Case report

Efficacy and tolerability of Liraglutide in combination with other antidiabetic drugs in type 2 diabetes

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Abstract. We present a collection case report performed in 29 inadequately controlled diabetic and obese outpatients. The aim of this study was to verify metabolic effects of liraglutide in combination with other antidiabetic drugs. Across this study, liraglutide effectively and rapidly improves glycemic control (both fasting glycemia and HbA1c), body weight and systolic blood pressure, thus promoting the achievement of therapeutic targets proposed by the American Diabetes Association and European Association for the study of Diabetes and reducing cardiovascular risk profile of diabetic patients. (www.actabiomedica.it)

Key words: type 2 diabetes, GLP-1 receptor agonists, liraglutide

Introduction

Targeting the incretin system has become an important therapeutic approach for treating type 2 diabetic (T2DM) patients. Two drug classes have been developed: incretin hormone Glucagon-Like Peptide-1 (GLP-1) receptor agonists and dipeptidyl-peptidase 4 (DPP-4) inhibitors (1).

American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) guidelines recommend metformin as first-line pharmacotherapy for T2DM. Sulfonylureas and/or thiazolidinediones are combination therapy options, but both can elicit weight gain, whereas sulfonylureas can induce hypoglycemia (2).

Liraglutide, a GLP-1 analog, is currently approved for treatment of type 2 diabetes at doses up to 1.8 mg, demonstrating improvements in glycemic control, systolic blood pressure and weight loss (3, 4). A phase II clinical trial has recently shown the potential efficacy and safety of this drug in the treatment of obesity (5), although this disease is not among the approved indications. Furthermore, incidence of hypoglycemia is relatively low because of its glucose-dependent mechanism of action. Liraglutide is generally well tolerated, with transient nausea experienced toward the beginning of the treatment (6).

Case collection report

The aim of this study was to verify metabolic effects of Liraglutide in patients affected by type 2 diabetes referring to our Diabetologic outpatient clinic (Diabetology Unit, Sacro Cuore Hospital, Negrar, VR, Italy) from 1st January 2011 until 31th May 2011.

In this 32-weeks study, we analyzed 29 obese outpatients affected by type 2 diabetes inadequately controlled with one or more antidiabetic drugs (average baseline HbA1c: 8.5±1.1%). The majority of the analyzed subjects were treated with metformin (38%) or with metformin plus sulfonylureas (48%). Concomitant antihypertensive treatment was reported in 66% of the study group without achieving systolic blood pressure values recommended by international guidelines.

Baseline demographic characteristics of participants are reported in Table 1.

Table 1. Baseline demographic characteristics of participants. Data are reported as mean values ± standard deviation

N	29
Age (years)	55.6 (8.6)
Sex (male %)	52%
Diabetes duration (years)	11.8 (6.4)
HbA_{1c} (%)	8.5 (1.1)
Body weight(kg)	100.0 (17.2)
BMI (kg/m^2)	35.6 (4.5)
Concomitant antihypertensive therapy (%)	66%
Systolic blood pressure (mmHg)	136.7 (18.6)
Diastolic blood pressure (mmHg)	78.4 (8.0)

Liraglutide was administered starting with a daily dose of 0.6 mg for the first week and then 1.2 mg accordingly to drug label. Subjects were encouraged to inject liraglutide into the abdomen, thigh or abdomen at the same time each time. Patients were treated with liraglutide for 32 weeks until the end of the study. Body weight, fasting blood glucose, HbA1c values, systolic and diastolic blood pressure were recorded at baseline and after 16 and 32 weeks. Blood pressure was measured in the sitting position after at least 10 min of rest. At each visit, hypoglycemic episodes were recorded: self-treated hypoglycemia was classified as minor, while those requiring third-party assistance were considered major.

Results

At the first follow-up, 16 weeks after introducing Liraglutide, HbA1c decreased rapidly from 8.5±1.1 to 7.4±1.2% reaching statistical significant (p<0.01) lower value (6.7±0.7%) at the end of the study.

By the first follow-up, subjects treated with Liraglutide had rapid and larger decrease in fasting plasma glucose throughout the study, in comparison to baseline levels (p< 0.01 for both). At 32 week, a 52 mg/dl reduction in fasting glycemia was achieved without occurrence of severe and minor hypoglycemic episodes.

Mean body mass index at baseline was 35.6 ± 4.5 kg/m^2. Mean decrease in weight from baseline to first follow-up was 2.7 kg, further declining to 6.1 kg at the end of the study (p<0.01). Although reduction in diastolic blood pressure was reported at both 16 and 32 week, they resulted not statistically different in comparison to baseline values. Conversely systolic blood pressure significantly improved during Liraglutide treatment at 16 week (p<0.01), thus reaching mean value lower than 130 mmHg at 32 week.

Demographic and biochemical parameters at 16 and 32 week are reported in Table 2.

No serious adverse events were reported during the trial.

Statistical analyses were performed using the Wilcoxon t Test. Data are expressed in mean ± Standard Deviation (SD).

Discussion

In this series of cases, liraglutide effectively and rapidly improved glycemic control when used in combination with oral antidiabetic drugs. This treatment has also been demonstrated to promote weight loss

Table 2. Demographic and biochemical parameters at 16 and 32 week. Data are reported as mean values ± standard deviation

	At 16 week	p*	At 32 week	p*
HbA1c (%)	7.4±1.2	<0.01	6.7±0.7	0.01
HbA1c in patients with less than 10 year diabetes duration (%)	7.4±0.9	<0.01	6.6±0.7	0.02
HbA1c in patients with more than 10 year diabetes duration (%)	7.4±1.4	0.02	6.9±0.8	ns
Fasting plasma glucose (mg/dL)	145.2±38.8	<0.01	129.8±21.9	<0.01
Body weight (kg)	97.5±16.8	<0.01	93.6±17.8	<0.01
BMI (kg/m^2)	34.7±4.3	<0.01	34.2±4.2	<0.01
Systolic blood pressure (mmHg)	130.6±20.4	0.06	126.2±12.6	0.06
Diastolic blood pressure (mmHg)	75.4±14.8	ns	78.2±4.6	ns

* In comparison to baseline values; ns= not significant

and reduce systolic blood pressure, which could be of benefit to patients with type 2 diabetes, thus reducing cardiovascular risk profile. Moreover, although nausea is a common side effect, liraglutide tends to be transient and this drug was generally well tolerated throughout the follow-up period.

The American Diabetes Association and the European Association for the Study of Diabetes define therapeutic goals of therapy in type 2 diabetes that include HbA1c levels less than 7%, systolic blood pressure less than 130 mmHg and no weight gain (or, in case of obese subjects, weight loss). Liraglutide treatment, as confirmed by our clinical experience, can promote achievement of these therapeutic targets by offering weight reduction, blood pressure reduction, and low hypoglycemic risk in addition to significant and rapid improvement on glycemic control.

Moreover, the greater HbA1c reduction observed in patients with a duration of diabetes of less than 10 years and higher HbA1c baseline levels supported the early use of this drug when a poor glycemic control is revealed after metformin failure.

In animal studies, liraglutide has shown protective effects on pancreatic β-cells, thus promoting β-cell mass and reducing apoptosis (7). Recent T2DM diagnosis with residual pancreatic function should obtain greater efficacy on glycemic control by incretin treatment, thus reducing/avoiding exogenous insulin requirement.

Clinical trials of sustained-release formulations are in progress suggesting long term effects on HbA1c and weight loss with fewer gastrointestinal symptoms (in particular nausea) than twice-daily formulation (1).

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