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Comparative Real World Effectiveness of Liraglutide *versus* Sitagliptin in Patients with Type 2 Diabetes as an Add-On to Metformin Monotherapy in the United States

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Abstract

Objective: Limited real-world evidence is available on the effectiveness of liraglutide compared with sitagliptin as an add-on therapy to metformin in clinical practice for adult patients with Type 2 diabetes mellitus (T2DM). The purpose of this study was to compare clinical outcomes 6 months after initiating treatment with liraglutide or sitagliptin for patients uncontrolled on metformin monotherapy in the United States (US).

Methods: We used the General Electric Centricity electronic medical records database to analyze the effectiveness of liraglutide and sitagliptin in adult (≥18 years) patients with T2DM who started either drug between January 1, 2010 and January 31, 2013 (index period) as an add-on to metformin monotherapy. Changes in A1C, body weight, and the proportion of patients reaching ADA A1C target of <7.0% 6 months after starting treatment with liraglutide or sitagliptin, adjusted for differences in demographic and baseline clinical characteristics, were evaluated.

Results: 395 patients treated with liraglutide (mean age: 52.9 years, female: 57.5%) and 1,896 patients treated with sitagliptin (mean age: 58.0 years, female: 51.1%) were identified during the index period. After adjusting for baseline factors, patients treated with liraglutide experienced greater reductions in A1C (-1.18% vs. -0.94%, p<0.001) and body weight (-3.0 kg vs. -1.6 kg [6.6 lbs vs. -3.4 lbs], p<0.001) at 6 months from baseline than patients treated with sitagliptin. Significantly more patients treated with liraglutide met the A1C <7.0% target after 6 months follow-up (49.4% vs. 40.0%, p=0.001).

Conclusions: As in clinical trials, this real-world study found that among adult patients with T2DM uncontrolled on metformin monotherapy liraglutide was associated with significantly greater reductions in A1C and body weight and improved glycemic goal attainment compared to sitagliptin.

Keywords: Liraglutide; Sitagliptin; Type 2 diabetes; Metformin; A1C; Weight; Comparative effectiveness; Clinical effectiveness

Introduction

Diabetes is the most common metabolic disorder and the global prevalence rates have been increasing [1]. According to the CDC report, diabetes is the seventh leading cause of death in the United States (US) [1]. Currently about 190 million people globally have diabetes and this number is expected to increase to 330 million in 2025 and 366 million in 2030 [2]. In the US alone, about 29 million people, or about 9% of the population, had diabetes as of 2014 [1]. Type 2 diabetes mellitus (T2DM) comprises about 90-95% of all diabetes cases [1]. The American Diabetes Association (ADA) reported that the total estimated cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in indirect costs or reduced productivity [3].

Metformin, due to its ability to control A1C without weight gain, overall favorable benefit-risk profile, and low cost, is the gold standard first-line agent for treating T2DM [4,5]. Since 2005 two classes of incretin-based therapies have become available: injectable glucagon-like peptide-1 (GLP-1) receptor agonists (RA) and oral dipeptidyl peptidase-4 (DPP-4) inhibitors. Both classes have a glucose-dependent mode of action that minimizes the risk of hypoglycemia while GLP-1 RAs also lead to weight loss. Januvia® (sitagliptin), an oral DPP-4 inhibitor was approved by the FDA in 2006 [6], while Victoza® (liraglutide), a once-daily injectable GLP-1 analogue was approved by the FDA in 2010. Both these agents are used alone or in combination with metformin or other oral agents and can be used as an adjunct to diet and exercise to improve glycemic control in T2DM [7,8].

A randomized 26-week open-label head-to-head clinical trial compared liraglutide (1.2 or 1.8 mg/day) with sitagliptin (100 mg/day), as add-on therapies to metformin monotherapy and showed that liraglutide was associated with greater reduction in A1C from baseline (-1.24% and -1.50% vs. -0.90%, l p<0.001 respectively) than sitagliptin [9]. The same trial also found that the reduction in body weight, as a secondary endpoint, was significantly greater among patients treated with liraglutide 1.2 mg (-2.86 kg [-6.29 lbs]) and 1.8 mg (-3.38 kg [-7.26 lbs]) than sitagliptin (-0.96 kg [-2.11], p<0.001) [9]. However, as clinical trials are conducted in selected populations following a strict protocol with the intention to document safety and efficacy, data

demonstrating clinical effectiveness in a real-world setting can provide valuable additional information to health care providers and payers.

Limited evidence is available on the effectiveness of liraglutide compared with sitagliptin as an add-on therapy to metformin for patients not reaching treatment targets in clinical practice. The objective of this study was to investigate whether the clinical trial results can be confirmed using real-world data. We used an electronic medical record (EMR) database to compare changes from baseline in A1C, body weight, and the proportion of patients reaching A1C target 6 months after initiating treatment with liraglutide or sitagliptin in addition to background metformin monotherapy.

Methods

Data source

We used the General Electric (GE) Centricity EMR database, which contains data on a wide range of demographic and clinical measures from more than 10,000 general practitioners in the US. These data represent the clinical experiences of over 20 million patients in 47 US states. In addition to medical and pharmacy claims that include over-the-counter medications, the database contains demographic and clinical information on age, sex, race/ethnicity, region, health plan type, smoking status, body weight, body mass index (BMI), and A1C.

This study was exempt from ethics approval from an institutional review board and informed consent since it involved assessment of existing data, and the subjects could not be identified directly or through identifiers linked to the subjects (45 CFR 46.101(b)).

Sample selection

The study population included adult (≥18 year) patients with T2DM who initiated treatment with liraglutide or sitagliptin. Patients were required to have their first prescription order for either of the two treatments of interest between January 1, 2010 and January 31, 2013 (the date of the first prescription order is referred to as the index date and prior time periods are referred to as the pre-index period). T2DM was defined by at least one of the following criteria: diagnosis of T2DM based on International Classification of Diseases, Ninth Revisions, Clinical Modification (ICD-9-CM) codes 250.x0 or 250.x2; one or more prescription orders for a non-insulin antidiabetic drug; or two consecutive fasting blood glucose levels of ≥126 mg/dL [10]. Other inclusion criteria included continuous eligibility during the 12-month pre-index period and 6-month follow-up period, A1C values available 45 days prior to the index date to 7 days after the index date for baseline measures and within ± 45 days around day 180 after starting treatment with liraglutide or sitagliptin for the follow-up measures (baseline and 6-month follow-up measurements may have been misclassified because the start and end dates of liraglutide and sitagliptin treatment that were recorded by physicians may have differed from when members of our sample actually started or stopped using their medications). We excluded patients with any diagnosis codes for type 1 diabetes (ICD-9 codes: 250.x1 or 250.x3), pregnancy or gestational diabetes, or polycystic ovarian syndrome (ICD-9 code 256.4) without the presence of T2DM ICD-9 diagnosis codes 250.x0 or 250.x2.

Additional restrictions were applied to limit the study sample to incretin-naïve patients (during the one-year pre-index period): individuals were required to be naïve to both GLP-1 receptor agonists and DPP-4 inhibitors. Patients with T2DM included in this study were limited to those treated with metformin monotherapy prior to the index date and those with baseline A1C>7% as of the index date.

Study measures

Demographic characteristics like age, sex, race, geographic region, and healthcare plan type were assessed at baseline. Clinical characteristics such as A1C, body weight, BMI, and common diabetes-related comorbidities (Table 1) were also measured at baseline [11]. Changes from baseline to 6 months follow-up were calculated for A1C, body weight (kg, absolute and relative changes), and the proportion of patients reaching A1C of ≤6.5%, and <7.0%, using the American Association of Clinical Endocrinologists (AACE) [12], and the [13], (ADA) targets respectively.

	Liraglutide (N=395)	Sitagliptin (N=1,896)	p-value
Age (%)			<0.001
18-39 years	10.9	6.3	
40-49 years	26.8	16.8	
50-59 years	34.9	31.1	
60-69 years	20.0	29.2	
70-79 years	6.6	13.0	
80+ years	0.8	3.6	
Age in years	52.9 (11.0)	58.0 (11.8)	<0.001
Gender (%)			0.021
Male	42.5	48.9	
Female	57.5	51.1	
Race/ethnicity (%)			0.052
Caucasian	63.8	63.8	
African American	5.3	8.5	
Hispanic	2.5	2.2	
Other	1.8	3.3	
Unknown	26.6	22.3	
Region (%)			<0.001
Midwest	17.7	20.1	
Northeast	20.3	39.1	
South	50.4	31.2	
West	11.7	9.6	
Plan type (%)			0.002
Commercial	36.2	30.4	
Medicare	16.5	24.2	
Medicaid	0.5	1.7	
Self-pay/other	0.5	1.1	

Unknown	46.3	42.6	
Smoking status (%)			0.306
Never smoked	23.5	24.5	
Former smoker	30.9	34.6	
Current smoker	8.9	8.9	
Other/unknown	36.7	32.0	
Presence of comorbidities (%)			
Retinopathy	0.5	0.4	0.817
Nephropathy	0.7	1.8	0.138
Neuropathy	1.7	2.3	0.54
Cerebrovascular	0.3	0.2	0.87
Cardiovascular	1.3	1.0	0.64
Peripheral vascular disease	0.0	0.2	0.429
Metabolic	0.0	0.1	0.518
BMI (%)			
Overweight (25.0-29.9)	8.1	24.4	<0.001
Obesity class I (30.0-34.9)	28.6	32.7	
Obesity class II (35.0-39.9)	25.8	21.5	
Obesity class III (≥40.0)	37.5	21.4	
BMI, kg/m^2	39.2 (8.8)	35.2 (7.00)	<0.001
Weight in kg	112.2 (27.1)	100.1 (22.3)	<0.001
A1C%	8.58 (1.49)	8.37 (1.32)	0.004
Note: Data expressed as mean (standard deviation) unless otherwise noted.			

Table 1: Baseline demographic and clinical characteristics

Statistical analysis

We summarized the data by calculating and presenting the means and standard deviations (SD) for continuous variables and frequency distributions for categorical variables. Differences in continuous variables between groups were assessed using the paired sample t-test and differences in categorical variables were assessed using McNemar's test; differences with $p<0.05$ were considered statistically significant. Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

Regression methods

Multiple ordinary least squares (OLS) regression models were used to assess the relationships between (liraglutide or sitagliptin) groups and the continuous outcomes (change in A1C and absolute and relative changes in body weight from baseline). The continuous outcomes were first graphed to verify that OLS regression was the appropriate method to use multiple logistic regression models to assess the relationship between treatment and achieving A1C<7.0%. All regression models were adjusted for demographics characterstics such as age, gender, race/ethnicity, health plan, region, smoking status, and baseline clinical characteristics such as comorbidities, BMI, and A1C (Appendix). Because the GE Centricity EMR database does not contain prescription fill and refill information, we were unable to adjust for medication adherence. As a result, we used an intent-to-treat approach.

For ease of interpretation, we calculated and presented, adjusted predicted outcomes, also known as predictive margins or recycled predictions (Table 2). The method of predictive margins is a type of standardization in which predicted outcomes of regression models are computed for certain values of key predictor variables, such as treatment group (liraglutide or sitagliptin), while holding others constant at their observed values. Standard errors of the predictive margins (and their functions) were computed using the delta method [14].

	Liraglutide (N=395)	**Sitagliptin (N=1,896)**	**p-value**
A1C			
Mean % (SD) A1C, %	7.34 (1.42)	7.44 (1.27)	0.18
Mean % (SD) absolute change in A1C from baseline, %	-1.24 (1.71)	-0.93 (1.47)	<0.001
≤6.5% goal attainment, %	29.6	21.2	<0.001
<7.0% goal attainment, %	47.1	40.5	0.015
Body Weight			
Mean (SD) weight, kg	108.1 (25.7)	98.5 (21.6)	<0.001
Mean (SD) absolute change in body weight from baseline, kg	-3.4 (4.8)	-1.5 (5.2)	<0.001
Mean (SD) relative change in body weight from baseline, %	-3.0 (4.9)	-1.4 (4.9)	<0.001
Relative change (=absolute change divided by baseline value). SD: Standard deviation.			

Table 2: Unadjusted Clinical outcomes at 6 months follow-up

Results

A total of 2,291 patients with T2DM were included in the analysis, of which 395 initiated treatment with liraglutide and 1,896 initiated treatment with sitagliptin; their demographic and clinical characteristics at baseline are shown in Table 1. Patients initiating liraglutide were younger than patients initiating sitagliptin (52.9 vs. 58.0, $p<0.001$) and more likely to be female (57.5% vs. 51.1%, $p=0.021$). There were no statistically significant differences in race/ethnicity, smoking status, or the presence of comorbidities at baseline between the two groups. At baseline, the mean A1C values of the two cohorts were significantly different. Patients who initiated liraglutide had significantly higher mean A1C (8.58% vs. 8.37%, $p=0.004$) and significantly higher mean BMI (39.2 kg/m^2 vs. 35.2 kg/m^2, $p<0.001$) than sitagliptin patients.

During the 6-month follow-up period (Table 3), patients treated with liraglutide experienced a significantly greater unadjusted mean change in A1C from baseline (-1.24% vs. -0.93%, $p<0.001$) than patients treated with sitagliptin. The liraglutide cohort also had

significantly more patients achieving A1C ≤6.5% (AACE target) during the study period (29.6% vs. 21.2%, p<0.001) than the sitagliptin cohort. The same significant finding (47.1% vs. 40.5%, p=0.015) was observed for the proportion of patients achieving A1C <7.0% (ADA target). The liraglutide cohort experienced a significantly greater mean absolute change in body weight at 6 months than the sitagliptin group (-3.4 kg vs. -1.5 kg [-7.4 lbs vs. -3.3 lbs], p<0.001). The liraglutide group also lost relatively more body weight after 6 months follow up than the sitagliptin cohort (3.0% vs. 1.4%, p<0.001).

	Liraglutide (N=395)	Sitagliptin (N=1,896)	p-value
A1C			
Mean absolute change in A1C from baseline, %	-1.18	-0.94	<0.001
<7.0% goal attainment, %	49.4	40.0	0.001
Body Weight			
Mean absolute change in body weight from baseline,kg	-3.0	-1.6	<0.001
Mean relative change in weight from baseline,%	-2.9	-1.4	<0.001
Note: Adjusted for baseline demographic and clinical characteristics using ordinary least squares for continuous outcomes (A1C and body weight) and multiple logistic regression for binary outcomes (A1C<7.0%).			

Table 3: Adjusted clinical outcomes at 6-months follow-up

These findings remained unchanged after adjusting for differences in demographic and baseline clinical characteristics (Table 3). Patients treated with liraglutide experienced greater reductions in A1C from baseline (-1.18% vs. -0.94%, p<0.001) and were more likely to achieve A1C< 7.0% (49.4% vs. 40.0%, p=0.001) than patients treated with sitagliptin after 6 months follow-up. Liraglutide patients also lost more absolute and relative body weight than sitagliptin patients after 6 months (-3.0 kg vs. -1.6 kg [-6.6 lbs vs. -3.4 lbs;] and -2.9% vs. -1.4%, both p<0.001).

Discussion

This is the first study in the US to compare the real-world clinical effectiveness of liraglutide with sitagliptin as add-ons to metformin monotherapy to lower A1C and body weight in patients with T2DM. As in head-to-head clinical trials with liraglutide and other GLP-1 RAs [15,16], this study found that patients with T2DM who added liraglutide to their metformin treatment regimen experienced significantly greater reductions in A1C and body weight and were more likely to attain A1C goals after 6 months follow-up than those who added sitagliptin.

Lee et al. compared real-world glycemic outcomes over 6 months of treatment after starting liraglutide versus exenatide or sitagliptin with or without use of other oral anti-diabetics. The study utilized the PharMetrics database, but was not able to assess changes in body weight and was not restricted to metformin monotherapy background treatment as in our study [17]. They found that patients treated with liraglutide experienced significantly greater mean reductions in A1C levels after 6 months follow-up than patients treated with sitagliptin (-1.08% vs. -0.68%, p<0.001) [17]. Differences in the absolute reductions between these studies are most likely due to differences in patient characteristics (particularly baseline A1C levels, which were lower in the study by Lee et al and could have impacted A1C outcomes at follow up). Evans et al. conducted a retrospective, case-note survey to compare outcomes for inpatients with T2DM who were treated with liraglutide, exenatide, or DPP-4 inhibitors (sitagliptin, saxagliptin, and vildagliptin). They found that the reduction in A1C level and body weight, from baseline to 12 months, was significantly greater in patients treated with liraglutide (1.15% and -3.5 kg [7.7 lbs], respectively) than in patients treated with DPP-4 inhibitors (0.74% and -0.6 kg [1.3 lbs], respectively) [18]. However, unlike the current study, the patients were not incretin-naïve, neither were they limited to metformin background monotherapy.

Pratley et al reported on an open-label head-to-head clinical trial comparing liraglutide and sitagliptin in patients with uncontrolled T2DM on metformin monotherapy (1500 mg/day). The observed mean reductions in A1C over 26 weeks were comparable to our results, although we could not differentiate between liraglutide doses: -1.50% for liraglutide 1.8 mg, -1.24% for liraglutide 1.2 mg, and -0.90% for sitagliptin. Mean absolute reductions in body weight were also similar to our results: -3.4 kg [-8.1 lbs]) for liraglutide 1.8 mg, -2.9 kg [-6.12 lbs] for liraglutide 1.2 mg, and -1.0 kg [-2.20 lbs] for sitagliptin [15].

Study Limitations

We used observational data to compare the real-world clinical effectiveness of liraglutide with that of sitagliptin. Because these data are non-experimental and the GE Centricity EMR database was not designed with our specific research questions in mind, our conclusions are subject to causal limitations inherent to the analysis of observational data. Although we adjusted for important patient clinical and demographic characteristics, we were unable to adjust for unmeasured, confounding factors such as diet, exercise, and some comorbidities. Despite this, and the fact that the liraglutide patients had higher A1C levels and weighed more at baseline, we nevertheless observed lower A1C levels and larger relative weight reductions after 6 months for liraglutide patients. Other limitations that we have already noted may have impacted our ability to accurately assess the differences between liraglutide and sitagliptin, such as a lack of information on prescription fills or refills and the potential mismatch between physician-recorded medication start and end dates. However, it is unlikely that these limitations would have varied between the treatment groups in any systematic way and they are therefore unlikely to bias our results.

Conclusion

This study presents the first real-world evaluation of changes in A1C and body weight in uncontrolled T2DM patients in the US on metformin monotherapy who initiated treatment with liraglutide or sitagliptin. We found that liraglutide initiation was associated with significantly greater reductions in A1C and body weight as well as improved glycemic goal attainment compared with sitagliptin. These results suggest that liraglutide may prove to be more effective than sitagliptin in clinical practice when initiated early in the treatment algorithm.

Disclosure Summary

Abhishek S. Chitnis, Michael L. Ganz and Nicole Benjamin are employees of Evidera, which provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In this salaried position, they work with a variety of companies and organizations and are precluded from receiving payment or honoraria directly from these organizations for services rendered. Mette Hammer and Jakob Langer are employees of Novo Nordisk Inc. and are shareholders of Novo Nordisk.

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