NEW DRUGS FOR LOWERING LDL-CHOLESTEROL

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NEW DRUGS FOR LOWERING LDL-CHOLESTEROL (Abstract): LDL-Cholesterol (LDL-C) is a well-known risk factor for cardiovascular disease. Although statins are the mainstream treatment for lowering LDL-C level, additional LDL-lowering therapies are needed to reduce residual cardiovascular risk, especially in patients at very high risk, or with hereditary lipid disorders or statin intolerance. The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator for LDL-Receptor activity and an attractive target for the treatment of hypercholesterolaemia. From its discovery in 2003, several therapeutic approaches to the inhibition of PCSK9 have been proposed. Monoclonal antibodies that bind to PCSK9 received marketing approval in 2015 (alirocumab and evolocumab) or are being evaluated in phase III trials (bococizumab). Many other molecules are in preclinical studies, phase I or II clinical trials. Another point of interest carefully investigated is the cardiovascular benefit of reducing LDL-C using these new molecules. High hopes are invested in them. Keywords: LDL-CHOLESTEROL, PCSK9 INHIBITORS, ALIROCUMAB, EVOLOCUMAB.

Low-density lipoprotein (LDL) is removed from the circulation mainly by hepatic uptake. LDL binds to the LDL receptor (LDLR) and the LDL-LDLR complex is internalized into clathrin-coated vesicles by endocytosis. In the endosomes, LDL is separated from its receptor. Further, LDL is degraded in the lysosomes and the LDLR is recycled for later reuse.

The proprotein convertase subtilisin/kexin type 9 (PCSK9) was identified in 2003 by Seidah et al. (1) and is a key regulator for LDLR activity. The major function of PCSK9 is the degradation of the LDLR (2). Secreted PCSK9 binds to the LDLR. When LDL-LDLR complex is formed, the PCSK9 is internalized together with it. The binding of PCSK9 to LDLR induces a change in LDLR conformation, avoiding normal recycling of LDLR to the plasma membrane and enhancing the LDLR lysosomal degradation (3). Consequently, it reduces the number of LDLR on the cell surface and the liver uptake of LDL, thereby increasing the plasma levels of LDL-C. As high LDL-C levels have consistently been associated with an increased risk of coronary heart disease,
PCSK9 is an attractive target for the treatment of hypercholesterolaemia. Recent data suggest that its involvement in lipid metabolism is even greater, PCSK9 having a role in triglyceride metabolism and triglyceride accumulation in visceral adipose tissue (4).

Several therapeutic approaches to the inhibition of PCSK9 have been proposed.

**MONOCLONAL ANTIBODIES**

The most successful approach was the monoclonal antibodies that bind to PCSK9 near the catalytic domain, interact with LDLR and hence inhibit the function of PCSK9.

Alirocumab (Praluent) and evolocumab (Repatha) are fully human monoclonal antibodies that specifically bind to PCSK9. In 2015 they received marketing approval from European Medicines Agency and the U.S. Food and Drug Administration. Bococizumab is a humanized monoclonal antibody that specifically binds to PCSK9 that is currently in phase 3 clinical trials.

Alirocumab and evolocumab are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The ODYSSEY Programme was designed to assess the efficiency and safety of alirocumab in a broad spectrum of patient populations. When alirocumab was compared with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance due to muscle symptoms, it was found that alirocumab reduced mean LDL-C by 45.0% vs 14.6% with ezetimibe (p<0.0001), with fewer skeletal-muscle adverse events vs atorvastatin (5).

When alirocumab was added to atorvastatin, it provided significantly greater LDL-C reductions vs adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin and enabled greater LDL-C goal achievement (6). ODYSSEY Combo II compared the efficacy and safety of alirocumab vs ezetimibe, as add-on therapy to maximally tolerated statin therapy in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia and again, alirocumab achieved significantly greater reductions in LDL-C compared with ezetimibe, with a similar safety profile (7).

ODYSSEY FH I and FH II assessed the long-term alirocumab treatment in patients with HeFH and inadequate LDL-C control on maximally tolerated lipid-lowering therapy. Patients without a history of cardiovascular events and those who had suffered a myocardial infarction or ischemic stroke were eligible to enroll in the study if their LDL-C levels were not at goal according to current guidelines for primary or secondary prevention. Patients received stable high-dose statin therapy with or without other lipid-lowering therapy (fenofibrate, ezetimibe). The study demonstrated that alirocumab reduced LDL-C levels from baseline by 57.9% (FH I) and 51.4% (FH II) vs placebo. Alirocumab was generally well tolerated, with consistent LDL-C reductions observed throughout the study. By doubling the antibody dose when LDL-C goal was not achieved on the starting dose, some 59–68% of patients achieved an LDL-C goal of <70 mg/dL (8). Alirocumab also reduced apolipoprotein B levels (by 54%, p<0.0001) and plasma Lp(a) levels.
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(by 20.5–30.3%) (9).

A major study, the ODYSSEY Long Term Trial, enrolled 2341 high-risk patients with HeFH, known coronary artery disease or coronary artery disease risk equivalent, in a randomized, double-blind, placebo-controlled trial. Eligible patients had LDL-C levels above 70mg/dL and were currently taking either high-dose statins or maximum tolerated dosages. Other lipid lowering therapies were also allowed. A post-hoc analysis of cardiovascular events that included a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke or unstable angina requiring hospitalization showed lower rates with alirocumab. Heart failure requiring hospitalization and ischemia-driven revascularization were not included as cardiovascular events in this post hoc analysis. When these events were included, the difference between groups was no longer significant (10). Therefore, a hope for an enlightening response is expected from ODYSSEY Outcomes (currently in the period of enrollment), an ongoing trial that is intended to provide an assessment of the cardiovascular benefit of alirocumab in approximately 18,000 patients over a period of 5 years.

The PROFICIO Programme was designed to assess the efficiency and safety of evolocumab. Comparing evolocumab with ezetimibe in statin intolerant patients due to muscle symptoms, it was found that evolocumab reduced LDL-C from baseline by 55% to 56% (corresponding to treatment differences: 140 mg sc q2weeks = Q2W dose, respectively 420 mg sc once monthly = QM dose) vs ezetimibe, with low incidence of muscle adverse events (12). Evolocumab also reduced Lp(a) levels by 22% to 27% compared to 1.7 - 5.8% in ezetimibe-treated patients. Of the evolocumab-treated patients at high risk, more than 75% achieved LDL-C <100 mg/dl compared with less than 10% of ezetimibe-treated patients.

When evolocumab was added to a guideline-recommended lipid-lowering therapy (10 mg atorvastatin, 80 mg atorvastatin with or without 10 mg ezetimibe, according to the patient’s ATP III defined cardiovascular risk), percent reductions in LDL-C in the evolocumab group vs placebo were 48.5% in the group receiving atorvastatin 80 mg plus ezetimibe, 56.8% in the group receiving atorvastatin 80 mg and 61.6% in the group receiving atorvastatin 10 mg (13). The LDL-C mean reduction in evolocumab group vs placebo was 57%. There were also significant reductions from baseline in apolipoprotein B, Lp(a) and triglycerides, as well as 5.4% increases in HDL-C and 3.0% in apoA1. In patients undergoing moderate or high intensity statin therapies, the favorable effect of evolocumab vs placebo or ezetimibe in lowering uncontrolled LDL-C levels was once again proven without a doubt (14).

RUTHERFORD-2 Study assessed the safety and efficacy of evolocumab in patients with HeFH and inadequate LDL-C control on maximally tolerated lipid-lowering therapy. Evolocumab achieved mean percent reductions of LDL-C of 60.2% (Q2W dose) and 65.6% (QM dose), compared to placebo (p < 0.0001). LDL-C <70 mg/dl was achieved by 68% of patients in the evolocumab Q2W group and by 63% in the evolocumab QM group, compared to only 2% in each of the placebo groups. Patients with receptor-negative mutations had a similar response to treatment compared to those with receptor-defective mutations or those with mutations in apolipoprotein B (15). TESLA study was conducted in pa-
patients with HoFH receiving stable background lipid-lowering treatment and not on apheresis. Evolocumab significantly reduced LDL-C by 30.9%. Patients with defective receptor mutation had the best response to treatment and had significantly higher reduction in LDL-C compared to those with single LDLR negative mutation (16).

Patients enrolled into a longer-term extension trial were re-randomized to the evolocumab plus standard therapy vs standard therapy alone without placebo control. 70% of patients were receiving background statin therapy. LDL-C was reduced by 61% to a mean of 48 mg/dL. Approximately 80% of patients had other cardiovascular risk factors including hypertension, diabetes, metabolic syndrome, current cigarette use, family history of premature coronary artery disease or familial hypercholesterolemia. The cardiovascular events (death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack and heart failure requiring hospitalization) occurred in a 1% of the evolocumab group vs 2% of the standard therapy group (17). The FOURIER Study is ongoing to confirm this finding and to determine if adding a PCSK9 inhibitor to standard statin therapy with will further decrease cardiovascular events over long-term follow-up.

Very little data is available on efficacy and safety of bococizumab. In a phase 2b dose-ranging study of subjects with hypercholesterolemia on stable doses of statin, compared with placebo, bococizumab significantly reduced LDL-C levels across all doses (18).

**GENE INHIBITORS**

Several other agents inhibit the gene responsible for the synthesis of the PCSK9 protein. Antisense oligonucleotides looked promising after the initial preclinical studies, but two phase I trials were terminated and development of the drugs had not been continued. ALN-PCS is a small interfering RNA that inhibits PCSK9 synthesis. ALN-PCS02 was successfully tested in a phase I trial on healthy volunteers with raised cholesterol who were not on lipid-lowering treatment (19).

**MIMETIC PEPTIDES**

The catalytic domain of mature PCSK9 binds to the first epidermal growth factor-like repeat A domain (EGF-A) of the LDLR, while the C-terminal domain binds to cell surface proteins, including annexin A2 (20). In order to induce its internalization and degradation, PCSK9 binds to EGF-A domain of LDLR. A mimetic peptide, which mimics the actions of EGF-A, was demonstrated to competitively inhibit PCSK9-mediated degradation of LDLR in HepG2 cells. Mimetic peptides currently being investigated are: EGF-AB peptide fragment, LDLR (H306Y) subfragment and LDLR DNA.

**SMALL MOLECULE INHIBITORS AND ADNECTINS**

Small molecule inhibitors and adnectins targeting circulating PCSK9 are currently being developed. Orally administered small-molecule inhibitors may act by altering the sequence of PCSK9 auto-catalytic intracellular processing, PCSK9 secretion or LDLR interaction. SX-PCK9 and TBD are in preclinical studies (21). Adnectins are genetically engineered target-binding proteins, similar to monoclonal antibodies, including binding to targets with similar affinity and specificity, but differ in terms of sequence and lack of
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disulphide bonds in their single-domain structure (22). The adnectin BMS-962476 has recently completed its phase 1 clinical trial and demonstrated good tolerability.

CONCLUSIONS
Multiple large studies have declared statins as the mainstream treatment for lowering LDL-C level, but additional therapies are certainly needed in order to reduce residual CV risk, especially in patients at very high risk, or with hereditary lipid disorders or statin intolerance. As we highlighted in this brief material, the addition of alirocumab or evolocumab to the existing lipid-lowering therapy has resulted in a significant, consistent and sustained reduction in LDL-C levels in patients with varying levels of CV risk. Even if at the moment the cardiovascular benefit of using these new drugs is still under investigation, high hopes are invested in them.

REFERENCES

10. Clary JM. PCSK9 Inhibition and CVD Events. JACC 2015 (epub)
CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Cardiovascular (CV) risk constitutes a major concern in patients with dermatomyositis and polymyositis. A multicentric Danish study evaluated cardiovascular risk factors and coronary artery calcification (CAC) in 76 patients with idiopathic inflammatory myopathies (IIM) and a control group formed of 48 sex- and age-matched healthy subjects. Obesity was more frequent among IIM patients than in healthy individuals (33% in patients as opposed to 11% healthy individuals, p<0.05). Waist/hip ratios and serum tryglicerides also had higher values in patients with IIM compared to healthy controls (p<0.05). Arterial hypertension and diabetes mellitus were more prevalent in IIM patients (p<0.05). The extent of coronary artery calcification was estimated using the Agatston score which showed higher mean values in patients compared to controls but results did not reach statistical significance. It was shown that glucocorticoid therapy, higher age at the moment of diagnosis, high levels of glycated hemoglobin (HbA1c) and smoking status correlate with higher coronary artery calcification scores in patients (p<0.05). However, C-reactive protein levels did not associate with a greater risk of CAC in the study group. Although not elucidating the mechanism behind increased CV mortality in IIM, the study brings to attention a series of important modifiable CV risk factors in patients with IIM. (Diederichsen L.P. et al. Traditional cardiovascular risk factors and coronary artery calcification in adults with polymyositis and dermatomyositis: a Danish multicenter study. Arthritis care & research 05.2015, doi:10.1002acr.22520. 67: 6 : 848-854).

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