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Original Article

Long-term effects of GLP-1 receptor agonists in type 2 diabetic patients: A retrospective real-life study in 131 patients

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ABSTRACT

Aim: We evaluate retrospectively long-term effects of GLP-1 receptor agonists in type 2 diabetic patients treated between 2008 and 2016.
Methods: 131 patients treated by GLP-1 receptor agonists (GLP-1RAs) were included. The objective was to evaluate the evolution of glycated hemoglobin (HbA_{1c}) during a period up to 4 years. The secondary objectives consisted of analysing the long-term effects of treatment on body mass index (BMI), blood pressure and lipids; reporting the proportion of patients who reached HbA_{1c} objectives; estimating the time before treatment failure and determining predictive factors of failure. We also compared twice-daily exenatide to once-daily liraglutide on the major parameters.
Results: HbA_{1c} improved significantly, mostly during the first year of treatment (−1.2%), and this effect was maintained after 4 years (−1.4% *vs*. baseline). At 1 year, 26% and 47% of subjects achieved HbA_{1c} levels <7.0% and 7.5%, respectively. Treatment failure was observed in 51% of patients after a mean duration of GLP-1RA treatment of 50 months. Half of patients had failed after 42 months. Baseline HbA_{1c} greater than 9.0% and male gender were predictive factors of treatment failure. BMI also decreased: −0.9 kg/m^2 the first year, −1.9 kg/m^2 after 4 years. No significant difference was found between patients treated with exenatide and liragutide over time.
Conclusions: The beneficial effects of GLP-1RAs on HbA_{1c} reached a plateau after the first year of treatment and are maintained at 4 years only in one third of patients. Failure occurred predominantly in men with a baseline HbA_{1c} greater than 9%.

1. Introduction

Type 2 diabetes (T2D) is a chronic disease leading to devastating micro- and macrovascular complications. Obesity and insulin resistance appear to be major risk factors involved in the disease onset while a progressive decline in pancreatic β-cell function explains overtime deterioration of glycaemic control, requiring stepwise intensification of glucose-lowering therapies. Despite stringent guidelines as well as improvement therapeutic arsenal, a high percentage of patients still do not achieve optimal glycaemic targets [1,2].

Glucagon like peptide-1 (GLP-1) is an intestinal incretin hormone deficient in T2D patients [2,3]. GLP-1 receptor agonists (GLP-1RAs) resisting to enzymatic degradation have been synthesized during the last years. In randomised controlled trials as well as in short-term real-life observational studies, their administration significantly improves glycaemic control and induces weight loss [3–7]. In Belgium, six GLP-1RAs (twice-daily exenatide, liraglutide, once-weekly exenatide, lixisenatide, albiglutide and dulaglutide) have been approved as third-line therapy, in association with metformin and sulfonylureas or thiazolidinediones [3–7].

Very long term data on the efficacy of GLP-1RAs are still scarce. The aim of the present study was to analyse the evolution of glycaemic control and weight changes in patients treated up to 8 years with a GLP-1RA.

2. Subjects, materiels & methods

This observational retrospective study included T2D patients aged 18–80 years, treated for the first time with a GLP-1RA during at least one year, in association with metformin and sulfonylureas or thiazolidinediones, between October 2008 and September

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2016 at the Cliniques universitaires Saint-Luc in Brussels, Belgium.

Data at baseline included demographic characteristics and type of GLP1-RA prescribed. Some patients also underwent combined assessment of insulin sensitivity and β-cell function using the *Homeostasis Model Assessment* (HOMA-2) computer-based version [8]. The following data were collected on a yearly basis from GLP1-RA initiation up to withdrawal or last visit: weight, body mass index (BMI), systolic and diastolic pressure, glycated haemoglobin (HbA_{1c}) and lipid parameters. Duration of GLP1-RA treatment as well as the reason for interruption were also reported.

The primary objective of this study was to evaluate the long-term evolution of HbA_{1c} after initiation of the GLP-1RA. Secondary objectives consisted of (i) analysing the long-term effects of GLP1-RAs on weight, BMI, blood pressure and lipids; (ii) reporting the proportion of patients who reached HbA_{1c} objectives $\leq 7.0\%$ and $\leq 7.5\%$; (iii) estimating the time before treatment failure as well as (iv) determining predictive factors of failure. Primary failure to GLP1-RA was defined as a deterioration of the glycaemic balance during treatment ($HbA_{1c} > 7.5\%$ or a decrease of less than 1.0% after one year treatment). A separate dataset included a subgroup of patients with a treatment duration of four years and all data collected each year (n = 30). We also compared long-term evolution of subgroups of patients treated with twice-daily exenatide (Byetta®) and liraglutide (Victoza®) regarding these major parameters.

The study was approved by the Ethics Committee of UCL (Université Catholique de Louvain) (2016/25JAN/024) and conducted in accordance with the Good Clinical Practice guidelines.

2.1. Statistical analysis

Continuous variables are presented as mean, standard deviation, median and quartiles (0.25 and 0.75) whereas discrete variables are presented as frequency. In accordance with the central limit theorem, the data distribution was considered normal if the sample size was greater than or equal to thirty. For accuracy and reproducibility, statistical analysis was performed only on the first treatment with GLP1-RA, as some patients received another trial of a distinct GLP1-RA after a primary failure. In order to analyse the effects of GLP1-RAs on clinical and biological parameters over time, paired samples t-tests or non-parametric Wilcoxon's tests for paired samples were used to compare continuous variables, whereas Pearson's chi-squared tests or non-parametric Fisher's exact tests were used to compare discrete variables. Among all GLP1-RAs, only liraglutide and twice-daily exenatide were compared because the sample size was sufficient (respectively n = 65 and n = 60). In order to compare those two groups, unpaired samples t-tests and Mann Withney U-tests were used. Kaplan-Meier's survival analysis allowed estimating the probability of primary failure to GLP1-RA treatment. Patients were censored at data collection closure or in case of side effects, loss of follow-up, non-compliance to the treatment, bariatric surgery as well as renal function deterioration. The log-rank test was used to compare the subgroups survival curves (patients treated with liraglutide and those with twice-daily exenatide). A multivariate logistic regression allowed the identification of potential predictive factors to treatment primary failure. Variables included in the final model were selected from univariate analysis ($p<0.20$) after verifying the absence of multicolinearity.

All statistical analyses were conducted with IBM SPSS Statistics (version 23.0) at a level of statistical significance of 0.05 and with bilateral p-values. For multiple comparisons, the level of statistical significance was adjusted by Bonferroni's method.

3. Results

One hundred and thirty-one patients (69 males) were included. Their age was 58 ± 9 years (mean ± SD) and duration of diabetes was 9 ± 6 years. Body weight and BMI were 94 ± 18 kg and 33.4 ± 5.9 kg/m^2, respectively. Blood pressure was 135 ± 15/78 ± 10 mmHg. Baseline HbA_{1c} was 9.0 ± 1.2%. HOMA-B and HOMA-S values (n = 52) were 34 ± 22% and 55 ± 32%, with a hyperbolic product reduced at 15 ± 7%. Total cholesterol, LDL and HDL-cholesterol as well as triglycerides were respectively 173 ± 45, 91 ± 34, 43 ± 10 and 197 ± 117 mg/dl.

Micro-albuminuria was present in 58 patients, and 14 had a glomerular filtration rate <60 ml/min/1.73 m^2. Retinopathy, peripheral and autonomous neuropathies were present in 18%, in 24% and 7% of patients, respectively. Twenty percent of subjects had a past history of macrovascular disease.

HbA_{1c} as well as body weight and BMI decreased over time in all treated patients, as shown in Table 1. For HbA_{1c}, the maximal effect was reached after one year (−1.19% *vs.* baseline) and no further reduction was observed over the following years (−1.37% at four years).

After one year of treatment, 26% (33/128) of patients reached the goal of $HbA_{1c} \leq 7.0\%$. This percentage rose to 47% (33/70) at two years and 38% (17/45) and 41% (14/34) after three and four years of treatment, respectively (Fig. 1A). Forty-seven percent (60/128) of the participants achieved a HbA_{1c} level $\leq 7.5\%$ after one year of treatment while 51% (36/70), 62% (28/45) and 74% (25/34) reached the goal after two, three and four years respectively (Fig. 1B).

During the follow-up period, 91 patients (69%) suspended their GLP1-RA treatment (32%, 49% and 58% after two, three and four years, respectively) for the following reasons: primary failure with deterioration of glycaemic control (n = 67), side effects (n = 6), loss of follow-up (n = 10), non-compliance (n = 5), bariatric surgery (n = 2) and renal deterioration (n = 1). Mean duration of treatment in this group was 50 months (95% CI [44; 57]). Fifty percent had failed after 42 months (Fig. 2A). At the end of the study period, 40 patients (31%) were still treated with a GLP1-RA.

In a multivariate analysis, including gender, age over the median of 59 years, baseline HbA_{1c} over 9.0% and BMI, male gender *(p=0.014)* and baseline HbA_{1c} over 9.0% *(p=0.053)* were independent predictors of primary failure to GLP1-RA therapy. More specifically, men and patients with a baseline $HbA_{1c} > 9.0\%$ had a 2.55- and 2.09-fold higher risk to fail, respectively.

At four years, 40 patients were still treated with GLP-1RA. In this subgroup, the reduction in HbA_{1c} (*vs.* baseline) reached a nadir after two years (mean change −1.8%) and was −1.37% after four years, as shown in Fig. 3. This long-term subgroup of "responders" differed clinically from the 91 patients who discontinued treatment earlier: they were older and their mean HbA_{1c}, diastolic blood pressure, total cholesterol as well as LDL-cholesterol and HDL-cholesterol were lower at baseline (data not shown).

In the total group of patients (n = 131), weight and BMI continued to decrease up to four years after initiation. This was also observed in the subgroup of long-term responders. A reduction in systolic blood pressure was also observed in all patients during follow-up. Lipid profile was slightly improved with a significant increase in HDL cholesterol at four years (Table 1).

Baseline characteristics were similar in the two subgroups of patients treated with once-daily liraglutide (n = 65) and twice-daily exenatide (n = 60). BMI were 34.3 ± 6.2 and 33.0 ± 5.4 kg/m^2 and HbA_{1c} levels were 9.1 ± 1.3% and 8.9 ± 1.1% in the liraglutide group and in the twice-daily exenatide groups, respectively. Liraglutide and exenatide led to significant decrease in HbA_{1c} during the first year (liraglutide −1.33%; exenatide −1.07% *vs.* baseline) and after four years of treatment (liraglutide −1.54%;

Table 1
Changes in main clinical and biological parameters over time.

	0–12 months	0–24 months	0–36 months	0–48 months
Delta HbA_{1c} (%)	−1.19*	−1.14*	−1.32*	−1.37*
(Nb of evaluated patients)	(128)	(70)	(45)	(34)
Delta body weight (kg)	−2.56*	−3.31*	−4.89*	−5.24*
Delta body mass index (kg/m^2)	−0.94*	−1.24*	−1.77*	−1.91*
Changes in systolic blood pressure (mm Hg)	−2.07	−5.52*	−1.28	−7.06
Changes in diastolic blood pressure (mm Hg)	0.04	−1.12	−0.21	1.16
Changes in triglycerides (mg/dl)	−16.30	−5.12	1.43	−24.44
Changes in total cholesterol (mg/dl)	−7.77	−12.41	−5.79	−5.96
Changes in LDL-cholesterol (mg/dl)	−6.20	−10.26	−10.58	−6.09
Changes in HDL-cholesterol (mg/dl)	−3.86*	4.58	3.04	5.48*

Results are presented as difference of means.
* Significant difference after adjustment of the level of significance by Bonferroni's method $p < 0.0125$ *vs.* baseline - no significant difference was observed in any parameter between the 1, 2, 3 and 4 year-time-points.

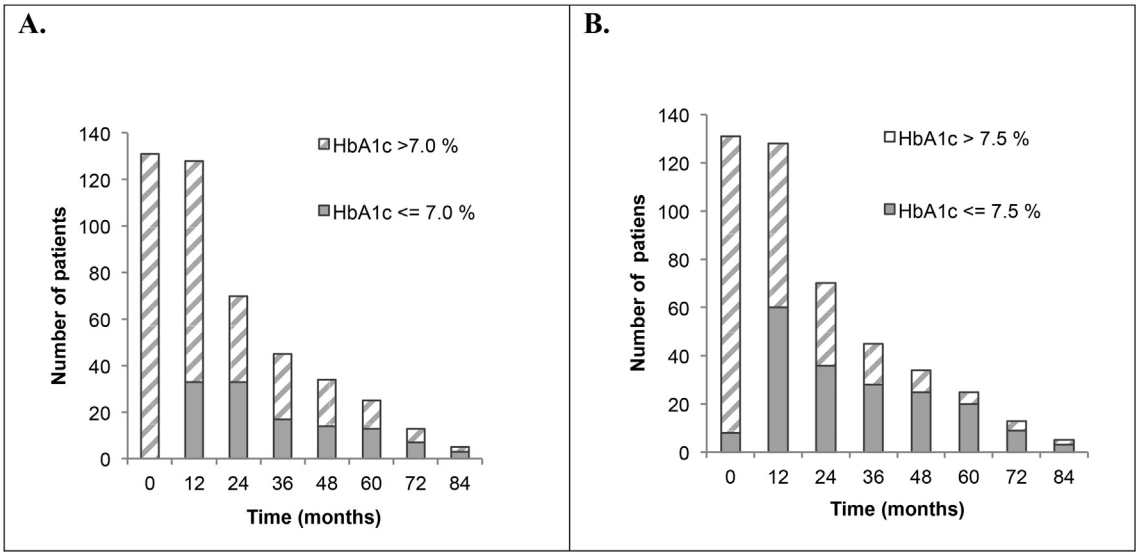

Fig. 1. Number of patients reaching HbA_{1c} goals over time.

exenatide −1.14% *vs.* baseline). The HbA_{1c} reduction tended to be more marked with liraglutide than exenatide at three years (−1.65% in the liraglutide group; −1.04% in the exexenatide group in particular at three years, *p=0.051*). Both treatments were associated with weight and BMI reduction *vs.* baseline during follow-up, with no statistical significance between the groups (Table 2). There was no difference in failure level between the two groups. However, patients treated with liraglutide tended to have longer treatment duration before primary failure than those treated with exenatide (*p=0.078)* (Fig. 2B).

4. Discussion

GLP1-RAs, introduced in the treatment of T2D over the past decade have demonstrated their efficacy on glycaemic control and weight loss. Most randomised and observational studies were conducted with a short duration of follow-up. The purpose and strength of the present study is to evaluate long-term efficiency of GLP-1RAs in type 2 diabetic patients, over a four years period in real life.

Our sample was composed at baseline of obese type 2 diabetic patients with poor glycaemic control (baseline HbA_{1c}: 9.0%), despite oral bitherapy. Our results demonstrate significant reductions over time in HbA_{1c} and weight, in agreement with previous trials [4–7]. As far as HbA_{1c} is concerned, the most marked reduction was observed after one year, with subsequently stable levels over four years follow-up. In contrast, weight and BMI progressively decreased with a nadir at the end of follow-up. Our long-term data have however to be considered with caution since many subjects discontinued their treatment. The subgroup of patients who achieved the four years follow-up were not only good responders but also likely compliant and tolerant to the treatment. This subgroup was older and had a lower baseline HbA_{1c}, despite similar duration of diabetes than the other groups.

Treatment failure, defined by an insufficient improvement or deterioration of the glycaemic balance ($HbA_{1c} > 7.5\%$ or a decrease less than 1.0% after one year treatment), concerned more than half of the entire cohort (n = 67). Male gender was a predictive factor associated with primary failure to GLP1-RA treatment with an odds ratio of 2.55 *(p=0.014)*. It is of interest to mention that a female gender was reported by Ratner et al. as a factor of good responsiveness to liraglutide [9]. At this stage however, we have no obvious explanation about the potential influence of gender on the efficacy of GLP-1RAs. We also found that a baseline HbA_{1c} higher than 9.0% was a predictive factor of failure. This observation is in agreement with another study showing that baseline HbA_{1c} was a major predictor of response to twice daily exenatide [10] and to liraglutide [9]. According to Dupuy et al., the greater the baseline HbA_{1c}, the greater the response to treatment was [11].

Regarding secondary endpoints, long term improvement in

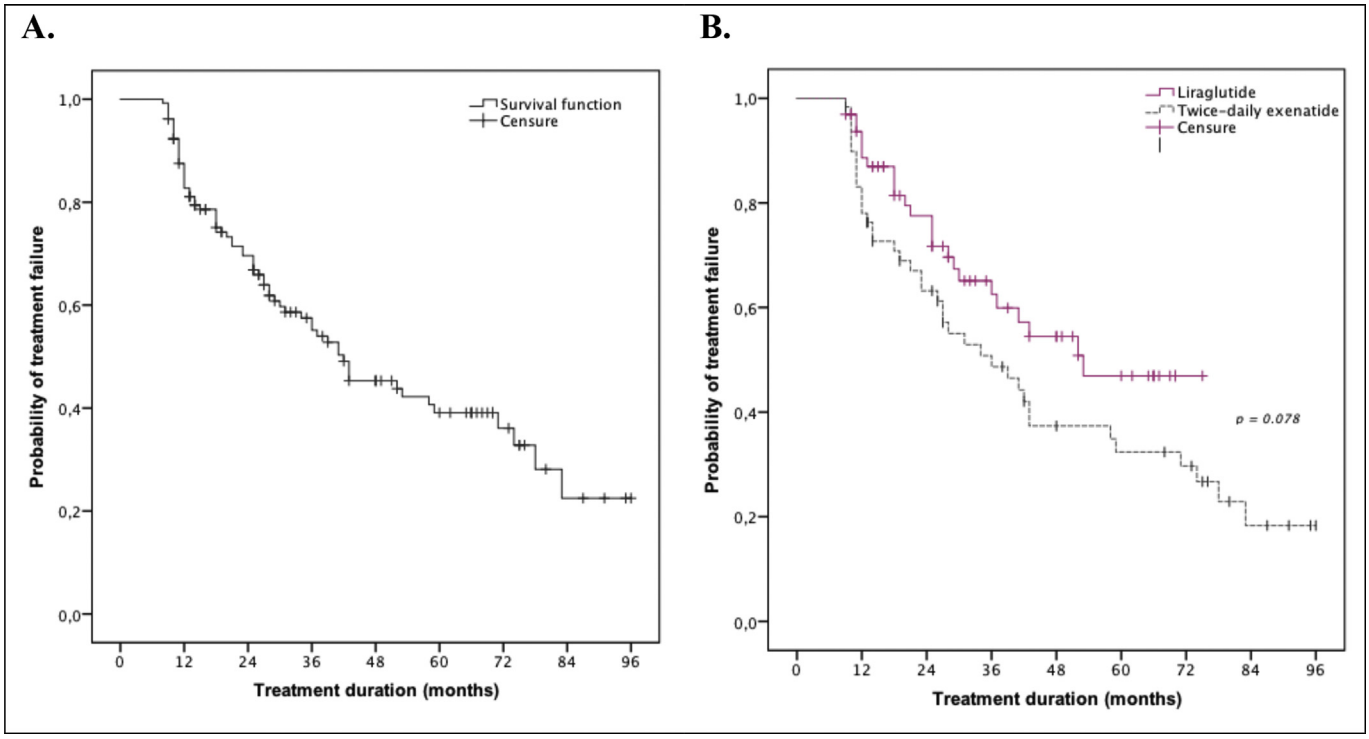

Fig. 2. Estimation of the probability of failure to the GLP1-RA treatment and comparison between liraglutide and exenatide.

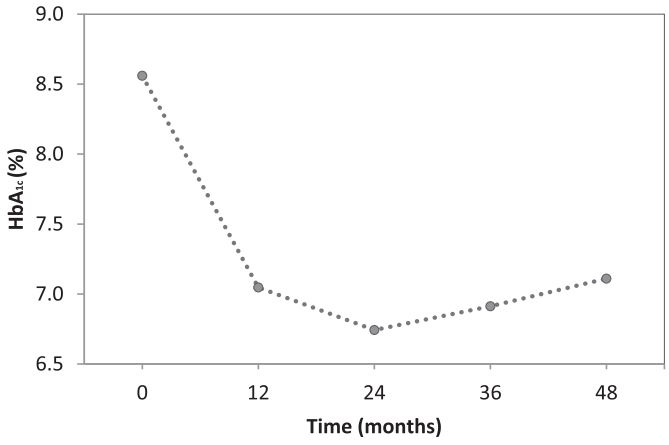

Fig. 3. Evolution of mean HbA_{1c} concentrations from baseline until four years of GLP1-RA therapy.

blood pressure and lipid profile *vs*. baseline did not reach statistical significance, except for systolic blood pressure after two years (−5.5 mmHg) and HDL-cholesterol after four years (+5.5 mg/dl).

Among all GLP1-RAs, only liraglutide and twice-daily exenatide could be compared in view of sample size.

HbA_{1c} and weight evolution in patients treated with exenatide (n = 60) are in phase with previous studies [5,6], including a Belgian multicentre trial [12]. The LEAD-6 study showed however a higher decrease in HbA_{1c} after two years than the present trial [13]. In contrast, our long term results are in agreement and extended those of Klonoff et al. who reported a similar reduction in HbA_{1c} of 1.0% after three years of follow-up [14].

Our liraglutide results are also comparable to previous data, in particular the ROOTS study [15]. In France, the prospective study EVIDENCE reported a reduction in HbA_{1c} after two years of 1.0% (*vs*. 1.43% in the present study) [16]. Rondinelli et al. also observed a decrease of 1.0% in HbA_{1c} at three years (*vs*. 1.65% in our study) [17]. Baseline HbA_{1c} levels could potentially account for the difference between those studies and our own trial. Results with liraglutide indicate a trend for a more marked effect on HbA1c and weight than exenatide, in particular after three years. These results are in agreement with the LEAD-6 prospective study [13].

In conclusion, we demonstrate that, in daily clinical practice, GLP1-RAs remain efficient after four years only in one third of patients. Clinicians should be aware of this limited long-term efficiency. Male gender and high baseline HbA_{1c} are potential risk

Table 2
Comparison between exenatide and liraglutide on HbA1c, BMI and body weight changes.

	0–12 months		0–24 months		0–36 months		0–48 months	
	Exenatide	Liraglutide	Exenatide	Liraglutide	Exenatide	Liraglutide	Exenatide	Liraglutide
Delta HbA1c (%)	−1.07*	−1.33*	−0.81*	−1.43*	−1.04*	−1.65*	−1.14*	−1.54*
Delta body weight (kg)	−2.69*	−2.53*	−3.87*	−2.91*	−2.90	−3.23*	−2.42	−3.62*
Delta body mass index (kg/m^2)	−0.97*	−0.94*	−1.37*	−1.10*	−1.49*	−2.06*	−1.24	−2.46*

Results are presented as difference of means.
* Significant difference after adjustment of the level of significance by Bonferroni's method $p<0.0125$ *vs*. baseline - no significant difference was observed in any parameter between twice-daily exenatide and liraglutide at different time.

factors for failure. Modest differences were observed between liraglutide and twice daily exenatide. Due to the paucity of long-term studies on real-life GLP1-RA efficiency, larger scale multicentre studies should be performed to confirm these long-term results.

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