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Design and methods of a randomised double-blind trial of adding liraglutide to control HbA1c in patients with type 2 diabetes with impaired glycaemic control treated with multiple daily insulin injections (MDI-Liraglutide trial)

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ABSTRACT

Aims: Patients with type 2 diabetes are generally treated in primary care setting and as a final treatment step to obtain good glycaemic control, multiple daily insulin injections (MDI) are generally used. The aim of this study is to evaluate the effect of GLP-1 analogue liraglutide on glycaemic control in patients with type 2 diabetes treated with MDI with inadequate glycaemic control.

Methods: Overweight and obese patients with type 2 diabetes and impaired glycaemic control treated with MDI were randomised to liraglutide or placebo over 24 weeks. Masked continuous glucose monitoring was performed at baseline and during the trial. The primary endpoint was the change in haemoglobin A1c from baseline to week 24. Additional endpoints include changes in weight, fasting glucose, glycaemic variability, treatment satisfaction, insulin dose, hypoglycaemias, blood pressure and blood lipid levels.

Results: Recruitment occurred between February 2013 and February 2014. A total of 124 patients were randomised. Study completion is anticipated in August 2014.

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Conclusions: It is expected that the results of this study will establish whether adding liraglutide to patients with type 2 diabetes treated with MDI will improve glycaemic control, lower body weight, and influence glycaemic variability.

1. Introduction

Good glycaemic control is a cornerstone to the prevention of complications among individuals with type 2 diabetes [1–3]. To obtain good glycaemic control, patients with type 2 diabetes are generally treated with metformin and diet as the first-line therapy [4–6]. Sulphonylureas (SU) have traditionally been recommended as first second line therapy [4–6] and after metformin SU has generally been the most commonly used non-insulin glucose lowering therapy [7]. However, consensus guidelines from the ADA and EASD in recent years have focused on an individualised perspective in the choice of non-insulin glucose lowering drugs after metformin [6]. SU, incretin-based therapies, glitazones and basal insulin are all potential treatment options where individualised needs, various advantages and disadvantages with respect to effects on weight, hypoglycaemia, haemoglobin A1c (HbA1c) and costs are considerations in the choice of therapy [6].

After metformin, a second non-insulin lowering drug is typically added before initiating insulin therapy [4–6]. When insulin therapy is initiated, it usually includes a basal or premixed formulation [6]. As a final step, multiple daily insulin injections (MDI) with basal and prandial insulin have become standard when glycaemic control does not meet targets [6]. Obesity is another co-morbid condition in patients with type 2 diabetes [8]. The United Kingdom Prospective Diabetes Study (UKPDS) illustrated that insulin therapy (mostly basal insulin alone) is accompanied by significant weight gain in patients with type 2 diabetes [1]. MDI generally results in even greater weight gain. Today there are few studied treatment options in patients with type 2 diabetes on MDI with poor glycaemic control.

Adding a dipeptidyl peptidase-4 (DPP-4) inhibitor or the GLP-1 analogues exenatide or lixisenatide to patients treated with insulin therapy has been shown to result in an approximate 5 mmol/mol (0.5%) lower HbA1c compared to placebo [9]. In a few trials where DPP-4 inhibitors were used, only minor subgroups of patients were treated with MDI, and there are no double blind clinical trials including patients on MDI where a GLP-1 analogue was added [9]. Hence, evidence from double-blind clinical trials of adding incretin-based therapies to patients with advanced insulin therapy in the form of MDI is lacking.

This question is of particular concern since currently there are no treatment options for reducing weight and insulin doses while simultaneously improving glycaemic control for this challenging patient group. Further, many clinicians today use a therapeutic strategy consisting of MDI as a final treatment option, but many patients do still not reach target HbA1c and some even continue to have very poor glycaemic control [10]. Therefore, the aim of this study is to study the effect on HbA1c when adding liraglutide to MDI in overweight and obese patients with type 2 diabetes and with impaired glycaemic control.

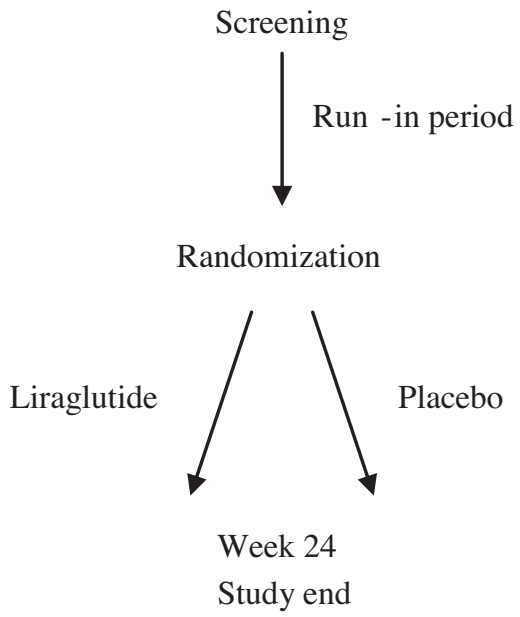

Fig. 1 – Overall study design of the MDI-Liraglutide trial.

2. Methods

The present study was a randomised, double-blind, placebo controlled trial with a parallel group design conducted at 14 sites in Sweden experienced in treating adult patients with type 2 diabetes. After a run-in period of up to 8 weeks, patients were followed for 24 weeks (Fig. 1). The ClinicalTrials.gov ID is NCT02113332.

2.1. *Screening*

Patients with type 2 diabetes, HbA1c greater than or equal to 58 mmol/mol (7.5%) and less than or equal to 102 mmol/mol (11.5%), a body mass index (BMI) of 27.5–45 kg/m^2 and treatment with (MDI) were included. MDI was defined as separate basal and meal-time insulin components including at least two daily meal-time insulin doses. Therefore, patients using premixed insulin were excluded. Patients were required to have a fasting C-peptide level of 0.1 nmol/l or higher. Other inclusion and exclusion criteria are shown in Table 1.