Sweetless’n low LDL-C targets for PCSK9 treatment

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Online publish-ahead-of-print 31 March 2015

This editorial refers to ‘Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial’¹, by C.P. Cannon et al., on page 1186.

In their trial, Cannon et al. report the superiority of the anti-PCSK9 monoclonal antibody (mAb) alirocumab (SAR236553/REGN722; s.c. 75 mg every 2 weeks) over ezetimibe (oral 10 mg once a day) in the reduction of LDL-cholesterol (LDL-C) levels among 720 patients at high cardiovascular risk who were inadequately controlled despite maximally tolerated statin dosage.¹ At week 24, mean reduction in LDL-C from baseline was 50.6% for alirocumab vs. 20.7% for ezetimibe (P < 0.001), while 77.0% of the alirocumab treatment arm achieved the recommended LDL-C target of < 1.8 mmol/L vs. 45.6% for ezetimibe (P < 0.001). Mean LDL-C at week 24 was 1.3 mmol/L for alirocumab compared with 2.1 mmol/L for ezetimibe, yielding an additional 30% lipid-lowering effect for patients treated with the anti-PCSK9. The findings of the ODYSSEY COMBO II trial add to the evidence of alirocumab as a safe and efficacious option for patients whose LDL-C is insufficiently controlled under maximally dosed statin therapy, as is the case for an increasing number of high-risk patients.

Available data indicate that fully human antibodies targeting PCSK9 are very effective in reducing LDL-C, apolipoprotein B (apoB), and lipoprotein(a) [Lp(a)] concentrations.² Their efficacy has been demonstrated alone or in addition to statins in hypercholesterolaemic patients.³ Used alone in the primary setting, anti-PCSK9 treatments yielded LDL-C reductions up to 70% greater than placebo.⁴

The ODYSSEY COMBO studies are among the longest duration placebo/ezetimibe-controlled trials of PCSK9 inhibitors in high-risk patients with poorly controlled LDL-C despite maximally tolerated statin treatment. ODYSSEY COMBO I reported the benefit of alirocumab (75 mg s.c. every 2 weeks) over placebo in patients poorly controlled despite maximally tolerated statin therapy or other concomitant lipid-lowering therapies. In ODYSSEY COMBO I, LDL-C levels < 70 mg/dL were reached more frequently for alirocumab than for placebo (75% vs. 9%, P < 0.001).⁵ ODYSSEY COMBO II compared alirocumab with the active substance ezetimibe. Using ezetimibe as the control substance is of particular interest in view of the IMPROVE-IT trial outcomes recently presented at the American Heart Association (AHA) 2014 congress.⁶ IMPROVE-IT is the first trial having demonstrated the benefit of adding a non-statin lipid-lowering agent (ezetimibe 10 mg) to a statin (simvastatin 40 mg), compared with a statin alone (simvastatin 40 mg) in patients with recent acute coronary syndrome (ACS) and LDL-C values < 125 mg/dL (3.2 mmol/L).⁷ Adding ezetimibe to the statin therapy further reduced LDL-C by an average of 0.4 mmol/L, yielding an additional improvement of 2% for the absolute rate of major composite cardiovascular endpoints. This result is remarkable in light of the fact that the study was intention-to-treat driven with a 40% drop-out rate, and all patients were already well controlled by optimal medical therapy. By treating 50 patients during 7 years, IMPROVE-IT demonstrated that the addition of a non-statin lipid-lowering agent to a statin could prevent one additional event. The relative risk reduction for IMPROVE-IT was, however, more modest (6%). As limitations, we can mention that patients in the control arms were not on a high-intensity statin therapy regimen as currently recommended by American and European guidelines.

The adage ‘lower is better’ seems to be confirmed also for non-statin lipid-lowering agents in the light of the ODYSSEY LONG TERM trial results (Figure 1) presented at the European Society of Cardiology 2014 congress and recently published.⁸ The ODYSSEY LONG TERM trial randomized 2341 patients with familial hypercholesterolaemia (FH) or coronary heart disease to alirocumab 150 mg every 2 weeks vs. placebo for 78 weeks. All participants had poorly controlled LDL-C at inclusion despite maximum tolerated statin dosages. At week 78, differences in LDL-C were significant (1.5 mmol/L for alirocumab vs. 2.1 mmol/L for placebo, P-value < 0.001), which translates into a significant additional 60% LDL-C reduction with PCSK9 inhibition. In a post-hoc analysis, the rate of

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

¹ doi:10.1093/eurheartj/ehv028

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adjudicated major cardiovascular events requiring hospitalization was 1.7% for alirocumab vs. 3.3% for placebo [hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.31–0.90, P = 0.02]. Recently, evolocumab (another monoclonal antibody that inhibits PCSK9) significantly reduced LDL-C by 61% and cardiovascular events (HR 0.47, 95% CI 0.28–0.78, P = 0.003) after one year of therapy compared to standard therapy. The ongoing phase III ODYSSEY OUTCOMES trial (NCT01663402) will randomize 18,000 patients with poorly controlled LDL-C on maximally tolerated statin dosages to receive either alirocumab (75–150 mg every 2 weeks) or placebo. ODYSSEY OUTCOMES is expected to provide the definitive answer on the impact of alirocumab on clinical outcomes when added to statins.

In terms of safety, alirocumab was generally well tolerated, with no evidence of excess treatment-emergent adverse events. Patients were compliant to self-administration by s.c. injection. Whatever the frequency of administration, anti-PCSK9 therapies may prove more attractive in patients who suffer from statin side effects and require lifelong treatment. Both statin inhibition of the HMG-CoA reductase pathway and ischaemic attack, and heart failure. In CTT Collaboration, MACE was defined as coronary death or non-fatal myocardial infarction, coronary revascularization, stroke, transient ischaemic attack, and heart failure. In CTT Collaboration, MACE was defined as coronary death or non-fatal myocardial infarction, coronary revascularization, and ischaemic attack.

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Figure 1 Relative risk reduction of major adverse cardiovascular events (MACE) according to the lipid-lowering strategy adopted for reducing LDL-cholesterol (LDL-C). In the IMPROVE-IT trial, MACE was defined as coronary death or non-fatal myocardial infarction, coronary revascularization, stroke, or hospitalization for unstable angina.

In ODYSSEY LONG-TERM, MACE was defined as cardiac death, myocardial infarction, ischaemic stroke, and unstable angina requiring hospitalization. In OSLER-1 and OSLER-2, MACE was defined as death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischaemic attack, and heart failure. In CTT Collaboration, MACE was defined as coronary death or non-fatal myocardial infarction, coronary revascularization, stroke, transient ischaemic attack, and heart failure.

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In terms of safety, alirocumab was generally well tolerated, with no evidence of excess treatment-emergent adverse events. Patients were compliant to self-administration by s.c. injection. Whatever the frequency of administration, anti-PCSK9 therapies may prove more attractive in patients who suffer from statin side effects and require lifelong treatment. Both statin inhibition of the HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA) reductase enzyme and mutations of the HMG-CoA reductase gene have been shown to induce body weight increase and the onset of type 2 diabetes.

In this regard, neither ezetimibe nor PCSK9 inhibitors act on the HMG-CoA-CoA pathway, and thus are not at risk of inducing type 2 diabetes through this route. However, there is matter for controversy surrounding the potential impact of anti-PCSK9 treatment on the onset of type 2 diabetes due to intracellular accumulation of lipids in pancreatic cells. In humans, PCSK9 loss-of-function mutation has not shown to increase the onset of type 2 diabetes or insulin resistance. In mice, gene inactivation of PCSK9 reduced insulin levels, resulting in glucose intolerance, which in turn was associated with malformation, apoptosis, and inflammation of pancreatic islets.

It is also of interest to evaluate systematically the role of PCSK9 inhibitors in the pathogenesis of diabetes, obesity, hypertension, inflammation and endothelial dysfunction. In the ODYSSEY COMBO II trial, week 24 results showed no significant differences for glycated haemoglobin levels between both groups (6.14 ± 1.00% for alirocumab vs. 6.15 ± 0.88% for placebo, P > 0.05). More data are needed from large trials to detect possible metabolic events related to PCSK9 inhibition. Long-term efficacy and safety trials are critical, as patients generally require lifelong treatment. In particular, the large ongoing phase III trials should eventually provide information on antibody development and adverse events. Additional studies will also be necessary to better understand the physiological role of PCSK9 and how its inhibition may impact specific populations, such as patients with diabetes or chronic kidney disease. The pooling of individual participant data analysis of different PCSK9 inhibitor trials will provide significant insight into the efficacy of PCSK9 inhibitors in subgroup populations, as well as the occurrence of adverse events such as hyperglycaemia.

The ODYSSEY COMBO II trial demonstrated that PCSK9 inhibitors are more effective than ezetimibe in terms of LDL-C lowering for patients not reaching their target LDL-C levels despite maximally tolerated statin dosages. The candidate populations who would most benefit from PCSK9 inhibition are patients with heterozygous FH, high-risk patients with documented statin intolerance, or patients with poorly controlled LDL-C on maximally tolerated statin dosages. Further medico-economic analyses will need to address cost-effectiveness issues of different lipid-lowering strategies once PCSK9 inhibitors are on the market. For example, patients treated with a PCSK9 mAb may show better adherence to injections every 2 or 4 weeks compared with daily p.o. therapies. In this regard, patient-related outcomes such as health-related quality of life will be relevant for the evaluation of PCSK9 inhibitors by policy makers. The latest AHA/ACC 2013 guidelines on cholesterol treatment abandoned the LDL-C target strategy in favour of the statin intensity strategy. In the meantime, PCSK9 inhibitors have proven beneficial for patients with poorly controlled LDL-C despite maximal statin therapy, rendering LDL-C targets once again a key indicator for lipid management. The next prevention guidelines may have to reconsider the LDL-C target strategy when integrating PCSK9 inhibitors into clinical decision-making algorithms.

Approval of PCSK9 inhibitors for the treatment of FH and for patients intolerant to statins is imminent. As declared by the Food and Drug Administration (FDA), approval will be based on the potential for PSCK9 inhibitors to reduce LDL-C and their safety profile rather than clinical outcomes. The three ongoing large phase III programmes in patients with ACS and inadequately controlled LDL-C values will prove critical in determining the place of PCSK9 inhibitors in secondary prevention of ACS patients. In this regard, the results of the FOURIER study (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk, NCT01764633) and ODYSSEY OUTCOMES (Evaluation of
Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553/REGN727, NCT01663402) will determine the a wider application of PCSK9 inhibitors.

If PCSK9 therapies continue to demonstrate their impressive LDL-C-lowering effect while having little or no impact on glycaemia, physicians can anticipate dyslipidaemia treatments to reach new, unprecedented sweet/s low targets.

Conflict of interest: F.M. has received honoraria for advisory boards and conferences on dyslipidaemia from Agenon, AstraZeneca, BMS, Eli Lilly, MSD, Sanofi, and Pfizer, and was a Principal Investigator for the IMPROVE-IT trial. B.G. has no conflicts to declare.

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Acknowledgements
The research of F.M. and B.G. is supported by the Swiss National Science Foundation (SNSF 33CM10-124112 and SPUM 33CM10-140336, ‘Inflammation and acute coronary syndromes – Novel strategies for prevention and clinical management’), and by a grant of the Geneva University Hospitals (Department of Specialties in Medicine). Special gratitude is expressed to Aliki Buhayer for excellent support.

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