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Editorial Open Access

PCSK9 Inhibitors

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Editorial

Numerous studies have demonstrated that a high serum total cholesterol or low-density lipoprotein (LDL) cholesterol is a risk factor for cardiovascular events in men and in women [1-3]. Numerous randomized, double-blind, placebo-controlled secondary prevention and primary prevention studies and observational studies have also shown that statins reduce cardiovascular events in high-risk patients with hypercholesterolemia [4-14]. The American College of Cardiology/American Heart Association 2013 Lipid Guidelines recommend use of statins for treatment of hypercholesterolemia to lower cardiovascular events in 4 major groups [15]. However, some patients on statins do not achieve their treatment goals or are intolerant to statins. Therefore, new therapies for treatment of hypercholesterolemia are under investigation.

PCSK9 is a serine protease synthesized mainly by the liver which binds to the epidermal growth factor-like repeat A (EGFA) domain of the LDL receptor. Binding to the LDL receptor initiates receptor internalization to lysosomal/endosomal organelles for intracellular degradation. Its function decreases the surface density of the LDL receptor on the hepatocytes and,therefore, increases the LDL clearance. Gain of function mutations can cause a phenotype similar to familial hypercholesterolemia, whereas loss of function mutation results in a significant reduction of LDL cholesterol associated with a significant reduction in cardiovascular risk [16,17]. In the past decade, several approaches have been developed to inhibit PCSK9 including gene silencing, small molecule inhibitors, EGFA mimetic peptides, and monoclonal antibodies against PCSK9. Among these approaches, the monoclonal antibodies are leading the way.

PCSK9 inhibition by specific antibodies showed significant lowering of serum LDL cholesterol levels without significant short -term safety concerns. Inhibition of PCSK9 has also been found to reduce endothelial apoptosis, lower serum insulin levels, and lower blood pressure. Since these drugs do not affect liver metabolism, they do not interfere with traditional lipid- lowering therapy [18]. These antibodies are administered subcutaneously and are degraded presumably through lysosomal digestion. Antibodies engineered to escape lysosomal degradation, and therefore, a longer life span, are being developed [19].

Several monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) have lowered serum LDL cholesterol levels 50% to 70% across various patient populations and background lipid-lowering therapy [20]. A meta-analysis of 24 randomized clinical trials including 10,159 patients found that PCSK9 inhibitors lowered serum LDL cholesterol 47.49% [21].

The Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)-1 and OSLER-2 randomized 4465 patients in a 2:1 ratio to evolocumab given subcutaneously at a dose of 140 mg every 2 weeks or 420 mg monthly plus standard lipid-lowering therapy or to standard lipid-lowering therapy alone [22]. Compared with standard lipid-lowering therapy alone, evolocumab plus standard lipid-lowering therapy decreased serum LDL cholesterol 61% from 120 mg/dL to 48 mg/dL. The incidence of cardiovascular events at 1 year was lowered 53% from 2.18% in the standard lipid-lowering therapy group alone to 0.95% in the group treated with evolocumab plus standard lipid-lowering therapy [22].

The 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) study randomized 2, 341 patients at high risk for cardiovascular events who had serum LDL cholesterol levels of 70 mg/dL or higher despite treatment with statins at the maximum tolerated dose in 2:1 ratio to receive alirocumab 150 mg or placebo subcutaneously every 2 weeks for 78 weeks [23]. Compared to placebo, alirocumab reduced serum LDL 62%. At week 78, a post hoc analysis found that the incidence of death from CHD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina rneeding hospitalization was 1.7% on alirocumab versus 3.3% on placebo (a 48% reduction by use of alirocumab) [23].

At this time, there are 4 ongoing placebo-controlled phase 3 trials in more than 70,000 patients investigating whether PCSK9 inhibitors on a background of statin therapy decrease cardiovascular events [21]. These trials are investigating the PCSK9 inhibitors alirocumab, evolocumab, and bococizumab (2 trials) [21]. The completion of these cardiovascular endpoint trials is expected in 2018 [21].

Despite absence of long-term clinical trial data on efficacy and safety, alirocumab and evolocumab have been approved by the USA Food and Drug Administration for use in addition to diet and maximally-tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who need additional reduction of serum LDL cholesterol. Alirocumab will cost approximately $14,600 per year and evolocumab approximately $14,100 dollars per year.

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