return back through the ABCG5 and ABCG8 efflux transporters.

Options available for statin intolerance:
Many trails have been conducted to combat statin induced side effects, one of them being "Switching Therapy" in which a change in the statin therapy is advocated that is switching from mild to high lipophilic statin, from cytochrome P 450 metabolized to non-cytochrome P450 metabolised statin, or shifting to a lower dose of a more potent

statin. Other strategies include "Alternate Day Dosing" with a statin with longer half- life (Atorvastatin, Rosuvastatin)[3]. Many non-statin lipid lowering drugs like Fibrates, Bile Acid Sequestrants, Niacin, Mipomersen[4] (antisense oligonucleotide inhibiting the synthesis of Apolipoprotein B-100 administered 200mg once weekly via subcutaneous route), Lomitapide (inhibits the lipid transfer activity of Microsomal triglyceride transfer protein (MTP) thereby inhibiting the assembly of intestinal chylomicrons and hepatic VLDL resulting in reduced secretion of these lipoproteins into the circulation. Lomatapide is effective in reducing LDL C levels as a monotherapy as well as in combination with ezetimibe.[5] A new drug group called as PCSK9 inhibitors (evolocumab, alirocumab), injected subcutaneously every 2 weeks or every 4 weeks, target a protein PCSK9 , involved in the regulation of LDL receptors(LDL-R) on the hepatocytes. As interaction of PCSK9-LDLR triggers the intracellular destruction of LDL-R, lower levels of circulating PCSK9 will result in less intracellular degradation of the LDL-R and more LDL-R will be available at the cell surface to scavenge and reduce the level of circulating LDL.[6] Currently statin intolerance is an approved indication for the use of PCSK9 inhibitors.

The current position of Ezetimibe:

Patients on statin therapy (who express an up regulation of LDL-R as a consequence of decreased hepatic cholesterol production) also express an up regulation of the NPC1L1 gene and thereby increased cholesterol absorption to counteract the endogenous cholesterol deficit. Ezetimibe inhibits cholesterol absorption by preferentially blocking the binding of the NPC1L1 protein with AP2 and Clathrin, thereby augmenting a reduction in cholesterol delivery to the liver. As a compensatory mechanism to obtain more cholesterol, the liver up-regulates LDL-R, which results in clearance of LDL from the blood. Ezetimibe (10-20mg) daily was approved initially by US FDA based on the drug's consistent efficacy to reduce LDL cholesterol by 20 % and probably due to its novel mechanism of action and as well as synergistic action with statins, prompting a dose reduction of the statins thereby a way to limit statin induced side effects. Statins, Ezetimibe and certain anti- diabetic drugs reduce epicardial fat volume, however most dramatic and consistent reduction in epicardial fat volume is achieved by atorvastatin, in comparison to simvastatin, pravastatin and Ezetimibe The negative outcomes of the ACCORD trial with fenofibrate and the AIM- HIGH and HPS2 THRIVE trials with nicotinic acid gave a solid foundation to statin hypothesis; however the conditions became favourable for Ezetimibe with the results of the SANDS, VYCTOR, SHARP and SEAS trials. The IMPROVE IT trials[7] provided the greatest thrust and opened the doors for ezetimibe into the arena of antilipidemic drugs and as a potent answer to the problematic question of statin intolerance. This trial also established that the increased occurrence of cancer with ezetimibe in the SEAS trial was a chance occurrence.

Finally, the statin hypothesis was relegated to the background. Target LDL goal is to be achieved, regardless of the use of statins or non statin antilipidemic drugs. 2016 ESC lipid guidelines have endorsed ezetimibe as the first option add on drug in those patients who don't reach the targeted LDL goal with statins alone, particularly in patients with familial hyper cholesterolemia.

Probiotics and Herbal Medications as an adjunct to antilipidemic therapy:

The human microbiome project has opened the era of designing organ specific probiotics, which can be administered to susceptible individuals and thereby prevent the pathology to develop in that organ system and forms an essential part of regenerative medicine. [8] Probiotics assist in digestion and boost the body's immunity in diarrhoea and infections. There are probiotics that confer beneficial effect on the cardiovascular system, a specific strain of Lactobacillus called Lactobacillus reuteri 30242 has been found to work in two distinct ways to lower cholesterol: It removes excess cholesterol from the body and increases the metabolism of cholesterol [9] Clinical studies demonstrate that Lactobacillus reuteri effectively lowers levels of total and LDL-cholesterol, while driving down inflammation and reducing other metabolic disturbances that raise cardiovascular risks. A safe, natural probiotic, Lactobacillus reuteri is one of the first "condition-specific" probiotics, designed and developed specifically to fight risk factors that lead to heart attacks, strokes, and other cardiovascular catastrophes [10]

Herbo-mineral drug like Prabhakar vati along with lekhana basti possesses potent antianginal and cardio protective activities[11] and it can be used effectively in the management to slow down the progress of pathogenesis of atherosclerosis leading to various coronary artery diseases especially stable angina [12] Supplementation of Shilajit significantly reduces serum triglycerides level, cholesterol, LDL cholesterol and VLDL cholesterol levels and significant improvement in HDL cholesterol level [13] Commiphora mukul decreased the total cholesterol level, LDL, triglycerides and the total cholesterol and HDL cholesterol ratio [14] Curcuma longa is useful in endothelial inflammation and also helps to keep interleukins and TNF under control.

Draksharishta is useful in keeping the oxidation of LDL under control [15] the herb Gymnema sylvestre possesses cardio protective activity [16]

Conclusion:

It is imperative to have a holistic approach with non-conflicting cooperation of effective antilipidemic therapy (ezetimibe alone or in combination with statins) along with cardiovascular probiotics, herbal medications and dietary supplements with proven efficacy to target LDL cholesterol and develop effective screening tools to measure total cholesterol load on heart and its impact in causing severe coronary artery disease. Epicardial fat emerges as an effective screening tool, especially in developing countries to measure the total visceral adiposity as it is metabolically active and is in dynamic equilibrium with the total body fat reserve, traversing along the adeventia of the coronary arteries.[17]

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