The ODYSSEY DM-DYSLIPIDEMIA trial: confirming the benefits of alirocumab in diabetic mixed dyslipidemia

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The role of triglycerides in the development of atherosclerotic cardiovascular disease (ASCVD) has been a controversial issue for many years, but recent evidence from epidemiology and Mendelian randomization studies has confirmed that elevated triglycerides, and perhaps more importantly triglyceride-rich lipoproteins, are strong and independent predictors of ASCVD and all-cause mortality (1). Hypertriglyceridemia is often related to genetic factors which are typically polygenic in mild-to-moderate hypertriglyceridemia or monogenic in severe hypertriglyceridemia with triglyceride concentration >10 mmol/L (>885 mg/dL) (2). Lifestyle, other diseases and medications also influence triglyceride levels and diabetes is typically associated with elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein (LDL) particles which are small and dense resulting in atherogenic diabetic dyslipidemia (3).

The contribution of cholesterol carried in triglyceride-rich lipoproteins in addition to LDL cholesterol (LDL-C) can be estimated by calculating the non-HDL-C which should then reflect the total burden of cholesterol transported in atherogenic lipoproteins. Non-HDL-C levels provide better prediction of ASCVD events than LDL-C levels in statin-treated patients (4) and in an analysis of changes in atheroma volume determined by coronary intravascular ultrasonography, the achieved non-HDL-C levels were more closely associated with coronary atheroma progression than LDL-C levels (5). Based on the current understanding, some international lipid management guidelines recommend non-HDL-C levels as alternative primary or secondary targets of treatment in addition to LDL-C levels in all patients (6,7) or specifically in patients with diabetes (8).

The ODYSSEY DM-DYSLIPIDEMIA trial was designed to examine the effects of alirocumab in an important group of patients with type 2 diabetes mellitus (T2DM) with mixed dyslipidemia at high cardiovascular risk, a group that has not previously been studied prospectively in the development programs with the proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies (mAbs) (9). Likewise, the other ODYSSEY trial in diabetic patients, the ODYSSEY DM-INSULIN trial, focused on another novel group of patients with either type 1 diabetes mellitus (T1DM) or T2DM who

were treated with insulin, again a group that has not been studied prospectively before (10). Both trials have now been completed and the results were presented at the meetings of the American Diabetes Association (ADA) in San Diego and the European Association for the Study of Diabetes (EASD) in Lisbon in 2017. The ODYSSEY DM-INSULIN trial has been published recently (11).

Other trials in the ODYSSEY program for alirocumab (12) and the PROFICIO clinical trial program with evolocumab (13) have focused on the reduction in LDL-C in patients with primary hypercholesterolemia, either familial or non-familial. The inclusion criteria usually included a baseline LDL-C above the target according to the level of cardiovascular risk, such as LDL-C ≥1.8 mmol/L (70 mg/dL) for very high-risk patients. Sometimes a target for non-HDL-C which was 0.8 mmol/L (30 mg/dL) above the LDL-C target was an alternative lipid inclusion criterion. This difference in values between LDL-C and non-HDL-C targets is based on the threshold for elevated fasting triglycerides being >1.7 mmol/L (>150 mg/dL) which converts into these figures for cholesterol carried in triglyceride-rich lipoproteins using the Friedewald formula. These trials did not exclude patients with T2DM but generally excluded patients with baseline fasting triglyceride levels >4.5 mmol/L (>400 mg/dL), partly because calculated baseline LDL-C levels become inaccurate with levels of triglyceride about this value.

Considering that the PCSK9 mAbs have a primary effect to reduce circulating PCSK9 and thus reduce LDL-C by upregulating the LDL receptors (LDLRs) (14), the primary endpoint of most of the studies was the change in LDL-C, which was assessed after 24 weeks with alirocumab or after 12 weeks with evolocumab (12,13). The studies also reported significant decreases in other atherogenic lipid parameters including total cholesterol, non-HDL-C, apolipoprotein (apo) B, triglycerides and lipoprotein(a) [Lp(a)], and there were usually increases in HDL-C and apoAI (15). The average relative reductions in LDL-C with alirocumab given in subcutaneous doses of 75 or 150 mg every 2 weeks have been fairly consistent at about 40% to 60% in most patient groups, irrespective of baseline values, although there is a considerable variation in response between individuals. Patients with homozygous familial hypercholesterolemia usually respond less well and those with null mutations in the LDLR gene did not respond at all in the studies with evolocumab (16). Patients on statin treatment show some differences in the pharmacokinetics but not the pharmacodynamics with alirocumab and evolocumab (12,13). However, there is no a priori reason to expect that any other group of patients would show a diminished response to PCSK9 mAbs.

A recent analysis evaluated the efficacy of alirocumab on non-HDL-C and apoB from data derived from 4,983 patients enrolled in ten randomized, placebo- or ezetimibe-controlled phase 3 ODYSSEY trials. The primary end point for this pooled analysis was percent reduction in non-HDL-C and apoB at week 24 (17). For the trials in which alirocumab was compared to placebo in the ODYSSEY COMBO I, FH I, and FH II studies, the alirocumab starting dose was 75 mg every 2 weeks (Q2W) and it was then increased to 150 mg Q2W at week 12 if the pre-defined ASCVD risk-based LDL-C goals were not achieved at week 8. In the ODYSSEY LONG TERM and HIGH FH trials, the starting dose of alirocumab was 150 mg Q2W. In these two groups of placebo-controlled ODYSSEY trials, the least squares mean differences [95% confidence intervals (CI)] compared to placebo were, respectively, –46.4% (–49.6% to –43.2%) and –51.6% (–53.7% to –49.5%) for non-HDL-C, –41.3% (–44.0% to –38.6%) and –52.9% (–55.2% to –50.7%) for apoB, –10.3% (–14.0% to –6.6%) and –17.0% (–19.7% to –14.3%) for triglyceride, –52.7% (–56.3% to –49.2%) and –60.9% (–63.3% to –58.5%) for LDL-C and 7.6% (5.6% to 9.6%) and 4.5% (3.3% to 5.8%) for HDL-C (17).

This analysis and other trials with the PCSK9 mAbs have generally shown relative reductions in triglycerides that are substantially less than the reductions in LDL-C, a situation similar to the effects of statins (18). Mechanistic studies in healthy subjects showed that alirocumab increased the clearance of intermediate-density lipoprotein (IDL) as well as LDL and there was also an increase in the fractional clearance rate of Lp(a) with no change in the production rate, suggesting increased LDLRs may play a role in the reduction of plasma Lp(a) (19). A study with evolocumab showed similar findings but also showed increased fractional catabolism of very-low-density lipoprotein (VLDL)-apoB and reduced production rate of IDL-apoB suggesting that the clearance of VLDL particles from the circulation may also be increased (20). PCSK9 also interacts with other members of the LDLR superfamily including the VLDL receptor (VLDLR), apolipoprotein E receptor 2 (ApoER2), and lipoprotein receptor-related protein 1 (LRP1), and effects of PCSK9 mAbs to reduce the PCSK9 interaction with these receptors may contribute to increased triglyceride-rich lipoprotein catabolism, and thereby reduction of triglyceride levels, as well as the effects on the

LDLR (21).

There are no previous trials with PCSK9 mAbs in patients selected for mixed hyperlipidemia but an analysis was performed of the effects of evolocumab in 1,148 patients selected from four 12-week phase 3 randomized studies which compared those with mixed hyperlipidemia who had fasting triglyceride levels ≥1.7 mmol/L (≥150 mg/dL) to those with triglycerides <1.7 mmol/L (22). The mean of the change from baseline in LDL-C at weeks 10 and 12 with evolocumab was approximately –67% versus placebo and –42% versus ezetimibe (all P<0.001) compared to –65% versus placebo and –39% versus ezetimibe in participants with and without elevated triglycerides, respectively. There was a similar pattern of treatment differences for evolocumab versus placebo and ezetimibe for non-HDL-C and apoB so that overall the reductions of atherogenic lipids with evolocumab were similar in patients with and without mixed hyperlipidemia.

Likewise, no previous trials have only enrolled patients with T2DM but a meta-analysis based on individual participant data of the clinical trials with evolocumab in adult patients with or without T2DM, excluding trials that included patients with homozygous familial hypercholesterolemia, identified three trials that included 413 patients with T2DM and 2,119 patients without T2DM (23). The mean reductions in LDL-C were 60% (95% CI, 51–69%) versus placebo in patients with T2DM and 66% (95% CI, 62–70%) versus placebo in those without T2DM. Reductions in non-HDL-C were 55% (95% CI, 47–63%) versus placebo in patients with T2DM and 58% (95% CI, 55–61%) in those without T2DM and reductions in triglycerides were 23% (95% CI, 12–34%) in patients with T2DM compared with 17% (95% CI, 14–21%) in those without T2DM. Findings were similar across diabetes subgroups based on glycemia, insulin use, renal function, and cardiovascular disease status so overall the lipid responses were not different between patients with and without T2DM.

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9) trial with evolocumab included 11,031 patients (40%) who had diabetes and 16,533 (60%) who did not have diabetes at baseline and a pre-specified analysis investigated the effect of evolocumab on cardiovascular events by diabetes status (24). Evolocumab reduced cardiovascular outcomes significantly and to the same extent in patients with and without diabetes at baseline. The hazard ratios (HRs) were 0.83 (95% CI, 0.75–0.93; P=0.0008) and 0.87 (0.79–0.96; P=0.0052) for patients with and without diabetes (P interaction =0.60), respectively, for the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization. The HRs for the key secondary endpoint, which was a composite of cardiovascular death, myocardial infarction, or stroke, were also similar in patients with and without diabetes (P interaction =0.65). There was no increased risk of new-onset diabetes with evolocumab in patients without diabetes at baseline, including in those with prediabetes and levels of glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were similar between the evolocumab and placebo groups over time in all patients grouped according to baseline glycemic status.

In the ODYSSEY DM-INSULIN study, there were 441 participants with T2DM and 76 with T1DM with baseline LDL-C ≥70 mg/dL (≥1.8 mmol/L) and increased cardiovascular risk (11). They were randomized to receive subcutaneous alirocumab or placebo in a 2:1 ration Q2W for 24 weeks. The alirocumab dose was initially 75 mg Q2W and this was increased to 150 mg Q2W at week 12 if necessary, as in other alirocumab studies. The mean (± standard error) reductions in LDL-C from baseline to week 24 were 49.0%±2.7% and 47.8%±6.5% versus placebo (both P<0.0001) in patients with T2DM and T1DM, respectively. There were also significant reductions in non-HDL-C, apoB, triglycerides and Lp(a). The non-HDL-C target of <100 mg/dL (<2.6 mmol/L) was achieved in 79% and 71% of T2DM and T1DM patients, respectively. Most of the T2DM (80%) and T1DM (63%) patients did not need the dose of alirocumab to be increased and remained on the starting dose of 75 mg Q2W. There was no significant change in HbA1c and FPG levels and concomitant administration of alirocumab and insulin did not raise any safety concerns.

Taken together, the available data indicate that the lipid changes with alirocumab would be similar in patients with and without mixed hyperlipidemia and in patients with and without T2DM. Moreover, the cardiovascular outcome with alirocumab might be expected to be similar in patients with and without diabetes, based on the FOURIER cardiovascular outcome trial with evolocumab. There is also no evidence to date that the PCSK9 mAbs increase the risk of development of new onset diabetes or worsen glycemic control in patients with established diabetes or impaired glucose tolerance.

The design of the ODYSSEY DM-DYSLIPIDEMIA study was to enroll 420 individuals with T2DM with

documented ASCVD or ≥1 additional cardiovascular risk factor and mixed dyslipidemia, defined as non-HDL-C ≥2.59 mmol/L (100 mg/dL) and triglycerides ≥1.7 and <5.65 mmol/L (≥150 and <500 mg/dL), with non-HDL-C inadequately controlled despite maximally tolerated statin therapy (25). Participants were randomized (2:1) to additional treatment with alirocumab 75 mg every 2 weeks (Q2W) with a blinded dose increase to 150 mg Q2W at week 12 if non-HDL-C ≥100 mg/dL at week 8, or to lipid-lowering usual care. The usual care allowed the option of adding the pre-specified choice of ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid, in accordance with local standard-of-care. In the 413 patients recruited from 14 countries worldwide, the primary efficacy endpoint reported was a reduction in non-HDL-C of 33.3% with alirocumab compared with fenofibrate (P<0.0001).

In conclusion, the ODYSSEY DM-DYSLIPIDEMIA trial fills an important gap in the development programs of the PCSK9 mAbs. Patients with T2DM are a group with high ASCVD risk and typically have mixed dyslipidemia. It may be relatively easy to achieve target LDL-C levels in these patients but it is important to consider non-HDL-C targets, which are less often attained with current therapies. The results presented from the ODYSSEY DM-DYSLIPIDEMIA trial with alirocumab are encouraging and considering the data available from the analysis of completed trials with alirocumab and evolocumab, the findings were not surprising. We await the final publication of the trial with interest.

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Footnote

Conflicts of Interest: B Tomlinson has received research funding from Amgen, AstraZeneca, Merck Serono, Merck Sharp and Dohme, Novartis, Pfizer and Roche, and he has acted as consultant, advisor or speaker for Amgen, AstraZeneca, Merck Serono, Merck Sharp and Dohme and Sanofi. The other authors have no conflicts of interest to declare.

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