Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Comparison of efficacy and safety of once- versus twice-daily insulin detemir added on to oral antidiabetics in insulin-naive type 2 diabetes patients: 24-week, crossover, treat to target trial in a single center

Soner Cander[a,b,*], *Oguzhan Sitki Dizdar*[c], *Ozen Oz Gul*[a,b], *Metin Guclu*[a,b], *Oguz Kaan Unal*[a], *Ercan Tuncel*[a], *Erdinc Erturk*[a], *Sazi Imamoglu*[a], *Canan Ersoy*[a]

[a] *Uludag University Medical School, Department of Endocrinology and Metabolism, Bursa, Turkey*
[b] *Bursa Sevket Yilmaz Education and Research Hospital, Division of Endocrinology and Metabolism, Bursa, Turkey*
[c] *Uludag University Medical School, Department of Internal Medicine, Bursa, Turkey*

ARTICLE INFO

Article history:
Received 11 November 2013
Received in revised form
17 January 2014
Accepted 18 January 2014
Available online 9 February 2014

Keywords:
Detemir
Once daily
Type 2 diabetes
HbA1c
Insulin dose
Hypoglycemia

ABSTRACT

Aim: To compare once- versus twice-daily insulin detemir added on OADS therapy in insulin-naive type 2 diabetes patients in terms of efficacy and safety.
Methods: An open-label study performed at a single center, comprised a randomized, crossover 24 week with insulin-naive type 2 diabetes patients. Insulin detemir was initiated with mean 0.12 U/kg in all patients (Group I once-daily, Group II twice-daily) and titrated for 24 week.
Results: A total of 50 patients completed the study (Group I *n*:25, Group II *n*:25). With use of once- and twice-daily insulin, HbA1c values were decreased by 1.8% (±2.0) and 1.5% (±1.4) within the first 12 weeks ($p < 0.01$), whereas increased by 0.21% (±0.7) and 0.14% (±0.8) in the second 12 weeks ($p > 0.05$). The increases in the insulin doses were found as 0.22 U/kg and 0.35 U/kg with once- and twice-daily insulin use, respectively (p:0.04). Although minor hypoglycemic events were similar in both groups in the first 12 weeks, 2-fold increase was found in the patients shifting from once- to twice-daily dose. Within the first and second periods, the body weight of the patients was observed an increase of 0.4 and 1.6 kg with once-daily dose, whereas a decrease of 0.1 and 2.1 kg in the twice-daily dose, in the same period.
Conclusion: Once-daily use of insulin detemir up to 0.4 U/kg was found to have similar efficacy and safety as twice-daily use. Twice dose use of insulin did not provide a prominent glycemic control advantage on 1.5-fold higher use of insulin.

* *Corresponding author at*: Uludag University Medical School, Department of Endocrinology and Metabolism, 16059 Gorukle, Bursa, Turkey. Tel.: +90 224 2951163; fax: +90 224 2951249.
E-mail address: drcander@gmail.com (S. Cander).
1751-9918/$ – see front matter
http://dx.doi.org/10.1016/j.pcd.2014.01.010

1. Introduction

Insulin therapy is the key step in the management of type 2 diabetes (T2DM) and a natural progression in treatment. One simple regimen that is frequently adopted is the use of basal insulin in combination with oral antidiabetic drugs (OADs). Excessive liver glucose production is the primary reason for the elevated fasting glucose concentrations in patients with type 2 diabetes and basal insulin suppresses this production [1]. All insulin regimens have the risk of hypoglycaemia and weight gain [2]. The basal insulin analogs glargine and detemir were developed to improve upon the limitations of neutral protamin Hagedorn (NPH) insulin and other conventional basal insulins, which have an inadequate duration of action, a marked peak glucose-lowering effect and variability in response from one injection to another [3,4]. Long-acting insulins such as glargine and detemir are effective for basal control of glucose, but do not target glucose fluctuations that occur after a meal [5]. Insulin detemir, a basal insulin analog differs from human insulin by a single amino acid deletion and the acylation of myristic acid to the B terminus of the molecule. These changes affect the pharmacokinetics of the insulin, prolonging absorption from a subcutaneous depot through a unique mechanism involving self-association of detemir molecules and reversible binding to albumin [6]. The result is a more prolonged, less peaked absorption (and hence pharmacodynamic) profile compared with that of NPH insulin (NPH) [7].

The detemir prescribing information recommends that, changing the basal insulin to detemir can be done on a unit-to-unit basis for patients with diabetes mellitus currently receiving only basal insulin. Detemir should be initiated at a dose of 0.1–0.2 U/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets for insulin-naive patients with T2DM who are inadequately controlled on oral antidiabetic drugs [8]. Most initial studies of detemir involved a twice-daily regimen, but recent pharmacological analyses [3,9] suggest that detemir has a pharmacodynamic profile similar to that of insulin glargine that is routinely injected once-daily. In recent clinical studies, it has been stated that once-daily dose of insulin detemir have similar results on glycemic control as twice-daily dose for basal insulin + OADs and basal-bolus insulin regimens [10,11]. A recent analysis of basal insulin studies by DeVries et al. [12] suggested that, although a percentage of patients may benefit from twice-daily basal insulin dosing, the routine use of twice-daily basal regimens tends to drive up the total unit dose of insulin without corresponding gains in glycemic control.

As a result of these observations, the reasons to prefer twice-daily dose of insulin detemir over once-daily dose, face question marks. In this study, it has been aimed to compare the efficacy and safety of once-daily dose versus twice-daily dose of insulin detemir added on OADs therapy among insulin-naive type 2 diabetes patients.

2. Methods

2.1. Study protocol

This was an open-label study performed at a single center (Uludag University, Medical School, Endocrinology and Metabolism Department, Bursa, Turkey) between 2009 and 2010. It comprised of a randomized 12-week, parallel group period comparing once-daily with twice-daily detemir, followed by a second 12-week crossover extension period. The study included 60 insulin-naive people with type 2 diabetes, who were randomized (1:1) and treated with insulin detemir (Levemir; Novo Nordisk, Bagsværd, Denmark) as add-on therapy to oral glucose-lowering drugs, once- or twice-daily dosing. The trial was conducted in accordance with the Declaration of Helsinki and principles for Good Clinical Practice and was approved by local ethics committee. All the cases were included in the study after they gave written informed consent.

2.2. Participants

Insulin-naive patients with type 2 diabetes and the following characteristics were recruited: Patients with type 2 diabetes diagnosed for >1 year and with A1C 7.5–10%. They were ≥18 and <65 years old with a BMI ≤ 40.0 kg/m^2. For inclusion, they had to be receiving two oral agents (to standardize the prestudy medication the same dose gliclazide and metformin that the patients were using was allowed) ≥4 months on at least one-half the maximum recommended dose. Exclusion criteria included treatment with other antidiabetic drugs, hypoglycaemic unawareness or other medical conditions likely to interfere with trial conduct, congestive heart failure, chronic renal failure, hepatic insufficiency and known malignancies. In addition, patients in the pregnancy and lactation and those planning to become pregnant during the trial period were also excluded from the study. Withdrawal criteria included pregnancy, HbA1c > 11.0% after the first 12 weeks of treatment and initiation of medication interfering with glucose metabolism.

2.3. Treatment regimen and insulin dosing

At the 4-week screening visit, 60 patients included were trained about the study, their adherence to diet and exercise was revised and the initial examinations and routine assays were completed. OADs used by the patients were continued with the same doses. Patients randomly assigned in Group I were put on once a day and Group II patients twice a day 0.12 U/kg insulin detemir under supervision of a physician. Subsequent dose titrations were carried out by the same physician through phone conversations and/or clinic visits every other week according to eight-point capillary blood glucose measurements. Insulin dose titration scheme is illustrated in Table 1. The groups were alternatively changed without changing the doses administered at that time after the 12th week and dose titration was continued (Fig. 1).