Twelve-Week Treatment With Liraglutide as Add-on to Insulin in Normal-Weight Patients With Poorly Controlled Type 1 Diabetes: A Randomized, Placebo-Controlled, Double-Blind Parallel Study

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OBJECTIVE

This study investigated the efficacy and safety of once-daily liraglutide 1.2 mg versus placebo as add-on to insulin treatment in normal-weight patients with poorly controlled type 1 diabetes.

RESEARCH DESIGN AND METHODS

In a randomized (1:1), double-blind, placebo-controlled design, 40 patients with type 1 diabetes (HbA_{1c} ≥8% [64 mmol/mol]) received once-daily liraglutide 1.2 mg or placebo for 12 weeks. Continuous glucose monitoring was performed before and at the end of treatment. The primary end point was change in HbA_{1c}. Secondary end points included change in insulin dose, weight, glycemic excursions, heart rate, and blood pressure.

RESULTS

Baseline HbA_{1c} was similar in the liraglutide and placebo group (8.8 ± 0.2 and 8.7 ± 0.1% [72.5 ± 2.2 and 71.8 ± 1.5 mmol/mol]). Change in HbA_{1c} from baseline was −0.6 ± 0.2% (−6.22 ± 1.71 mmol/mol) with liraglutide and −0.5 ± 0.2% (−5.56 ± 1.67 mmol/mol) with placebo (P = 0.62). Variation in glycemic excursions did not change in either group. Change in body weight was −3.13 ± 0.58 and +1.12 ± 0.42 kg (P < 0.0001) with liraglutide and placebo, respectively. The bolus insulin dose decreased in liraglutide-treated patients and did not change with placebo treatment (4.0 ± 1.3 vs. 0.0 ± 1.0 IU, P = 0.02). Heart rate increased within the liraglutide group (P = 0.04) but not compared with placebo, whereas mean systolic blood pressure decreased compared with placebo (between-group difference 3.21 mmHg [95% CI −8.31 to 1.90], P = 0.04). Liraglutide was more frequently associated with gastrointestinal adverse effects. The incidence of hypoglycemia did not differ between groups.

CONCLUSIONS

Liraglutide significantly reduces body weight and insulin requirements but has no additional effect on HbA_{1c} in normal-weight patients with type 1 diabetes inadequately controlled on insulin alone.

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Type 1 diabetes is characterized by destruction of the pancreatic β-cells (1) and severely impaired or absent insulin secretion in combination with abnormal α-cell function and hyperglucagonemia (2–4). Both defects contribute to abnormal glucose metabolism (5). Tight glycemic control using intensive insulin treatment reduces the rates of late diabetic complications (6).

However, achieving and maintaining strict glycemic control is very demanding for patients, even when using multiple daily injections with basal and prandial insulin analogs or insulin pumps. Despite improved absorption profiles with new insulin analogs, intra- and interday blood glucose variability remains high, with an associated risk of hypoglycemia (7,8).

Insulin treatment only partly corrects the disturbed α-cell function, and even the most rapid-acting insulins peak too late to match the postprandial glucose absorption rate, resulting in large glucose excursions. Thus, a large proportion of individuals with type 1 diabetes still have suboptimal glycemic control. In addition, intensive insulin treatment is associated with weight gain and hypoglycemia in many patients (9). On this background, novel treatments as add-ons to insulin therapy are of interest to improve glycemic control.

In type 2 diabetes, GLP-1 receptor agonists (GLP-1RA), when added to insulin, result in improved glycemic control, weight loss, and a reduction in the insulin dose (10–12), most likely explained by the pleiotropic effects of GLP-1RA, which include enhancement of glucose-induced insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and induction of satiety, resulting in weight loss (13–17).

At present, few clinical trials have assessed the efficacy and safety of GLP-1RA in people with type 1 diabetes (18–24). These open-label studies have indicated that GLP-1RA treatment induces weight loss, improves postprandial glucose excursions, and reduces insulin requirements, with improved or unaltered glycemic control (18–24). Notably, GLP-1RAs have been shown to be effective in patients with and without β-cell function (18). A confounder in all previous studies is that the design has not been randomized and double-blinded with a placebo-treated group. Accordingly, we undertook a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the efficacy and safety of the GLP-1RA liraglutide 1.2 mg once daily as add-on to insulin treatment in normal-weight patients with poorly controlled type 1 diabetes without residual β-cell function.

RESEARCH DESIGN AND METHODS

The study was conducted using a randomized, double-blind, placebo-controlled, parallel design in normal-weight patients with poorly controlled type 1 diabetes. Patients were recruited from outpatient clinics in the Capital Region of Denmark. Medical records of 1,147 patients were reviewed, 67 patients were screened, and 40 patients were enrolled (Fig. 1). Informed consent was obtained from all participants after oral and written information was provided.

Participants were randomly assigned to liraglutide 1.2 mg or placebo for 12 weeks as an as add-on to their usual basal/bolus insulin regimens, except for one patient, whose usual regimen consisted of basal insulin alone. The primary outcome was change in HbA_{1c} from baseline (week 0) to week 12. Secondary and exploratory outcomes were change in insulin dose, weight, glycemic excursions and variability, heart rate and blood pressure, self-monitored blood glucose (SMBG) profiles, and frequency of hypoglycemia (glucose levels <70 mg/dL [3.9 mmol/L]) on SMBG or continuous glucose monitoring (CGM).

Inclusion criteria were age 18–70 years, BMI 18–28 kg/m^2, poor glycemic control (HbA_{1c} ≥8% [≥64 mmol/mol]), no residual β-cell function (defined as stimulated plasma C-peptide <60 pmol/L), Caucasian descent, diabetes diagnosed between the ages of 5 and 40 years, and no use of additional medication known to affect glucose metabolism. Exclusion criteria were overt late diabetes complications (except for microalbuminuria or background retinopathy), clinically significant cardiac disease, any medical or psychological condition that made the patient unsuitable for study participation according to the investigator's assessment, anemia, pregnancy or lactation, epilepsy, use of antiepileptic medication, use of β-blockers, previous stroke, use of benzodiazepine within the last month, use of neuroleptic drugs within the last 6 months, and alcohol or drug abuse.

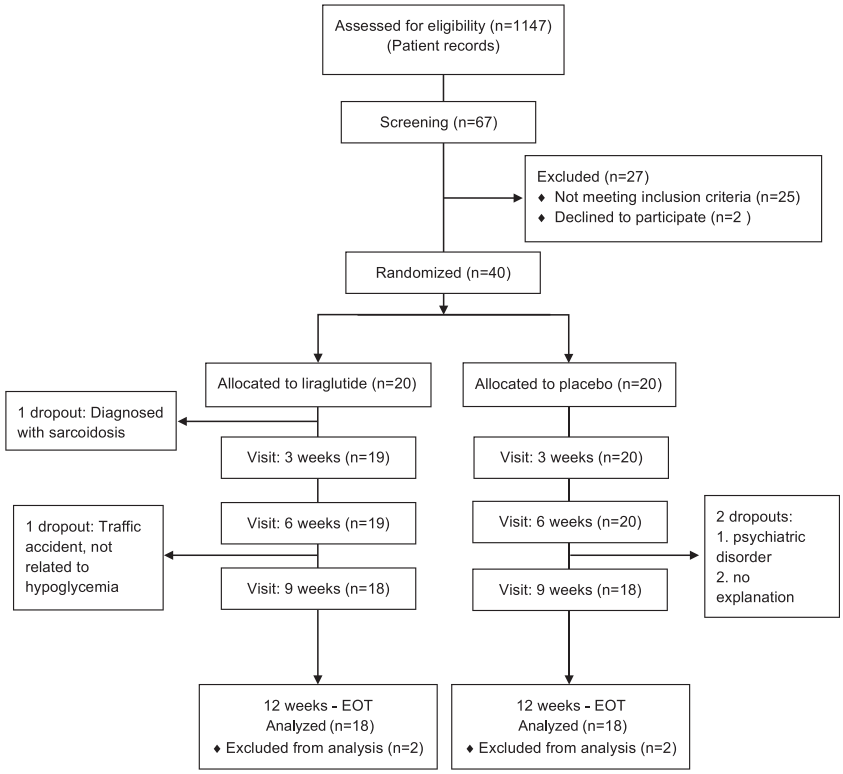

Figure 1—Trial profile. EOT, end of trial.

The study was approved by the Danish Medicines Agency (EudratCT: 2012-002526-67), the Scientific Ethical Committee of the Capital Region of Denmark (H-2-2012-068), and the Danish Data Protection Board (HVH-2012-023), and was supervised by the Good Clinical Practice unit, Bispebjerg University Hospital, Copenhagen, Denmark. The study complied with the principles of the Declaration of Helsinki 2.

Screening Procedures

Screening was performed after an overnight fast. The usual basal insulin dose was administered the night before, but no insulin was administered on the morning screening was performed. Medical history, demographic data, and information on the frequency of hypoglycemia were obtained, and hypoglycemic awareness status was determined by the Gold (25), Clarke (26) and Pedersen-Bjergaard (27) methods. Measurements of blood pressure, height, weight, abdominal circumference, and a 12-lead electrocardiogram (ECG) were performed. Autonomic neuropathy was defined as beat-to-beat variation during deep breathing of $<$10 bpm (mean R-R interval difference between maximal inspiration and expiration on ECG tracing) and/or an orthostatic blood pressure drop of $>$20 mmHg after 0, 1, 3, 5, 7, or 10 min of standing.

Blood was sampled for analyses of HbA_{1c}, leukocyte count, CRP, lactate dehydrogenase, liver parameters (alanine transaminase, alkaline phosphatase, bilirubin), albumin, pancreatic amylase, sodium, potassium, creatinine, carbamide, hemoglobin, total cholesterol, HDL, LDL, VLDL, islet cell antibodies, GAD-65, and thyroid-stimulating hormone. Urine was sampled for analyzes of albumin and creatinine, and urinary human chorionic gonadotropin was measured in women of childbearing potential.

β-Cell function was determined by measurements of C-peptide at baseline (0 min) and 8 min after increasing blood glucose to 282 mg/dL (15 mmol/L) using an intravenous glucose bolus infused over 1 min, followed by an intravenous bolus of 1 mg glucagon injected 2 min after the glucose infusion was initiated. Absent residual β-cell function was defined as a stimulated C-peptide $<$60 pmol/L (28,29).

Randomization and Study Medication

If patients were eligible after screening, a randomization list provided by the drug manufacturer, Novo Nordisk A/S, was used to randomly assign patients in block sizes of four to receive one daily subcutaneous injection of liraglutide 1.2 mg or placebo. Patients were instructed to administer the study medication at bedtime. The placebo pen was indistinguishable from the liraglutide pen. Assignment of patients was done by a person not otherwise involved in the study. The participants did not meet each other during the study.

Liraglutide or placebo was titrated to a maximum dose of 1.2 mg (0.6 mg once daily for 1 week, and 1.2 mg once daily thereafter) if tolerated. In case of intolerable side effects, the study medication dosage was reduced until recovery from symptoms occurred. We adjusted study medication according to the labeling and reduced the dose of study medication to 0.6 mg for 1 week if 1.2 mg was not tolerated. Subsequently, dose escalation to 1.2 mg was again attempted. The individual participant and investigators evaluated whether side effects were acceptable with respect to the participant's daily life. Moreover, investigators judged if a side effect was medically and ethically safe and whether dose adjustment of the study medication was required. Adherence to study medication was evaluated at each visit, and all used pens had to be returned. The investigators were responsible for assessing medication distribution and use.

Patients continued their prestudy brands of insulin throughout the study. At the introduction of the study medication, bolus insulin was reduced by 25% and basal insulin by 10%. Once daily for the following 3 days and once in the second week of treatment, patients received a follow-up telephone call to adjust the insulin dosage, with the purpose of attaining adequate glycemic control (i.e., treat-to-target). During the entire study, the participants and investigators collaborated to titrate insulin, aiming at morning, bedtime, and preprandial capillary blood glucose concentrations of 70–130 mg/dL (3.9–7.2 mmol/L) and peak postprandial capillary glucose concentrations of $<$180 mg/dL ($<$10 mmol/L) (30).

Glycemic Variability, SMBG, Hypoglycemia, Insulin Dose

At week 0 (before initiation of study medication) and week 12, patients wore a CGM (iPro2; Medtronic, Copenhagen, Denmark) for 4 days. The monitoring was performed in a blinded fashion (i.e., the CGM device had no display and no alarm functions). During the CGM periods, patients were asked to continue their daily life as usual. Food intake and physical activity were neither standardized nor predefined in the study protocol. However, participants were encouraged to maintain similar food intake and physical activity across the two CGM periods. Patients kept logbook recordings of insulin injections, physical activity, and food intake and performed at least four daily blood glucose measurements, with premeal and bedtime values advised. iPro2 uses a retrospective algorithm to convert the sensor signal to glucose values based on self-monitored capillary blood glucose readings (iPro2 Manual Guide, 2011). Patients were requested to maintain the same level of glycemic control during the two CGM periods and to adjust their insulin dose according to SMBG readings. Changes in mean insulin dose, mean blood glucose concentration, 24-h glucose profiles, and glycemic variability and excursions were evaluated using the logbook and CGM data. Time spent in hypoglycemia ($<$70 mg/dL [3.9 mmol/L]), near normoglycemia (70–180 mg/dL [3.9–10 mmol/L]), and hyperglycemia ($>$180 mg/dL [$>$10 mmol/L]) was calculated from the 24-h glucose profiles. Intraday glycemic variability was calculated using the mean amplitude of glycemic excursions (MAGE) and continuous overall net glycemic action (CONGA) (60 min) methods (31,32).

All patients were requested to use an identical glucose meter throughout the study (Contour; Bayer Diabetes Care, Lyngby, Denmark) to ensure uniform measurements for conversion of sensor signals during the CGM periods and to obtain comparable data regarding the average number of total glucose meter readings and the percentage of hypoglycemic, near-normoglycemic, and hyperglycemic readings. Hypoglycemia (any type) was defined as SMBG glucose levels $\leq$70 mg/dL ($\leq$3.9 mmol/L). Severe hypoglycemia was defined as any event

requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions with or without measurement of blood glucose levels (33). The provided glucose meter had to be used for no less than 75% of the trial to be considered valid data.

Trial Visits, Clinical Examinations, and Blood Samples

At all visits (weeks 0, 3, 6, 9, 12), adverse events, hypoglycemic events, concomitant medication, body weight, basal and bolus insulin doses, blood pressure, heart rate, and 12-lead ECG were recorded, and blood samples were collected.

Statistical Analyses

For the analysis of the continuous variables of HbA_{1c}, weight, and blood pressure, we used a mixed-model repeated-measures analysis with effects for treatment, time (from start of treatment), and treatment-by-time interaction and included all enrolled patients, including those who dropped out during the intervention period. Heart rate did not fulfill the assumption of linearity, and a parametric test was applied on the change from baseline. Single parameter comparisons were done per protocol. Differences between normally distributed data were assessed using a two-tailed Student *t* test (paired within groups and unpaired between groups). Differences between nonnormally distributed data were done using a Wilcoxon test for paired differences within groups and a Mann-Whitney *U* test between groups.

The safety analyses were based on all randomized patients who took at least one dose of the study drug.

We calculated that with 20 patients in each group and an SD of 0.38 HbA_{1c} percentage point, a predicted change in HbA_{1c} of 0.5 percentage point would be detected at a 5% significance level with >90% probability. All data are presented as mean ± SE unless otherwise stated. A two-tailed *P* value of <0.05 was considered statistically significant. The data were analyzed using RStudio 0.98.1091 statistical software (RStudio Inc., Boston, MA).

RESULTS

A total of 67 patients were screened, 40 of whom were enrolled (Fig. 1). Two patients assigned to liraglutide withdrew because of adverse events not related to the study medication. Two patients in the placebo group withdrew; one patient because of adverse events and one patient for unspecified reasons (Fig. 1). Baseline characteristics were similar between groups (Table 1). Residual β-cell function was negligible in all patients in both groups.

Glycemic Control

After 12 weeks, HbA_{1c} fell from 8.8 ± 0.2 to 8.2 ± 0.2% (72.5 ± 2.2 to 66.3 ± 2.5 mmol/mol) in the liraglutide group and from 8.7 ± 0.1 to 8.2 ± 0.2% (71.8 ± 1.5 to 66.3 ± 2.0 mmol/mol) in the placebo group. Accordingly, at the end of treatment, the change in HbA_{1c} from baseline was −0.6 ± 0.2% (−6.2 ± 1.7 mmol/mol) (*P* = 0.002, within-group comparison) with liraglutide and −0.5 ± 0.2% (−5.6 ± 1.7 mmol/mol) (*P* = 0.004, within-group comparison) with placebo (*P* = 0.62, for comparison between groups).

Two patients in the liraglutide group achieved the glycemic goals (HbA_{1c} <7% [53 mmol/mol]), but none of the placebo-treated patients reached this target.

The mean 24-h blood glucose profiles obtained by CGM did not differ at any time points within or between groups. The absolute time spent in near normoglycemia, hypoglycemia, and hyperglycemia (h/day) was 10.8 ± 0.9 vs. 11.0 ± 1.0, 2.2 ± 0.5 vs. 2.6 ± 0.6, and 11.0 ± 1.1 vs. 10.4 ± 1.1 in the liraglutide group compared with 11.3 ± 0.7 vs. 12.0 ± 1.2, 1.6 ± 0.4 vs. 1.4 ± 0.4, and 11.1 ± 1.1 vs. 10.5 ± 1.3 with placebo at baseline versus end of treatment. Accordingly, the change in glycemic excursions from baseline to 12 weeks did not differ within or between the groups; changes in time spent in near normoglycemia, hypoglycemia, and hyperglycemia in the liraglutide and placebo groups were +0.2 ± 0.9 and +0.7 ± 1.0 h/day (*P* = 0.72), +0.4 ± 0.5 and −0.1 ± 0.4 h/day (*P* = 0.42), and −0.6 ± 1.2 and −0.6 ± 1.2 h/day (*P* = 0.98), respectively. Furthermore, glycemic variability estimated with MAGE, CONGA, and SD of mean glucose did not differ between groups (data not shown).

Two patients lost their glucose meters, and three patients refused to use the provided glucose meter or used it for less than 75% of the study period.

Table 1—Baseline characteristics

	Liraglutide group	Placebo group	*P* value
N (% males)	18 (61)	18 (72)	0.48
HbA_{1c}, % (mmol/mol)	8.8 ± 0.2 (72.5 ± 2.2)	8.7 ± 1.4 (71.8 ± 1.5)	0.80
BMI, kg/m^2	24.17 ± 0.64	22.75 ± 0.41	0.08
Weight, kg	75.83 ± 2.89	74.89 ± 1.66	0.78
Diabetes duration, years	18.33 ± 2.0	19.56 ± 1.6	0.64
Hypoglycemic awareness status,* % aware	83	78	0.29
Basal insulin, IU/day	34.5 ± 2.4	33.5 ± 3.6	0.82
Bolus insulin, IU/day	27.5 ± 3.2	23.6 ± 1.7	0.29
Age, years	39.5 ± 2.7	36.1 ± 1.6	0.30
Total cholesterol, mmol/L	4.6 ± 0.2	4.4 ± 0.1	0.41
HDL, mmol/L	1.7 ± 0.1	1.5 ± 0.1	0.12
LDL, mmol/L	2.5 ± 0.2	2.4 ± 0.1	0.68
VLDL, mmol/L	0.45 ± 0.04	0.53 ± 0.08	0.46
Triacylglycerol, mmol/L	1.0 ± 0.1	1.2 ± 0.1	0.49
GAD-65, positive/negative	11/6†	12/6	0.90
ICA, positive/negative	1/13‡	2/14§	0.66
Blood pressure, mmHg			
Systolic	129.4 ± 2.5	127.3 ± 2.2	0.5
Diastolic	75.5 ± 1.7	72.5 ± 1.4	0.2
Heart rate, bpm	73.2 ± 2.2	69.7 ± 2.1	0.27
C-peptide (pmol/L)‖	11.2 ± 4.6	7.6 ± 3.7	0.55

Variables are described as mean ± SE or as number (percentages), as appropriate. ICA, pancreatic islet-cell antibodies. *Classified by the Clarke method (26). †Data missing for 1 patient. ‡Data missing for 4 patients. §Data missing for 2 patients. ‖Stimulated plasma C-peptide (see text).

The average number of SMBG readings per day was 4.2 ± 0.3 in the liraglutide group and 4.6 ± 0.5 in the placebo group (P = 0.21). The percentages of SMBG readings in near normo-, hypo-, and hyperglycemia were 42 ± 3 vs. 45 ± 4% (P = 0.17), 9 ± 2 vs. 10 ± 2% (P = 0.87), and 49.0 ± 4.0 vs. 45 ± 4% (P = 0.23) in patients treated with liraglutide versus placebo.

The hypoglycemia event rate did not differ significantly between groups. The incidence of any hypoglycemia was 11.2 ± 1.2 and 12.8 ± 1.7 episodes per patient per month (P = 0.45) in the liraglutide and placebo groups, respectively. One episode of severe hypoglycemia occurred in the liraglutide group.

Insulin Dose and Body Weight

At the end of treatment, the bolus insulin dose decreased significantly in liraglutide-treated patients from 27.5 ± 3.2 to 23.6 ± 2.6 IU/day (P = 0.006) (from 0.363 ± 0.040 to 0.326 ± 0.037 IU/kg per day [P = 0.02]), equivalent to a mean relative reduction of −11.0 ± 5.6% (range −41.7 to +35.9%). In comparison, the bolus insulin dosage did not change in patients receiving placebo (23.6 ± 1.7 and 23.7 ± 1.5 IU/day, P = 0.84; 0.321 ± 0.022 and 0.317 ± 0.018 IU/kg per day, P = 0.79). The change from baseline with liraglutide persisted when the absolute change between groups was compared (4.0 ± 1.3 vs. 0.0 ± 1.0 IU, P = 0.02). There was a tendency toward a correlation between the change in the bolus insulin dose and BMI (r = 0.40, P = 0.12).

The basal insulin dose did not differ from baseline to week 12 within or between groups (liraglutide: 34.5 ± 2.4 and 34.4 ± 3.0 IU/day, P = 0.82; placebo: 33.5 ± 3.6 and 33.4 ± 3.1 IU/day, P = 0.99, respectively; change from baseline [liraglutide vs. placebo]: −0.1 ± 1.6 vs. −0.1 ± 1.5 IU, P = 0.99) (Fig. 2).

Body weight decreased with liraglutide (from 75.8 ± 2.9 to 72.7 ± 2.9 kg) but increased with placebo (from 74.9 ± 1.7 to 76.0 ± 1.7 kg); hence, the change in body weight was −3.1 ± 0.6 vs. +1.1 ± 0.4 kg (between-group difference: 4.3 kg [95% CI −5.7 to −2.8], $P < 0.0001$) with liraglutide and placebo, respectively (Fig. 2). Accordingly, BMI decreased in liraglutide-treated patients from 24.2 ± 0.6 to 23.2 ± 0.6 kg/m^2 compared with an increase from 22.8 ± 0.4 to 23.3 ± 0.5 kg/m^2 in patients taking placebo. There was no correlation between starting BMI and the change in body weight (r = 0.08, P = 0.76).

Blood Pressure, Heart Rate, and Lipids

In patients receiving liraglutide, ambulatory heart rate increased significantly, from 73 ± 2 to 77 ± 2 bpm (P = 0.04), and the absolute change with placebo was 70 ± 2 to 71 ± 2 bpm (P = 0.51) (between-group difference for change from baseline: 2.4 bpm [95% CI −1.9 to 6.8], P = 0.26).

Mean systolic blood pressure decreased from baseline to week 12 with liraglutide, from 129.4 ± 2.5 to 127.1 ± 2.6 mmHg, compared with an increase in placebo-treated patients, from 127.4 ± 2.2 to 128.2 ± 2.4 mmHg (between-group difference: 3.2 mmHg [95% CI −8.3 to 1.9], P = 0.04). Changes in diastolic blood pressure did not differ between groups (P = 0.46). At 12 weeks, diastolic blood pressure changed from 75.5 ± 1.7 mmHg at baseline to 74.2 ± 2.0 mmHg with liraglutide compared with 72.5 ± 1.4 to 72.0 ± 1.5 mmHg in participants taking placebo.

Lipids did not differ between groups after 12 weeks. Data on lipids are provided in Supplementary Table 1.

Adverse Events

Adverse events occurred in 90% of patients in the liraglutide group and in 65% of patients in the placebo group. Gastrointestinal adverse events were the most common in both groups. In most patients, adverse events were transient. However, in five patients the dose of liraglutide was temporarily reduced (range 17–85 days), and one patient only tolerated 0.9 mg of liraglutide because of gastrointestinal adverse events. Five serious adverse events occurred, but all were judged to be unrelated to the investigational medicinal product. Adverse events of special interest in relation to GLP-1RA therapy are presented in Table 2, and details of all adverse events are provided in Supplementary Table 2.

CONCLUSIONS

This randomized, placebo-controlled, double-blind study evaluated the efficacy and safety of once-daily 1.2 mg liraglutide added to pre-existing insulin treatment in normal-weight patients with poorly controlled type 1 diabetes and without residual β-cell function. The current study was inspired by previous clinical and physiological studies suggesting that GLP-1 and GLP-1RAs decrease postprandial glucose and glucagon levels, slow the gastric emptying rate, and decrease meal-related insulin requirements in patients with type 1 diabetes, regardless of residual β-cell function (14,15,18,34). Contrary to our hypothesis, the present results indicate that concomitant treatment with liraglutide 1.2 mg once daily and insulin does not improve HbA_{1c} levels during 12 weeks of follow-up more than insulin treatment alone. These results are consistent with two previous studies (18,20) that also found no difference in glycemic control between patients treated with a GLP-1RA as add-on to insulin compared with patients on insulin alone. In contrast, other studies have suggested that adding a GLP-1RA to insulin improves glycemic control compared with insulin treatment alone (19,21,22). Notably, none of these studies used a randomized, double-blind, placebo-controlled design.

The participants included in the current study were selected from among patients in poor glycemic control before study entry, and insulin treatment was continually optimized during the study without a run-in period, possibly causing a substantial effect on HbA_{1c}. This treat-to-target approach could potentially have masked a beneficial effect of adding GLP-1 to insulin treatment. Furthermore, we found no change in glycemic variability in the liraglutide- or placebo-treated patients. We speculated that the enrolled participants would display abnormal α-cell function, with excess fasting plasma glucagon and inappropriate suppression of glucagon during meal ingestion, where the benefit of the suppressive effect of a GLP-1RA on glucagon release should become evident in the clinical efficacy outcomes. Nevertheless, the current study does not support the improvements in glycemic excursions or variability reported by Kielgast et al. (18) and Varanasi et al. (19).

Another notable finding was a significant reduction in body weight in liraglutide-treated patients, providing supporting evidence for the weight-reducing potential of GLP-1RA in patients with type 1 diabetes (18–23). Importantly, our patients were normal weight, and even patients with lower starting BMIs lost weight,

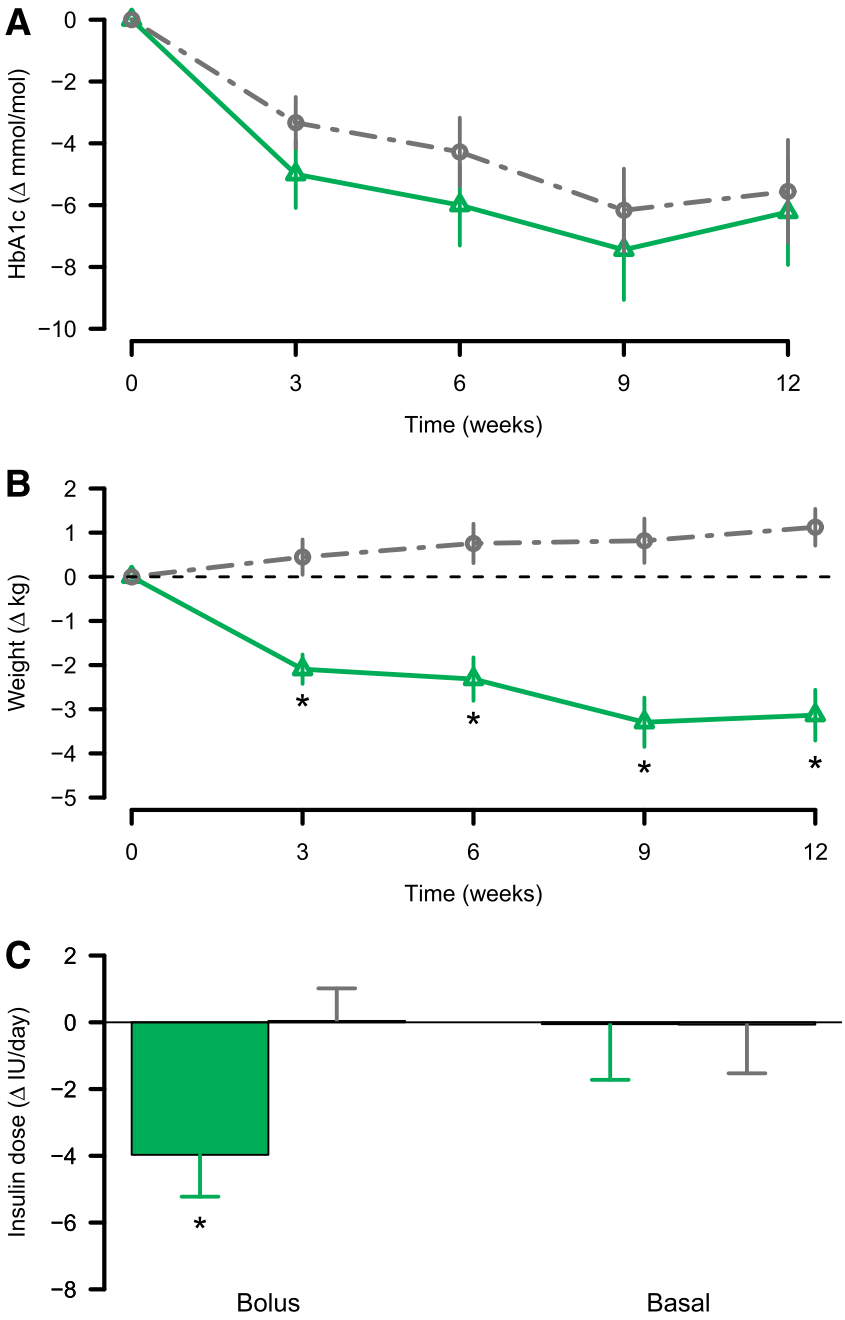

Figure 2—Changes in HbA_{1c} (*A*), weight (*B*), and dose of insulin (*C*) during 12 weeks of treatment with liraglutide ($n = 18$) or placebo ($n = 18$) in patients with type 1 diabetes. *A* and *B*: Green triangles and solid line, liraglutide group; gray circles and dashed line, placebo group. *$P < 0.001$. *C*: Change in bolus (bars to the left) and basal insulin (bars to the right) at 12 weeks (green bars, liraglutide; gray bars, placebo). *$P = 0.02$ for comparison between groups. Data are mean ± SE.

suggesting that this mechanism to some extent is independent of the starting weight. This implies that caution should be paid to the patient's baseline weight if initiation of GLP-1 treatment is considered.

We found a significant reduction in the bolus insulin dose; in contrast, the basal insulin dose did not change in patients treated with liraglutide. A comparison of these findings with those of other studies confirms that liraglutide reduces bolus insulin doses (18–22). Nonetheless, the relative dose reduction was markedly smaller in the current study than in previous studies. From the current study, it is unclear whether the reduction in bolus insulin was explained by a reduced food intake, improved insulin sensitivity, the weight loss, or suppression of glucagon during meals. Regarding the dose of basal insulin, our results are in contrast with all (18,19,21,22) but one (20) of the previous clinical trials, in which concomitant GLP-1 and insulin treatment has proven very effective in reducing the insulin dose. Taken together, the clinical results of the current study differ slightly from what we previously have shown when using a GLP-1RA in the management of type 1 diabetes (18). We speculate that differences in trial design and duration, baseline glycemic control, and residual β-cell function may explain the somewhat contradictory results.

We found that liraglutide 1.2 mg resulted in an increase in heart rate of 2–3 bpm and a placebo-adjusted reduction in systolic blood pressure of ~3 mmHg, which concurs with previous results in patients with type 1 and type 2 diabetes (22,35–37). The clinical significance of these cardiovascular effects is unknown; consequently, it is currently an area of active research in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (38), Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL; ClinicalTrials.gov Identifier: NCT01144338), Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA; ClinicalTrials.gov Identifier: NCT01147250), and Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND; ClinicalTrials.gov Identifier: NCT01394952) trials.

We chose liraglutide 1.2 mg as the maximal dose based on our experiences from an earlier study (18) where almost all patients had gastrointestinal adverse events with liraglutide 1.2 mg. Hence, increasing the dose would almost certainly not be tolerated in this population. Liraglutide 1.2 mg once daily was generally well tolerated. However, as expected, gastrointestinal adverse events were more frequent in liraglutide-treated patients compared with placebo. Consequently, five patients had to reduce the dose of liraglutide for a period of time, and one patient only tolerated 0.9 mg of liraglutide.

The strength of the current study was the double-blind, placebo-controlled research design. A limitation may be the relatively short duration of the study—an extension period of 12 weeks or more could have been of interest with regard to the long-term effects on efficacy

Table 2—Adverse events of special interest

Adverse events	Liraglutide 1.2 mg	Placebo
Gastrointestinal		
Nausea	13	9
Dyspepsia	7	2
Diarrhea	0	4
Vomiting	2	3
Hypoglycemia		
SMBG, per patient-day	0.37 ± 0.04	0.42 ± 0.06
CGM, h		
Baseline	2.2 ± 0.5	1.6 ± 0.4
Week 12	2.6 ± 0.6	1.4 ± 0.4
Severe	1	0
Heart rate, bpm		
Baseline	73 ± 2	70 ± 2
Week 12	77 ± 2	71 ± 2

Variables are described as number of patients or as mean ± SE. Hypoglycemia SMBG defined as SMBG glucose levels ≤70 mg/dL (≤3.9 mmol/L). Hypoglycemia CGM defined as mean time spent in hypoglycemia (<70 mg/dL [<3.9 mmol/L]) per 24 h.

outcomes. The current study does not provide data on fasting and postprandial glucagon levels, but this is currently an area of active research in our and other groups (39).

In conclusion, liraglutide 1.2 mg once daily as add-on to insulin treatment in normal-weight patients with poorly controlled type 1 diabetes, without endogenous insulin secretion, has no significant effect on HbA_{1c}, has a minor but significant effect on the dose of bolus insulin, and induced a significant reduction in body weight with an incidence of hypoglycemia similar to placebo.

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Author Contributions. C.S.F. was the principal investigator, contributed to the conceptual design, recruited participants, conducted the study, researched the data, performed the data analysis, and wrote the manuscript. T.F.D. was the subinvestigator, recruited participants, contributed to data analysis and conducting the study, and wrote the manuscript. J.J.H., B.T., and S.M. contributed to the conceptual design and data analysis and wrote the manuscript. H.U.A. contributed to recruitment and enrollment of participants. All authors contributed significantly to the creation of the manuscript, data collection or analysis, and to the review and editing of the manuscript. C.S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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