EDITORIAL COMMENT

Realizing the potential of PCSK9 inhibition: a novel oral macrocyclic peptide on the horizon

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Brief title: An oral macrocyclic peptide inhibitor of PCSK9

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The authors declare no funding for this contribution. Prof Chapman reports honoraria from Amgen, Amarin, AstraZeneca, Daiichi-Sankyo, Kowa, Lexicon, MSD, Regeneron, Sanofi, and Pfizer. Prof Packard reports honoraria from Amgen, Amarin, MSD, Dalcor, Novartis and Daiichi-Sankyo.

No Twitter handle available.

Contributors: All authors contributed equally to the design and writing of the manuscript. All authors critically reviewed and edited the manuscript.

ApoB-containing lipoproteins and atherosclerotic cardiovascular disease.

Current statistics for morbidity and mortality resulting from cardiovascular disease (CVD) make stark reading. In the United States alone, one person dies every 34 seconds from CVD, coronary heart disease accounting for more than half of all deaths. Total average annual direct and indirect healthcare costs were estimated at $378.0 billion in 2017-18. (1) Worldwide, about 19 million deaths were attributed to CVD in 2020, an increase of almost 20% from 2010. (1)

A 2004 landmark study conducted across 52 countries determined that atherogenic apoB-containing lipoproteins account for a major proportion of the population-attributable risk for acute myocardial infarction. (2) Within this lipoprotein class, the main cholesterol-transporting particle, low-density lipoprotein (LDL), has been identified unequivocally as a principal causal factor in the pathophysiology of atherosclerotic CVD (ASCVD). (3) More recently, genetic and epidemiological studies have revealed that less abundant apoB-containing lipoproteins, notably lipoprotein (a) (Lp(a), an LDL-like particle with an additional protein apolipoprotein (a)), and cholesterol-rich 'remnant' particles generated by lipolysis of triglyceride-rich lipoproteins (TRL), are also causal factors for ASCVD (Figure 1). (4-6)

This new, expanded landscape of lipoprotein-associated risk on the one hand emphasizes the complexity of hypercholesterolemia (which involves more than LDL), and on the other highlights the need for lipid lowering agents which not only efficaciously reduce LDL-cholesterol (LDL-C), but also address the need to decrease plasma levels of Lp(a) and TRL remnant lipoproteins. Additionally, evidence-based guideline recommendations for management of hypercholesterolemia in patients in secondary prevention now mandate ever-lower goals for LDL-C to maximize reduction in cardiovascular events. (7,8)

In this scenario, the entry of inhibitors of Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) in 2015/2016 into clinical practice, in the form of monoclonal antibodies (MABs), was a most welcome and timely development. (9,10) More recently, a small interfering RNA (siRNA), inclisiran, has become available which, like the aforementioned MABs, is also administered as an 'injectable'. (11) In contrast to evolocumab and alirocumab, inclisiran acts intracellularly in liver cells, to which it is specifically targeted, inducing degradation of the messenger RNA for PCSK9. (11) It is therefore of considerable interest that in this issue of the *Journal of the*

*American College o*f *Cardiology*, Ballantyne et al. (12) present phase 2b studies of the efficacy and safety of MK-0616, a novel orally administered macrocyclic peptide inhibitor of PCSK9 that adds a further approach to regulating this target protein.

Why is PCSK9 an effective target for lipid-lowering?

PCSK9, a 692 kDa protein abundantly expressed by hepatocytes, is a key regulator of circulating levels of LDL-C via its control of hepatic LDL receptor activity. (9,10) Indeed, inhibition of PCSK9 offers a magnitude of reduction in LDL-C - routinely >50% - not seen with other agents including most statins. (10) This effect is accompanied by substantial decreases in TRL remnants, an expected effect since these particles are also cleared by LDL receptors (5,6,13). The ancillary action of PCSK9 inhibitors on Lp(a) was not predicted since the metabolism of this lipoprotein particle was thought to be independent of the LDL receptor pathway. (4,10) Indeed, plasma concentrations of Lp(a) are not altered, and may even be moderately increased, by statin therapy. (4) However, clinically relevant reductions of some 25-30% are seen with monoclonal antibody-based PCSK9 inhibition, and recent PCSK9 inhibitor trials have attributed a portion of the clinical benefit seen in ASCVD risk reduction to the lowering of Lp(a) as well as that of LDL-C (10). At present we have no other means to address the risk linked to high Lp(a) levels. Thus, the therapeutic strategy of reducing Lp(a) even moderately with PCSK9 inhibitors has attraction until specific agents are approved for clinical use.

Why has the full potential of PCSK9 inhibition not been realized?

PCSK9 inhibitor therapy is effective and provides substantial LDL lowering in virtually all patient subgroups. (10) Further, the safety profile of five years or more for both monoclonal antibodies, alirocumab and evolocumab, indicates that very low levels of LDL-C can be achieved and maintained with no apparent adverse effects. (10)

Guidelines such as those from the ESC (7), and most recently the American Diabetic Association (8) recommend that in patients at highest risk, ie. those with established ASCVD, the LDL-C treatment goal should be <55 mg/dl. In most subjects, such goals cannot be achieved with statin monotherapy or even with the combination of statin plus ezetimibe, making it implicit that PCSK9 inhibitors should be widely used in the majority of secondary prevention patients. This has not been the case to date for reasons including cost, complex approval processes, and limits on which healthcare actors can initiate therapy. Some of the slow uptake may equally be

attributed to the fact that currently available agents are 'injectables', a novel approach in cholesterol management where oral agents are the norm.

There is increasing recognition that combination lipid-lowering therapy needs to be instituted early in a patient's treatment plan if the new aggressive LDL-C goals are to be achieved. A recent position paper from the European Atherosclerosis Society set out a strategy in which the combination of statin plus ezetimibe or statin plus PCSK9 inhibitor is initiated as first-line therapy in patients at highest risk. (14) It is possible to predict the LDL reduction achievable on most regimens – moderate dose statin, high dose statin, ezetimibe, PCSK9 inhibitor – and so with the optimum goal in mind and knowing the patient's starting LDL-C, it is good practice to move quickly to the combination that will deliver a patient to goal first time. Such an approach also addresses the implementation gaps where patients, once discharged from a cardiology division, are passed to primary care where aggressive LDL-C -lowering, especially with PCSK9 inhibitors, is unlikely to be initiated.

A novel oral macrocyclic PCSK9 inhibitor, MK-0616

Phase 1 studies of MK-0616 involving single doses showed rapid reduction in free circulating PCSK9 levels (>90%) (12). The present phase 2b randomized, double-blind, placebo-controlled, clinical trial of the efficacy and safety of this orally administered macrocyclic peptide inhibitor of PCSK9 was performed over a dose range of 6 to 30 mg QD in a small cohort (n=380) of hypercholesterolemic subjects exhibiting a wide range in CVD risk (12). Significantly, the placebo-adjusted reductions in LDL-C, apoB and non-HDL-C over the 8-week study (with 8 weeks of follow-up) were ≈61%, ≈52% and ≈56% respectively; as such they compare favorably to findings with anti-PCSK9 MABs and inclisiran (10, 11). Adverse events (AEs) occurred to a similar degree in subjects in both treatment and placebo arms (≈44%) (12). Discontinuation due to AEs occurred in 2 or fewer participants in any treatment group. Although the effect of MK-0616 on Lp(a) was an exploratory endpoint, nonetheless mean Lp(a) reduction was 23% at the highest dose. The ability of this macrocyclic peptide to reduce Lp(a) is thus shared with MABs, and likely to be clinically relevant. Parameters of blood chemistry and hematology, and biomarkers of renal and liver function and glycemic control were similar across treatment arms, supporting the clinical safety profile of the drug.

Potential implications for clinical practice

Will the availability of an oral agent increase the likelihood that successful goal-orientated combination therapy be instituted early in the patient pathway, possibly by the cardiologist on discharge after an ASCVD event? This will depend, of course, on the drug maintaining an advantageous efficacy and safety profile, on issues involving product cost, and on willingness to adopt novel therapeutic strategies for effective lipid lowering.

A phase 3 cardiovascular outcome trial and longer-term safety data across a range of patients at risk for ASCVD will be key components of the profile of this new agent. The launch of a cost-effective oral drug such as this macrocyclic peptide, MK0616, is eagerly awaited, as it may widen the strategic implementation of PCSK9 inhibitor therapy.

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KEY WORDS Atherosclerotic cardiovascular disease, PCSK9, LDL cholesterol, Lipoprotein (a), Remnant lipoproteins.

Legend to Figure

Figure 1. PCSK9 monoclonal antibody-mediated reductions in LDL-C, in Lp(a) and in TRL remnants and the potential clinical benefit which results by virtue of reduction in cardiovascular events. Evidence for the contribution of both PCSK9 inhibitor-mediated reduction in LDL-C and in Lp(a) to clinical benefit has been documented in cardiovascular outcome trials, notably the FOURIER trial involving evolocumab and the ODYSSEY OUTCOMES trial involving alirocumab. (10) *Although abundant evidence supports the causal role of TRL remnants in ASCVD, it is yet to be proven that PCSK9 inhibitor-mediated lowering of remnant levels – which may approach 40% - translates to reduction in major adverse cardiovascular events. (5,6, 13) ApoB is a common component to all three lipoprotein particles.

Figure 1.

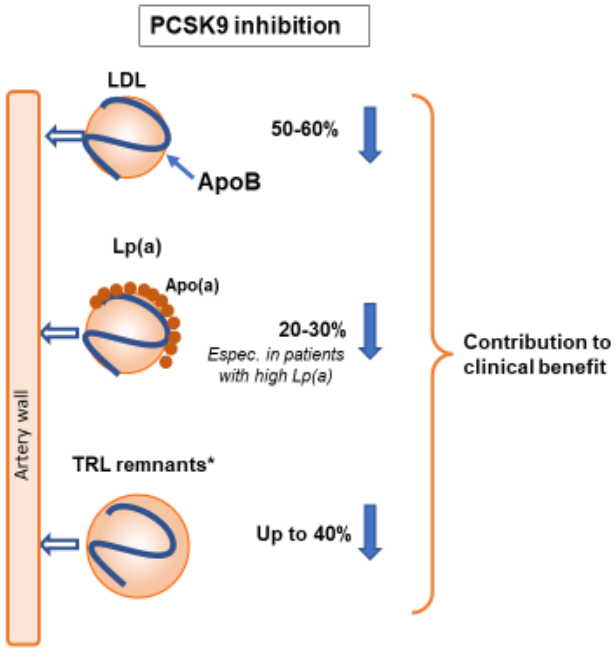
PCSK9 inhibition
LDL
ApoB
50-60%
Lp(a)
Apo(a)
20-30%
Espec. in patients with high Lp(a)
TRL remnants*
Up to 40%
Artery wall
Contribution to clinical benefit

Figure 2: Prof M.J. Chapman