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REVIEW

The role of proprotein convertase subtilisin/kexin type 9 inhibitors in managing cardiovascular risk

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Abstract

Hypercholesterolaemia and dyslipidaemia, marked by decreased levels of high-density lipoprotein and elevated levels of low-density lipoprotein (LDL), increase the risk of cardiovascular disease. Familial hypercholesterolaemia (FH), diagnosed based on the clinical features seen in patients with a positive family history, constitutes a heritable disorder involving a single gene. FH can exist in either the heterozygous or homozygous form, and may be differentiated based on clinical features and genetic studies. A novel drug target, proprotein convertase subtilisin/kexin type 9 (PCSK9), has resulted in the development and subsequent approval of new, targeted monoclonal antibodies in the treatment of FH. Targeting PCSK9 with monoclonal antibodies, i.e. evolocumab and alirocumab, inhibits the degradation of LDL receptors, and against a background of optimised statin therapy, increases the life expectancy of patients with hypercholesterolaemia by reducing the incidence and severity of coronary artery disease.

Keywords: alirocumab, evolocumab, cardiovascular risk factors, familial hypercholesterolaemia, PCSK9, proprotein convertase subtilisin/kexin type 9, LDL cholesterol, LDL receptor

Introduction

The highest mortality rate globally is attributed to atherosclerotic cardiovascular disease (CVD). Ischaemic heart disease is the leading cause of death worldwide.[1–3] Atherosclerotic CVD represents 28% of global all-cause mortality.[2] Estimates predict that by the year 2020, CVD, and more notably atherosclerosis, will become the leading cause of the world's total disease burden.[1]

Risk factors for CVD were introduced in 1961 by the Framingham Heart Study, which linked the presence of specific antecedent conditions, e.g. elevated cholesterol levels, arterial hypertension, diabetes mellitus and tobacco use, with future CVD. These risk factors may be classified as being either traditional or non-traditional. Traditional risk factors include constitutional factors (a family history of atherosclerosis, age and gender); behavioural or lifestyle factors (nutrition, physical activity and tobacco exposure); and physiological factors (blood pressure, lipids, obesity and glucose metabolism, including diabetes mellitus). In addition, medical diagnoses, such as diabetes mellitus and chronic kidney disease, are included.[4]

Conversely, the non-traditional risk factors, or novel biomarkers, which may be of value in predicting CVD , include adipocyte dysfunction, mitochondrial dysfunction and oxidative stress, inflammation, haemostasis and thrombosis, as well as insulin resistance. The clinical utility of the non-traditional risk factors remains limited because of an inconsistent association with CVD, especially in children. The role of these biomarkers, especially in identifying childhood risk factors, is increasingly being studied.[4]

The pathogenesis of coronary heart disease (CHD) remains largely unknown, but it is generally accepted to be a polygenetic disease, resulting from several gene interactions, in addition to environmental and psychosocial factors.[5] Circulating blood lipid levels and atherosclerosis are consistently being recognised as two risk factors for the development of CHD.[5]

Atherosclerosis as a risk factor

Atherosclerosis is an inflammatory disease associated with lipid and metabolic abnormalities, which cause alterations in the arteries, and is considered to be a major cause of CVD.[2] Atherosclerotic plaques are initiated by the so-called fatty streak or initial lesion. These initial lesions arise from localised increases in the lipid content of lipoproteins, and in particular, in the fraction of lipoprotein pertaining to low-density lipoprotein (LDL). Lipoprotein binds to the constituents of the extracellular matrix in the intima of arteries, increasing the lipid-rich particles within the arterial wall. Lipoprotein particles in the extracellular space of the intima may undergo oxidative modification, forming oxidised lipoprotein, which supports a pathogenic role in atherogenesis.[1] Oxidative stress plays an important role in cholesterol metabolism. Oxidised LDL is toxic to the vascular network, whereas high-density lipoprotein (HDL) acts as an antioxidant. Oxidative stress is believed to be a major cause of

plaque rupture and resultant thrombosis. Both are late events in the progression of atherosclerosis.[4]

Reduced levels of HDL cholesterol are an important risk factor for CVD, because the so-called reverse cholesterol transport which is mediated by the HDL provides an independent pathway for lipid removal, away from atheroma formation.[1,3]

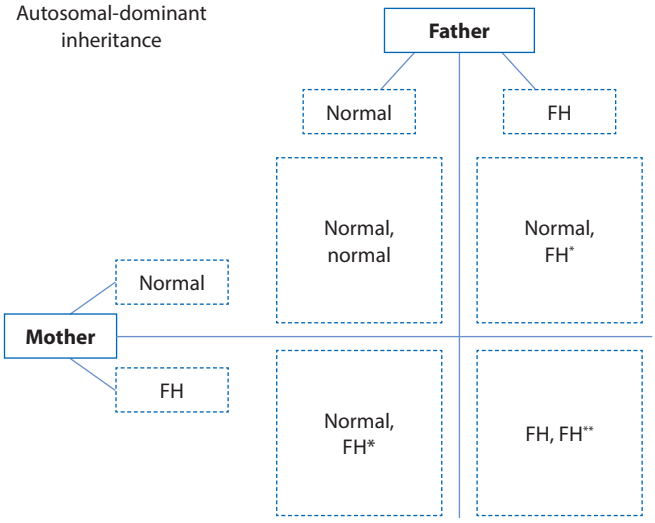
Familial hypercholesterolaemia

FH is an autosomal dominant trait, with the mutation of the LDL receptor gene on chromosome 19, which can often be identified by elevated levels of umbilical cord blood cholesterol.[6] Therefore, FH is characterised by defects of the LDL receptors, and some individuals produce non-functional and kinetically impaired receptors.[7]

FH may either be homozygous (HoFH) or heterozygous (HeFH). The latter has a 1 in 500 prevalence in most populations, with higher incidences described in Afrikaner South Africans and French Canadians. The underlying genetic disorder seems to be attributed to a loss-of-function mutation in the LDL receptor alleles. More than 1 600 mutations have been identified. Other causes which occur less frequently include defects in apolipoprotein B100 (ApoB100) and the gain-of-function mutation in proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease.[8]

Affected children with the HoFH form inherit the abnormal gene from both their parents, i.e. both alleles are pathogenic, and therefore suffer from the most severe form of this disease (Figure 1). The clinical manifestations of HeFH versus HoFH are listed and compared in Table 1.[6]

LDL levels tend to increase throughout childhood, while triglyceride levels are usually normal. Tendon xanthomas may be present and *arcus corneae* and xanthelasma may appear in the third decade. Levels of cholesterol often exceed 25.8 mmol/l.[7]



FH: familial hypercholesterolaemia
*Normal, FH: Heterozygous familial hypercholesterolaemia
**FH, FH: Homozygous familial hypercholesterolaemia

Figure 1: The mode of inheritance of familial hypercholesterolaemia, showing both the heterozygous and homozygous forms of the disease

Table 1: A comparison of heterozygous versus homozygous clinical manifestations of familial hypercholesterolaemia[6]

Clinical manifestations	HeFH	HoFH
Tendon xanthoma	Present	Present
Cutaneous xanthoma	–	Present
Coronary disease	Aged ≥ 25 years	Aged ≤ 25 years
LDL cholesterol levels	5–12 mmol/l	≥ 12 mmol/l

HeFH: heterozygous familial hypercholesterolaemia,HoFH: homozygous familial hypercholesterolaemia, LDL: low-density lipoprotein

Adipocyte dysfunction

Pathophysiological and metabolic consequences of excess adiposity appear as central phenomena in the pathway to CVD. Excessive levels of circulating glucose and triglycerides cause energy imbalances, which lead to adipocyte hypertrophy and hyperplasia. The subsequent result is an inflammatory process within the adipose tissue.[4] Excesses of circulating nutrients cannot be absorbed, and the capacity of the adipocyte to store triglycerides and glucose is overwhelmed, causing adipocyte dysfunction. This dysfunction is characterised by infiltration of the inflammatory cells and elevated proinflammatory cytokines which activate additional inflammatory pathways.[4]

Transport and metabolism of lipoproteins

The most important lipids in the body are phospholipids, cholesterol and the triglycerides. The latter two also constitute the major plasma lipids. These lipids are transported in the blood stream by lipoprotein complexes. The liver is the primary organ responsible for the metabolism of lipoprotein. The lipoprotein complexes mostly fall into one of three categories, namely HDL, LDL and VLDL (Table 2). The category of intermediate-density lipoprotein (IDL) is typically grouped with LDL in the clinical practice setting. (IDL is also referred to as LDL_1, while LDL actually refers to LDL_2).[9,10]

Table 2: Important terminology pertaining to the density of commonly occurring lipoprotein complexes[9,10]

Term or acronym	Definition or description
LDL	Low-density lipoprotein. LDL is subdivided into LDL_1 (or IDL) and LDL_2 (the typical LDL that constitutes the major component of LDL)
VLDL	Very low-density lipoprotein
HDL	High-density lipoprotein. (Subfractions of HDL also exist, i.e. HDL_2 and HDL_3)

HDL: high-density lipoprotein, IDL: intermediate-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein

The significance of dyslipidaemia

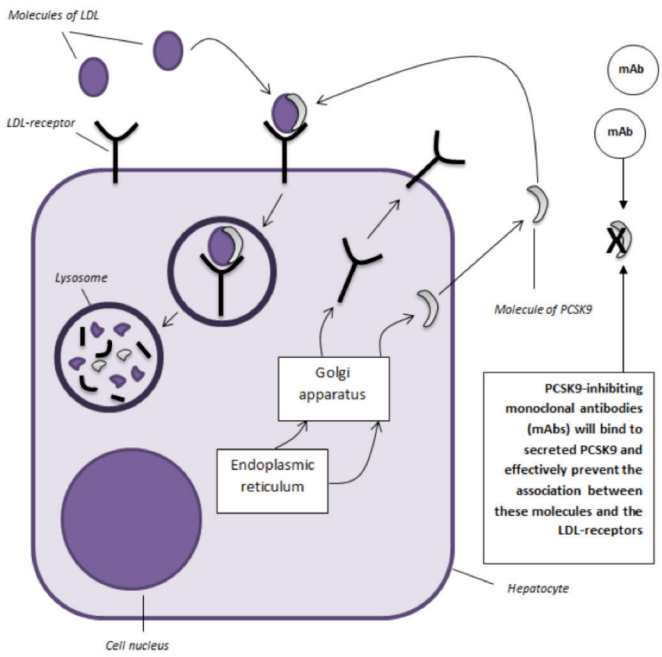
Dyslipidaemia refers to the combination of elevated levels of total and LDL cholesterol (as well as the triglycerides), combined with decreased levels of HDL cholesterol, and is considered to be a disorder of lipoprotein metabolism. There is an undisputed association between the elevated levels of total and LDL cholesterol (as a major modifiable risk factor) and CHD.

LDL cholesterol transports approximately two thirds of all the circulating cholesterol in the human body. Elevated levels of LDL, in particular, are considered to constitute a primary risk factor for the occurrence of atherosclerosis and associated ischaemic coronary events.[9–12]

The pivotal role of the low-density lipoprotein receptor and proprotein convertase subtilisin/kexin type 9

The protein constituents of lipoprotein complexes are referred to as apolipoproteins, which are grouped into four different classes, namely A, B, C and E. ApoB100 is the most significant apolipoprotein associated with LDL cholesterol. The latter provides an attachment to the binding site for LDL on its LDL receptor.[9,10]

When LDL binds to its receptor on the cell surface of selected tissue cells, especially hepatocytes, the resultant internalisation of LDL provides its lysosomal degradation. This is subsequently followed by the so-called recycling of the LDL receptor back to the cell's plasma membrane. Once repositioned, it is able to bind to yet another molecule of LDL. This is an ongoing process. However, in an attempt to maintain normal, stable levels of LDL cholesterol in the body, the uncontrolled recycling of the LDL receptor may be counteracted by the effects of PCSK9, which promotes the breakdown of these receptors (Figure 2). Therefore, PCSK9, a serine protease, which is expressed in particularly significant quantities within the liver (the main source of circulating PCSK9), intestines and kidneys, may be regarded as a modulator of LDL cholesterol levels in the plasma. It effectively acts to reduce the number of LDL receptors on the cell surface of hepatocytes.[11,12]



LDL: low-density lipoprotein, mAb: monoclonal antibody, PCSK9: proprotein convertase subtilisin/kexin type 9

Figure 2: A simplified diagram of a prototypical hepatocyte, illustrating the production and release of proprotein convertase subtilisin/kexin type 9, with its subsequent role in the degradation of the low-density lipoprotein receptor, and showing the site of action of the proprotein convertase subtilisin/kexin type 9-inhibiting monoclonal antibodies (X)

In turn, PCSK9 undergoes endogenous inactivation by two different proprotein convertases, referred to as furin and PC5/6A, within hepatocytes.[12]

Proprotein convertase subtilisin/kexin type 9 antibody therapy

PCSK9 is a member of the proteinase subfamily of subtilisin-related serine endoproteases, and participates in the regulation of LDL cholesterol.[13] PCSK9 has emerged as a target when preventing and treating coronary heart disease. Elevated serum levels of LDL cholesterol have been implicated in various human genetic studies as gain-of-function mutations which can lead to premature incidences of CHD. The opposite holds true for reduced serum levels of LDL cholesterol.[14] The complete loss of PCSK9 results in a very low serum LDL cholesterol level of ≤ 1 mmol/l in healthy subjects.[14] PCSK9 targets the LDL receptor for degradation in the liver by lysosomes, thereby preventing expression of the receptor on the cell membrane. PCSK9 binds to the receptor on the cell membrane, and the complex is then internalised and destroyed by the lysosomes.[15] Targeted monoclonal antibodies then have the ability to bind to PCSK9, thereby inhibiting its interaction with LDL cholesterol receptors.[16] Outcomes with regard to their efficacy indicate a reduction in LDL cholesterol of greater than 50% and an elevation in HDL cholesterol levels, especially when administered against a background of statin therapy. Gene silencing and mimetic peptides are other potential strategies currently under investigation.[11]

The human monoclonal antibodies, evolocumab (IgG_2 isotype) and alirocumab (IgG_1 isotype), which target PCSK9, have been identified as treatment options, as an adjunct to diet, for patients diagnosed with HeFH and HoFH, where LDL cholesterol levels could not be reduced to target using statins alone, or in combination with other agents, e.g. ezetimbe, newer bile acid sequestrants and extended-release formulations of niacin. In addition, they may also be used in patients diagnosed with clinical atherosclerotic CVD which requires the additional lowering of LDL cholesterol.[17–19] Both of these agents received approval from the US Food and Drug Administration in the latter half of 2015.

Following the introduction of the novel, injectable PCSK9 inhibitors, concerns were raised with regard to the potential for eliciting neurocognitive impairment. PCSK9 is involved in cortical regeneration, and cholesterol is an important component of neurons. A low rate of neurocognitive-related adverse events was reported in the Open-Label Study of Long-Term Evaluation Against LDL-C (i.e. the OSLER-1 and -2 studies) and the ODYSSEY Long-Term study. However, such events were still higher than those in the matching placebo arms. Monoclonal antibodies and lipoproteins do not cross the blood-brain barrier, and PCSK9 loss-of-function variants have not been associated with a decline in cognitive performance.[16] Other reported adverse events include allergic reactions,

inherent to the use of monoclonal antibodies, and other forms of protein therapeutics.[19,20]

The use of PCSK9 inhibitors against a background of statin therapy significantly reduces cardiovascular risk factors, by significantly reducing LDL cholesterol.[17,18]

Conclusion

The use of statin treatment in patients suffering from FH has greatly reduced the mortality rate by decreasing the incidence of coronary events. This article provided a brief introduction to lipoprotein metabolism and the genetic differences involved in the phenotypic expression of patients suffering from FH. The use of the novel PCSK9 inhibitors has brought new hope for patients suffering from FH as coronary incidences are greatly reduced when these monoclonal antibodies are used against a background of statin therapy and dietary modification.

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