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PCSK9 Inhibitors or Cardiovascular Disease Inhibitors?

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Abstract

Cardiovascular disease (CVD) is well documented as the leading cause of adult mortality and morbidity worldwide and it remains a substantial public health issue with enormous financial impact to global economy. Statins remain the cornerstone of lipid management for both primary and secondary prevention of CVD. A variety of other lipid modifying therapies are available which can be added to statin therapy to further reduce CV risk. Nowadays, PCSK9 inhibitors (evolocumab and alirocumab recently approved) appear promising agents with multiple trials demonstrating that these agents -in combination with statins or monotherapy- can modify lipids substantially with an unprecedented optimal safety profile.

Several large PCSK9 inhibitor clinical outcomes trials (ODYSSEY-OUTCOMES, FOURIER and the SPIRE-I and II trials) are currently ongoing, which should elucidate their place in clinical practice. However, it remains non negotiable that keeping CVD therapy affordable necessitates restricted use of PCSK9 antibodies to select patient groups such as Familial Hypercholesterolemia (FH), statin intolerance and very high CVD risk with residual LDL burden, [1] until those currently ongoing outcome trials and future randomized survival trials elucidate the high rank place of these inhibitors in our cardiovascular armamentarium.

Abbreviations: CVD: Cardiovascular Disease; FH: Familial Hypercholesterolemia; MR: Mendelian Randomisation; MoAbs: Monoclonal Antibodies; RNAi: RNA Interference; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; LDL-C Low Density Lipoprotein Cholesterol; GAUSS: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; DESCARTES: Durable Effect of PCSK9 Antibody Compared with Placebo Study; RUTHERFORD-2: Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; OSLER: Open-Label Study of Long-Term Evaluation Against LDL-C; SPIRE: Studies of PCSK9 Inhibition and the Reduction of Vascular Events

Introduction

Cardiovascular disease (CVD) is well documented as the leading cause of adult mortality and morbidity worldwide and it remains a substantial public health issue with enormous financial impact to global economy. Preventive measures such as reduction of smoking, blood pressure and atherogenic lipids, as well as advances in treatments and healthcare have led to large reductions in age-standardized death rates for CVD, particularly in high income regions [2,3]. However its prevalence is rising in developing countries [2,3] with all the expected consequences. The aetiological relationship between long-term average blood cholesterol concentrations and risk of cardiovascular (CV) morbidity and mortality has been established reliably by the more than 60 years of evidence from observational, randomized and genetic studies. Many of the older prospective observational studies which established these relationships were incorporated into comprehensive meta-analyses of the lipid risk factors for CVD undertaken by the Emerging Risk Factors Collaboration (ERFC) [4].

The pooled data from the ERFC observational studies of about 10 years follow-up shows a hazard ratio of 1.5 (1.39 - 1.61) per 1 standard deviation (43 mg/dL or 1.1 mmol/L) higher in non-HDL-cholesterol; whereas more recent Mendelian Randomisation [MR] studies show that life-long differences in LDL-cholesterol, based on genetics, are associated with CHD risk even more strongly with about a 2-fold increase in risk per mmol/L higher LDL-C. This indicates approximately a 3-fold greater reduction in the risk of CHD associated with a unit lower LDL-C than that observed during treatment with a statin started

later in life [5]. This implies that residual risk following standard LDL-lowering treatment may be partly explained by treating late in the course of the disease, and that earlier treatment would increase benefit.

The association between non HDL-C and risk of ischaemic stroke, although also positive, is much less strong although LDL-C lowering clearly reduces ischaemic stroke in the randomized trials [4,6]. By contrast, observational data indicates that HDL-C levels are strongly inversely associated with CHD and also, although less clearly so, with ischaemic stroke [4]. The positive associations between triglyceride levels and risk of vascular disease typically disappear on adjustment for the other lipid factors [4], although recently it has become clear that remnant cholesterol, the cholesterol content of triglyceride-rich lipoproteins, is independently associated with CHD even after adjustment for HDL-C [7,8] and MR studies also support the importance of triglyceride pathways in CHD risk [9].

In light of these associations, interventions to modify lipids have been a key component of CVD treatment and prevention. People whose diet is relatively high in saturated fat can achieve some reduction in blood cholesterol and LDL-C through dietary intervention, but this effect is modest [10,11]. Statins are the cornerstone of lipid modification but, despite intensive statin therapy, many high risk patients remain at significant risk or suffer from unsupportable drug-related symptoms. Until today there were various drug options for the management of this residual risk through further lipid modification. Nevertheless, it should be noted that effective CVD reduction strategies need to adopt a multi-faceted approach to address other major CVD risk factors, such as blood pressure or diabetes, ensure smoking cessation and constant physical activity and avoidance of obesity as well.

Equally, any intervention is only as effective as its associated compliance, highlighting the importance of patient understanding of any treatment and its acceptability in clinical practice. Nevertheless, there are patients in everyday's clinical practice who are on maximally tolerated statin therapy and cannot achieve their attributed specific LDL targets, or even more, patients intolerant to statins or those patients with familial hypercholesterolemia,who apparently have unmet need for lipid lowering therapies beyond statins. PCSK9 inhibitors such as evolocumab (Repatha, Amgen) and alirocumab (Praluent, Sanofi/Regeneron) and are potentially good choices in these populations since the drugs' effect on LDL reduction is potent and prolonged and a few associated adverse and post hoc analyses have shown signals of reduced CV events.

The history of the PCSK9 inhibitors is brief

Discovery in 2003 by a company conducting screenings for genes involved in cholesterol synthesis and fast forward drug approval in 2015. Then early findings on transcription factors SREBP-1 and SREBP-2, respectively regulating fat synthesis and activating all enzymes involved in the creation of a cholesterol molecule, and experiments in animal models that led to gene identification. Formally, proprotein convertase subtilisin/kexin type 9 serine protease PCSK9 is actually the 9th member of its family. But the big breakthrough in learning about its function happened in France, where researchers found mutations in the PCSK9 gene associated with hypercholesterolemia, suggesting they were functional mutations.

Upon researchers realized that LDL was being affected, the pathway was relatively straightforward. Many investigators took approaches looking at PCSK9 expression in relation to LDL in the liver and they've noticed that when PSCK9 was deleted, the LDL receptor protein went up regulated by two-and-a-half to threefold. The proprotein convertase subtilisin/kexin type 9 (PCSK9) enzymes is encoded in humans by the PCSK9 gene. It plays a significant role in regulating LDL-C levels by binding to hepatic LDL receptors and promoting their degradation, leading to increased LDL-C levels [12,13]. These findings have led to the development of PCSK9 inhibitors, including using monoclonal antibodies (MoAbs), antisense oligonucleotides [14] and by RNA interference (RNAi) mechanisms.

The most extensively studied of these PSCK9 inhibitors are the subcutaneously administered, either fully human or humanized, PCSK9 MoAbs. Multiple trials have been conducted with these agents, which principally involve alirocumab, bococizumab and evolocumab, all of which are either in late stage of development or have been recently approved. The phase 3 programme for alirocumab is known as ODYSSEY, whilst that for bococizumab is called Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE), with each programme containing multiple trials prefixed by the associated programme names (e.g. ODYSSEY FH [15], ODYSSEY LONGTERM [16], SPIRE-FH [17] and SPIRE-LDL [18] trials). The evolocumab phase III trials are encompassed by the Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9.

In Different Populations (PROFICIO, which includes the completed Monoclonal Antibody Against PCSK9 to Reduce Elevated Low density Lipoprotein Cholesterol (LDL-C) in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels [MENDEL]-2 [19],Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects [GAUSS] [20], Durable Effect of PCSK9 Antibody Compared with placebo Study [DESCARTES] [21], LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy [LA-PLACE-2] [22], Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder [RUTHERFORD]-2 [23] and Open-Label Study of Long-Term Evaluation Against LDL-C [OSLER] [24] trials). The development of PCSK9 MoAbs and associated trial results to date are comprehensively summarized elsewhere 78-90.

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In summary, PCSK9 MoAbs have been shown to significantly reduce LDL-C levels against both placebo and background lipid therapies, with further LDL-C reductions of ~60% when used in combination with statin compared to statin alone being reported [13,16,22,25]. Neutralizing antibodies have not been observed, and based on evidence to date; they appear to be well tolerated. Two studies have specifically looked at PCSK9 MoAbs in statin intolerant patients (the GAUSS-2 [26] and ODYSSEY ALTERNATIVE [27] trials), with reported results indicating good efficacy and favourable muscle symptomatology compared to other therapies. However, injection site reactions can occur, and studies have shown clinical outcomes when used in combination with statin therapy.

New studies and complementary analyses of phase III trials have consistenly shown that evolocumab and alirocumab are highly effective in reducing LDL - C and to some extent Lp (a). Some preliminary findings coming from exploratory and post-hoc analyses of the longer-term safety phase III trials and meta-analyses suggest that these mAbs can decrease the incidence of cardiovascular events itself. Whether or not mAbs targeting PCSK9 definitely reduce the incidence of cardiovascular events without any safety concerns, shall be demonstrated and documented with the results of the ongoing cardiovascular outcome trials. Waiting the results of these outcome trials and given the high cost of these mAbs, groups of experts have proposed as priority groups of patients to treat those with familial hypercholesterolemia (FH) and those with atherosclerotic cardiovascular disease who have substantially elevated LDL-C on maximally tolerated statin/ezetimibe therapy.

Conclusion

Statins remain the cornerstone of lipid management for both primary and secondary prevention of CVD. A variety of other lipid modifying therapies are available which can be added to statin therapy to further reduce CV risk. Ezetimibe is the most effective and evidence-based treatment that can be safely added to statins, and is increasingly used in clinical practice. Other options include fibrates, resins or nicotinic acid. Fibrates remain widely used in lipid clinics to manage significant hypertriglyceridaemia but their role for further CV reduction in the absence of high triglycerides or low HDL-C has not been proven. Bile acid sequestrants, such as the newer tablet preparations of colesevelam, also have a role in a limited number of patients and are effective LDL-C lowering agents if given at sufficiently high dose, but without recent trial data to support their use.

In contrast, nicotinic acid, despite modifying lipids, has not been shown to reduce CV risk when added to statins and has been shown to be associated with significant hazards. Several large phase 3 trials of CETP inhibitors have been initiated, but only one (REVEAL) remains ongoing after the ILLUMINATE trial was stopped for safety concerns and the dal-OUTCOMES and ACCELERATE trials stopped for futility. A variety of novel anti-sense oligonucleotides are also in development, with vaccines offering a further potential opportunity for lipid intervention in the future. Nowadays, PCSK9 inhibitors (evolocumab and alirocumab recently approved) appear promising agents with multiple trials demonstrating that these agents -in combination with statins or monotherapy- can modify lipids substantially with an unprecedented optimal safety profile. Several large PCSK9 inhibitor clinical outcomes trials (ODYSSEY-OUTCOMES, FOURIER and the SPIRE-I and II trials) are currently ongoing, which should elucidate their place in clinical practice.

However, it remains non negotiable that keeping CVD therapy affordable necessitates restricted use of PCSK9 antibodies to select patient groups such as Familial Hypercholesterolemia (FH), statin intolerance and very high CVD risk with residual LDL burden, [1] until those currently ongoing outcome trials and future randomized survival trials elucidate the high rank place of these inhibitors in our cardiovascular armamentarium. In light of this exciting era, which the medical community is facing in lipid disorders treatment and generally in cardiovascular disease, we should all serve a unique vision:

Educate (in details), identify (early), support and manage patients with high and very high CV risk, not only for short and long-term but aggressively as well. Reduction of total mortality and CV mortality will become reality only with early, persistent, aggressive, safe and efficient management.

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