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Original article

Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: Rationale and design of the ODYSSEY DM–INSULIN trial

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ABSTRACT

Aims. – The coadministration of alirocumab, a PCSK9 inhibitor for treatment of hypercholesterolaemia, and insulin in diabetes mellitus (DM) requires further study. Described here is the rationale behind a phase-IIIb study designed to characterize the efficacy and safety of alirocumab in insulin-treated patients with type 1 (T1) or type 2 (T2) DM with hypercholesterolaemia and high cardiovascular (CV) risk.

Methods. – ODYSSEY DM–INSULIN (NCT02585778) is a randomized, double-blind, placebo-controlled, multicentre study that planned to enrol around 400 T2 and up to 100 T1 insulin-treated DM patients. Participants had low-density lipoprotein cholesterol (LDL-C) levels at screening $\geq$ 70 mg/dL (1.81 mmol/L) with stable maximum tolerated statin therapy or were statin-intolerant, and taking (or not) other lipid-lowering therapy; they also had established CV disease or at least one additional CV risk factor. Eligible patients were randomized 2:1 to 24 weeks of alirocumab 75 mg every 2 weeks (Q2W) or a placebo. Alirocumab-treated patients with LDL-C $\geq$ 70 mg/dL at week 8 underwent a blinded dose increase to 150 mg Q2W at week 12. Primary endpoints were the difference between treatment arms in percentage change of calculated LDL-C from baseline to week 24, and alirocumab safety.

Results. – This is an ongoing clinical trial, with 76 T1 and 441 T2 DM patients enrolled; results are expected in mid-2017.

Conclusion. – The ODYSSEY DM–INSULIN study will provide information on the efficacy and safety of alirocumab in insulin-treated individuals with T1 or T2 DM who are at high CV risk and have hypercholesterolaemia not adequately controlled by the maximum tolerated statin therapy.

Abbreviations: AE, adverse event; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; I-TAQ, Injection-Treatment Acceptance Questionnaire; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LDL-P, LDL particle; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); MI, myocardial infarction; mITT, modified intention-to-treat; MMRM, mixed-effects model with repeated measures; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; TG, triglyceride; T1, type 1; T2, type 2; UA, unstable angina.

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Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 1 (T1) or type 2 (T2) diabetes mellitus (DM) [1–3], and insulin-treated patients have an even higher CV risk [4]. Furthermore, the presence of comorbid DM among those who have atherosclerotic CVD (ASCVD) significantly increases the risk of CV events [4,5].

As in the general population, dyslipidaemia is a risk factor for CVD in both T1DM and T2DM [2,6]. The development of dyslipidaemia is associated with insulin resistance that precedes the development of T2DM; once hyperglycaemia is present, increased hepatic free fatty acid influx and synthesis, driven by concomitant loss of insulin sensitivity and glycaemic control, cause dyslipidaemia to deteriorate further [1,7]. Although T2DM is usually characterized by elevated non-high-density lipoprotein cholesterol (non-HDL-C) and triglyceride (TG) levels, along with low HDL-C, elevation in low-density lipoprotein cholesterol (LDL-C) can be variable and rather modest [7]. Nonetheless, small, dense LDL particles are increased, along with other qualitative lipid changes: LDL is more likely to be glycated and oxidized, and HDL undergoes increased catabolism [8]. As a result, two scenarios probably contribute to increased CV risk in T2DM:

- increased TG levels result in increased levels of intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) remnants, which are atherogenic [8];
- whether smaller LDL particles (LDL-P) are more atherogenic on an individual level remains to be fully elucidated; however, a shift to smaller LDL-P at any given level of LDL-C is associated with a greater number of LDL particles and thereby an increased atherogenic risk.

Patients with T1DM under good glycaemic control often have a 'supernormal' lipid profile, and subcutaneous administration of insulin is known to increase lipoprotein lipase activity and, as a consequence, the turnover of VLDL particles [5]. However, there may be potentially atherogenic changes in the composition of both HDL and LDL particles [5]. Recent evidence has also suggested that components of metabolic syndrome (MetS) are often present in adults with T1DM [9]. Under conditions of poor glycaemic control or declining renal function, T1DM may also be accompanied by dyslipidaemia with a lipid profile that resembles what is seen in T2DM [1].

Several studies and meta-analyses have shown that lowering LDL-C by statins has led to significant reductions in CV events in those with DM [10–12], with further CV risk reduction associated with additional LDL-C-lowering by concomitant ezetimibe [13]. Guidelines generally recommend an LDL-C goal of < 70 mg/dL (1.81 mmol/L) and/or a reduction of $\geq 50\%$ from baseline in patients with T1DM or T2DM considered to be at high or very-high CV risk [5,14,15]. However, even with the currently available treatments, many patients with DM continue to have persistent lipid abnormalities [16–18] and are therefore exposed to a residual risk of CV events.

Alirocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is approved in several regions, including the US, Europe and Japan, for the management of patients with hypercholesterolaemia on maximum tolerated doses of statin. In phase-III clinical studies, alirocumab reduced LDL-C by up to 61% in patients treated with statins [19]. Significant reductions in apolipoprotein (Apo) B, non-HDL-C and lipoprotein(a) [Lp(a)], trends for TG reduction, and modest increases in HDL-C and ApoA-I were also observed. It is hoped that these robust lipid changes will translate into significant reductions in CV events, as the preliminary results were promising [19]. Indeed, the ongoing ODYSSEY OUTCOMES study (NCT01663402) is evaluating the effect of alirocumab on major CV events in $\geq$ 18,000 patients 4–52 weeks post-acute coronary syndrome, including a significant number with DM [20].

There is conflicting evidence regarding the possible association of PCSK9 with alterations of glucose homoeostasis. The CODAM study [21] found that plasma levels of PCSK9 do not differ between those with recently diagnosed T2DM, normal glucose metabolism and impaired glucose metabolism. In contrast, the ILLUMINATE study [22] found that plasma PCSK9 levels were elevated in patients with DM compared with those without DM, with a significant association between PCSK9 levels and LDL-C, TGs, glucose, insulin and homoeostasis model assessment of insulin resistance (HOMA-IR) scores. In addition, a study evaluating the impact of a short-term high-calorie, high-fructose diet showed that plasma PCSK9 levels were increased with this diet independently of cholesterol synthesis, and associated with insulin resistance, hepatic steatosis and TG levels [23]. Thus, the potential interaction between PCSK9 inhibitors and exogenously administered insulin is of considerable interest.

Based on currently available data, there is no evidence of any effect of alirocumab on glycaemia after a maximum follow-up of 78 weeks [24]. Nevertheless, despite no safety signals to date, the safety of the coadministration of a biological agent (insulin) with a monoclonal antibody (alirocumab) warrants further study. Of the 5296 participants in the phase-III ODYSSEY programme, around one-third had DM, and 28% of those DM patients receiving alirocumab were insulin-treated (8% of the overall alirocumab-treated population). In these phase-III studies, 56% of the insulin-treated patients received alirocumab at a starting dose of 150 mg every 2 weeks (Q2W). However, as a 75 mg Q2W dose is expected to be sufficient for most patients with DM, given their relatively lower elevations in LDL-C, the present study is using a starting dose of 75 mg Q2W, with an increase to 150 mg Q2W if LDL-C goals are not achieved. Given the high CV risk in DM patients who require insulin treatment, it is important to collect sufficient efficacy and safety data for alirocumab in such patients to inform clinical practice.

The present report describes the design of a placebo-controlled study — ODYSSEY DM–INSULIN — initiated to further characterize the efficacy and safety of alirocumab in insulin-treated patients with T1DM or T2DM who are at high CV risk and have failed to reach LDL-C goals despite maximum tolerated statin doses, with or without other lipid-lowering therapy (LLT).

Material and methods

Study design

ODYSSEY DM–INSULIN (ClinicalTrials.gov identifier: NCT02585778) is a phase-IIIb randomized double-blind, placebo-controlled, parallel-group multicentre trial being conducted in Europe and the US. It is evaluating the efficacy and safety of alirocumab in insulin-treated DM patients at high CV risk with hypercholesterolaemia not adequately controlled with the maximum tolerated LLT (Fig. 1). The study planned for a population of approximately 500 subjects, comprising 400 with T2DM and up to 100 with T1DM. Randomization began in November 2015 and ended in August 2016.

The study is being performed in accordance with the ethical principles outlined at the 18th World Medical Assembly (WMA) in Helsinki (1964), and all the relevant amendments laid down by the WMA and International Conference on Harmonization guidelines for Good Clinical Practice (GCP). Institutional review board or independent ethics committee approval of the protocol and informed consent forms were obtained from each study site

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