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

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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

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

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>HeFH</th>
<th>HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Cutaneous xanthoma</td>
<td>–</td>
<td>Present</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>Aged ≥ 25 years</td>
<td>Aged ≤ 25 years</td>
</tr>
<tr>
<td>LDL cholesterol levels</td>
<td>5–12 mmol/l</td>
<td>≥ 12 mmol/l</td>
</tr>
</tbody>
</table>

HoFH: 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 bloodstream 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, while LDL actually refers to LDL1).9,10

Table 2: Important terminology pertaining to the density of commonly occurring lipoprotein complexes9,10

<table>
<thead>
<tr>
<th>Term or acronym</th>
<th>Definition or description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein. LDL is subdivided into LDL1 (or IDL) and LDL2 (the typical LDL that constitutes the major component of LDL)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low-density lipoprotein</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein. (Subfractions of HDL also exist, i.e. HDL2 and HDL3)</td>
</tr>
</tbody>
</table>

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.
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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 (lgG2 isotype) and alirocumab (lgG1 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.\textsuperscript{19,20}

The use of PCSK9 inhibitors against a background of statin therapy significantly reduces cardiovascular risk factors, by significantly reducing LDL cholesterol.\textsuperscript{17,18}

\textbf{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.

\textbf{References}