

EDITORIAL

## Novel Hypolipidemic Agents: Focus on PCSK9 Inhibitors

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was recently discovered as the third gene involved in autosomal dominant familial hypercholesterolemia. The encoded PCSK9 protein binds and induces degradation of the low-density lipoprotein (LDL) receptor and thereby modulates the plasma levels of LDL-cholesterol. Some of the naturally occurring PCSK9 mutations increase the function of this protein (gain of function) and cause hypercholesterolemia, whereas loss of function mutations produce hypocholesterolemia. Since the loss of a functional PCSK9 in humans is not associated with apparent deleterious effects, this protease is an attractive target for the development of hypocholesterolemic agents, either alone or in combination with statins. Thus, inhibition of PCSK9 with monoclonal antibodies is emerging as a novel strategy for the treatment of hypercholesterolemia. Other novel hypolipidemic agents include mipomersen, an antisense oligonucleotide inhibitor targeted to human apolipoprotein B-100, and lomitapide, an oral microsomal triglyceride transfer protein inhibitor. Data obtained from preliminary studies show that these new therapeutic approaches are effective in reducing LDL-cholesterol. An overview of these novel hypolipidemic agents is herein attempted with a focus on PCSK9 inhibition.

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*bococizumab; mipomersen; lomitapide*

ABBREVIATIONS

Apo B-100 = apo-lipoprotein B-100  
FH = familial hypercholesterolemia  
HDL = high density lipoprotein  
HMG-CoA = 3-hydroxy- 3-methylglutaryl  
coenzyme A  
LDL = low density lipoprotein  
MTTP = microsomal triglyceride transfer  
protein  
PCSK9 = proprotein convertase subtilisin/  
kexin type 9  
SREBP-2 = sterol regulatory element-  
binding protein-2  
VLDL = very low density lipoprotein

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INTRODUCTION

Familial hypercholesterolemia (FH) is the most common and severe form of monogenic hypercholesterolemia.<sup>1</sup> FH was the first genetic disease of lipid metabolism to be clinically and molecularly characterized. A scientific breakthrough happened in the mid-1970s, when Brown and associates described the low-density lipoprotein (LDL)-receptor pathway;<sup>2</sup> Goldstein and Brown demonstrated that defects in the LDL-receptor cause FH,<sup>3</sup> a landmark discovery that earned the authors the Nobel Prize in Physiology or Medicine in 1985.<sup>4</sup>

The main biochemical abnormality in FH is elevated LDL-cholesterol in plasma, caused by reduced function of the LDL-receptor pathway, which removes LDL particles from the circulation into the liver.<sup>1</sup> The majority (>90%) of cases of FH are caused by mutations in the gene of the LDL receptor; however, less commonly the etiology of FH may also include mutations in the gene of apolipoprotein B (*apo B*), and the proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*). In addition to having an important structural role in LDL, apo B-100 also acts as a ligand for the LDL receptor

to facilitate clearance of LDL particles from plasma. Finally, rare heterozygous gain-of-function mutations in PCSK9 cause a severe form of FH by causing accelerated degradation of the LDL receptor. Patients with FH are characterized by a decreased clearance of LDL from the circulation and an increase in LDL synthesis; changes in homozygotes are more marked than in heterozygotes (a gene dosage effect).<sup>1</sup> If untreated, patients develop premature atherosclerotic coronary artery disease.

Hypercholesterolemia of whatever cause, typically due to a combination of environmental and genetic factors, is a major cardiovascular risk factor that accelerates the process of formation of atherosclerotic plaque,<sup>5</sup> thus increasing the incidence of cardiovascular events (myocardial infarction and stroke). Reduction in plasma LDL-cholesterol is a mainstay of treatment for the prevention of these potentially catastrophic events. Currently, statins constitute the cornerstone of hypolipidemic drug therapy,<sup>6,7</sup> as they reduce LDL-cholesterol levels by inhibiting the rate-limiting step in hepatic cholesterol synthesis; they block the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate by inhibiting the enzyme HMG-CoA reductase, resulting in increased expression of hepatic LDL receptors and increased clearance of circulating LDL-cholesterol.

Although statin therapy confers significant protection against acute coronary events in both primary and secondary prevention,<sup>6,7</sup> a considerable residual risk remains after intensive therapy. In addition, a significant proportion of high-risk patients do not achieve the optimal LDL-cholesterol goal recommended in the current guidelines.<sup>8</sup> Hence, novel LDL-cholesterol-lowering agents that act via mechanisms distinct from HMG-CoA reductase inhibition are under investigation.

**Apolipoprotein B-100** (Apo B-100) is the major apolipoprotein and an essential component of all atherogenic lipoproteins, namely very low density lipoproteins (VLDL), LDL, intermediate-density lipoprotein (IDL), and lipoprotein(a) - Lp(a).<sup>9,10</sup> Apo B-100 drives many of the functions of lipoproteins, including interaction with the LDL receptor. Plasma levels of apoB-100 are associated with a risk for cardiovascular disease. Incorporation of apoB-100 is necessary for the production and secretion of VLDL particles into the circulation. Hence, inhibition of apo B-100 synthesis would lead to decreased circulating levels of VLDL and all its remnant lipoproteins, including IDL, LDL, and Lp(a).

**Microsomal triglyceride transfer protein (MTTP)** is an endoplasmic reticulum-associated protein with a central role in the biosynthesis and the secretion of apolipoprotein B-containing lipoproteins.<sup>9,11</sup> Expressed in hepatocytes and enterocytes, MTTP mediates the transfer of neutral lipids (triglycerides and cholesterylesters) to the nascent apoB-100 and apoB-48 polypeptides, thereby promoting the assembly

of VLDL and chylomicrons, respectively. Owing to its pivotal role in VLDL assembly and secretion, MTTP inhibition has been considered as an efficacious strategy for the treatment of dyslipidemia. Its pharmacological inhibition is associated with a decrease in LDL cholesterol and triglycerides. The concept of MTTP inhibition has been further validated by reports in patients with abetalipoproteinemia, a rare autosomal recessive disorder characterized by defective and nonfunctional MTTP activity.<sup>9</sup> These patients have very low levels of apoB-containing lipoproteins in the circulation due to the absence of VLDL secretion and almost complete protection against atherosclerosis, albeit with significant hepatic accumulation of triglycerides, with ensuing steatosis and hepatomegaly, steatorrhea, elevated hepatic enzyme levels, and deficiencies of fat-soluble vitamins, untoward effects which are very similar to the side-effects of MTTP inhibitors.

**Proprotein convertase subtilisin/kexin type 9 (PCSK9)** is a proteinase K-like enzyme of the secretory subtilase family.<sup>12</sup> This protein is primarily synthesized and secreted by hepatocytes. The best-known biological function of PCSK9 is regulation of cholesterol homeostasis via accelerating the degradation of the LDL receptor by direct binding. PCSK9 decreases the LDL receptor density on the surface of hepatocytes either through inhibition of receptor recycling or through directing LDL receptors to lysosomal catabolism. Dominant gain-of-function mutations in the PCSK9 gene cause a phenotype similar to familial hypercholesterolemia (FH),<sup>13</sup> while loss-of-function variants are associated with hypocholesterolemia and prevention of coronary artery disease.<sup>14</sup>

Agents that inhibit PCSK9, apolipoprotein (apo) B, and MTTP are the most promising therapies. Inhibition of PCSK9, apoB, and MTTP has been achieved mostly via fully humanized monoclonal antibodies, antisense oligonucleotides, and synthetic compounds, respectively. PCSK9 inhibitors increase the hepatic uptake of LDL-cholesterol, while apoB and MTTP inhibitors decrease the synthesis and secretion of apoB-containing lipoproteins. These 3 mechanisms lead to marked reductions in plasma LDL-cholesterol in patients with hypercholesterolemia at risk for acute coronary events, particularly those with familial hypercholesterolemia. Moreover, these agents can exert additional benefits by decreasing plasma levels of apoB, triglycerides, and lipoprotein(a). Mipomersen and lomitapide have recently been approved by the United States (US) Food and Drug Administration (FDA) for use in patients with homozygous familial hypercholesterolemia. PCSK9 inhibitors are currently under final evaluation in clinical outcomes studies and are anticipated to find wide application either as monotherapy or as an adjunct to statins. A main safety concern is the risk for hepatic steatosis with apoB and MTTP inhibitors, which needs to be explored in prospective, long-term trials.

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**PROPROTEIN CONVERTASE SUBTILISIN  
KEXIN TYPE 9 (PCSK9)**


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Proprotein convertase subtilisin kexin type 9 (PCSK9), as described above, is a protein (serine protease) synthesized and secreted mainly by the liver which binds to hepatic low-density lipoprotein (LDL) receptors.<sup>15-17</sup> It regulates plasma LDL-cholesterol levels by diverting cell surface LDL receptors to lysosomes for degradation. In so doing, PCSK9 prevents the normal recycling of LDL receptors back to the cell surface. This process results in reduced LDL receptor density, decreased clearance of LDL-cholesterol, and, consequently, accumulation of LDL-cholesterol in the circulation. Thus, PCSK9 levels tend to correlate directly with LDL-cholesterol levels.<sup>18</sup>

Several mutations in the PCSK9 gene have been identified which are associated with either a hypocholesterolemic or hypercholesterolemic phenotype.<sup>13,15,19</sup> “Loss-of-function” mutations in PCSK9 decrease LDL receptor degradation and patients with these mutations have life-long low levels of LDL-cholesterol and appear to be protected from coronary artery disease with significantly reduced cardiovascular risk. Conversely, “gain-of-function” mutations accelerate LDL receptor degradation and carriers of these mutations present with elevated LDL-cholesterol levels and increased cardiovascular risk. In these patients, the clinical features are similar to those observed in FH patients with LDL receptor mutations.

Statins do not only upregulate LDL receptors, but they also simultaneously upregulate expression and secretion of PCSK9 via a process involving the sterol regulatory element-binding protein-2 (SREBP-2) transcription factor.<sup>19,20</sup> Elevation in PCSK9 levels further diminishes the number of LDL receptors, thereby blunting the efficacy of statins. This may explain why most LDL-cholesterol reduction is achieved with the starting dose of a given statin and why doubling the statin dose only further reduces LDL-cholesterol concentrations modestly. It has been alleged that statins follow a rule of 6% in that whatever LDL-cholesterol reduction is achieved at a starting dose of a given statin is only improved upon an additional approximate 6% with each doubling of the dose. Statin-induced increases in PCSK9 levels may, therefore, account for the less than expected incremental reduction of LDL-cholesterol concentrations in response to increasing doses of statins.<sup>19</sup> Therefore, introducing a PCSK9 antagonist on top of a statin is predicted to be additive to statins and further lower LDL-cholesterol.

Thus, the search for a novel lipid-lowering therapy has recently focused on developing pharmacological approaches that block the capacity of PCSK9 to degrade LDL receptors.<sup>21-28</sup> Several monoclonal antibodies are being currently assessed in human clinical trials. These studies indicate that PCSK9 inhibition could be an alternative monotherapy for hypercholesterolemic patients who cannot tolerate statins. It might also be an effective therapy for patients who have not

reached desirable LDL-cholesterol targets with use of statins. PCSK9 inhibitors used in combination with statins could reduce LDL-cholesterol levels further and may be of added benefit in the treatment of these high-risk patients.

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**PCSK9 INHIBITING AGENTS  
AND STUDIES**


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The particular biology of the PCSK9 protein has hindered efforts to find a small molecule and produce an oral PCSK9 inhibitor. However, the fact that this protein operates outside cells points to its vulnerability to attack by monoclonal antibodies. Indeed, the most promising therapeutic strategy to inhibit PCSK9-mediated degradation of the LDL receptor appears to be the use of injectable monoclonal antibodies, a proven successful, albeit very expensive, form of biological medicine.<sup>15</sup> Several monoclonal antibodies to PCSK9, which mimic the effects of genetic mutations by inhibiting PCSK9, have been developed and are in clinical trials (Table 1). Amgen Inc (Thousand Oaks, CA, USA) developed a humanized anti-PCSK9 monoclonal antibody that blocked the PCSK9:LDL-receptor interaction. In Phase I studies, Amgen’s antibody (AMG145, now named **Evolocumab**) lowered LDL-cholesterol by up to 64% in healthy subjects and by up to 81% in hypercholesterolemic statin-treated subjects with or without heterozygous FH. Evolocumab also significantly reduced ApoB (~55%) and lipoprotein(a).<sup>17</sup> Subsequently, evolocumab was tested in several 12-week Phase II studies. The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-intolerant Subjects (GAUSS) trial assessed the efficacy and tolerability of the antibody as a monotherapy in statin-intolerant hypercholesterolemic patients.<sup>21</sup> The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) trial tested evolocumab in patients with heterozygous FH with LDL-cholesterol  $\geq 100$  mg/dL despite statin therapy with or without ezetimibe.<sup>22</sup> The Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels (MENDEL) trial tested the antibody as a monotherapy in patients with hypercholesterolemia.<sup>23</sup> The LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-Thrombolysis in Myocardial Infarction 57 (LAPLACE-TIMI 57) trial assessed the antibody in combination with a statin in patients with hypercholesterolemia.<sup>24</sup> All four trials demonstrated that subcutaneous injections of evolocumab could reduce LDL-cholesterol by >50% either alone or in addition to other LDL-cholesterol-lowering therapies. Evolocumab was reported to be well tolerated, with no major adverse effects compared with placebo.

According with the results of phase II trial extension

TABLE 1. Novel Hypolipidemic Agents

Agent	Evolocumab (AMG 145)	Alirocumab (REGN727/SAR236553)	Bococizumab (RN 316)	LGT-209	RG7652 (MPSK3169A)	Mipomersen	Lomitapide
<b>Mechanism of action</b>	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor	Apolipoprotein-B inhibitor	MTTP inhibitor
<b>Type of inhibitor</b>	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody	Antisense oligonucleotide	9H-fluorene-carboxamide derivative
<b>Manufacturer</b>	Amgen	Sanofi/Regeneron	Pfizer/Rinat	Novartis/KaloBios	Roche/Genentech	Genzyme	Acertion
<b>Study Phase</b>	3	2/3	2/3	1/2	1/2	3	3
<b>Administration</b>	sc	sc	sc	sc	sc	sc	p.o.
<b>Studies</b>	GAUSS, <sup>21</sup> RUTHERFORD, <sup>22</sup> MENDEL, <sup>23</sup> LAPLACE-TIMI 57, <sup>24</sup> OSLER, <sup>25</sup> PROFICIO, DESCARTES (NCT01516879), FOURIER (NCT01764633), <sup>26</sup> TAUSSIG (NCT01624142), GLAGOV (NCT01813422), TESLA (NCT01588496)	3 phase I studies, <sup>27</sup> 2 phase II studies, <sup>28,29</sup> ODYSSEY Outcomes program (NCT01663402)	NCT01592240, SPIRE-LDL (NCT01968967), SPIRE-HR (NCT01968954), SPIRE-1 (NCT01975376), SPIRE-2 (NCT01975389)	NCT01979601 & NCT01859455	NCT01609140 http://eurheartj.oxfordjournals.org/content/34/suppl_1/P4183?	16 studies @: http://clinicaltrials.gov/ct2/results?term=mipomersen&Search=Search	10 studies @: http://clinicaltrials.gov/ct2/results?term=Lomitapide&Search=Search
<b>Liver metabolism</b>	No	No	No	No	No	No	CYP450/ CYP3A4
<b>Half-life</b>	2.5-11.5 d	3.2 d	7-13 d	?	?	30 d	29 h
<b>Dose</b>	140 mg q 2 weeks or 420 mg q 1 month	75/150 mg q 2 weeks	150 mg q 2 weeks	50/300 mg q ?	? mg q 4 weeks	200 mg q 1 week	5-60 mg/d
<b>Indications</b>	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	Severe familial hypercholesterolemia	Severe familial hypercholesterolemia

CVD = cardiovascular disease; MTTP = microsomal triglyceride transfer protein; PCSK9 = proprotein convertase subtilisin/kexin type 9; p.o. = per os; sc = subcutaneously

studies (Open-Label Study of Long-term Evaluation Against LDL-C / OSLER), recently presented at the American Heart Association Meeting in Dallas and simultaneously published online in *Circulation*,<sup>25</sup> evolocumab maintained drastically reduced cholesterol levels over 1 year. Mean reduction in LDL cholesterol was 52.1% over baseline at 1 year in the extension phase, similar to the 50.4% reduction seen in the initial 12-week phase II studies. Furthermore, patients in the control group in the initial studies who were switched onto the drug in the extension phase also demonstrated a mean 52.3% reduction in LDL over baseline by 1 year ( $P < 0.0001$ ). On the other hand, switching to statin therapy after initially being on evolocumab led to a return to baseline without rebound. There were no neutralizing anti-drug antibodies or other safety issues emerging during the extension phase. The OSLER study included 1,104 patients from four separate phase II dose ranging studies that lasted 12 weeks (GAUSS, LAPLACE-TIMI 57, RUTHERFORD, and MENDEL trials). All were randomized to either standard of care alone (including statin therapy) or open-label evolocumab subcutaneous injections at 420 mg every 4 weeks plus standard of care, regardless of their prior trial randomization. In the evolocumab group, LDL cholesterol levels dropped from a mean of 140 mg/dL to  $< 100$  mg/dL at week 52 for 86% of patients and to  $< 70$  mg/dL for 63%. For the standard-of-care arm, LDL cholesterol fell from a mean of 144 mg/dL at baseline to  $< 100$  mg/dL for 16% by 52 weeks and to  $< 70$  mg/dL for just 1%. The PCSK9 inhibitor also reduced lipoprotein(a) by 30-33% in the extension phase, compared with a 9-11% reduction among patients on standard of care in the extension ( $P < 0.0001$ ). Evolocumab also reduced apolipoprotein A and B and triglycerides significantly more than the control therapy. Adverse events and serious adverse events occurred in 81.4% and 7.1% of the evolocumab-plus-standard-of-care group patients and 73.1% and 6.3% of the standard-of-care-group patients, respectively. Musculoskeletal and connective tissue disorders were observed in 33.0% and 34.7% of patients when LDL dropped below 50 or 25 mg/dL, respectively, compared with ~25% in those with levels of  $\geq 50$  mg/dL. Injection site reactions occurred in ~5% of patients with evolocumab.

The effects of evolocumab on clinical outcomes will be assessed in the large phase 3 PROFICIO study program.<sup>15</sup> A very important trial is the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) study testing the effects of evolocumab on cardiovascular events in  $> 20,000$  patients with prior myocardial infarction or stroke, with at least 1 major or 2 minor coronary risk factors, and fasting LDL-cholesterol level  $\geq 70$  mg/dl or non-high-density lipoprotein cholesterol level of  $\geq 100$  mg/dl receiving maximal tolerated doses of atorvastatin with or without ezetimibe (NCT01764633).<sup>9,26</sup>

**Alirocumab** (formerly SAR236553/REGN727) is a highly specific, human monoclonal antibody to PCSK9 developed

by Regeneron Pharmaceuticals, Inc (Tarrytown, NY, USA) / Sanofi SA (Paris, France).<sup>27-29</sup> In a study, reporting the results of three phase 1 trials, the administration of alirocumab significantly reduced LDL cholesterol levels in healthy volunteers and in patients with familial or nonfamilial hypercholesterolemia; the effect was also significant in subjects who were concomitantly taking atorvastatin (further reduction of LDL-cholesterol concentrations by up to 68%).<sup>27</sup> A recent placebo-controlled study evaluated the LDL-cholesterol-lowering effect of 5 dosing regimens of alirocumab (50, 100, or 150 mg every 2 weeks; or 200 or 300 mg every 4 weeks) vs placebo for a total treatment period of 12 weeks in 183 patients with LDL-cholesterol  $\geq 100$  mg/dl maintained on stable atorvastatin therapy (10, 20, or 40 mg for  $\geq 6$  weeks).<sup>28</sup> This novel agent demonstrated a clear dose-response relationship with respect to percentage LDL-cholesterol lowering for both every 2 and 4 weeks regimens: 40%, 64%, and 72% with 50, 100, and 150 mg every 2 weeks, respectively, and 43% and 48% with 200 and 300 mg every 4 weeks. LDL-cholesterol reduction with placebo at week 12 was 5%. Alirocumab also substantially reduced non-HDL cholesterol, apolipoprotein B, and lipoprotein(a). The drug was generally well tolerated. One patient on the drug experienced a serious adverse event of leukocytoclastic vasculitis. The authors concluded that PCSK9 inhibition with alirocumab added to atorvastatin therapy further reduces LDL-cholesterol by 40-72%. These additional reductions were both dose- and dosing frequency-dependent.

In another phase 2 study, 77 patients with heterozygous FH were randomly assigned to receive alirocumab 150 mg, 200 mg, or 300 mg every 4 weeks, or 150 mg every 2 weeks, or placebo every 2 weeks. LDL-cholesterol reduction from baseline to week 12 ranged from 29% for 150 mg every 4 weeks to 68% for 150 mg every 2 weeks ( $p < 0.0001$ ), compared with 10.65% with placebo.<sup>29</sup> No increases of  $> 3$  times the upper limit of normal were observed for hepatic transaminases or creatinine kinase. The most common adverse event was injection-site reaction with one patient in the group of 300 mg alirocumab terminating treatment. The authors concluded that the new drug was well tolerated and achieved substantial further LDL-cholesterol reduction in patients with heterozygous FH treated with high-dose statins, with or without ezetimibe. Finally, the effects of alirocumab on clinical events are being assessed in the large phase 3 ODYSSEY study program including the ODYSSEY Outcome trial in 18,000 patients with a recent acute coronary syndrome (NCT01663402) (Table 1).<sup>9,15,17</sup>

More programs using monoclonal antibodies inhibiting PCSK9 are in development, some of which are included in Table 1. To date, the two different commercial development programs presented above, which have produced the bulk of clinical data, have demonstrated significant success in lowering LDL-cholesterol in phase 1 and 2 trials with similar agents (Evolocumab and Alirocumab). When administered subcutaneously at doses ranging from 50 to 150 mg every 2 weeks or 200

to 400 mg every 4 weeks, respectively, these agents produced similar dose-responses in LDL-cholesterol lowering. In hypercholesterolemic patients, LDL-cholesterol reductions ranged up to 60%, and, as would be expected, an even greater response was reported for statin-treated hypercholesterolemic patients with up to 70% decrease. LDL-cholesterol has typically shown a gradual increase after the nadir as monoclonal antibodies are cleared from the circulation. Results to date indicate that the PCSK9 monoclonal antibody approach appears safe, well-tolerated, and significantly lowers LDL-cholesterol levels while also favorably affecting apolipoprotein B, triglycerides, lipoprotein (a), and HDL-cholesterol. This novel hypolipidemic therapy is expected to meet an important clinical need for patients unable to achieve adequate LDL-cholesterol-lowering with currently available therapies.

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#### OTHER NOVEL HYPOLIPIDEMIC AGENTS

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Several other new agents are under investigation for their potentially beneficial treatment of homozygous familial hypercholesterolemia. Just recently, about 1 year ago, the first microsomal triglyceride transfer protein inhibitor, lomitapide, and the first antisense therapy to target apolipoprotein B, mipomersen, were granted FDA approval for the treatment of homozygous familial hypercholesterolemia, whereby LDL-cholesterol levels are extremely elevated.

Mipomersen (Kynamro™, Genzyme), administered as once-weekly subcutaneous injection, is a second-generation antisense oligonucleotide inhibitor targeted to human apolipoprotein B (apoB)-100.<sup>10,30,31</sup> Basically it is a nucleotide that is the mirror image of the mRNA that encodes the apoprotein B-100 protein and blocks its formation. Mipomersen is distributed mainly to the liver where it silences apoB mRNA, thereby reducing hepatic apoB-100 and leading to decreases in plasma total cholesterol, LDL-cholesterol, and apoB concentrations in a dose- and time-dependent manner. When given to FH patients on maximally tolerated doses of lipid-lowering therapy, LDL-cholesterol decreased by an additional 25%. The short-term efficacy and safety of mipomersen appears to have been established, however, injection site reactions are common and concern exists regarding the long-term potential for hepatic steatosis. Thus, mipomersen given alone or in combination with standard lipid-lowering medications shows promise as an adjunct therapy in patients with homozygous or refractory heterozygous FH at high risk of coronary artery disease, who are not at target or are intolerant of statins.

Lomitapide (Juxtapid™/Lojuxta™, Aegerion Pharmaceuticals), an oral inhibitor of the microsomal triglyceride transfer protein, inhibits the synthesis of chylomicrons and very low-density lipoprotein, thus reducing plasma levels of LDL-cholesterol by 40% in homozygous FH, as demonstrated

in a multinational single-arm, open-label, 78-week, phase III trial, including 23 adults with homozygous FH.<sup>32</sup> The initial dosage of lomitapide in the study was 5 mg once daily for two weeks, with upward titration up to 60 mg within 2-14 weeks as tolerated. Prior to commencing treatment with lomitapide, therapy with other lipid-lowering interventions (including LDL apheresis) was stabilized over a 6-week period, and continued throughout the lomitapide treatment phase. Lomitapide was generally well tolerated; the most common adverse events were gastrointestinal side-effects; importantly, transaminase elevation was noted in 34% of patients; it also caused hepatic steatosis with or without transaminase elevation.

These new hypolipidemic agents (lomitapide and mipomersen) have the ability to significantly lower LDL-cholesterol, apo B, and non-HDL cholesterol levels, when administered concurrently with other lipid-lowering therapies. However, these agents carry a black box warning regarding the risk for transaminase elevations and hepatic steatosis, and are currently restricted by the FDA for use only in patients with homozygous FH. Long-term safety and tolerability remain dubious. Inordinately high cost and potential risk for hepatotoxicity are currently the major limiting factors for their wider use.<sup>11</sup>

The cholesteryl ester transfer protein (CETP) transfers cholesteryl esters from high-density lipoprotein (HDL) to the apoB-containing lipoproteins. CETP deficiency leads to increased levels of HDL-cholesterol. Thus, inhibition of CETP was considered to be a target to increase HDL-cholesterol and potentially reduce atherosclerosis. Unfortunately, CETP inhibitors, like torcetrapid and dalcetrapid, either produced harm or failed to show any clinical benefit.<sup>10</sup> Anacetrapib added to statin therapy has been demonstrated to reduce LDL-cholesterol by a further ~40% and increase HDL-cholesterol by ~140%.<sup>33</sup> Whether it confers any clinical benefit by preventing cardiovascular events, is currently being investigated in the REVEAL trial.<sup>34</sup>

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#### PERSPECTIVE

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Most recently, new guidelines on cholesterol management were issued by the American Heart Association and the American College of Cardiology recommending strong measures for patients at particularly high risk of cardiovascular events, which include more aggressive therapy with the most potent statins, which are the only class of cholesterol-lowering drugs that the guidelines recommend for patients who can tolerate them.<sup>35</sup> The guidelines dropped an emphasis on specific targets for lowering LDL levels. Instead, they suggest that individual patient risk assessment of developing heart disease rather than an LDL number should be used to determine the need for more intensive treatment. Thus, there is a concern that these guidelines that favor potent statins may threaten use or even approval of any new class of investigational cholesterol drugs

even if they are presented as more potent than conventional statin therapy. A potential drawback of the new agents is their injectable form compared to the convenience of oral formulation of statins. Another major issue pertains to the results of future outcome studies with these novel agents. It is not just the degree of reduction in LDL-cholesterol that these agents confer, but the main point relates to whether this indeed impressive reduction translates into an improved patient outcome. The regulatory authorities may not approve the new agents on the basis of their ability to lower LDL cholesterol, but when and if the evidence of these ongoing “outcomes studies” eventually proves that the new agents actually lower the risk of cardiovascular events and the prediction is that these results will not be available before late 2017 or early 2018. Of course, there is always a safety issue with any new drug, and the results of just one-year follow-up is too short to draw any conclusions at all. Finally, cost issues will also prevail when these drugs become available, while the subcutaneous route of administration might be a problem and some may wish to wait for other oral alternatives,<sup>15,36</sup> and many may put forth the issue of pleiotropic effects of statins which these newer agents do not seem to possess.

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### CONCLUSION

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Proprotein convertase subtilisin/kexin type (PCSK9) protein plays an important role in the degradation of the LDL receptor and therefore in the LDL cholesterol catabolism. Preliminary clinical data of PCSK9 inhibition are quite promising and indicate that the novel hypolipidemic agents targeting PCSK9, i.e. the PCSK9 inhibitors, may be a most effective treatment modality for dyslipidemia, particularly for those patients with refractory hypercholesterolemia, statin intolerance, or an elevated lipoprotein(a) level and associated cardiovascular diseases. The most promising approach to inhibit PCSK9 activity appears to be the use of monoclonal antibodies, which produce a 50 - 70% LDL cholesterol reduction in addition to and to a greater extent than what has previously been attainable by maximal doses of statins. The most recent results of phase II clinical studies are promising and indicate a significant effect of LDL cholesterol reduction sustained over one year. However, apart from exuberant cost issues that need to be settled, safety and outcomes studies are needed with much longer clinical follow-up, before these agents are more widely adopted.

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