Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Review

PCSK9 inhibition in the management of familial hypercholesterolemia

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ARTICLE INFO

Article history:
Received 3 July 2017
Accepted 3 July 2017
Available online xxx

Keywords:
PCSK9
Familial hypercholesterolemia
Therapeutic target
Lipoprotein apheresis

ABSTRACT

Familial hypercholesterolemia (FH) is a frequent hereditary metabolic disease characterized by high serum low-density lipoprotein (LDL) cholesterol concentration and premature atherosclerotic cardiovascular disease (ASCVD). The discovery of the LDL receptor as one of the causative genes of FH enabled us to understand the pathophysiology of FH and paved the way for developing statins. Similar to LDL receptor, discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) also created an opportunity for developing its inhibitors. Since PCSK9 degrades LDL receptor protein, inhibiting PCSK9 will be an effective strategy. Evolocumab and alirocumab, anti-PCSK9 antibodies that inhibit binding between PCSK9 and LDL receptors, are now available in Japan. Adding an anti-PCSK9 antibody to standard therapy with statin alone or statin combined with ezetimibe further reduced serum LDL cholesterol levels by around 60% and they significantly decrease cardiovascular event incidence as compared with placebo. Additionally, the strong LDL cholesterol lowering effect of anti-PCSK9 antibody therapies has reportedly enabled the frequency of lipoprotein apheresis to be reduced or to be discontinued. As alternative strategies against PCSK9, antisense oligonucleotide agents that inhibit PCSK9 protein synthesis as well as a small interfering (or short interference) RNA (siRNA) for PCSK9 are also being developed. While relatively high cost can be given as a problem, PCSK9 inhibitors are able to reduce LDL cholesterol dramatically even in FH patients who could not achieve targets until now. To ensure that these drugs are given to the patients who really need them, it is necessary to raise the diagnosis rate and family screening has to be more actively conducted. Finally, it has been reported that PCSK9 is expressed not only in hepatocytes but also in other cells such as epithelial cells in small intestine and vascular smooth muscle cells in atherosclerotic plaque. Further research regarding extra-hepatic pathophysiology of PCSK9 is expected.

Contents

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http://dx.doi.org/10.1016/j.jjcc.2017.07.002
0914-5087/

Please cite this article in press as: Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.07.002

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary metabolic disease characterized by markedly high serum low-density lipoprotein cholesterol (LDL-C) concentration, xanthomas including Achilles tendon thickening and premature coronary artery disease (CAD). In FH patients, as the prevalence of CAD is extremely high and its age of onset is 15–20 years earlier than usual, early diagnosis and appropriate treatment to prevent atherosclerosis or delay its progression is necessary. Various studies have reported high rates for FH heterozygotes of 1 in 200–500 persons and that 10% of patients with acute coronary syndrome have FH. Thus, from the aspect of public health, it can be said that FH is one of the most important underlying diseases of CAD in Japan.

The discovery of the LDL receptor as one of the causative genes of FH enabled us to understand the pathophysiology of FH and paved the way for developing 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Similar to LDL receptor, discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) also created an opportunity for developing its inhibitors. Thus, we have to recognize that patients with single gene disorder such as FH have given some clues to develop new pharmacological interventions that reduce LDL-C (Table 1). This review focuses on PCSK9, a novel therapeutic target for dyslipidemia and atherosclerosis. In it, we outline the pathologies arising from genetic abnormalities in PCSK9 as well as the new drugs that have been developed based on clues gained from such pathologies, and finally look at the issues in the treatment of FH and its future prospects.

Discovery of PCSK9 and description of its physiological actions

In 2003, Abifadel et al. [1] found that gene mutations in the PCSK9 genes were shown to cause dominant hypercholesterolemia in pedigree analysis, and also demonstrated that a gain of function due to a missense mutation in this gene was the cause of this disease.

To date, a number of gain of function mutations associated with hypercholesterolemia and premature atherosclerotic cardiovascular disease (ASCVD) have been identified [2]. Among Japanese patients with FH, it has been reported that a PCSK9 E32K variant affects LDL-C levels and could exacerbate the clinical phenotype of heterozygous FH carrying 3 types of LDL receptor mutations [3]. We reported that the additional PCSK9 V4I variant carrying LDL receptor mutations was linked to a significantly increased prevalence of ASCVD in accord with the elevation of the LDL-C level [4].

We also found that the prevalence of PCSK9 gain of function variants such as V4I and E32K was 9% in the patients without LDL receptor mutations [4]. Patients carrying only PCSK9 V4I or E32K variants were 2.7% and 5.8%, respectively, of the 224 unrelated FH patients. Interestingly, the distribution of PCSK9 gain of function variants among Japanese heterozygous FH patients is different from that in previous reports of PCSK9 gain of function mutations (S127R, D129G, F216L, R218S, R357H, and D374H) in FH studies from other countries. In a French population, the reported prevalence of FH patients carrying only PCSK9 gain of function variants without LDL receptor mutations was 0.7% [5]. The prevalence of PCSK9 gain of function variants among Japanese FH patients may be higher than that in FH patients from other countries.

Table 1
What have the single gene disorders taught us?

Single gene disorders	Gene	Phenotype	Drugs
FH1	*LDLR*	LDL-C↑	Statin
FH2	*APOB*	LDL-C↑	ApoB synthesis inhibitor
FH3	*PCSK9*	LDL-C↑	PCSK9 inhibitor
Familial hypobeta-lipoproteinemia	*APOB*	LDL-C↓	ApoB synthesis inhibitor
MTP deficiency	*MTP*	LDL-C↓	MTP inhibitor

FH, familial hypercholesterolemia; MTP, microsomal triglyceride transfer protein; LDLR, low-density lipoprotein receptor; ApoB, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9.

Two years after the identification of gain of function mutations, PCSK9 loss of function mutations were reported to be associated with lower levels of LDL-C and reduced incidence of ASCVD. In a study comparing the incidence of coronary heart disease over 15 years among individuals taking part in the Atherosclerosis Risk in Communities (ARIC) study, nonsense mutations in PCSK9 were associated with a 28% reduction in LDL-C and an 88% reduction in the rate of coronary events among African Americans [6]. Similarly, the R46L variant was associated with a 15% reduction in LDL-C and a 47% reduction in ASCVD risk in whites [6]. In a Japanese population, it has been reported that a PCSK9 R93C variant was associated with low LDL-C concentration [7]. In this regard, there has been the case of a 32-year-old African American woman who was a compound heterozygote for a PCSK9 loss of function mutation and although her LDL-C levels were markedly low at 14 mg/dL, she was not affected intellectually and graduated from university, was able to become pregnant and give birth and liver and renal function were normal [8]. Based on observations in the PCSK9-deficient mouse [9], loss of PCSK9 in mammals is not considered to influence viability or health.

Molecular biology research on PCSK9 has found that it promotes the degradation of LDL receptors by forming a complex with them, mainly in the liver. Localized on the cell surface, LDL receptors bind with LDL, and afterwards, the complex is transported to the endosomes via endocytosis and release the LDL under acidic conditions. LDL is degraded to amino acids and cholesterol while LDL receptors are transported to the cell surface, bind with LDL and taken into cells. This recycling of LDL receptors to the cell surface occurs approximately 150 times [10,11] (Fig. 1, left). PCSK9 is secreted by the endoplasmic reticulum in liver cells, binds with LDL receptors on the cell membrane, and is taken into cells. LDL receptors that PCSK9 has bound to are degraded in lysosomes without being recycled (Fig. 1, right).

Regarding gene mutations causing FH, the first to be discovered was that in the LDL receptor itself (FH1), next a mutation in apolipoprotein (apo) B (FH2), a ligand of LDL receptors, was discovered and the gain of function mutation in PCSK9 that promotes degradation of LDL receptors was the third one to be discovered and called FH3.

Relationship between statins and PCSK9 and difficulty of treating FH

Let us review the pharmacological action of HMG-CoA reductase inhibitors (statins) in order to better understand PCSK9 inhibitors. As shown in Fig. 2, cholesterol is mainly synthesized in the liver via the mevalonate pathway. The rate-limiting enzyme is HMG-CoA reductase and if there is a decrease in intracellular cholesterol in the liver, this is sensed by sterol regulatory-element binding protein 2 (SREBP2), a sensor molecule, and the expression of HMG-CoA reductase is increased to promote the intracellular synthesis of cholesterol. At the same time, intracellular cholesterol levels are elevated through increased expression of LDL receptors, which promotes intake of cholesterol from the blood. Statins are HMG-CoA reductase inhibitors and they decrease intracellular cholesterol by inhibiting cholesterol synthesis. Thus statins enhance SREBP2 activation and stimulate recovery of cholesterol from the blood via LDL receptors. As a result, the LDL-C level in the blood decreases and the intracellular cholesterol amount recovers.

Please cite this article in press as: Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.07.002