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Review

Atherosclerosis: Recent trials, new targets and future directions

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ABSTRACT

Mortality from cardiovascular diseases (CVD) represents the primary cause of death worldwide. Prevention or treatment of atherosclerosis and its clinical sequelae is a central goal in the management of patients with established vascular disease or those at high-risk for vascular events. This paper provides a review of the contemporary pharmacological armamentarium targeting atherosclerosis and also highlights strategies to support future clinical trial design. Powering future trials targeting LDL-cholesterol to its absolute reduction and including patients with a higher LDL-C despite optimal medical therapy (or unable to tolerate statins) will increase the odds of meaningful results. Mendelian randomization studies may identify new causal risk factors for CVD that would help in the selection of the patients most likely to benefit from a specific new compound. Furthermore, imaging techniques integrating a morphological and functional assessment such as IVUS, OCT, PET/CT and PET/MRI may represent in a near future robust "soft" endpoints to support successful translation of early research into meaningful phase III clinical outcome trials.

1. Introduction

Clinical complications of atherosclerosis like myocardial infarction (MI), stroke and peripheral arterial disease represent the leading cause of mortality and morbidity in the world [1]. Therefore, the development of drugs targeting the atherosclerotic process has been an important area of contemporary clinical research.

While statins are the cornerstone of prevention they are not the panacea for eliminating atherosclerotic cardiovascular disease (ASCVD) [2]. A meta-analysis published in 2004 including patients on standard statin therapy showed a 21.7% 5-year event rate for major adverse cardiovascular event (MACE) in patients with prior ASCVD [3]. Furthermore, almost 1 in 10 high-risk patients treated with intensive statin therapy with low LDL-C after an acute coronary syndrome (ACS) suffers a subsequent adverse event within a 2-year period [4]. In this way, there is significant residual cardiovascular risk that persists despite low LDL-C, highlighting the role of "atherogenic dyslipidemia" that includes low HDL-C and high triglycerides [5].It is likely that longer duration of statin therapy combined with early introduction of LDL-C lowering will reduce residual risk, and with inexpensive and effective statins now available, recent guidelines in the USA has expanded such treatment to lower risk patients [6].

The utilization of complex imaging techniques including anatomical and functional evaluations and a better selection of high-risk patients may foster the successful design of trials. Indeed, a large number of lipid-associated new targets or targets reflecting other pathways of the complex atherosclerotic process are being evaluated in mechanistic imaging studies as well as in large outcome trials in the endeavor of residual vascular risk reduction (see Tables 1, 2 and 3). The latter will definitely include patient-tailored approaches in order to modulate the complex atherosclerotic process, emphasizing a strategy of personalized medicine [7].

This paper results from a discussion at the 2013 Cardiovascular Clinical Trialists' Forum held in Paris, France and aims to provide an

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overview of the most recent clinical data on antiatherosclerotic compounds, emphasizing new targets and strategies for robust clinical trial design.

2. Lipoprotein metabolism

2.1. Cholesterol absorption inhibition

Ezetimibe is a selective inhibitor of cholesterol absorption at the brush border of the small intestine mediated by the Niemman–Pick C1-like 1 protein, thus impairing the uptake of intestinal lumen micelles into the enterocyte [8,9] (Fig. 1). Lower cholesterol absorption depletes the hepatic pool of cholesterol and upregulates hepatic LDL receptors, therefore boosting LDL-C clearance from the circulation. Ezetimibe is able to induce a significant LDL-C reduction of 15–20% alone or by approximately 50% combined with simvastatin [10].

Although the results of ezetimibe and simvastatin in Hypercholesterolemia Enhances Atherosclerotic Regression (ENHANCE) Trial including patients with familial hypercholesterolemia showed a reduction in LDL-C and hsCRP when a combination therapy of simvastatin and ezetimibe was compared to simvastatin alone, yet it was not associated with a significant change in carotid intima-media thickness (cIMT) [11]. These results challenged not only the role of ezetimibe in CVD prevention but also pointed to the limitations of biomarkers and surrogate non-invasive markers to assess the efficacy of a lipid-lowering drug.

However, the results of the Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) Trial comparing simvastatin plus ezetimibe with simvastatin alone in 18,144 patients included within 5 days post-ACS showed a modest 6.4% relative risk reduction (RRR) of the primary endpoint and thus demonstrated a beneficial role of ezetimibe in vascular protection [12]. Baseline LDL-C was 95 mg/dl and was reduced to 69.5 mg/dL in the simvastatin group and to 53.7 mg/dL in the combination group during 7 years of follow-up with a good safety profile.

Table 1
Drug targets for atherosclerosis and current research development phase.

Target	Clinical research phase
LDL lowering	
PCSK9 antibodies	
Alirocumab (SAR236553/REGN727)	3
Evolocumab (AMG145)	3
Bococizimab (PF-04950615/RN316)	3
MTTP (microsomal triglyceride transfer protein) inhibitors	3
Antisense apoB (mipomersen)	3
ATP-citrate lyase inhibitor (ETC-1002)	2
TR-β agonist (MGL-3196)	1
Lp(a)	
Antisense apo(a)	1
Triglycerides	
Antisense apo C-III (ISIS 304801)	2
PPAR agonists (α:K877, α/δ:GFT505, δ:CER-002)	2
Omega-3 free fatty acids (eicosapentaenoic acid and docosahexaenoic acid)	3
Acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1) inhibitors (LCQ908)	2
Angiopoietin-like proteins (ANGPTLs) 3 and 4 inhibitors	Pre-clinical
HDL	
Reconstituted HDL (CSL-112)	2
Recombinant HDL (CER-001)	2
Apo A-I inducer (RVX-208)	2
Apo A-I milano (ETC-216/MDCO-216)	1
Apo A-I mimetics (D6F APP018, ATI-5261, …)	2
ABCA1 inducer	Pre-clinical
Antagomir miR-33	Pre-clinical
CETPi (evacetrapib, anaceptrapib)	3
rLCAT (APC-501)	Pre-clinical
LXR-623	Pre-clinical
SR-B1 inhibitor (ITX5061)	1
Inflammation/atherosclerosis	
Inflammation	
sPLA2 (varespladib)	3
LpPLA2 (darapladib)	3
ox-LDL antibodies	2
5-lipoxygenase inhibitors (VIA-2291)	2
Methotrexate (CIRT)	3
CCR-2 inhibition	2
CRP antisense	2
IL1b/IL1RA/Inflammasome inhibition (canakinumab)	3
Immunization strategies	
Antibodies against modified apoB epitopes (MLDL1278A)	2
ApoB vaccination strategies	Pre-clinical

2.2. PCSK9 inhibition

The proprotein convertase subtilisin/kexin (PCSK) type 9 is a serine protease which modulates lipoprotein metabolism by its circulating component binding with LDL to the hepatic LDL receptor promoting hepatic internalization and intracellular degradation of the LDL receptor, preventing its recycling (Fig. 1) [9,13]. The latter is a fundamental player in LDL clearance from the circulation. In addition, pre-clinical research has also identified roles for PCSK9 in peripheral tissues. For instance, PCSK9 is induced by inflammation [14] and small interfering RNA (siRNA) knockdown of PCSK9 in human macrophages attenuates the inflammatory response elicited by oxidized LDL (oxLDL) [15]. Lastly, statin therapy increases the expression of PCSK9 [16]. The integration of these data, together with overwhelming evidence that patients with loss-of-function mutations of PCSK9 have 15–30% reductions in LDL-C and 47–88% reduction in the risk of coronary heart disease (CHD) [19], supports a role for PCSK9 as an interesting target for antiatherosclerosis drug therapy.

There are several ways to interfere with PCSK9: mimetic peptides and adnectins (with similarities to small monoclonal antibodies), small-molecule inhibitors, gene silencing (e.g., antisense oligonucleotides and siRNA) and monoclonal antibodies [13]. To date, the most promising strategy to impair the action of PCSK9 appears to be the use of monoclonal antibodies. Indeed, two monoclonal antibodies targeting PCSK9, AMG145 (evolocumab, Amgen), SAR236553/REGN727 (alirocumab, Sanofi/Regeneron) and bococizumab (Pfizer) reported encouraging results in phase 1 and 2 trials. The body of evidence accumulated since 2009 has shown that these drugs elicit a significant and sustained 40–70% reduction of LDL-C in patients with familial hypercholesterolemia (FH) [18–22] and non-FH [21,23–26]. LDL-C lowering was observed in patients with PCSK9 inhibitors, alone or in combination with a statin, and also in statin-intolerant patients [27]. Phase 3 trials are currently in progress to assess the role of the following drugs on cardiovascular events: evolocumab (FOURIER; 28,000 patients with prior MI or stroke) [28], alirocumab (ODYSSEY OUTCOMES; 18,000 patients with recent ACS) [29] and bococizumab (SPIRE 1 and 2; 17,000 and 9,000 patients, respectively, with high CV risk as defined by LDL-C levels) [30,31].

The potential disadvantages of these agents include their subcutaneous administration (although it may be performed monthly or twice monthly, which may be an advantage compared to a daily drug use) and injection site reactions (in about 6% of patients both with evolocumab [32] and alirocumab [32]). Furthermore, long-term immune reactions even to fully human antibodies may appear, although available evidence from trials suggests that they are rare. The larger phase 3 trials underway may help to clarify the long-term tolerability of these drugs. The recently published results of a 52-week treatment with evolocumab (DESCARTES; every 4 weeks) showed sustained efficacy in reducing LDL-C with acceptable safety and tolerability [33]. Furthermore, recently announced findings showed that alirocumab on top of statin therapy (administered every 2 weeks) in very-high risk patients with hypercholesterolemia elicited a 48% reduction in MACE