Evolocumab and Alirocumab: A Review of the Emerging Role of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors in the Management of Hyperlipidaemia

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Abstract

This article reviews the emerging role of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors in the management of hyperlipaemia. Two PCSK9 inhibitors, Evolocumab and Alirocumab, have been recently approved by the National Institute for Health and Care Excellence (NICE) for patients who are at high risk of cardiovascular disease who cannot tolerate statins or those who fail to achieve appropriate levels of low density lipoprotein (LDL) despite maximum statin therapy. In this article we discuss the pathophysiology of PCSK9 Inhibitors as well as summarising the outcomes of the various clinical studies carried out on Evolocumab and Alirocumab. We also review the current NICE indications, contraindication, and the annual cost of each of these drugs.

Keywords: PCSK9 Inhibitors; Evolocumab; Alirocumab; Hyperlipaemia; Lipids; Cholesterol

Abbreviations

TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; NICE: National Institute for Health and Care Excellence; LDLR: Low-Density Lipoprotein Receptor; Q2W: Every Two Weeks; QM: Every Month; heFH: Heterozygous Familial Hypercholesterolemia; LMT: Lipid Modifying Treatment; CVD: Cardiovascular Disease; QALY: Quality Adjusted Life Years; ICER: Incremental Cost Effectiveness Ratio; NHS: National Health Service; ACS: Acute Coronary Syndrome

Introduction

Cardiovascular disease accounts for the largest proportion in terms of the cause of death in advanced countries [1]. Most cardiovascular risk estimation systems and virtually all drug trials are based on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). The reduction of TC or LDL-C is associated with statistically and clinically significant reductions in cardiovascular events and mortality. The European Society of Cardiology recommends that LDL-C has to be used as the primary lipid analysis. The greater the LDL-C reduction, the greater the cardiovascular risk reduction. Statins remain the first line treatment of hyperlipidaemia while bile acid sequestrants, cholesterol absorption inhibitors, and nicotinic acid are usually used as a combination therapy in patients with very high cardiovascular risk or those who are statin intolerant or are not able to tolerate higher statin doses. Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors are a new class of drugs that have become available for LDL-C reduction [2]. Two PCSK9 inhibitors have recently been approved by the National Institute for Health and Care Excellence (NICE): Evolocumab and Alirocumab. We will summarise the history and development as well as the main clinical trials and characteristics of these drugs.

Genetics, Structure, and Physiological function

The human 22-kb gene PCSK9 is located on the small arm of chromosome 1p32 and contains 12 exons and 11 introns. The gene encodes a 692-amino acid (aa) proteinase K-like serine protease named PCSK9. In the adult, PCSK9 is highly expressed in liver hepatocytes and less so in the small intestine and kidney [3,4].

The 692-amino acid preproPCSK9 undergoes signal peptidase cleavage, then autocatalytic cleavage in the endoplasmic reticulum into two products: the prodomain and the mature PCSK9 containing the catalytic domain and the C-terminal domain. Cleavage of the prodomain is required for the maturation and secretion of PCSK9. After cleavage, the prodomain or prosegment remains associated by hydrogen bonds with the mature active form and the protein is finally secreted as an inactive dimer complex [4,5]. The major function of PCSK9 is the degradation of the low-density lipoprotein receptor (LDLR) by two possible ways: the first is for PCSK9 to be secreted and immediately get bound to LDL-R in the liver, and the second is to enter the systemic circulation. The binding of PCSK9 to LDLR induces modification of LDLR conformation and enhances the LDLR lysosomal degradation rather than the normal recycling to plasma membrane. Therefore leading to fewer numbers of LDL-R present on the cell surface and so less uptake of the LDL-C resulting in an elevated LCL-C concentration [4,5]. PCSK9 circulating in the plasma can bind to LDL-R in various organ systems such as the liver, intestines, kidneys, lungs, pancreas, and adipose tissue. This mechanism explains an inverse relationship between PCSK9 concentrations in plasma and LDL-R [4] (Figure 1).

![Figure 1: The role of PCSK9 Inhibitors in lipids metabolism: PCSK9 binds to LDL-R at the surface of hepatocytes leading to the degradation of LDL-R and higher plasma LDL-L. PCSK9 Inhibitors interfere with this binding leading to recycling of LDL-R rather than degradation. This results in more LDL-R available at hepatocyte level leading to more LDL-C uptake and to reduction in plasma levels of LDL-C](image)

Discovery and early studies

In 2003 the ninth member of the protein convertase PCSK9 was identified [6]. In the same year, Abifadel, et al. reported two mutations in the gene PCSK9 causing autosomal dominant hypercholesterolemia (ADH) in two French families and with no detectable mutations in LDLR or ApoB. They were missense mutations favouring a gain-of-function or a dominant negative effect [7]. Further studies identified many PCSK9 gene mutations that have been classified as gain of function (GOF) resulting in high LDL-C levels or loss of function (LOF) when the lack of the gene resulted in low LDL-C levels [5,8]. The LOF association with hypercholesterolaemia made this protein an attractive target for the treatment of dyslipidaemia [8]. Animal studies in mice showed a direct relationship between PCSK9 and atherosclerosis as the overexpression of PCSK9 in mice resulted in an excess of atherosclerosis while mice lacking PCSK9 showed a marked reduction in aortic cholesterol esters [9]. Also, administering statins to mice lacking PCSK9 was found to result in an exaggerated increase in LDLRs in their liver and enhanced LDL clearance from plasma [9].

Human studies

After performing phase I and phase II studies, both Evolocumab and Alirocumab underwent multiple phase 3 studies. Tables 1 and 2 summarise the major phase 3 studies performed on Evolocumab and Alirocumab respectively.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Type</th>
<th>Design</th>
<th>Number of Patients</th>
<th>Study duration (Weeks)</th>
<th>Number of centres</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAPLACE-2 [11]</td>
<td>Double-blind, Randomised, Placebo and Ezetimibe Controlled</td>
<td>Evolocumab Q2W or QM in combination to a statin in patients with Primary Hypercholesterolemia and Mixed Dyslipidaemia</td>
<td>2067</td>
<td>12</td>
<td>Multinational</td>
<td>Evolocumab added to moderate- or high-intensity statin therapy resulted in additional LDL-C lowering</td>
</tr>
<tr>
<td>GAUSS-2 [12]</td>
<td>Double-blind, Randomised</td>
<td>Evolocumab Q2W and QM vs Ezetimibe in hypercholesteraemic adults unable to tolerate an effective dose of a statin</td>
<td>307</td>
<td>12</td>
<td>Multicentre multinational</td>
<td>Evolocumab resulted in a significant reduction in LDL-C in hypercholesteraemic patients who were unable to tolerate effective doses of at least 2 statins</td>
</tr>
<tr>
<td>GAUSS-3 [13]</td>
<td>Randomized, double-blind, ezetimibe-controlled, parallel group study</td>
<td>Evolocumab vs Ezetimibe in patients with muscle related statin intolerance</td>
<td>511</td>
<td>24</td>
<td>Multicentre multinational</td>
<td>Evolocumab resulted in a significantly greater reduction in LDL-C levels after 24weeks</td>
</tr>
<tr>
<td>RUTHERFORD-2 [14]</td>
<td>Double-blind, Randomised, Placebo-controlled</td>
<td>Evolocumab Q2W or QM vs Placebo Q2W or QM in patients with heFH on a statin with or without ezetimibe</td>
<td>331</td>
<td>12</td>
<td>Multicentre multinational</td>
<td>Evolocumab administered either biweekly or monthly yielded significant reductions in LDL-C with no notable difference in the adverse events profile compared with placebo</td>
</tr>
<tr>
<td>Descartes [15]</td>
<td>Double-Blind, Randomised, Placebo-controlled</td>
<td>Evolocumab vs placebo in patients on lipid lowering therapy</td>
<td>905</td>
<td>52</td>
<td>Multicentre multinational</td>
<td>Evolocumab added to diet alone, to low-dose atorvastatin, or to high dose atorvastatin with or without ezetimibe significantly reduced LDL cholesterol levels in patients with a range of cardiovascular risks.</td>
</tr>
<tr>
<td>FOURIER [16]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Evolocumab vs placebo in patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 1.8 mmol/l or higher on statin therapy</td>
<td>27564</td>
<td>26</td>
<td>Multicentre multinational</td>
<td>The addition of Evolocumab was associated with a 59% reduction in LDL cholesterol levels. This was associated with a significant reduction of the risk of cardiovascular event. Apart from a higher rate of injection-site reactions, there was no significant difference in the rate of adverse effects.</td>
</tr>
</tbody>
</table>

Table 1: Phase 3 clinical trials of Evolocumab.

Q2w: Every two weeks; QM: Every month; LDL-C: Low Density Lipoprotein Cholesterol.
* The dose for Evolocumab twice weekly is 140mg subcutaneously.
** The dose for Evolocumab once a month is 250mg subcutaneously.
### Table 2: Published Phase 3 Clinical trials of Alirocumab.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Type</th>
<th>Design</th>
<th>Number of Patients</th>
<th>Study duration</th>
<th>Location and centres</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odyssey Mono [17]</td>
<td>Randomised double blind, active -controlled, Parallel group study</td>
<td>Alirocumab vs Ezetimibe</td>
<td>103</td>
<td>24 weeks</td>
<td>Multicentre Multinational</td>
<td>%47.2 reduction in LDL compared to %15.6 with Ezetimibe</td>
</tr>
<tr>
<td>Odyssey Combo 1 [18]</td>
<td>Randomised double blind, placebo-controlled, Parallel Group study</td>
<td>Alirocumab vs placebo in patients on maximally tolerated statin therapy in high CVD risk patients</td>
<td>316</td>
<td>24 weeks</td>
<td>Multicentre USA</td>
<td>Alirocumab treatment achieved a significantly greater reduction in LDL-C compared to placebo %45.9 vs %2.3</td>
</tr>
<tr>
<td>Odyssey Combo II [19]</td>
<td>Double blind, double-dummy, active controlled parallel group trial</td>
<td>Alirocumab vs Ezetimibe in patients on maximal tolerated statin therapy and high CVD risk</td>
<td>720</td>
<td>24 weeks</td>
<td>Multicentre Multinational</td>
<td>Alirocumab achieved a significantly greater reduction in LDL-C compared with Ezetimibe (%50.6 vs %20.7) with a similar safety profile</td>
</tr>
<tr>
<td>Odyssey FH I [20]</td>
<td>Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study</td>
<td>Alirocumab vs Placebo in Patients With heFH Not Adequately Controlled With Their Lipid-Modifying Therapy</td>
<td>486</td>
<td>24 weeks</td>
<td>Multicentre Multinational</td>
<td>Alirocumab achieved a significantly greater reduction in LDL-C compared with Placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was ~57.9% (p &lt; 0.0001) with Alirocumab compared with placebo</td>
</tr>
<tr>
<td>Odyssey FH II [20]</td>
<td>randomized, double-blind, placebo-controlled, parallel-group</td>
<td>Alirocumab vs Placebo in patients with heFH who are not adequately controlled with their LMT.</td>
<td>249</td>
<td>24 weeks</td>
<td>Multicentre Multinational</td>
<td>Alirocumab achieved a significantly greater reduction in LDL-C compared with Placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was ~57.9%.</td>
</tr>
<tr>
<td>ODYSSEY HIGH FH [21]</td>
<td>Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study</td>
<td>Alirocumab vs Placebo in Patients with heFH and LDL-C Higher or Equal to 160mg/dL</td>
<td>107</td>
<td>24 weeks</td>
<td>Multicentre Multinational</td>
<td>Alirocumab achieved significantly greater reduction in LDL-C compared with Placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks was ~57.9% (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

**heFH**: Heterozygous Familial Hypercholesterolemia; **LMT**: Lipid Modifying Treatment; **CVD**: Cardiovascular Disease; **LDL-C**: Low Density Lipoprotein Cholesterol

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Indications
NICE recommends using Evolocumab and Alirocumab in specific situations as follows:

Evolocumab:
Evolocumab is recommended, only if:

- The dosage is 140 mg every 2 weeks and
- The person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and:
  - A history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; or peripheral arterial disease and
  - A low-density lipoprotein cholesterol (LDL-C) concentration persistently above 4.0 mmol/litre
- The person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and
  - Recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease) and
  - An LDL-C concentration persistently above 3.5 mmol/litre
- The person has primary heterozygous-familial hypercholesterolaemia and
  - A history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, or peripheral arterial disease and
  - An LDL-C concentration persistently above 3.5 mmol/litre
- The person has primary heterozygous-familial hypercholesterolaemia and
  - No cardiovascular disease (CVD) and
  - An LDL-C concentration persistently above 5.0 mmol/litre
- The company provides Evolocumab with the discount agreed in the patient access scheme [22].

Alirocumab
Alirocumab in combination with other lipid-lowering therapies:

- Is not recommended for treating non-familial hypercholesterolaemia or mixed dyslipidaemia in adults without a history of cardiovascular disease.
- Is recommended for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in adults with a high risk of cardiovascular disease and persistent LDL-C levels of at least 4.0 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in adults with a very high risk of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating heterozygous-familial hypercholesterolaemia in adults without a history of cardiovascular disease and persistent LDL-C levels of at least 5.0 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating heterozygous-familial hypercholesterolaemia in adults with a history of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- In all cases, Alirocumab is recommended only if the company provides the drug with the discount agreed in the patient access scheme [23].

Table 3 compares the main characteristics of Evolocumab and Alirocumab.

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab</th>
<th>Alirocumab</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>140 mg every two weeks or 420 mg once a month by subcutaneous injection*</td>
<td>75 mg or 150 mg every two weeks</td>
</tr>
<tr>
<td><strong>Annual cost per</strong></td>
<td><strong>£4,422.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg monthly [22]</strong></td>
<td><strong>£4,383 for 75 mg or 150 mg every 2 weeks [23]</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity [24]</td>
<td>Hypersensitivity [25]</td>
</tr>
<tr>
<td><strong>Common Side effects-nice</strong></td>
<td>Nasopharyngitis, upper respiratory tract infection, influenza, back pain, arthralgia (joint pain), and nausea [24]</td>
<td>Local injection site reactions, upper respiratory tract signs and symptoms, and pruritus [25]</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Avoid unless the clinical condition of the woman requires treatment with Evolocumab [24]</td>
<td>Not recommended unless the clinical condition of the woman requires treatment with Alirocumab [25].</td>
</tr>
<tr>
<td><strong>Breast feeding</strong></td>
<td>It is unknown whether Evolocumab is excreted in human milk. Risk to breastfed newborns/infants cannot be excluded [24].</td>
<td>Not recommended in breast-feeding women in colostrum. For the remaining duration of breast-feeding the effects of Alirocumab on the breast-fed infant are unknown [25].</td>
</tr>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td>Use with caution in severe impairment [24]</td>
<td>Use with caution in severe impairment [25]</td>
</tr>
</tbody>
</table>

*Table 3: Comparison of the main characteristics of Evolocumab and Alirocumab.

*Only the 140 mg every two weeks is recommended by NICE.

Role of PCSK9 Inhibitors in different types of dyslipidemia

In patients with heterozygous familial hypercholesterolemia, both Evolocumab and Alirocumab achieved a higher LDL-C reduction in patients on maximum statin dose plus Ezetimibe compared to placebo [14,20,29].

In patients with homozygous familial hypercholesterolemia who took a maximum statin dose and Ezetimibe; Evolocumab reduced LDL-C significantly more than placebo at 12 weeks [26,29]. There were no studies of Alirocumab in patients with homozygous familial hypercholesterolemia [29].

In patients with Statin intolerance, The GAUSS and GAUSS-2 studies showed that Evolocumab, led to a greater reduction LDL-C than placebo [12,27,29] with similar changes in HDL-C and harm. The GAUSS study also showed that the combination of Evolocumab 420mg every 4 weeks, plus Ezetimibe was superior to Ezetimibe in LDL-C reduction [27,29]. There was no evidence for Alirocumab in patients who were intolerant to statins [29].

When considering the role of PCSK 9 inhibitors in patients with high cardiovascular risk, the initial studies were based on LDL-C reduction. These trials showed that Alirocumab resulted in a higher proportion of patients with high cardiovascular risk reaching an LDL-C Target of less than 70 mg/dl at 24 weeks compared to Ezetimibe [ODYSSEY COMBO II [19]] and to placebo [ODYSSEY COMBO I [18]]. Similar results were found when comparing the usage of Evolocumab with statins to Ezetimibe with statins [11].

More recent studies have addressed cardiovascular events and mortality and morbidity reduction. The FOURIER study concluded that the addition of Evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 1.8 mmol/l or higher was associated with a 59% reduction in LDL cholesterol levels. This was associated with a significant reduction of

the risk of cardiovascular event when compared to placebo [16]. More recently, the ODYSSEY OUTCOMES study that was presented at the American College of Cardiology Annual Scientific Session ACC 2018) showed that the use of Alirocumab significantly reduced ischemic events, including all-cause mortality and myocardial infarctions, compared with placebo among patients with an ACS event within the preceding 1 - 12 months [28].

Cost effectiveness

In the United States, a study looking at the cost-effectiveness of PCSK9 inhibitors in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. Found that PCSK9 inhibitors did not meet generally acceptable incremental cost-effectiveness thresholds for this group of patients and was estimated to increase US health care costs substantially. The study suggested that the cost of PCSK9 inhibitors needed to be reduced from $14,350 to $4,536, or less, per patient per annum for PCSK9 inhibitors to be cost effective at less than $100,000 per QALY [30].

Further cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial suggested a 71% price reduction was required to make PCSK9 inhibitors therapy cost effective [31].

In the United Kingdom, the price of PCSK9 inhibitors is cheaper (Evolocumab costs £4,422.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg monthly and Alirocumab costs £4,383) but so is the maximum acceptable ICER considered to represent a cost effective use of NHS resources (£20,000 - 30,000) [22,23]. The specific conditions under subheading 8 where NICE recommends the use of PCSK9 inhibitors represent conditions where usage of Evolocumab and Alirocumab resulted in an acceptable QALY gained below the maximum ICER. Reducing the cost of PCSK9 inhibitors could potentially reduce the QALY of using Evolocumab and Alirocumab in other lipid disorders to below the acceptable ICER.

Conclusion

This review summarises the rapid evolution of PCSK9 inhibitors with large clinical outcome trials along with future utilisation of these exciting new drugs. While clinical trials are showing promising results, the high costs of PCSK9 inhibitors is currently limiting their use in clinical practice to the highest risk patients who are most likely to benefit. If the cost of PCSK9 inhibitors was to be reduced, this would potentially result in a huge increase in their market.

As these are all injectable medications; compliance can be a significant limitation in daily practice. It would be useful to gather post launch registry data to understand what proportion of patients can manage with self-injections in a real world setting. The long term safety data on PCSK9 inhibitors is also awaited with eagerness as well as further trials to further assess their efficacy on clinical outcomes. Despite these limitations, a 50 - 70% reduction in LDL appears to be an exciting prospect in certain high risk patients. PCSK9 inhibitors could well represent the start of a new era in lipids management.

Conflict of Interest

None of the authors have a financial interest or any conflict of interest.

Bibliography

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