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PCSK9 Inhibitors: Heralding A New Era In Dyslipidemia Management

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Dyslipidemia is a well known risk factor for cardiovascular disease. Till now statins were the sheet anchor of therapy for dyslipidemia. But there are a few patients who are intolerant to statins and some who develop cardiovascular disease in spite of maximally tolerated dose of statins. Still there are some others like those with familial hypercholesterolemia who do not achieve adequate reduction of cholesterol levels with statins alone or in combination with ezetimibe. Now we have a new group of medications - proprotein convertase subtilsin-kexin type 9 (PCSK9) inhibitors, to cater to these group of patients.

Two drugs belonging to this novel class of PCSK9 inhibitors have been approved by the United States Food and Drug Administration in the last few years: Evolocumab and Alirocumab. These are monoclonal antibodies targeting PCSK9, which is a hepatic protease involved in the internalization of LDL (Low Density Lipoprotein) cholesterol receptors into the lysozymes. Blockage of PCSK9 prevents the destruction of LDL receptors by lysozymes and hence can achieve LDL-C reduction 50-60% above that achievable by statin therapy [1].

Over the years, it has been noted that patients with genetically lower LDL have correspondingly better cardiovascular event reductions than in those who have pharmacologically lower LDL. This is possibly due to lifetime lower LDL levels. PCKS9 mutations (rs11591147 T allele) producing lower levels of LDL have been shown to have markedly lower cardiovascular event rates [2].

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial [3], evaluated 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg/dl or more who were receiving statin therapy. They were randomised to evolucumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. Median follow up period was 2.2 years and the primary efficary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. LDL cholesterol levels were reduced to a median level of 30 mg/dl. There were no significant increase in the adverse events including new onset diabetes mellitus and neurocognitive events. But injection-site site reactions were more common with evolocumab. Evolocumab reduced primary endpoint by 18% [4]. It may be noted that all these patients were on statin therapy, with 69% of them taking high-intensity statin therapy.

An analysis of FOURIER trial investigated the efficacy and safety of evolocumab in patients with peripheral artery disease (PAD) as well as the effect on major adverse limb events [5]. Around thirteen percent of patients (3642 out of 27564) had PAD, of which 1505 had no prior myocardial infarction or stroke. As these patients were at higher risk, they had larger absolute reductions of primary end point (3.5% with PAD, 1.6% without PAD). Evolocumab reduced the risk of major adverse limb events in all patients (HR, 0.58; P=0.0093) and there was consistent relationship with lower LDL levels.

Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) involved 2341 patients at high risk of cardiovascular events and LDL cholesterol of 70 mg/dl or more while on maximum tolerated dose of statins [6]. They were randomised in a 2:1 ratio to receive either alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. Though higher rates of injection-site reactions were noted in the active treatment group, they had significant reductions of LDL cholesterol levels (mean reduction of 62 percentage points, P<0.001). A post hoc analysis also documented lower rates of cardiovascular events (1.7% vs. 3.3%; nominal P=0.02). Reduction in lipoprotein (a) was 26 percentage points in this trial.

An often raised question has been regarding the safety of profound reductions in LDL-C levels. Reductions to levels below 25 mg/dl noted commonly in trials of PCSK9 inhibitors have been accompanied by low rates of atherosclerotic coronary events, suggesting that there may be no lower limit for LDL-C reduction [7].

Important limitation of PCSK9 inhibitors is the cost of therapy. Moreover no benefit on cardiovascular or all-cause mortality has been demonstrated so far in the relatively shorter duration of follow up compared to statins. But they are useful in achieving good reductions of LDL cholesterol in those with atherosclerotic cardiovascular disease not at goal despite maximally tolerated statin therapy. They do have a role in familial heterozygous and homozygous hypercholesterolemia as well.

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