Liraglutide, a Long-Acting Human Glucagon-Like Peptide-1 Analog, Given as Monotherapy Significantly Improves Glycemic Control and Lowers Body Weight Without Risk of Hypoglycemia in Patients With Type 2 Diabetes

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Liraglutide is a long-acting human glucagon-like peptide-1 (GLP-1) analog (1–4), and the current study was undertaken to evaluate efficacy and safety after 14 weeks' treatment with liraglutide in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Main inclusion criteria were patients aged ≥18 years with type 2 diabetes and A1C ≥7.5 and ≤10.0% (diet) or ≥7.0 and ≤9.5% (mono–oral antidiabetes drug); previous therapy was discontinued. Fasting plasma glucose (FPG) at randomization was 7–13 mmol/l. If FPG was >15 mmol/l during the study, the patient was withdrawn. The study was conducted in accordance with the Declaration of Helsinki (5). The study was double-blind, randomized (1:1:1:1), and placebo-controlled using three doses of liraglutide (0.65, 1.25, or 1.90 mg). The following main efficacy parameters were assessed: A1C, insulin, proinsulin, glucagon, fructosamine, lipids, home-measured seven-point plasma glucose profiles, and body weight. Safety parameters (adverse events, hypoglycemic episodes, clinical laboratory parameters, antibodies against liraglutide, vital signs, electrocardiogram, and thyroid (including ultrasonography) and parathyroid parameters were assessed. Liraglutide or placebo was administered in the evening (as in the most recently completed phase 2 study) (6) as once-daily subcutaneous injections in the abdomen or thigh.

RESULTS — Baseline characteristics are given in Table 1. The placebo group accounted for almost one-half of the patient withdrawals, primarily due to ineffective therapy. Withdrawals due to adverse events were infrequent and occurred at a comparable level in all groups (Table 1).

After 14 weeks of treatment, estimated change in A1C for placebo, 1.90, 1.25, or 0.65 mg was +0.29, −1.45, −1.40, and −0.98%, respectively (change for 1.90 mg vs. placebo: −1.74% [95% CI −2.18 to −1.29], $P < 0.0001$; 1.25 mg vs. placebo: −1.69% [−2.13 to −1.24], $P < 0.0001$; and 0.65 mg vs. placebo: −1.27% [−1.72 to −0.82], $P < 0.0001$). The proportion of patients reaching A1C <7% was 46% (1.90 mg), 48% (1.25 mg), 38% (0.65 mg), and 5% (placebo) in the four groups, respectively. FPG was significantly reduced (1.90 mg vs. placebo: −3.4 mmol/l [−4.4 to −2.4], $P < 0.0001$; 1.25 mg vs. placebo: −3.4 mmol/l [−4.4 to −2.4], $P < 0.0001$; and 0.65 mg vs. placebo: −2.7 mmol/l [−3.7 to −1.7], $P < 0.0001$). For the 1.90 mg group, the fractions of patients reaching 90 min postmeal glucose values below the American Diabetes Association treatment goal of <10 mmol/l was 46, 51, and 56% of patients after breakfast, lunch, and dinner, respectively. Corresponding values were 15, 23, and 23%, respectively, in the placebo-treated group. For both the 1.90 and 1.25 mg groups, the fraction of patients with FPG <10 mmol/l was significantly different from that of patients given placebo ($P < 0.05$) at each meal, respectively. Analysis of homeostasis model assessment showed a significant increase (1.90 mg vs. placebo: 86% [48–134], $P < 0.0001$; 1.25 mg vs.placebo: 134% [86–93], $P < 0.0001$; and 0.65 mg vs. placebo: 75% [40–120%], $P < 0.0001$). A dose-dependent decrease in insulin resistance (homeostasis model assessment) was observed (not significant [NS]). The median change from baseline in proinsulin-to-insulin ratio was significant for all three liraglutide groups versus placebo (1.90 mg: −0.19, $P = 0.0111$; 1.25 mg: −0.28, $P = 0.0062$; and 0.65 mg: −0.15, $P = 0.0218$).

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Abbreviations: FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient disposition and characteristics*

	All	Liraglutide 1.90 mg	Liraglutide 1.25 mg	Liraglutide 0.65 mg	Placebo
Patient disposition	—	—	—	—	—
Screened	377	—	—	—	—
Randomized	165	—	—	—	—
Exposed	163	41	42	40	40
Withdrawn	25	6	3	5	11
Adverse event	7	2	1	1	3
Noncompliance	2	1	0	0	1
Ineffective therapy	14	2	2	3	7
Other	2	1	0	1	0
Completed	140	37	39	35	29
Included in ITT population	163	41	42	40	40
Baseline characteristics	—	—	—	—	—
Age (years)	—	55.4 ± 11.4	53.8 ± 10.7	56.5 ± 9.3	57.7 ± 8.2
Sex (male/female) (*n*)	—	30/11	23/19	27/13	19/21
BMI (kg/m^2)	—	29.9 ± 4.2	31.2 ± 4.7	28.9 ± 3.9	30.4 ± 4.0
A1C (%)	—	8.5 ± 0.9	8.3 ± 0.8	8.1 ± 0.6	8.2 ± 0.7
Duration of diabetes (years)	—	4.0 (1–29)	7.0 (0–21)	6.0 (1–25)	5.0 (1–23)
Previous diabetes treatment	—	—	—	—	—
Diet	—	7	8	9	7
OAD (metformin)	—	14	19	15	17
OAD (SU)	—	19	14	16	15
OAD (repaglinide)	—	1	1	0	1
FPG (mmol/l)	—	12.3 ± 3.1	11.9 ± 2.4	11.3 ± 2.7	11.3 ± 2.2
Insulin (pmol/l)	—	63 ± 35	60 ± 37	59 ± 45	70 ± 51
Proinsulin (pmol/l)	—	45 ± 28	38 ± 19	34 ± 24	35 ± 20
Proinsulin-to-insulin ratio	—	0.74 ± 0.26	0.70 ± 0.30	0.88 ± 0.52	0.59 ± 0.33
Glucagon (pmol/l)	—	23 ± 7	21 ± 7	23 ± 9	19 ± 6
C-peptide (pmol/l)	—	1138 ± 455	1076 ± 405	1176 ± 640	1260 ± 515
Fructosamine (μmol/l)	—	360 ± 75	341 ± 74	358 ± 75	330 ± 59

Data are means ± SD or median (range) unless otherwise indicated. Data for age, sex, duration of diabetes, and previous treatment were recorded at screening and diabetes characteristics at baseline. Two patients withdrew from the study before receiving study medication; one because of withdrawal of consent and one because of noncompliance. The adverse event withdrawals were as follows: placebo: blood glucose increased (2 patients), hyperglycemia/nausea; 0.65 mg: diarrhea; 1.25 mg: injection site rash; and 1.90 mg: tachypnoea/gastrooesophageal reflux disease, constipation. ITT, intent to treat.

Body weight decreased in all treatment groups, with a maximum estimated loss of 2.99 kg in the 1.90 mg liraglutide group. The difference compared with placebo was significant for the 1.90 mg group (−1.21 kg [95% CI −2.36 to −0.06], $P = 0.0390$). There was a significant lowering in fasting glucagon concentrations in the 1.90 mg liraglutide group compared with placebo (−3.26 pmol/l [−6.52 to 0.00], $P = 0.0497$). Systolic blood pressure decreased significantly (1.90 mg vs. placebo: −7.9 mmHg [−12.9 to −2.9], $P = 0.0023$; 1.25 mg vs. placebo: −5.2 mmHg [−10.2 to −0.2], $P = 0.0417$; 0.65 mg vs. placebo: −7.4 mmHg [−12.4 to −2.4], $P = 0.0041$). Diastolic blood pressure dropped 2–3 mmHg using all doses of liraglutide when compared with placebo (NS). There was no significant effect on pulse or clinically relevant changes in electrocardiogram. Lipid parameters (total, LDL, VLDL, and HDL cholesterol; free fatty acids, and apolipoprotein B) showed no consistent changes among treatment. Triglyceride levels decreased compared with placebo (1.90 mg vs. placebo: −22% [−35 to −6%], $P = 0.0110$; 1.25 mg vs. placebo: −15% [−30 to 2%], $P = 0.0854$; and 0.65 mg vs. placebo: −19% [−33 to −2%], $P = 0.0304$).

The overall fractions of patients with adverse events were comparable across the four groups, ranging from 43 to 51% of patients. The fractions of patients reporting a gastrointestinal adverse event were 37, 29, 38, and 23% of patients for 1.90 mg, 1.25 mg, 0.65 mg, and placebo, respectively (NS), with a higher event rate reported at the highest dose group in comparison with placebo ($P < 0.05$). The individual gastrointestinal adverse events were reported at similar frequencies across the liraglutide treatment groups, although nausea seemed somewhat higher in the 1.90 and 0.65 mg groups (10% of subjects vs. 2–3% in the 1.25 mg and placebo groups, respectively). Diarrhea was reported by 26 of 123 and 5 of 40, nausea by 9 of 123 and 1 of 40, and vomiting by 4 of 123 and 0 of 40 subjects treated with liraglutide and placebo, respectively. Only 4 of 123 liraglutide-treated patients withdrew from the study because of gastrointestinal adverse events. The incidence of gastrointestinal adverse events decreased over time. The effect on body weight did not change when excluding patients with duration of gastrointestinal events >7 days. Three serious adverse events were reported by two patients (one in the placebo group and one in the 1.90 mg group [influenza]). No major or minor hypoglycemic episodes were reported. There was no treatment-

related effect on induction of antibodies and no clinically relevant changes in safety laboratory parameters, including thyroid ultrasonography, were observed after treatment with liraglutide.

CONCLUSIONS — The present study demonstrated sustained effect of the long-acting GLP-1 analog liraglutide on glycemic control in patients with type 2 diabetes without any major or minor hypoglycemic episodes. At the highest dose, liraglutide monotherapy reduced the estimated average A1C levels by 1.74% from an average A1C of 8.5%, when compared with placebo. When given one of the two highest doses of liraglutide, almost one-half of the patients managed to reach the American Diabetes Association target for postprandial control (7), confirming a full 24-h coverage of liraglutide on glycemic control (2). Furthermore, in spite of improved glycemic control, which is often associated with an increase in body weight (8), a dose-dependent decrease in body weight was seen. Adverse events related to the gastrointestinal system and headaches were the most frequently reported adverse events. In addition to a beneficial effect of liraglutide on β-cell function, in current and in previous studies (9–11), a potential effect on lowering of blood pressure was observed in the current study. The mechanism behind the effect on blood pressure remains unknown. However, since the effect on blood pressure occurred earlier than the effect on body weight, it suggests that the effect cannot only be ascribed to the lowering in body weight. In conclusion, the long-acting, once-daily GLP-1 analog, liraglutide, targets well-described abnormalities in the type 2 diabetes phenotype.

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