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Switching from twice-daily glargine or detemir to once-daily degludec improves glucose control in type 1 diabetes. An observational study

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Abstract *Background and aims:* Degludec is an ultralong-acting insulin analogue with a flat and reproducible pharmacodynamic profile. As some patients with type 1 diabetes (T1D) fail to achieve 24-h coverage with glargine or detemir despite twice-daily injections, we studied the effect of switching T1D patients from twice-daily glargine or detemir to degludec.
Methods and Results: In this prospective observational study, T1D patients on twice-daily glargine or detemir were enrolled. At baseline and 12 weeks after switching to degludec, we recorded HbA1c, insulin dose, 30-day blood glucose self monitoring (SMBG) or 14-day continuous glucose monitoring (CGM), treatment satisfaction (DTSQ), fear of hypoglycemia (FHS). We included 29 patients (mean age 34 ± 11 years; diabetes duration 18 ± 10 years). After switching to degludec, HbA1c decreased from 7.9 ± 0.6% (63 ± 6 mmol/mol) to 7.7 ± 0.6% (61 ± 6 mmol/mol; $p = 0.028$). SMBG showed significant reductions in the percent and number of blood glucose values <70 mg/dl and in the low blood glucose index (LBGI) during nighttime. CGM showed a significant reduction of time spent in hypoglycemia, an increase in daytime spent in target 70–180 mg/dl, and a reduction in glucose variability. Total insulin dose declined by 17% ($p < 0.001$), with 24% reduction in basal and 10% reduction in prandial insulin. DTSQ and FHS significantly improved.
Conclusion: Switching from twice-daily glargine or detemir to once daily degludec improved HbA1c, glucose profile, hypoglycemia risk and treatment satisfaction, while insulin doses decreased.
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Introduction

Insulin analogues have improved the quality of life in people with type 1 diabetes (T1D) [1], but severe hypoglycaemia and excessive glycaemic excursions remain a problem. Compared with NPH insulin, glargine and detemir have flatter pharmacologic profile and longer duration of action [2,3]. Though both glargine and detemir are

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thought to last 24 h [4], a direct comparison in patients with T1D found that the duration of action of detemir may be shorter than that of glargine [5]. For this reason, T1D patients may require two daily injections of insulin detemir. Even with insulin glargine 15–30% of patients may fail to achieve full day coverage and present pre-dinner hyperglycaemia, especially if long-acting analogue is injected at bedtime [6].

To overcome this inconvenience, several strategies have been applied, like adding a rapid insulin analogue injection at mid-afternoon or switching to twice daily long-acting analogues. However twice daily use is not indicated on the label for glargine and has uncertain efficacy and safety. For instance, Ashwell et al. found that twice-daily glargine was better than once-daily in outpatients, while there was no difference between the two regimens during a short hospital stay [7]. In fact, even when patients are on twice-daily basal insulin, undesirable glucose variability frequently remains [8–10].

New insulin formulations may improve glucose profiles in patients on basal-bolus insulin. Degludec is an ultralong-acting basal insulin analogue produced by modification of human insulin through deletion of one amino-acid and conjugation to hexadecanedioic acid. These modifications favour the formation of a multi-hexameric depot in the subcutaneous tissue, whence insulin is slowly released. As a result, degludec has no peak activity, a duration of action longer than 24 h [11] and is suitable for once-daily use. Meta-analyses of phase III randomized clinical trials (RCTs) show that, in pooled T1D and T2D patients, degludec use was non-inferior to glargine considering HbA1c, and was associated with ~10% lower daily insulin dose. In addition, degludec decreased nocturnal confirmed hypoglycaemia (total and non-severe episodes from 00:01 to 05:59) in the entire treatment period, overall confirmed hypoglycaemia in the maintenance period, and severe hypoglycaemia (requiring assistance in administering carbohydrates, glucagon or other resuscitative actions) only in insulin-naïve type 2 diabetic patients [12,13].

Heller et al. report that, in patients with T1D, the lower rate of nocturnal hypoglycaemia with degludec as compared with glargine was already evident at 8 weeks and was significantly lower by 25% (rate ratio 0.75; $p = 0.02$) at the end of treatment, whereas no significant effect was detected on overall and diurnal hypoglycaemia [14]. However, the meta-analysis by Ratner et al. indicates that, in the T1D population, the rate of nocturnal confirmed hypoglycaemia was not significantly lower with degludec versus glargine across the entire treatment period (0–15 weeks: RR 0.83; 95% C.I. 0.69–1.00), but significantly lower during the maintenance period (RR 0.75; 95% C.I. 0.60–0.94) [12].

At present, there is great interest in observational studies testing whether evidence gathered from RCTs translates in the real world [15]. We therefore performed an observational study wherein T1D patients on twice-daily glargine or detemir, were studied before and after switching to once-daily degludec, to detect changes in HbA1c, glucose variability, fear of hypoglycaemia and treatment satisfaction.

Methods

Study design and participants

This was a single-centre, non-controlled, observational study. Patients were enrolled among consecutive T1D patients attending the diabetes outpatient clinic of the University Hospital of Padova between October 2014 and May 2015. Inclusion criteria for switching to degludec were: age 18–65 years; diagnosis of T1D; ongoing twice-daily glargine or detemir, in addition to prandial insulin, from at least 6 months; HbA1c>7.0% and/or frequent hypoglycaemic episodes. Exclusion criteria were: hypoglycaemia unawareness, acute illnesses or infections, inability to provide informed consent, pregnancy and lactation. Each patient served as his own control. The indication to switch to degludec was given on clinical ground and the decision to start degludec was independent from enrolment.

Primary objective was the detection of a significant change in HbA1c from baseline to study end (3 months after starting degludec). Secondary objectives were: 1) changes in glucose variability derived from self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM); 2) changes in treatment satisfaction and fear of hypoglycaemia; 3) changes in total daily insulin dose.

In the two weeks preceding the shift to degludec, we retrieved from electronic records: age, sex, BMI, diabetes duration, type of basal-bolus therapy, total daily insulin dose, other medications, and chronic complications. HbA1c was measured in a centralized laboratory during the week before switching.

The study was approved by the local ethical committee and registered on ClinicalTrials.gov (NCT02360254). Informed consent was obtained for every individual. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975.

Study protocol

Once the caring diabetologist suggested the switch from twice-daily glargine or detemir to once-daily degludec, patients were referred for screening of inclusion/exclusion criteria. If eligible, patients were informed about the study protocol and objectives, and signed a written consent. Starting 2 weeks before switching to degludec, patients were asked to wear a Dexcom G4 Platinum (DG4P) CGM system (Dexcom Inc., San Diego, CA, USA) for 14 days in blinded modality. Patients refusing to wear the CGM system were shifted to degludec immediately.

Before switching to degludec, SMBG profiles of the preceding 30 days were recorded by glucometer download in 23/29 patients or from diaries in 6/29 patients. All patients were asked to complete the Diabetes Treatment

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