Therapy and clinical trials

Nishtha Sodhi[a] *and Richard A. Krasuski*[b]

Just over two-thirds of high-risk patients treated with statin monotherapy for more than 90 days achieve the ATP-III recommended LDL cholesterol (LDL-C) goal (<100 mg/dl), and only a fifth achieve the optional target (<70 mg/dl) [1▪]. Further limiting goal attainment is statin intolerance, which affects up to 20% of patients. As the prevalence of proatherogenic disease states such as metabolic syndrome continues to rise [2], the need for adjuvant therapy has never been greater.

Preliminary results from the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [3▪] parallels prior study data showing that niacin does not provide additional clinical benefit to statins [4▪], and may increase the risk of serious, although not fatal side-effects. Likewise, adding cholesterol ester transferase protein inhibitors (CETP-I) to statins has yet to demonstrate clinical benefit [5▪,6▪], although the final appraisal of CETP-I awaits completion of actively enrolling Phase III studies [7▪,8▪].

Given the disappointments targeting HDL cholesterol (HDL-C), investigators have refocused on further LDL-C modification utilizing novel molecules such as antibodies to proprotein convertase subtilisin/kexin (PCSK9) and antisense oligonucleotides (ASO). Studies with these agents have mostly targeted challenging groups such as familial hypercholesterolemia [9,10▪▪,11] and the statin intolerant [12▪▪].

The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) study showed that four doses of AMG145 administered 4 weeks apart resulted in dose-dependent reductions in LDL-C; 70 and 89% of patients achieved an LDL-C less than 100 mg/dl (2% with placebo) and 44 and 65% achieved less than 70 mg/dl (0% with placebo) with 350 and 420 mg doses, respectively [10▪▪]. The drug was well tolerated, with few patients experiencing liver enzyme or creatine-kinase elevations.

The effect of a monoclonal antibody to PCSK9 on LDL-C levels in a statin-intolerant patients (GAUSS) study demonstrated profound mean reductions in LDL-C after 12 weeks of AMG145: 67 mg/dl with 280 mg, 70 mg/dl with 350 mg, 91 mg/dl with 420 mg and 110 mg/dl with 420 mg and ezetimibe [12▪▪]. By comparison reduction was only 14 mg/dl with ezetimibe and placebo. Myalgia was the most common side-effect, occurring in 7% of antibody monotherapy patients (with no dose-effect), but increasing to 20% when combined with ezetimibe. Additionally, lipoprotein-a levels decreased by 20–26% and the 420 mg dose of AMG145 significantly increased HDL-C.

Mipomersen, an antisense apoB synthesis inhibitor, was US Food and Drug Administration approved in January 2013 as adjunctive therapy in homozygous familial hypercholesterolemia. Currently, PCSK9-abs and apoB-ASOs are mostly in injectable form, with transformation to oral form limited by biological enterases and protein fragility. Thus, administration issues which could impact cost and patient acceptance, as well as overall safety, including hepatic and immunological consequences, will need to be further addressed before either therapy becomes available and widely accepted. The most important determinant of all will be whether the impressive LDL-C reductions seen with these new agents is sustained and translates into improved cardiovascular outcomes. Nevertheless, both could be critical new adjunctive classes that expand our treatment armamentarium.

Acknowledgements

None.

Conflicts of interest

Dr Krasuski has served as a consultant to Actelion and Gilead and is on the speakers bureau of Actelion. He is also on the scientific advisory board for Ventripoint.

[a]Department of Internal Medicine and [b]Department of Cardiovascular Medicine, The Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to Richard A. Krasuski, MD, Department of Cardiovascular Medicine, Desk J2-4, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: +1 216 445 7430; e-mail: krasusr@ccf.org

Curr Opin Lipidol 2013, 24:281–282

DOI:10.1097/MOL.0b013e3283616351

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■ Jones PH, Nair R, Thakker KM. Coronary Heart Disease: Prevalence of dyslipidemia and lipid goal attainment in statin-treated subjects from 3 data sources: a retrospective analysis. J Am Heart Assoc 2012; 1:e001800; doi: 10.1161/JAHA.112.001800.

In this cross-sectional, retrospective study, three different data sources were examined: electronic medical records (2003 to September 2010), administrative claims data (2003–2010) and National Health and Nutrition Examination Survey data (2007–2008). This study nicely demonstrates our continued inability to get our highest risk patients to their ATP III LDL and non-HDL goals.

2. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999–2006. Diabetes Care 2011; 34:216–219.
3. ■ Treatment of HDL to reduce the incidence of vascular events HPS2-THRIVE. http://www.thrivestudy.org. [Accessed 1 March 2013].

The primary aim of this study was to assess the effects of raising HDL cholesterol with an extended release form of niacin combined with laropiprant (a D-type prostanoid receptor antagonist) on the risk of myocardial infarction, coronary death, stroke or the need for arterial bypass revascularization in patients with a history of cardiovascular disease. Preliminary results were released to the public in December 2012; and similar to AIM-HIGH, reported that the addition of niacin to statin therapy produced no perceived clinical benefit.

4. ■ The AIM-HIGH investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011; 365:2255–2267.

Three thousand four hundred and fourteen patients who had attained optimal on-treatment levels of LDL-C on statin therapy were randomized to either 36 months of extended release niacin or placebo. The study was prematurely discontinued due to lack of benefit and for concern of a possible increase in the incidence of ischemic stroke in niacin-treated patients (this did not actually achieve statistical significance). Despite a significant increase in HDL-C and further reductions in triglycerides and LDL-C, no effect on the primary end-point (first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome or symptom-driven coronary or cerebral revascularization) was seen.

5. ■ Schwartz GG, Olsson AG, Abt M, *et al.* Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012; 367:2089–2099.

Dal-OUTCOMES was the anticipated follow-up study to the dal-VESSEL Trial (a study that assessed the safety and efficacy of dalcetrapib to improve endothelial function as measured with brachial artery flow-mediated vasodilatation). In Dal-OUTCOMES 15 871 patients with acute coronary syndrome were randomized to receive the CETP inhibitor, dalcetrapib, or placebo. Although dalcetrapib increased HDL cholesterol levels, it did not reduce the risk of subsequent cardiovascular events.

6. ■ The ILLUMINATE investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109–2122.

This was a randomized, double-blind study of 15 067 patients at high cardiovascular risk who received either torcetrapib or placebo in addition to atorvastatin. The study was stopped prematurely as torcetrapib was found to increase the risk of mortality and morbidity by a still incompletely characterized mechanism.

7. ■ ACCELERATE: Assessment of Clinical effects of CholestEryL Ester transfeR protein inhibition with evAcetrapib in patienTs at a high-risk for vascular outcomEs. 2012. ClinicalTrials.gov Identifier: NCT01687998. ClinicalTrials.gov.

The purpose of this study is to evaluate the efficacy and safety of evacetrapib, a CETP inhibitor, in patients with high-risk vascular disease already receiving a statin. This is a Phase III, multinational, event-driven study which should help to define the future role of CETP inhibition as an adjuvant to statin therapy.

8. ■ REVEAL: Randomized EValuation of the Effects of Anacetrapib through Lipid-modification. 2010. ClinicalTrials.gov Identifier: NCT01252953. ClinicalTrials.gov.

The REVEAL trial is a multicenter, Phase III study aiming to determine whether lipid modification with anacetrapib (another CETP inhibitor) will reduce the risk of major coronary events in patients with cardiovascular disease who are already being treated with a statin.

9. Stein EA, Gipe D, Bergeron J, *et al.* Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomized controlled trial. Lancet 2012; 380:29–36.
10. ■■ Raal F, Scott R, Somaratne R, *et al.* Low-density lipoprotein cholesterol–lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation 2012; 126:2408–2417.

The RUTHERFORD Trial studied heterozygous familial hypercholesterolemia patients with elevated LDL and triglycerides despite at least 4 weeks of statin and adjuvant lipid-lowering therapy. Patients were randomized into three different groups: therapy with AMG 145 at a dose of 350 mg, therapy with AMG 145 at a dose of 420 mg or placebo. A dose-dependent reduction in LDL-C was found.

11. Stein EA, Dufour R, Gagne C, *et al.* Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation 2012; 126:2283–2292.
12. ■■ Sullivan D, Olsson AG, Scott R, *et al.* Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant Patients: The goal achievement after utilizing an anti-PCSK9 antibody in statin intolerant subjects (GAUSS). JAMA 2012; 308:2497–2506.

The GAUSS Trial was conducted to determine safety and efficacy of AMG 145 in patients intolerant to statins. Administration of AMG145 resulted in a dose-dependent reduction in LDL-C levels. All doses of AMG145 reduced lipoprotein(a) and the 420 mg dose increased HDL as well.

FURTHER RECOMMENDED READING

Koren MJ, Scott R, Kim JB, *et al.* Efficacy, safety, and tolerability of a ■ monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2012; 380:1995–2006.

The MENDEL Trial assessed the safety and efficacy of AMG145 as monotherapy in hypercholesterolemic patients. After 12 weeks, significant reductions in LDL-C was seen with all AMG145 doses, with clear evidence for a dose response. Significant improvements compared with placebo were also noted for multiple other lipid parameters including total cholesterol, apolipoprotein B, apolipoprotein A1, lipoprotein(a) and ratios of total cholesterol to HDL-C and apolipoprotein B to apolipoprotein A1.

Giugliano RP, Desai NR, Kohli P, *et al.* Efficacy, safety, and tolerability of ■ a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet 2012; 380:2007–2017.

LAPLACE (LDL-C Assessment with Pcsk9 monoclonaL Antibody inhibition Combined with statin thErapy) TIMI (Thombolysis In Myocardial Infarction)-57 examined combination statin (± ezetimibe) and AMG145 therapy. By week 12, the mean LDL-C concentrations were significantly reduced: ranging from 41.8 to 66.1% in the every second week administration group and from 41.8 to 50.3% in the ever 4th week administration group.

Marais DA, Blom DJ, Petrides F, *et al.* Proprotein convertase subtilisin/kexin type 9 ■■ inhibition. Curr Opin Lipidol 2012; 23:511–517.

The pharmacology, genetics, immunology and theory behind PCSK9 inhibitors are detailed in this excellent review.

Lambert G, Sjouke B, Choque B, *et al.* The PCSK9 decade. J Lipid Res 2012; ■ 53:2515–2524.

PCSK9 can be targeted via monoclonal antibodies (as described), via peptide mimics and via antisense oligonucleotides and gene slicing. Future investigation is very likely to target PCSK9 via peptide mimics and ASOs.