Journal of Clinical and Translational Endocrinology: Case Reports 2 (2016) 23–26

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jecr

New lipid therapies: PCSK9 inhibitors

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ARTICLE INFO

Article history:
Received 29 June 2016
Accepted 25 July 2016

Keywords:
LDL
LDL receptor
Atherothrombosis
Familial hyperlipidemia
Alirocumab
Evolocumab

ABSTRACT

Pharmacologic therapy reduces cardiovascular risk in a variety of primary and secondary prevention clinical situations in addition to lifestyle modifications. Low density lipoprotein cholesterol (LDL-C) is a key mediator of atherogenesis. Most cholesterol guidelines propose specific LDL-C while recently the ACC/AHA recommends statin therapy without a specific LDL-C target. Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that leads to LDL receptor degradation. The decreased availability of LDL receptors results in decreased clearance and an increase of circulating LDL-C particles. Monoclonal antibodies that inhibit PCSK9 (PCSK9 abs) reduce LDL-C levels and may be especially helpful in familial hypercholesterolemia and statin-intolerant patients. PCSK9 inhibition is an exciting and promising new therapy for protection against macrovascular events.

Abundant data indicate that, in addition to lifestyle modification, pharmacologic lipid-lowering therapy reduces cardiovascular risk in a variety of primary and secondary prevention clinical situations. Though the majority of the randomized controlled trials involve statins, there is some data supporting the efficacy of niacin and gemfibrozil in these situations [1].

Over the years there have been different recommendations regarding treatment of dyslipidemia. Most of the guidelines have proposed specific low density lipoprotein cholesterol (LDL-C) targets [2–4]. Recently, the American College of Cardiology/American Heart Association (ACC/AHA) recommended the use of specific statins for treatment of dyslipidemia without aiming for a specific LDL-C target [1].

While the ACC/AHA did not target a certain LDL-C level, we do not think that this was meant to imply that LDL-C was not important or not atherogenic, just that the many studies showing statin benefit did not show the benefit of *statin titration* to a certain LDL-C level.

Indeed, there is an excellent physiologic basis for believing that LDL-C is very atherogenic and, logically, that lowering LDL-C as much as possible would have incremental benefit. The major carrier of cholesterol in most humans is LDL-C. LDL-C particles are variable in size and contain a hydrophobic cholesterol core lined by a phospholipid coat containing the lipoprotein apolipoprotein B (apoB). Atherosclerotic plaque starts with LDL-C infiltration into arterial walls where LDL-C is able to bind to glycosaminoglycans followed by oxidative processes which lead to a modified apoB recognized and internalized by receptor-mediated macrophage endocytosis. These macrophages transform into cholesterol-laden foam cells that secrete cytokines leading to inflammation, smooth muscle proliferation, and plaque formation within the arterial wall [5]. A fibrous cap forms a barrier between prothrombotic material on the surface of the plaque and platelets which can facilitate thrombus formation [6]. Atherothrombosis can lead to arterial occlusion and end organ damage.

Most cells express the LDL-C receptor which recognizes the apoB portion of LDL-C and mediates LDL-C clearance from the circulation [7]. Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL-C receptors and subsequently to increased circulating LDL-C levels. It circulates in three forms: a PCSK9 monomer, LDL-C-bound PCSK9, and a 55 kDa furin-cleaved inactive fragment [8]. The transcription factor sterol regulatory element–binding protein 2 (SREBP2) regulates LDL-C receptor expression and increases PCSK9 synthesis. PCSK9 binds to an epidermal growth factor (EGF)–like repeat located at the extracellular domain of the LDL-C receptor and is subsequently internalized and prevents the recycling of LDL-C receptors to the cell surface. As displayed in Figure 1, the resultant decrease in the number of LDL-C receptors by means of lysosomal degradation leads to an increase of LDL-C particles in circulation which contributes to the generation of atherosclerotic plaque. Sequence variations that cause decreased activity of the PCSK9 gene leading to decreased serum LDL-C is associated with coronary heart disease risk reduction [9].

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2214-6245/
http://dx.doi.org/10.1016/j.jecr.2016.07.001

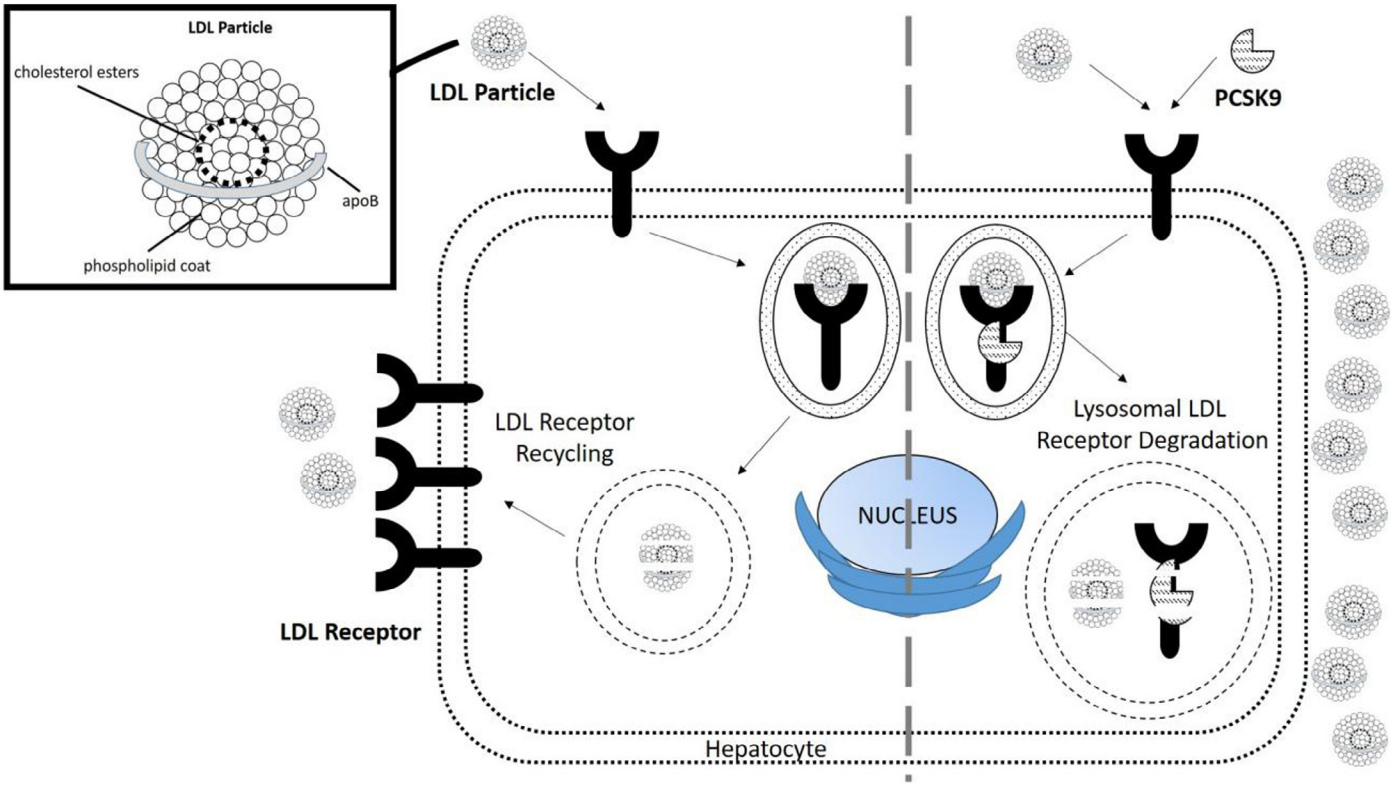

Figure 1. PCSK9 plays an important role in regulating the number of LDL-C receptors located at the hepatocyte cell surface. In the absence of PCSK9, the LDL particle binds to the LDL receptor followed by internalization. The LDL particle is targeted for degradation by the lysosome and the LDL receptor is recycled to the cell surface. In the presence of PCSK9, PCSK9 binds to the LDL particle-LDL receptor complex. The LDL receptor bound to PCSK9 is unable to recycle to the cell surface and is subject to degradation. A decrease in LDL receptors results in an increase of serum LDL particles.

Therapies that lower circulating PCSK9 levels significantly lower LDL-C levels. This category of lipid lowering therapy offers an important option not previously available and has demonstrated significant efficacy in lowering LDL-C and a large meta-analysis has suggested that this lowering might decrease adverse CV outcomes. Monoclonal antibodies that inhibit PCSK9 (anti-PCSK9 abs) reduce LDL-C by as much as 70% in a dose dependent manner. They have been shown to lower LDL-C by as much as 60% in statin treated patients [10]. A comprehensive meta-analysis of 24 randomized trials (n = 10,159) encompassing a large cohort of clinical situations including familial hypercholesterolemia, statin-intolerant patients, and those not on any statin therapy found that anti-PCSK9 abs lowered all-cause mortality (odds ratio [OR] 0.45, 95% CI 0.23–0.86), CV mortality (OR 0.50, CI 0.23–1.10), and MI (OR 0.49, CI 0.26–0.93) [11]. The benefits of anti-PCSK9 abs appear to be similar across a wide range of clinical situations and CV risks similar to what has been noted with statin therapy. Therapy with anti-PCSK9 abs appears to result in additional reductions in CV risk even in patients already on intensive or maximal statin therapy. Table 1 displays similarities and differences between the current FDA approved PCSK9 inhibitors in select placebo controlled trials.

Table 1
Comparison of the FDA-approved PCSK9 Inhibitors

	Alirocumab		Evolocumab	
Monoclonal Ab Characteristics	100% Human 4th generation IgG1		100% Human 4th gen IgG2	
Indications for Use	HeFH		HoFH, HeFH	
LDL-C Reduction				
Trial	Odyssey Long-Term		Mendel-2	
Duration	24 weeks		12 weeks	
Biweekly Therapy	Alirocumab	Placebo	Evolocumab	Placebo
Percentage (%)	–61.0	0.8	–57.0	0.1
Dosage and Administration	1. Injection: 140 mg/mL solution in a single-use prefilled syringe 2. Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector To administer the 420 mg dose, give three 140 mg/dL injections consecutively within 30 minutes		1. Injection: Single-dose pre-filled pen/syringe 75 mg/mL 150 mg/mL	
Cost	~ $15,000/year		~$14,500/year	
Adverse Effects	Nasopharyngitis, Bronchitis, Sinusitis, Influenza, Cough, Myalgia, Urinary tract infections, Diarrhea, Muscle spasms, Musculoskeletal pain, Injection site reactions, Neurocognitive effects			

HeFH = Heterozygous Familial Hypercholesterolemia; HoFH = Homozygous Familial Hypercholesterolemia.