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Non-Statin Treatments for Managing LDL Cholesterol and Their Outcomes

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ABSTRACT

Purpose: Over the past 3 decades reducing LDL-C has proven to be the most reliable and easily achievable modifiable risk factor to decrease the rate of cardiovascular morbidity and mortality. Statins are effective, but problems with their side effects, adherence, or LDL-C efficacy in some patient groups remain. Most currently available alternative lipid-modifying therapies have limited efficacy or tolerability, and additional effective pharmacologic modalities to reduce LDL-C are needed.

Methods: Recent literature on new and evolving LDL-C–lowering modalities in preclinical and clinical development was reviewed.

Findings: Several new therapies targeting LDL-C are in development. Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), a recently elucidated key regulator of plasma LDL-C, is the most promising and effective, with a number of approaches aimed at this target. The most advanced are monoclonal antibodies, which have demonstrated LDL-C reductions of ~60%, whether given alone or added to statins. Other PCSK9-targeted therapies in clinical development include adnectins and gene silencing techniques. Preclinical approaches involve vaccines, whereas a search remains for small molecule inhibitors. Other new pharmacologic approaches in Phase III clinical trials include a refocusing of cholesterol ester transfer protein inhibitors from primarily agents to increase HDL-C to their off-target effect on LDL-C and adenosine triphosphate citrate lyase inhibition. In earlier clinical development is new delivery of nicotinic acid-containing compounds. Additional agents are being developed as orphan indications expressly for patients with homozygous familial hypercholesterolemia, including peroxisome proliferator activated receptor-δ agonists, angiopoietin-like protein 3 inhibitors, and gene therapy.

Implications: Monoclonal antibodies that inhibit PCSK9 were shown to be very effective reducers of LDL-C and well tolerated despite subcutaneous administration, and no significant safety issues have yet emerged during large Phase II and III trials. They have the potential to substantially impact further the risk of cardiovascular disease. A number of additional new, but less effective, oral LDL-C–lowering agents are also in various stages of development, including some which are targeted only to patients with homozygous familial hypercholesterolemia. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: CETP inhibitors, LDL cholesterol, PCSK9 inhibitors, Familial hypercholesterolemia.

INTRODUCTION

Reducing LDL-C concentrations was well established in large, prospective clinical trials as a primary modality for decreasing the risk of cardiovascular morbidity and mortality.[1–3] Although hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, are the mainstay of LDL-C reduction, there are patient populations that either are intolerant or have contraindications to statins or are unable to achieve consensus based 'optimal' or 'target' LDL-C levels despite adequate response to statins and other currently available LDL-C reducing drugs.[4] The recent, still controversial and even in the United States not widely accepted, American Heart Association/American College of Cardiology guidelines recommend consideration of non-statin therapies that have demonstrated favorable benefit, compared with adverse effects, for reduction of atherosclerotic

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cardiovascular disease (CVD).[5,6] Currently available non-statin therapies for lowering LDL-C include bile acid sequestrants, cholesterol absorption transport inhibitors, niacin, and fibrates. However, with the exception of ezetimibe, these modalities are not well tolerated and often result in inadequate additional LDL-C reduction, and the benefit when added to statins has not shown to improve cardiovascular outcomes.[7–10] More recently, in specific and rare populations with homozygous familial hypercholesterolemia (HoFH), agents that target apolipoprotein B (apoB)-containing lipoprotein formation, mipomersen and lomitapide, have gained limited approval and have encountered significant postmarketing adverse side effects, further restricting their use even in these populations.[11] Thus, there remains an important need for efficacious agents to robustly and safely decrease LDL-C, and several compounds currently in clinical development are included in this review and are classified into those for widespread use in the general population and those specifically for patients with HoFH (Table I).

EVOLVING THERAPIES FOR REDUCING LDL-C IN THE GENERAL POPULATION

PCSK9 Inhibitors

Since its discovery in 2003 proprotein convertase subtilisin/kexin type 9 (PCSK9) was found to play a key role in the metabolism of LDL-C via its interaction with, and subsequent degradation of, the LDL receptor (LDLR).[12] The elucidation of the pathophysiologic role of PCSK9 via gain-of-function and loss-of-function (LOF) mutations has been extensively reviewed in the past few years and is not repeated here.[13–15] However, it was mostly the studies documenting that LOF mutations resulted in small but lifelong reductions in LDL-C which were associated with a 40% to 60% reduction in CVD risk that led to the search for, and development of, compounds that target PCSK9. The critical finding, by Legace et al[16] in 2006, that circulating PCSK9 was responsible for interaction with the LDLR resulted in the rapid development of highly targeted therapy to inhibit PCSK9 with the use of monoclonal antibodies (mAbs). Alternative mechanisms that reduce intrahepatic PCSK9

Table I. LDL cholesterol-lowering therapies: new drugs in development.

- General or widespread use (non-FH, HeFH, and HoFH)
  - PCSK9 inhibitors
    - Monoclonal antibodies
      - Approved (alirocumab, evolocumab)
      - Phase III (bococizumab)
      - Phase II (LY3015014, RG7652)
    - Adnectins: Phase I (BMS-962476)
    - siRNA: Phase I (ALN-PCS)
  - CETP inhibitors: Phase III (anacetrapib, evacetrapib, TA-8995)
  - Adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase modulator: Phase II (ETC-1002/ bempedoic acid)
  - New niacin-related agents: Phase I (CAT-2054); ARI-3037MO
- Specific or orphan use (HoFH only)
  - PPAR-δ agonist (MBX-8025): Phase II
  - ACC inhibitor (gemcabene): Phase II
  - ANGPTL3 inhibition: monoclonal antibody (REGN1500) Phase I; antisense (ISIS-ANGPTL3Rx); siRNA (ALN-ANG)

ACC, acetyl coenzyme A carboxylase; ANGPTL3, angiopoietin-like protein 3; CETP, cholesterol ester transfer protein; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; siRNA, small interfering RNA.