NEW CLASS OF DRUGS: THERAPEUTIC RNAi INHIBITION OF PCSK9 AS A SPECIFIC LDL-C LOWERING THERAPY

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NEW CLASS OF DRUGS: THERAPEUTIC RNAi INHIBITION OF PCSK9 AS A SPECIFIC LDL LOWERING THERAPY (Abstract): Hyperlipidemia is a well-known risk factor for coronary heart disease, the leading cause of death for both men and women. Current lipid-lowering treatment is not always efficient, therefore new pharmacological interventions that reduce LDL cholesterol (LDL-C) have been developed. This paper presents new class of specific LDL lipid-lowering drugs under investigation in phase II or III clinical trials. The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), a key enzyme in cholesterol homeostasis, improve the liver’s ability to clear LDL from the plasma, reducing LDL-C levels. Currently, three monoclonal antibodies PCSK9 inhibitors (alirocumab, evolocumab and bococizumab) are evaluated in clinical outcome trials. ALN-PCSsc, the new first-in-class therapeutic RNA interference (RNAi) inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) is also the first-in-class investigational medicine that acts by turning off PCSK9 synthesis in the liver. The development leadership of ALN-PCSsc has now transferred from Alnylam Pharmaceuticals® to The Medicines Company, who has initiated the ORION-1 Phase II study at the beginning of 2016. ALN-PCSsc has significant potential given its highly competitive profile as compared with monoclonal antibodies anti-PCSK9 MAbs, a recently approved class of LDL-C lowering drugs. Keywords: RNA INTERFERENCE (RNAi), PCSK9 PROTEIN, ALN-PCSsc.

Hyperlipidemia is a well-known risk factor for coronary heart disease, the leading cause of death for both men and women. Current lipid-lowering treatment is not always efficient, therefore new pharmacological interventions that reduce LDL-C have been developed.

The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme discovered almost a decade ago (1) as a key player in cholesterol homeostasis (2,3,4), is now considered an exciting approach (5,6,7) in the reduction of the incidence of cardiovascular events (8,9,10). The PCSK9 protein is a plasma protein synthesized by several organs in the body (liver, intestine, etc.) and it can bind to LDL receptors. This binding prevents the LDL receptors from continuously clearing LDL from the plasma, resulting in elevated LDL-C levels. The new class of drugs, PCSK9 inhibitor drugs, serves to improve the liver’s ability to clear LDL from the plasma, reducing LDL-C levels and reducing the risk of cardiovascular diseases.
New class of drugs: therapeutic RNAi inhibition of PCSK9 as a specific LDL-C lowering therapy

When added to a maximized statin regimen, PCSK9 inhibitors work synergistically with statins to provide additional LDL-lowering via a different mechanism of action (11). The progress from PCSK9 discovery to the development of targeted treatment (12, 13) has been unprecedented in terms of scale and speed. The first suggestion of a link between PCSK9 and hypercholesterolemia was published in 2003 (14); a decade later, two meta-analyses of clinical trials comparing anti-PCSK9 treatment to placebo or ezetimibe, including >10,000 hypercholesterolemic individuals, were published (15). This paper presents new groups of lipid-lowering drugs under investigation in phase II or III clinical trials.

**PCSK9 INHIBITION WITH MONOCLONAL ANTIBODIES**

Currently, three PCSK9 inhibitors (all anti-PCSK9 MAbs: alirocumab, evolocumab and bococizumab) are being evaluated in clinical outcome trials and the results will determine the future of these lipid-lowering therapies by establishing their clinical efficacy in terms of cardiovascular event reduction, safety, and the consequences of prolonged exposure to very low levels of LDL-cholesterol. Irrespective of their outcomes, the exceptionally rapid development of these drugs exemplifies how novel technologies, genetic validation, and rapid clinical progression provide the tools to expedite the development of new drugs.

Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of coronary artery disease, the leading cause of death in the world. However, a large proportion of patients with hypercholesterolemia are not achieving adequate LDL-C levels with currently available therapies such as statins, including genetic familial hypercholesterolemia patients, acute coronary syndrome patients, high-risk patient populations (e.g., patients with coronary artery disease, diabetes, symptomatic carotid artery disease, etc.) and other patients that are statin intolerant. There is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies. One potential drawback of monoclonal antibodies and other PCSK9 inhibitors in development is the need for repeated injections of the drugs.

**PCSK9 INHIBITION WITH RNA INTERFERENCE (RNAi) INHIBITORS**

In efforts to reduce the number of injections required for effective treatment, Alnylam Pharmaceuticals® and The Medicines Company recently reported positive results from their phase I clinical trial with ALN-PCSsc, an investigational RNAi therapeutic targeting PCSK9 which would likely be dosed quarterly. RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon (16).
Small interfering RNA (siRNA), known as short interfering RNA or silencing RNA, the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made (fig.1). RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way (17, 18, 19).

New delivery platforms were introduced for ALN-PCSsc. GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology enables subcutaneous dosing with increased potency and durability, and a wide therapeutic index. This ESC-GalNAc-conjugate delivery platform is being employed in nearly all of Alnylam's pipeline programs, including ALN-PCSsc and several other programs in clinical development (20).

**PHARMACOLOGICAL EFFECTS**

The effects of ALN-PCSsc were found to be highly durable, with clinically significant and clamped reductions in LDL-C, supportive of a potential bi-annual subcutaneous dose regimen. Specifically, an up to 53 percent maximal and 47 percent least squares mean reduction in LDL-C was achieved at day 180 after just a single, low volume injection (tab 1). In addition, ALN-PCSsc was shown to reduce a number of...
New class of drugs: therapeutic RNAi inhibition of PCSK9 as a specific LDL-C lowering therapy

atherogenic lipids, including lipoprotein (a) - or "Lp(a)" - and total cholesterol, which are associated with increased risk of cardiovascular disease. ALN-PCSsc was generally well tolerated with no clinically significant drug-related adverse events, but it is not known the long-term clinical benefit (21).

<table>
<thead>
<tr>
<th>Study name</th>
<th>PCSK9 inhibitor</th>
<th>Dosing</th>
<th>LDL-C reduction vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY (7)</td>
<td>Alirocumab</td>
<td>300 mg once-monthly</td>
<td>56%</td>
</tr>
<tr>
<td>RUTHERFORD (7)</td>
<td>Evolocumab</td>
<td>420 mg once-monthly</td>
<td>55%</td>
</tr>
<tr>
<td>Ballantyne et al.(7)</td>
<td>Bococizumab</td>
<td>300 mg once-monthly</td>
<td>27–53%</td>
</tr>
<tr>
<td>ORION-1 (18)</td>
<td>ALN-PCSsc</td>
<td>500 mg on days 0 and 90</td>
<td>59%</td>
</tr>
</tbody>
</table>

CONCLUSIONS
These anti-PCSK9 agents, now in phase II or III clinical trials, are still years away from approval. These new drugs appear to be promising in the reduction of the incidence of cardiovascular events because they reduce LDL-C, but there are basic facts not understood. Although the current recommendation for PCSK9 inhibitors is to be used in conjunction with statins and they have a steep price compared to statins, there are still not enough data about their long-term safety and efficacy and about the place of PCSK9s in the treatment of hypercholesterolemia.

REFERENCES


