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Efficacy and safety of once daily liraglutide versus twice daily exenatide in type 2 diabetic patients in Qatar: an observational study

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Abstract

Objective: Compare efficacy and saftey of liraglutide (1.8mg subcutaneous once daily) and exenatide (10mcg subcutaneous twice daily) in uncontrolled type 2 diabetes at 26 and 52 weeks

Method: A retrospective observation study of uncontrolled type 2 diabetes patients who took liraglutide or exenatide in addition to their anti-diabetic medications. This study was conducted at Hamad Medical Corporation (HMC), the predominant public healthcare organization in Qatar. The primary outcome was the change in HbA1C after 26 and 52 weeks.

Key finding: Two hundred and two patients were included in this study (liraglutide 98, exenatide 114). There was no significant HbA1C change observed between two groups at either 26 or 52 weeks (p= 0.23 and 0.40, respectively). However, more patients in the liraglutide group achieved HbA1C ≤7% at week 26. Liraglutide reduced the mean FBG more than exenatide at week 26 and 52. Although both medications were associated with some benefits in other studied variables at a certain point (e.g. weight losses, blood pressure), neither of them were able to show a significant change from baseline. No patients in either group reported drug-related side effects (e.g. nausea and vomiting) or episodes of hypoglycemia during the treatment period.

Conclusions: Exenatide and liraglutide resulted in similar glycemic effects (HbA1C and FPG changes) in patients with type 2 diabetes who were sub-optimally controlled with other anti-diabetic therapy. However, this study supports the effectiveness of both medications for weight reduction at both endpoints. A prospective large-scale study is recommended to overcome the study limitations.

Key words: liraglutide, exenatide, type 2 diabetes, HbA1C

Introduction

Type 2 diabetes is an increasingly common chronic disease characterized mainly by insulin resistance. Many anti hyperglycemic drugs are now available for type 2 diabetes management. Most adults with type 2 diabetes need to receive combination therapy of more than one class to achieve adequate glycemic control (1). To date, there is insufficient evidence to support any specific drug over another. Bayesian network meta-analysis found that glucagon like peptide 1 (GLP-1) receptor agonists and insulin were the most efficacious agents in lowering Hemoglobin A1C (HbA1C) after metformin failure (2).

Glucagon like peptide receptor agonists (e.g. exenatide and liraglutide) are injectable drugs that are similar to endogenous GLP-1 which usually decreased in patients with type 2 diabetes (3). It stimulates insulin secretion (in a glucose dependent fashion), suppresses glucagon secretion, inhibits gastric motility, and reduces appetite (4, 5). GLP-1 agonists lower HbA1C by approximately 1-2 % (6). It also appear to offer advantages over other drugs by either keeping weight stable or even reducing weight while achieving good glycemic control (7,8). GLP-1 receptor agonists influence weight reduction mainly through a centrally mediated mechanism that regulates the appetite, satiety, and food intake (9, 10). Another explanation of weight loss associated with GLP-1 receptor agonist treatment can be due to its gastrointestinal related adverse effects (e.g. nausea and vomiting). However, this explanation is considered weak since patients who did not experience nausea during the treatment duration lost weight as well (11). In clinical studies that focused on the cardio-protective benefits of diabetic medications, GLP-1 agonist (exenatide and liraglutide) showed their ability to reduce blood pressure and significantly reduced total cholesterol (TC), low density lipoprotein (LDL), and triglyceride (TG) levels compared with baseline (12). The most common side effect associated with GLP1-receptor agonists is gastrointestinal disturbances, in which 30– 45% of treated patients experiencing at least one episode of

nausea, vomiting, or diarrhea (13). GLP-1 agonists were rarely found to cause significant hypoglycemic episodes (14).

There is only one head to head study comparing liraglutide versus exenatide in type 2 diabetes (LEAD-6 study) (15). LEAD-6 results showed that the mean change of HbA1C values from baseline to week 26 was significantly greater in the group treated with liraglutide than in that treated with exenatide ($p<0.0001$) (15). On December 2006, exenatide (Byetta®) was dispensed for the first time at Hamad Medical Corporation (HMC). Later on (January 2010), liraglutide (Victoza®) was also available in the HMC pharmacy. It was unclear if liraglutide (Victoza®) is really more effective than exenatide (Byetta®) and needed to be added to the formulary as well. Thus the aim of this study was to compare the effects of exenatide versus liraglutide on glycemic control (defined as reduction in HbA1C) over 26, and 52 weeks in patients with type 2 diabetes who could not achieve adequate glycemic control despite the use of other anti-diabetic medications.

Method

Study Design

A retrospective observation study conducted at Hamad Medical Corporation (HMC), the predominant public healthcare organization in Qatar.

Patients

Patients with type 2 diabetes who took liraglutide or exenatide in addition to their anti-diabetic medications during the period of 1st of February 2010 till 30th of January 2012 were potentially eligible for this study. Pharmacy computer system was used to identify and generate list of patients who received liraglutide or exenatide during that period. Generated patient list was screened against inclusion and exclusion criteria. Inclusion criteria were: 1) type 2 diabetes patients using either Victoza® (liraglutide 1.8 mg subcutaneous once daily) or Byetta® (exenatide 10 mcg subcutaneous twice daily), 2) being compliant with studied drugs for at least 52 weeks (1 year), 3) had suboptimal glycemic control at baseline (HbA1C

7.1-11.0%), 4) had a body mass index (BMI) ≤45 kg/m^2, 5) had been treated with lifestyle modification (diet and exercise) and with at least one other anti-diabetic drug. Patients were considered to be compliant if the studied drugs were dispensed at regular basis and patients did not run-out of medication at any point during treatment duration.

Exclusion criteria were: 1) had been treated with herbals or drugs that promote weight loss within 3 months before the study baseline or throughout the duration of the study, 2) had been taking any herbals or alternative medication for any indications, 3) had done bariatric or bypass surgery, 4) were enrolled in or recently discontinued from a study involving use of an investigational drug or device, or any other type judged not to be scientifically or medically compatible with this study, 5) and had received long-term (more than 2 weeks) systemic glucocorticoid therapy.

Procedure

Medical records of eligible patients were retrospectively reviewed from both 1) the patient's paper-based medical file and 2) the patient's electronic file (i.e. medical database, e-viewer, and pharmacy database). Data-collection sheets were completed by the investigators. All data were rechecked twice to prevent any missed data.

Primary and secondary objectives

Primary: To compare the efficacy between liraglutide (1.8mg subcutaneous once daily) versus exenatide (10mcg subcutaneous twice daily) measured by the changing of hemoglobin A1C from baseline to 26 weeks, and 52 weeks.

Secondary**:** to compare the effects of liraglutide and exenatide at baseline, 26 weeks, and 52 weeks in terms of:

- Efficacy: Percentage of patients achieved target HbA1C ≤7%, Fasting plasma glucose (FPG), Body weight and body mass index (BMI), Systolic and diastolic blood pressure, Fasting lipids profile levels (total Cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG).

- Safety: Gastrointestinal disturbances (nausea, vomiting, or diarrhea), Hypoglycemic episodes (defined as FPG <3.9 mmol/L (70 mg/dL) at any time during the study period and/or dispensing of Glucagon showed on the pharmacy dispensing system, Kidney and liver function (e.g. serum creatinine, BUN, AST, and ALT).

Statistical analysis

Descriptive statistics were used to summarize demographic and all other clinical characteristics of the patients. Quantitative variables means between the two independent groups were analyzed using an unpaired 't' test and a Mann Whitney U test. Associations between two or more qualitative variables were assessed using a chi-square test or Fisher exact test as appropriate. Quantitative variables means at different time points (baseline, 26, and 52 weeks) were compared using repeated measure analysis of variance (ANOVA) followed by bonferroni corrections for a multiple comparison test. Relationships between two quantitative variables were examined using Pearson's correlation coefficients. A two-sided P value <0.05 was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 19.0 (SPSS Inc. Chicago, IL).

Ethical consideration

The study protocol, data-collection sheet, and waiver consent were approved by the HMC research and ethics committee.

Funding

This study was funded by Hamad research center allied to Hamad Medical Corporation. This study was not funded by any pharmaceutical industry.

Results

Patients' Characteristics

Out of 371 identified patients, only 212 patients met the inclusion criteria and were included in this study. There were 114 patients in Exenatide group, and 98 in liraglutide group. The most common reason for excluding patients was the duration use of exenatide or liraglutide was less than 1 year (n= 134). Female gender was dominant in this study, representing around 73% in both groups. The mean age for all of the study's patients was 53 years. A round half of the patients in this study were aged between 50–59 years. Patients were diagnosed with diabetes for a mean duration of 7.7 years. Generally, there were no significant differences in all of the patients' demographics, co-existing chronic diseases, and concurrent medications (including anti-diabetic medications) between the two groups except for renal impairment and diabetic neuropathy (Table 1).

Primary outcome

The mean HbA1C readings of both exenatide and liraglutide were statistically insignificant over the observation periods of 26 and 52 weeks (Table 2). However, comparing the mean change of HbA1C values between the two groups, HbA1C was increased from the baseline to 26 weeks interval (0.098±0.177) in the exenatide group, while it decreased in the liraglutide group (-0.213±0.180). Despite this; the treatment difference between the two groups was statistically insignificant (estimated treatment difference (ETD) -0.310; 95% CI -0.19 to 0.81; p= 0.23). At week 52, the opposite relationship was shown, in which HbA1C values increased more in the liraglutide group than in the exenatide group (Figure 1-A). The mean change from the baseline to 52 weeks interval was more in the liraglutide group (1.399±1.608) than in the exenatide group (0.077±0.203) and was statistically insignificant (ETD -1.322; 95% CI-4.30 to 1.65; p= 0.40).

The proportion of participants achieving HbA1C targets of 7% or less was higher in the liraglutide than in the exenatide group at 26 weeks (20% vs. 6.4%, respectively) and was statistically significant (p= 0.008). Similarly, a higher proportion of liraglutide participants

achieved HbA1C targets ≤7% at 52 weeks (16.4 % vs. 9%); however, it was statistically insignificant (p= 0.19) (Figure 1-B).

Secondary outcomes

Efficacy

1. Fasting Blood Glucose

The mean fasting plasma glucose (FPG) was reduced in both groups at 26 and 52 weeks. This reduction was statistically significant in the liraglutide group at the three time intervals: baseline to 26 weeks, baseline to 52 weeks (Table 3). The mean change from the baseline to 26 weeks interval was greater in the liraglutide group (-1.099±0.518) than in the exenatide group (-0.122 ±0.432) and was statistically insignificant (p= 0.15). Comparable results were found in exenatide and liraglutide groups at the 52 weeks interval (-0.616 ±0.618; 67, -1.150 ±0.519, p=0.52 respectively).

2. Body Weight

The mean BMI and body weight were reduced at 26 and 52 weeks, in which BMI reduction was statistically significant in both liraglutide and exenatide groups at both time intervals: 26 weeks (p=0.023, p=0.015, respectively), and 52 weeks (p=0.002, p=0.002, respectively). On the other hand, body weight reduction was statistically significant at both 26 and 52 weeks only in exenatide group, while the liraglutide group was statistically significant only at 52 weeks.

3. Blood pressure

At week 26, the systolic blood pressure (SBP) increased in the exenatide-treated group, while it slightly decreased in the liraglutide group. On the other hand, the diastolic blood pressure (DBP) decreased in the exenatide-treated group, while it increased in the liraglutide group (Figure 2-A,B). At 52 weeks, both the systolic and diastolic blood pressure reduced in

both treatment groups (compared with week 26) and the reduction was more in the liraglutide group than in the exenatide group (Figure 2-A, B). Comparing the change of blood pressure between the two groups retrieved no statistical difference at any time point.

4. Lipid level profile

Total cholesterol and LDL were reduced in the liraglutide group at both time points (26 and 52 weeks) but it was statistically significant only at the baseline–52 week's interval. Other parameters (HDL, Triglycerides) were statistically insignificant over the observation periods. All lipid profile parameters (TC, LDL, HDL, and TG) were statistically insignificantly changed in exenatide group at both time points (Figure 2-C, D). Comparing two groups together, none of the profile parameters showed any statistically significant difference.

Safety

None of the patients in either groups reported any GI side effects (nausea, vomiting, and diarrhea) or hypoglycemic episodes. For other safety parameters regarding kidney and liver functions, none of the changes in these parameters were significant at any time points except for creatinine in the liraglutide group at 52 weeks (p=0.001) (Table 4).

Overall, the exenatide group had a better safety profile than the liraglutide group in all kidney and liver function parameters in both time points, except for AST at 26 weeks. For example, at week 52, the mean reduction of ALT from baseline was (-1.483±1.278) in the exenatide group, which is better than the ALT elevation occurred in the liraglutide group (1.822±1.730) with ETD of -3.305±2.15, but it was statistically insignificant (p= 0.13).

Discussion

Patients Demographics

In this study, the mean age of the patients was 53 years, 73% of them were female, and more than 90% were Middle Easterners. These demographic findings are in line with the demographics of type 2 diabetic patients in general (16).

Primary Outcome

UKPDS found that a reduction of 1% in HbA1C was associated with a 37% decrease in micro-vascular complications and a 21% decrease in mortality associated with diabetes (17). Thus, selection of HbA1C reduction as a primary outcome is clinically relevant and well justified. In the current study, results showed that in type 2 diabetic patients with inadequate glycemic control on other anti-diabetic medications, neither the addition of 1.8 mg liraglutide nor 10 mcg exenatide provided significant glycemic control after 26 or 52 weeks of treatment compared to baseline. The beneficial effects of liraglutide over exenatide seen at week 26 were aligned with those reported in the only liraglutide versus exenatide head-to-head study (LEAD-6) (15). The LEAD-6 results showed that the mean change of HbA1C values from baseline to week 26 was significantly greater in the group treated with liraglutide than in that treated with exenatide ($p<0.0001$).

Unlike the previous studies of either liraglutide or exenatide when each drug was studied separately, in the present study, liraglutide 1.8 mg once daily reduced HbA1C by a mean of 0.213% after 26 weeks compared with a reduction of 1% in the LEAD-2 study (18), 1.1% in the LEAD-1 study (19), 1.3% in the LEAD-5 study (20) and 1.5% in both the LEAD-4 and DURATION-6 studies (21, 22).

Additionally, the current results and the previous studies' results, exenatide 10 mcg twice daily slightly increased HbA1C values by a mean of 0.098% and 0.077% at 26 weeks and 52 weeks, respectively. This increase was not consistent with other trials in which HbA1C was reduced by approximately 1% (12, 23-26). The reasons for this unexpected difference in HbA1C changes noted in this study for both liraglutide and exenatide are unknown; however, previous pharmacological exposure, study population, or medication compliance might have contributed to the differences.

Secondary Outcomes

- *Fasting Plasma Glucose*

Fasting plasma glucose (FPG) is an important measure of glycemic control, where fasting hyperglycemia contributes to the chronic complications of diabetes (11). In this study, FPG was decreased in both groups at 26 and 52 weeks, but the decrease achieved statistical significance only in the liraglutide group. Although liraglutide also showed greater FPG reduction over exenatide in the LEAD-6 study, the mean reduction at 26 weeks reported in the LEAD-6 study (3.2 mmol/L for liraglutide, and 2.9 mmol/L for exenatide) was much higher than what was shown in the current study (1.1 mmol/L for liraglutide, and 0.12 mmol/L for exenatide) (16).

In the current study, the mean reduction in FPG in the exenatide group was out of the reduction range (1-2 mmol/L) reported in other trials at both 26 and 52 weeks (11, 12, 25, 27,28). Unpredictably, liraglutide patients continued to have FPG reduction at week 52 despite the elevation of their HbA1C at that endpoint. Therefore, reduction in FPG is not always translated into a reduction in HbA1C.

- *Body Weight, blood pressure and lipid profile:*

In line with the beneficial effects of exenatide and liraglutide in weight reduction approved in previous trials (7, 8), the current study showed that patients' weights were significantly reduced at 26 and 52 weeks in both groups compared to their baseline weight, except for the liraglutide group at 26 weeks. However, there was no treatment differences between the two groups at both time points similar to the LEAD-6 study (p=0.2235) (16).

Noteworthy that both exenatide and liraglutide showed reductions in blood pressure (SBP and DBP) occurred in the two groups at both 26 and 52 weeks. Although the SBP reduction reported in the LEAD-6 trial was much greater in both groups than reported in this study (16). Moreover, they demonstrated beneficial effects on lipids parameters (e.g. TC, TG, and

LDL); liraglutide provided better non-significant lipid improvement versus exenatide with exception of HDL which improved more in exenatide patients. In spite of both groups experiencing an unpredicted elevation of TG at week 52, liraglutide produced a more substantial TG elevation than exenatide did. However, the mean change in lipid levels in this study was lower than that reported in previous trials (12, 25).

- *Hypoglycemic Episodes*

In previous trials, GLP-1 agonists were not associated with a significant increase of hypoglycemic episodes unless combined with other drugs that elicited hypoglycemia (27). There is no event of hypoglycemia in this study neither as minor no major episodes. In the LEAD-6 study, no major hypoglycemia occurred with liraglutide while only two episodes happened with exenatide patients (16).

- *Gastrointestinal Disturbances*

The proportion of patients experiencing nausea in LEAD-6 was initially similar in the two groups; however, nausea was resolved more quickly in patients treated with liraglutide than in those treated with exenatide (16). In the current study, unfortunately, none of the patients in both groups reported any GI side effects as nothing was documented in their files.

- *Strengths and limitations*

This study had several strengths that are worth mentioning. The notable strengths of this study that; it was being the first of its kind in Qatar, and indeed the entire Arabian Gulf region, to present a head-to-head comparison of exenatide (10 mcg twice daily) versus liraglutide (1.8 mg once daily) in type 2 diabetic patients other than the LEAD-6 study. Moreover, a longer duration when compared to the LEAD-6 study, which gives deep insight about the long-term effect of liraglutide and exenatide. In addition to, There were no statistically significant differences between the two groups regarding other anti-diabetic

medications that patients were concurrently taking with the studied drug, providing the study with the advantage of eliminating any possible confounder factors that could affect the reliability of the study results' and ensuring that the reported results truly represented the effect of the studied drugs rather than the effect of other underlined causes.

Conclusion

In conclusion and on the basis of the results of this study, it seemed that there was no statistically significant efficacy difference between liraglutide and exenatide in terms of reduction in HbA1C and FPG. However, this study supports the effectiveness of both medications for weight reduction where both medications caused weight loss (and consequently BMI reduction) at both endpoints (26 and 52 weeks). Although these medications were associated with some benefits in other studied variables at a certain point, neither of them was able to show a significant change from baseline. No patients in either group reported drug-related side effects (e.g. nausea and vomiting) or episodes of hypoglycemia during the treatment period.

Overall, the current study highlights the importance of further studies to be done to compare the efficacy and safety of liraglutide and exenatide in type 2 diabetic patients. A prospective large-scale study is recommended to overcome the previously mentioned limitations. Until that, this study hopefully will be used to better inform healthcare providers, and this will eventually translate into an increase in the health benefits and awareness for the patients.

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