The Role of PCSK9 in Lipid Metabolism and its Relationship to New Therapies for Lowering Cholesterol and Reducing Cardiac Disease

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ABSTRACT

The treatment of atherosclerosis includes changing lifestyle (e.g. changing diet and exercise regimens, losing weight, stopping smoking, managing stress), performing medical procedures (e.g. bypass surgery) and medical interventions involving primarily statins. Despite excellent safety profiles, the major limitation of statins is their muscle and liver toxicity that occurs in some patients. Since non-statin therapies only modestly reduce LDL cholesterol, alternatives are needed for patients not tolerating statins or in clinical cases of familial hypercholesterolemia where even statins are ineffective. Over the past 12 years, an amazing series of studies have identified proprotein convertase subtilisin/kexin type-9 (PCSK9) as a new target to treat high cholesterol that is the underlying cause of atherosclerosis and cardiovascular disease. The liver-derived PCSK9, a gene found on the short arm of chromosome 1 that encodes a 692 amino acid protein, was initially discovered as neural apoptosis-regulated convertase 1 (NARC-1) in cancer cell lines and implicated in the differentiation of cortical neurons in 2003. Subsequently, neutralizing PCSK9 antibodies were developed and proven clinically effective in pre-clinical studies. Since then, Phase I, II, and most recently Phase III human trials have tested applied anti-PCSK9 antibodies to patients intolerant of statins and familial hypercholesterolemia. In this review, we discuss the role of PCSK9 in regulating cholesterol and summarize the promising findings of blocking PCSK9 with antibodies in human clinical trials. While the efficacy of blocking PCSK9 using antibodies to treat high cholesterol is still forthcoming in at least 12 ongoing Phase III clinical studies, anti-PCSK9 antibodies appear effective with minimal safety or tolerance issues identified to date. Blocking PCSK9 may offer a viable complement to statin therapies, which are not universally tolerated or effective with all patient populations.

Key words: Atherosclerosis; PCSK9; Statin; Cholesterol; Lipid metabolism


Nonstandard Abbreviation and Acronyms

vLDL: very-low-density lipoprotein; IDL: intermediate density lipoprotein; LDL: low-density lipoprotein; HDL: high density lipoprotein; LDLR: low-density lipoprotein receptor; PCSK9: proprotein convertase subtilisin-like/kexin type 9; IHD: ischemic heart disease; TC: total cholesterol; PCR: polymerase chain reaction; CAD: coronary artery disease; IS: ischemic stroke
TREATING ATHEROSCLEROSIS: TODAY

The treatment of atherosclerosis, the underlying cause of cardiovascular disease, involves lifestyle changes (e.g., changing diet and exercise regimens, losing weight, stopping smoking, managing stress) and medical interventions involving primarily statins in those that can tolerate them. The goal in treating atherosclerosis is to slow the buildup of plaques, lower the risk of blood clots, relieve symptoms (if present), and prevent heart attacks (stroke, intestinal ischemia, peripheral artery disease). Lowering LDL, triglycerides, or overall cholesterol are the three primary ways in which medicines target atherosclerosis. Despite the excellent safety profile of statins, muscle toxicity is the major limitation for its use. Non-statin therapies are available, but their effectiveness in reducing LDL cholesterol concentrations is modest (15%-20%) compared with those obtained with a full-dose statin regimen. Thus, patients at high cardiovascular risk who are unable to achieve LDL cholesterol goals or to tolerate effective doses of statins because of muscle-related side effects represent a difficult population to treat. This class of medicine most widely used to lower cholesterol today are statins, which are HMG-CoA reductase inhibitors, which lower LDL cholesterol by reducing cholesterol synthesis in the liver.

TREATING ATHEROSCLEROSIS AND HIGH CHOLESTEROL: TARGETING PCSK9 IN THE FUTURE?

A number of studies were published recently investigating proprotein convertase subtilisin/kexin type-9 (PCSK9) as a new target to treat atherosclerosis. How it became a new target of interest has involved some new discoveries teaching us that our understanding of how lipid metabolism is regulated is more complex than previously thought. The liver-derived PCSK9, a gene found on the short arm of chromosome 1 that encodes a 692 amino acid protein, was initially discovered as neural apoptosis-regulated convertase 1 (NARC-1) in cancer.
cell lines and implicated in the differentiation of cortical neurons in 2003[17]. Since then, therapies targeting PCSK9 to lower LDL-C have been successfully developed in pre-clinical trials and more recently multiple ongoing and completed Phase III human trials, which we discuss here.

The role of regulation of PCSK9 in regulating lipid metabolism

PCSK9 influence on cholesterol was evident in observational Dallas Heart Studies of multi-ethnic probability-based sample of Dallas County[23]. One striking finding in these studies was the variability of circulating plasma PCSK9 concentrations found in patients. PCSK9 levels varied 100 fold, ranging from 33 to 2988 ng/mL (median 487 ng/mL), and correlating closely with LDL-C[13]. PCSK9 levels were significantly higher in women (517 ng/mL) than men (450 ng/mL) and correlated with LDL-C, plasma triglycerides, insulin, and glucose[13]. Follow-up studies identified patients with loss of function PCSK9 mutations and reduced plasma levels of LDL-C had significantly lower levels of PCSK9, adjusting for age, gender, and LDL-C levels (p<0.0001)[14]. While these results suggested that inhibiting PCSK9 activity may be therapeutically beneficial, the underlying mechanism at the time was unclear[14]. One of the unique characteristics of PCSK9 is that plasma PCSK9 concentrations vary minimally in response to short term high fat challenges and is not accompanied by changes in hypercholesterolemia induced by high-fructose diets[14]. Short term high-fructose diet, however, increases plasma PCSK9 suggesting that PCSK9 is regulated by SREBP-2, associated with insulin resistance, hepatic steatosis, and plasma triglycerides[14]. Together, these studies suggest that PCSK9 regulates triglyceride-rich lipoproteins, a common contributor to cardiovascular disease in diabetes mellitus and a difficult to control factor in its pathogenesis and disease progression.

PCSK9 and LDL-apoB Catabolism

The association between PCSK9 and the degradation of the LDL receptor in patients was investigated next in patients with a wide range of body mass index values[15]. Like the relationship identified in PCSK9 mutations, plasma PCSK9 concentration correlated with cholesterol, LDL-C, and LDL apoB-100 concentrations and inversely correlated with the LDL Apo B-100 fractional catabolic rate[15]. This association remained statistically significant after adjusting for age, obesity, plasma insulin, insulin resistance measures (HOMA), and dietary energy intake[15]. These studies were vital in determining that PCSK9 levels were independent of obesity, insulin resistance, energy intake and age and directly linked the Apo B-100 catabolism with PCSK9, accounting for nearly 50% of the correlation (r=-0.456, p=0.038)[15]. Subsequently, mice expressing human PCSK9 were created to identify how PCSK9 and LDLR interact. These studies supported a role for LDLR in eliminating PCSK9, which reciprocally reduces LDLR expression. In this way, serum PCSK9 levels and hepatic LDLR expression and serum LDL levels reciprocally balance each other's activity and offer a mechanism in which reducing PCSK9 results in the reduction of serum lipoproteins and cholesterol[15].

Critical Role of cleaving PCSK9 to inactivate in vivo

The formation and inactivation of PCSK9 is a multi-step process, with the 62 kDa proprotein secreted in liver, intestine, and kidney tissues[15]. As an escort protein to the lysosomal degradatory pathway, it is cleaved after the R218 residue, resulting in the detachment and formation of a 55 kDa inactive form of PCSK9[15]. The proteolysis of PCSK9 is mediated by two proprotein convertases in hepatocytes, named furin and PC5/6A[16,20]. Evidence supporting this cleavage site includes missense mutations in the R218 residue that prevent inactivation in PCSK9 (e.g. R218S), result in an autosomal dominant hypercholesterolemia[21]. Mechanistically, these studies indicate that PCSK9 inactivation by furin and PC5/6A lead to an increased in proteins degraded by PCSK9 (e.g. LDLR, VLDL, ApoER2) responsible for clearing circulating lipoproteins. In turn, hypercholesterolemia results.

In summary, PCSK9 was found to be responsible for inhibiting the clearance involved in lipid metabolism, at the level of the liver. Specifically, PCSK9 was found to clear the LDL receptor (LDLR), VLDL receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2), all of which are critical to clearing and ultimately reducing circulating cholesterol levels (see Figure 1)[22]. Since PCSK9 activity reduces the clearance mechanisms needed to prevent lipid accumulation, inhibiting its activity would be predicted to reduce cholesterol levels, as patients with PCSK9 loss of function mutations demonstrated. This hypothesis was tested by the development of therapies to reduce PCSK9 activity and expression.

TARGETING PCSK9 THERAPEUTICALLY TO REDUCE CHOLESTEROL AND RISK OF CV DISEASE

Cholesterol lowering drugs, such as statins, and fibrates lower PCSK9, despite being developed against other targets[23]. Statin therapies up-regulate PCSK9 in hepatocytes to a greater extent than they increase the expression of the LDLR itself[24]. This finding reveals the paradox of statins, which increase LDLR activity, resulting in lowering LDL-C on the one hand, while simultaneously increasing the expression of PCSK9 on the other hand, an effect resulting in LDLR degradation (and opposing LDL-C lowering effects[24]). Treating hypercholesteremic patients with statins results in increased PSCK9 vs. controls, while increasing statin dose and adding ezetimibe further enhanced PCSK9 levels, opposing the observed decreases in cholesterol seen[25]. Later studies reported different results. In these randomized clinical trials, it was confirmed that simvastatin, but not the fibrate ezetimib, resulted in upregulating circulating PCSK9 levels[26]. Since fibrates significantly modify PCSK9 concentrations, it may be by indirectly modifying cholesterol levels[24]. Bile acid binding resins have also been found to increase PCSK9 gene expression in human liver biopsies[26], while reduction of lipoproteins by apheresis results in a 50% reduction of PCSK9 levels by trapping LDL-bound and Apo B-free PCSK9 in the apheresis.

PCSK9 inhibitors in Clinical Trials

Phase I Clinical Trials. An anti-sense nucleotide targeting PCSK9 was begun in a Phase I clinical trial. However, it was terminated prematurely and no ongoing trials pursuing anti-sense oligonucleotides of PCSK9 are currently underway[27]. The use of small interfering RNA (siRNA) against PCSK9, which binds messenger RNA of PCSK9 and reduces protein expression, has been used to reduce LDL-C. In Phase I clinical trials, healthy volunteers given siRNA had significantly lower levels of PCSK9, adjusting for age, gender, and LDL-C. In Phase I clinical trials, healthy volunteers given siRNA had significantly lower levels of PCSK9, adjusting for age, gender, and LDL-C[18]. Mechanistically, these studies indicate that PCSK9 mutations and reduced plasma levels of LDL-C had significantly lower levels of PCSK9, adjusting for age, gender, and LDL-C levels (p<0.0001)[14]. While these results suggested that inhibiting PCSK9 activity may be therapeutically beneficial, the underlying mechanism at the time was unclear[14]. One of the unique characteristics of PCSK9 is that plasma PCSK9 concentrations vary minimally in response to short term high fat challenges and is not accompanied by changes in hypercholesterolemia induced by high-fructose diets[14]. Short term high-fructose diet, however, increases plasma PCSK9 suggesting that PCSK9 is regulated by SREBP-2, associated with insulin resistance, hepatic steatosis, and plasma triglycerides[14]. Together, these studies suggest that PCSK9 regulates triglyceride-rich lipoproteins, a common contributor to cardiovascular disease in diabetes mellitus and a difficult to control factor in its pathogenesis and disease progression.

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Phase II trials to assess the LDL-C lowering by PCSK9 inhibitors

**Frequency of administration**

Phase II trials to assess the LDL-C lowering by PCSK9 inhibitors using different administration frequencies have been completed\[56\]. SAR236553, a fully human monoclonal antibody to PCSK9, has been tested in a double-blind, parallel group, placebo controlled randomized trial of 183 patients with LDL-C ≥ 100 mg/dL on stable-dose atorvastatin 10, 20, or 40 for ≥ 6 weeks in Phase 2 clinical trials\[56\]. SAR236553 had a clear dose-response with respect to LDL-C lowering when given every 2 weeks (Q2W) or every 4 weeks (Q4W). Reductions in 40%, 64%, and 72% with 50, 100, and 150 mg Q2W were seen, with reductions in 43% and 48% with 200 and 300 mg Q4W\[56\]. Notably, patients enrolled found the drug generally well tolerated, with only myalgia occurring in 15.6% of the 280 mg mibe group compared to the -14 mg/dL seen in the placebo/ezetimibe group \(p<0.001\)\[56\]. The short-term tolerability was good in these studies, with only myalgia occurring in 15.6% of the 280 mg group, 3.2% in the 350 mg group, and 3.1% in the 420 mg group\[56\].

**Phase III clinical trials of monoclonal anti-PCSK9 antibodies**

Six (6) Phase III clinical trials investigating monoclonal antibodies against PCSK9 have been completed, with nine (9) ongoing, including Evolocumab, Bococizumab, and Alirocumab. In the completed studies, Alirocumab is the only drug that has been tested to date. The focus of these studies has been on patients with statin intolerance and familial hypercholesterolemia. Statin intolerance occurs in ~5-10% of patients taking statins resulting in myalgia, rhabdomyolysis, and elevated liver enzymes, while familial hypercholesterolemia, occurring in 1/200 – 1/500 people, is characterized by extremely high LDL-C concentrations and the development of atherosclerosis and cardiovascular disease at a young age\[56\]. Patients unable to reach LDL cholesterol goals with high dose statins may also benefit from PCSK9 inhibitors, which have also been investigated in these Phase III studies. Since PCSK9 inhibitors effectively reduce LDL-C when added to statins, they may be effective against cardiovascular disease complications.

In the ODYSSEY ALTERNATIVE (NCT01709513), the efficacy and safety of Alirocumab was tested against two comparator therapies: ezetimibe (a drug inhibiting cholesterol absorption from the gut) and a statin (atorvastatin), along with two placebos for 24 weeks in this Phase III trial\[57\]. In this ongoing randomized study, patients with primary hypercholesterolemia intolerant to statins are followed for the primary outcomes of change in LDL-C at baseline compared to 24 weeks of therapy.

In the ODYSSEY OPTIONS I trial, patients with inadequately controlled hypercholesterolemia and high cardiovascular disease risk were studied for Alirocumab LDL-C reduction as an add-on therapy to atorvastatin compared to ezetimibe as an add-on to atorvastatin, compared to double atorvastatin dose, compared to switching from atorvastatin to rosuvastatin after 24 weeks of treatment\[58\]. The ODYSSEY OPTIONS II trials tested Alirocumab in hypercholesterolemia not adequately controlled in patients with high cardiovascular disease risk to evaluate Alirocumab LDL-C reduction as an add-on therapy to rosuvastatin, ezetimibe as an add-on to rosuvastatin, compared to double atorvastatin dose, compared to switching from atorvastatin to rosuvastatin after 24 weeks of treatment\[58\]. Together, these studies demonstrated the long-term efficacy and safety in high-risk patients when given with a maximally tolerated statin, allowing for therapy based on the degree of LDL-C lowering needed on an individual basis to achieve the goal treatment response.

In the ODYSSEY FH I (NCT01623115), trials, patients with heterozygous familial hypercholesterolemia and inadequately controlled LDL-C with current lipid-modifying therapy were evaluated for the effect of Alirocumab compared to placebo on LDL-C after 24 weeks of treatment\[59\]. In this trial completed in Dec. 2014, heterozygous familial hypercholesterolemia patients inadequately controlled with maximally tolerated statin with or without other lipid-modifying therapy were treated with Alirocumab to demonstrate reduction in LDL-C compared to placebo as an add-on therapy to stable, maximally tolerated daily statin therapy with or without other lipid-modifying therapy for 24 hours\[60\]. The ODYSSEY FH II (NCT01709500) phase 3 trial comparing atorvastatin, simvastatin, or rosuvastatin vs Alirocumab, vs. placebo, was completed in January 2015. The ODYSSEY HIGH FH (NCT01617655) investigated Alirocumab in heterozygous familial hypercholesterolemia and LDL-C levels ≥ 160 mg/dL for its efficacy, safety, and tolerability.

**What Phase III Studies have learned: Safety and tolerance of anti-PCSK9 antibodies**

While the final clinical results have yet to be published, we do have information on the safety and tolerance of anti-PCSK9 preliminarily. Phase III trials have found that 36-75% of patients given PSCK9 inhibitors had adverse events, with 2-6% of them serious. Discontinuation of the drug occurred in 2-10% of patients, a rate comparable to the group being compared\[59\]. Liver function tests >3 times upper normal limit (aminotransferases) were found in <2% of the patients; abnormal elevations in creatine kinase were similarly rare\[60\]. Anti-drug antibodies were not detected, which could potentially alter PCSK9 inhibitor pharmacokinetics in either LDL-C concentrations or safety in any Phase III trials.

Injection site reactions were observed in 1/52 patients in the Odyssey MONO trials vs 2/51 in the placebo group at 24 weeks\[60\]. At 52 weeks, the OSLER trials reported only 1/38 patients with an injection-site reaction\[60\]. The DESCRUTES study found 34/599 patients (5.7%) in the Evolocumab group and 14/302 (5.0%) in the placebo group experienced injection-site reactions, with only 1 discontinuing Evolocumab\[60\]. In the ODYSSEY COMBO II Study, approximately 85% of patients were taking medication (or placebo) at 1 year, indicating a good tolerance of parenteral LDL-C lowering therapy\[60\]. While more detail of these profiles will be forthcoming, the studies have been suggestive of a generally safe and well tolerated therapy relative to currently available treatments.
A non-exhaustive list of the major trials underway accessed from clinicaltrials.gov (17 August 2015). Visit clinicaltrials.gov for updates.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th><a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> #</th>
<th>Status</th>
<th>Study description and basic outline</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLAGOV (Evolocumab)</td>
<td>NCT01813422</td>
<td>Active, not recruiting.</td>
<td>This study will evaluate whether low-density lipoprotein (LDL-C) lowering with Evolocumab (AMG 145) results in greater change from baseline in percent atheroma volume (PAV) at week 78 than placebo in subjects with coronary artery disease taking lipid lowering therapy. The primary hypothesis is that additional LDL-C lowering with Evolocumab (AMG 145) when used in addition to other treatment for dyslipidemia is well tolerated and decreases the risk of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization in subjects with clinically evident cardiovascular disease.</td>
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<tr>
<td>FOURIER (Evolocumab)</td>
<td>NCT01764633</td>
<td>Active, not recruiting.</td>
<td>A study to assess the long term safety and efficacy of Evolocumab (AMG145)on Low Density Lipoprotein-Cholesterol (LDL-C) in subjects with severe familial hypercholesterolemia.</td>
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<tr>
<td>TAUSSIG (Evolocumab)</td>
<td>NCT01624142</td>
<td>Ongoing, not recruiting participants</td>
<td>This study is a multicenter, randomized study in subjects with high cholesterol receiving highly effective statins to assess the efficacy, safety and tolerability of Bococizumab (PF-04950615;RN316) to lower LDL-C.</td>
</tr>
<tr>
<td>SPIRE-HF (Bococizumab)</td>
<td>NCT01968980</td>
<td>Recruiting participants</td>
<td>A 52 Week, Phase 3 Double-blind, Randomized, Placebo-controlled, Parallel-group Study To Assess The Efficacy, Safety And Tolerability Of PF-04950615 In Subjects With Heterozygous Familial Hypercholesterolemia</td>
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<tr>
<td>SPIRE-HR (Bococizumab)</td>
<td>NCT01968954</td>
<td>Recruiting participants</td>
<td>This study is a multicenter, randomized study in subjects with high cholesterol receiving highly effective statins to assess the efficacy, safety and tolerability of Bococizumab (PF-04950615;RN316) to lower LDL-C.</td>
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<tr>
<td>SPIRE-LDL (Bococizumab)</td>
<td>NCT01968967</td>
<td>Recruiting participants</td>
<td>This study evaluates the PCSK9 inhibitor, Bococizumab (PF-04950615;RN316), compared to placebo, in reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization, in high risk subjects who are receiving background lipid lowering therapy and have cholesterol laboratory values of LDL-C &gt;/= 70 mg/dL (1.8 mmol/L) and &lt; 100 mg/dL (2.6 mmol/L) or non-HDL-C &gt;/= 100 mg/dL (2.6 mmol/L) and &lt; 130 mg/dL (3.4 mmol/L).</td>
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<tr>
<td>SPIRE-1 (Bococizumab)</td>
<td>NCT01975376</td>
<td>Recruiting participants</td>
<td>This study evaluates the PCSK9 inhibitor, Bococizumab (PF-04950615;RN316), compared to placebo, in reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization in high risk subjects who are receiving background lipid lowering therapy and have cholesterol laboratory values of LDL-C &gt;/= 100 mg/dL (2.6 mmol/L) or non-HDL-C &gt;/= 130 mg/dL (3.4 mmol/L).</td>
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<tr>
<td>SPIRE-2 (Bococizumab)</td>
<td>NCT01975389</td>
<td>Recruiting participants</td>
<td>Primary Objective: To compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are treated with evidence-based medical and dietary management of dyslipidemia.</td>
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<tr>
<td>ODYSSEY OUTCOMES (Alirocumab)</td>
<td>NCT01663402</td>
<td>Recruiting participants</td>
<td>The primary hypothesis is that both dosing regimens of Evolocumab (AMG 145) subcutaneous will be well tolerated and will result in greater reduction of Low Density Lipoprotein-Cholesterol in subjects with primary hypercholesterolemia and mixed dyslipidemia.</td>
</tr>
<tr>
<td>LAPPLACE-2 LDL-C Assessment w/ PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2</td>
<td>NCT01763866</td>
<td>Completed</td>
<td>The study is divided into 3 parts (A, B, C). Part A is a double-blind, placebo-controlled, two-period cross-over rechallenge of atorvastatin 20 mg. Part B is a 24-week double-blind, double-dummy comparison of Evolocumab and ezetimibe. Part C is a 2-year open-label Evolocumab extension. The primary hypothesis is that Evolocumab will be well tolerated and will result in greater reduction of LDL-C than ezetimibe, defined by the mean percent change from baseline at Weeks 22 and 24 of Part B and percent change from baseline at Week 24 of Part B, in statin-intolerant hypercholesterolemic subjects.</td>
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<td>Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3</td>
<td>NCT01984424</td>
<td>Ongoing, not recruiting</td>
<td>A study to assess safety and efficacy of Evolocumab (AMG-145) in pediatric subjects aged 10-17 years diagnosed with heterozygous familial hypercholesterolemia.</td>
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<tr>
<td>HAUSER-RCT</td>
<td>NCT02392559</td>
<td>Not yet open for recruitment</td>
<td>This study evaluates change over time in neurocognitive testing in subjects receiving statin therapy in combination with Evolocumab (AMG 145), compared with subjects receiving statin therapy in combination with placebo.</td>
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<tr>
<td>EBBINGHAUS</td>
<td>NCT02207634</td>
<td>Currently recruiting participants</td>
<td>This study evaluates change over time in neurocognitive testing in subjects receiving statin therapy in combination with Evolocumab (AMG 145), compared with subjects receiving statin therapy in combination with placebo.</td>
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</table>
DISCUSSION

The major limitation of statin therapies has been their muscle and liver toxicity that occurs in some patients. Alternatives to statins only modestly reduce LDL-C, while patients with extreme hypercholesterolemia due to genetic mutations often need more than statins alone to reduce LDL-C. Here we presented the emerging evidence for PCSK9 as a new target to treat high cholesterol, in addition to specific therapies inhibiting PCSK9 activity to reduce cholesterol in Phase I-III clinical trials. While the efficacy of blocking PCSK9 using antibodies to treat high cholesterol is still forthcoming in at least 12 ongoing Phase III clinical studies (Table 1), anti-PCS9 antibodies appear effective with minimal safety or tolerance issues identified to date. Blocking PCSK9 may offer a viable complement to statin therapies, which are not universally tolerated or effective with all patient populations. While there is much to learn about PCSK9 before being accepted in practice, they offer a new hope and alternative to treating cardiovascular disease and atherosclerosis and will likely become a milestone on the road to curing hypercholesterolemia.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

10. Meyers CD, Moon YS, Ghanem H, Wong ND. Type of preexisting intolerance or tolerance issues identified to date. Blocking PCSK9 may offer a viable complement to statin therapies, which are not universally tolerated or effective with all patient populations. While there is much to learn about PCSK9 before being accepted in practice, they offer a new hope and alternative to treating cardiovascular disease and atherosclerosis and will likely become a milestone on the road to curing hypercholesterolemia.

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