The effect of Dulaglutide on glycemic and weight control in patients with type 2 diabetes

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Abstract

Background and aims. The objectives of type 2 diabetes treatment are to achieve adequate long-term glycemic control and to reduce the risk associated with comorbidities and complications. Once-weekly Dulaglutide showed a reduction in cardiovascular risk associated with diabetes in addition to improved glycemic control and bodyweight reduction in several clinical trials. We aimed to investigate the effect of Dulaglutide 1.5 mg on glycemic and weight control in type 2 diabetes patients inadequately controlled by antihyperglycemic treatment in real-world clinical practice.

Methods. We retrospectively reviewed the medical records of 50 patients with type 2 diabetes inadequately controlled by previous treatment and newly initiated on Dulaglutide. The data were collected at 6 months (n=50) and 12 months (n=40) after Dulaglutide therapy initiation.

Results. Dulaglutide treatment resulted in significant improvement of glycated hemoglobin (−1.3 %; $p<0.001$) after 6 months and after 12 months (−2.0 %; $p<0.001$). Significant bodyweight reduction was found after 6 months (−2.0 kg; $p=0.002$) and 12 months (−3.5 kg; $p=0.001$) of Dulaglutide treatment initiation. In addition, a reduction in insulin dose was observed.

Conclusions. Our clinical data showed that Dulaglutide 1.5 mg significantly improved glycemic and bodyweight control at 6 and 12 months after treatment initiation in patients with type 2 diabetes inadequately controlled by previous antihyperglycemic treatment.

Keywords: diabetes mellitus, dulaglutide, bodyweight, glycemic control

Introduction

Rapid economic development and increasing life expectancy worldwide, phenomena accompanied by accelerating urbanization and expanding prevalence of sedentary lifestyle, have resulted in a marked increase of type 2 diabetes incidence [1]. The objectives of type 2 diabetes treatment are to achieve adequate long-term glycemic control and to reduce the risk associated with comorbidities and complications. Novel therapeutic strategies take into consideration factors such as the effect on cardiovascular and renal disease, hypoglycemia risk, impact on weight, efficacy, and patient preferences [2].

Impairment of incretin hormone secretion or activity acts synergistically with insulin resistance and decreased insulin secretion in inducing chronic hyperglycemia in type 2 diabetes [3,4]. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) represent a new class of non-insulin antihyperglycemic drugs that exert their metabolic effect through incretin mechanism, a term that refers to the postprandial action of intestinal hormones to stimulate insulin and inhibit glucagon secretion in a glucose-dependent manner [4]. They are available as short-acting injectable agents with daily administration and long-acting injectable agents with weekly administration. Also, more recently

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an oral formulation of Semaglutide has been approved [5]. Due to their effect of reducing bodyweight, fasting, and postprandial glycemia, as well as a positive effect on atherosclerotic cardiovascular outcomes for some of the class representatives, current guidelines for the management of type 2 diabetes, recommend the GLP-1 RA as first-line injectable therapy even before insulin initiation [5,6].

Dulaglutide is a once-weekly GLP-1 RA that has been shown to improve glycemic control with a low risk of hypoglycemia [7] and with additional positive effects on cardiovascular outcomes [8]. In addition, weight reduction was an effect associated with Dulaglutide administration, with direct consequences on glucose control through improved insulin sensitivity and lower glycated hemoglobin (HbA1c) [8]. Thus, Dulaglutide treatment is a treatment option to be considered in most patients with type 2 diabetes due to its proven effectiveness in enhancing glycemic control in the AWARD (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes) clinical program [7,9-17] and reducing cardiovascular risk in the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) clinical trial [8].

Data provided by randomized controlled clinical trials have the highest levels of evidence for both efficacy and safety of Dulaglutide [7,8]. However, their result might not truly reflect the efficacy of Dulaglutide in all patients with type 2 diabetes who exhibit different characteristics and treatment behaviors [18]. Data from real-world clinical practice could bring new information regarding Dulaglutide effectiveness in terms of HbA1c reduction and changes in bodyweight [19,20]. Thus, the aim of our study was to investigate the effect of once-weekly Dulaglutide 1.5 mg on glycemic and weight control in type 2 diabetes patients inadequately controlled by previous antihyperglycemic treatment in real-world clinical practice.

Methods

Study design and patients

We retrospectively reviewed the medical records of type 2 diabetes consecutive patients (n=50) inadequately controlled by previous antihyperglycemic treatment and newly initiated on Dulaglutide between February 2019 and June 2021. Patients were selected from the outpatient clinic of the Center of Diabetes, Nutrition and Metabolic Diseases, Emergency Clinical County Hospital Cluj-Napoca, Romania. Patients were followed up at 6 months (n=50) and 12 months (n=40) of Dulaglutide treatment. Data at 12 months were not collected in all patients included in the study, being unavailable because of shorter observation time. Type 2 diabetes and its comorbidities (obesity, arterial hypertension) and macrovascular and microvascular complications (atherosclerotic cardiovascular disease, diabetic peripheral polyneuropathy, diabetic retinopathy, and diabetic chronic kidney disease) were diagnosed according to the American Diabetes Association criteria [21]. Patients were not included if they were diagnosed with any unstable clinical conditions, hematological diseases (e.g. anemia), liver cirrhosis, nephrotic syndrome, had an estimated glomerular filtration rate <30 ml/min/1.73 m^2, followed therapy with steroid drugs, or were pregnant or breast-feeding. In accordance with the World Medical Association Declaration of Helsinki and institutional guidelines, the local Ethics Committee of the Iuliu Hatieganu University of Medicine Cluj-Napoca, Romania approved the study protocol. The need for informed consent was waived due to the retrospective nature of the study.

Study protocol and assessments

Data related to personal medical history were collected accessing the patients' medical records. The following data were collected for the outpatients on Dulaglutide initiation : age, sex, type 2 diabetes duration, comorbidities, and chronic complications, treatment of type 2 diabetes (total dose of insulin measured in international units [IU] and non-insulin antidiabetic drugs). Height and bodyweight were recorded, body mass index (BMI) was calculated and classified according to World Health Organization [22]. HbA1c was assessed using commercially available methods. Fasting glycemia was measured using blood-glucose meters and it was self-reported by patients as mean fasting glycemia over the last three months.

HbA1c, fasting blood glucose, bodyweight, and total dose of insulin were monitored at 6 months (n=50) and 12 months (n=40) after once-weekly Dulaglutide 1.5 mg treatment was newly added to previous antihyperglycemic treatment in all patients.

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics and Microsoft Office for Windows, Version 22.0 (Armonk, NY: IBM Corp). To assess all variables' normal distribution, we used the Shapiro-Wilk test. Data were expressed as mean ± standard deviation, or median (25th, and 75th percentiles), or numbers and percentages. Data at baseline, 6, and 12 months whereas compared using the t-test for paired samples and related-samples Wilcoxon signed rank test, with the value of $p < 0.05$ being considered statistically significant.

Results

Baseline characteristics

We evaluated 50 patients with type 2 diabetes, 56.0 % of which were men, with a median age of 65.0 years and a mean duration of diabetes 12.0 years. When Dulaglutide was initiated, 49 of the patients were treated with Metformin 2g/day as the primary oral antihyperglycemic agent, 6 patients were treated with sulfonylureas and 35 patients were treated with insulin. All patients included in the study were evaluated after 6 months and 40 (80.0 %) were evaluated after 12 months of Dulaglutide 1.5 mg treatment, respectively. Baseline characteristics of patients included in this analysis are presented in table I.

Table I. Baseline characteristics.

Variables	N=50
Age, years	65.0 (60.0; 67.0)
Men, n (%)	28 (56.0%)
Diabetes duration, years	12.0±7.3
Arterial hypertension, n (%)	40 (80.0%)
Atherosclerotic cardiovascular disease, n (%)	27 (54.0%)
Diabetic peripheral polyneuropathy, n (%)	23 (46.0%)
Diabetic retinopathy, n (%)	16 (32.0%)
Diabetic chronic kidney disease, n (%)	12 (24.0%)
Type 2 diabetes treatment:	
Metformin, n (%)	49 (98.0%)
Sulfonylureas, n (%)	6 (12.0%)
Insulin therapy, n (%)	35 (70.0%)

Glycemic control

We found a statistically significant reduction in HbA1c and fasting glycemia at 6 months and 12 months after Dulaglutide treatment initiation, respectively (Table II, Figure 1). HbA1c significantly decreased by −1.3 (−2.5; −0.67) % after the first 6 months and by −2.0 (−2.9; −1.1) % after 12 months of treatment. Also, fasting glycemia decreased with −56.0 (−78.0; −0.16) mg/dl after first 6 months and −55.5 (−85.0; −14.0) mg/dl after 12 months of treatment. There were significantly more patients presenting with optimal glycemic control (HbA1c<7%) after 6 months (n=14 [28.0 %]; P<0.001) and after 12 months (n=14 [35.0 %]; p<0.001) of Dulaglutide treatment, respectively, compared to baseline (n=0).

Weight control

According to BMI at baseline, 39 patients, representing 78% of the study population, were diagnosed with obesity at baseline. Of these, 20 (40.0%) had obesity grade I, 12 (24.0%) obesity grade II and 7 (14.0%) obesity grade III.

When analyzing the effect that Dulaglutide had on weight control, we found statistically significant reductions after 6 months and 12 months of Dulaglutide treatment (Table II, Figure 2). Bodyweight significantly decreased by −2.0 (−5.0; 0.0) kg after first 6 months and −3.5 (−8.0; 0.0) kg after 12 months of Dulaglutide treatment. Similarly, BMI significantly decreased by −0.7 (−1.8; 0.0) kg/m^2 after 6 months and by −1.2 (−2.9; 0.0) kg/m^2 after 12 months of Dulaglutide treatment.

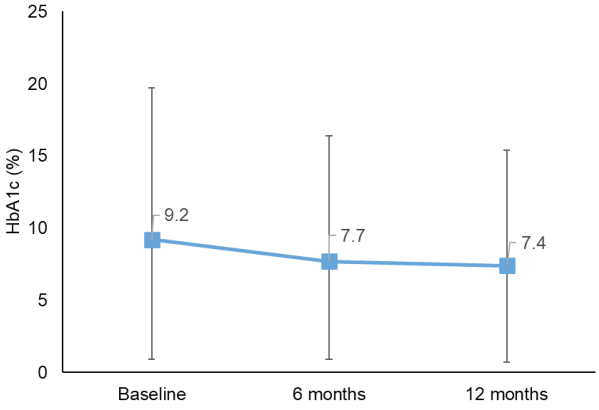

Figure 1. Median glycated hemoglobin (Q1; Q3) after Dulaglutide treatment initiation.

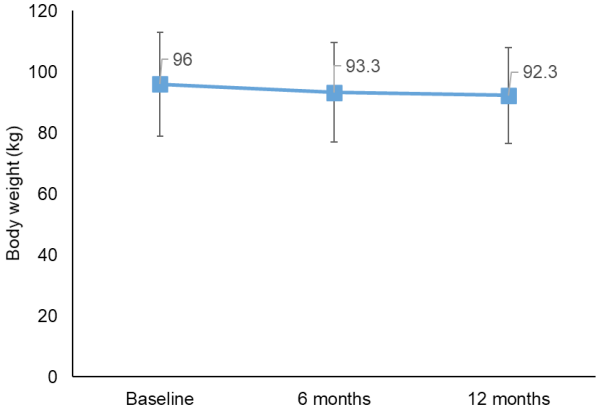

Figure 2. Changes in bodyweight (±standard deviation) after Dulaglutide treatment initiation.

Table II. Parameters at baseline,at 6 months and 12 months after Dulaglutide treatment initiation.

	Baseline (n=50)	After 6 months (n=50)	After 12 months (n=40)	p-value
Glycated hemoglobin (%)	9.2 (8.3; 10.5)	7.7 (6.8; 8.7)	7.4 (6.7; 8.0)	<0.001* <0.001#
Fasting glycemia (mg/dl)	182.0 (147.5; 200.0)	135.5 (123.0; 160.0)	137.0 (124.0; 150.0)	<0.001* <0.001#
Bodyweight (kg)	96.0±17.0	93.3±16.4	92.3±15.7	<0.001* 0.001#
Body mass index (kg/m^2)	33.9±5.4	32.9±5.1	32.1±5.0	0.002* 0.001#
Total daily insulin dose (IU) (n=35)	63.9±29.4	53.1±21.9	51.6±24.5	0.002* 0.013#
Insulin dose per kg bodyweight (IU/kg) (n=35)	0.7 (0.4; 0.9)	0.5 (0.3; 0.7)	0.5 (0.3; 0.7)	0.008* 0.102#

*p-value for comparison 6 months vs. baseline; #p-value for comparison 12 months vs. baseline.

Insulin dose

Total insulin dose decreased significantly by −4.0 (−16.0; 0.0) UI at 6 months (n=35) and by −2.0 (−20.0; 0.5) UI at 12 months (n=27) compared to baseline. Also, the insulin dose per bodyweight decreased both at 6 months and 12 months after Dulaglutide initiation, but the statistical significance was reached only at 6 months (Table II). The total insulin dose reduction was −4.0 (−14.0; 0.0) IU at 6 months and−2.0 (−20.0; 0.5) at 12 months. The insulin dose reduction per bodyweight was −0.03 (−0.14; 0.02) IU/kg at 6 months and −0.03 (−0.17; 0.06) IU/kg at 12 months.

None of the participants included in this analysis reported serious adverse events associated with Dulaglutide treatment.

Discussion

Our retrospective observational study evaluated the effects of Dulaglutide 1.5 mg on glycemic and weight control in type 2 diabetes patients inadequately controlled by antihyperglycemic treatment in real-world clinical practice. We found a significant improvement in glycemic control and bodyweight reduction at 6 months and 12 months after Dulaglutide treatment initiation. This is the first real-world study in Romanian population to report results of Dulaglutide treatment.

We report significantly lower levels of HbA1c at 6 months and 12 months compared to baseline.

A recent efficacy analysis of the studies from the Dulaglutide clinical program (AWARD-1 to AWARD-6 and AWARD-8 clinical trials) in patients with type 2 diabetes showed a significant reduction in HbA1c at 6 months from baseline in both men (−1.26%) and women (−1.33%), and among diabetes duration subgroups. In this pooled analysis, patients presenting with HbA1c higher than 8.5% (−1.86%) at baseline had a greater reduction at 6 months than their peers with HbA1c <8.5 % (−1.02 %) [7]. In the cardiovascular outcome clinical trial REWIND, 9901 participants from 24 countries were randomized either on Dulaglutide or placebo. In this trial, HbA1c decreased by −0.61 % in patients treated with Dulaglutide over a mean follow-up of 5.4 years [8]. A similar positive effect on HbA1c was reported in real-world data. A recent literature review investigating the real-world effectiveness of Dulaglutide reported a 0.5–2.2% reduction from baseline in HbA1c after 3 to 24 months across a number of 20 studies [19]. Two recent retrospective studies found a reduction of −1.13% [20] and −0.97% [23] in HbA1c after 6 months of Dulaglutide initiation. Different changes in HbA1c reported in these studies could be related to previous antihyperglycemic regimens associated with Dulaglutide, duration of diabetes, duration of follow-up, and factors such as lower treatment compliance and adherence. However, our findings regarding HbA1c reduction after Dulaglutide initiation are consistent with data reported in both randomized clinical trials and patient studies.

In our study population, 28% of the patients achieved optimal glycemic control (HbA1c <7%) at 6 months and 35% of the patients at 12 months. In comparison, a larger proportion of patients from AWARD-1 (78%) [9], AWARD-5 (61%) [13], AWARD-6 (68%) [14], AWARD-8 (55.3%) [15] clinical trials reached an HbA1c level of <7.0% at 6 months. Similarly, when evaluated at 12 months, more patients from AWARD-1 (57%) [9], AWARD-5 (58%) [13], AWARD-6 (53.2%) [14] and AWARD-11 (58.6%) [17] presented with optimal glycemic control. Data from real clinical practice indicate that 23.4–55.7% of patients achieved HbA1c below 7.0% during a follow-up period ranging from 3 to 24 months [19]. These findings reported from a clinical real-world setting are closer to those we found in our retrospective study. However, the disparity between data reported in randomized clinical trials and results from practice might be explained by patients' characteristics and factors influencing the real-world settings such as compliance and adherence to antihyperglycemic treatment.

Bodyweight reduction is an important and desired effect of Dulaglutide, particularly in patients with overweight and obesity. We found a significant bodyweight reduction after 6 months and 12 months of Dulaglutide treatment, resulting in a significant BMI reduction. In the pooled analysis of clinical trials from the Dulaglutide development program AWARD, Gallwitz et al. reported that weight loss was similar among subgroups of HbA1c and diabetes duration, while women presented greater changes in bodyweight compared to men [7], ranging between −0.24 kg in AWARD-8 [15] and −2.9 kg in AWARD-6 clinical trial [14]. In the AWARD-11 trial, patients treated with Dulaglutide 1.5 mg presented with −3.5 kg after 12 months [17]. The bodyweight reduction is maintained during the Dulaglutide therapy and not only during the first 6 or 12 months of therapy. For example, patients from the REWIND trial had −1.46 kg at the end of the follow-up period of 5.4 years [8]. Similar positive results are reported outside of clinical trials settings. In real-world settings, bodyweight was reduced by 2.1 to 6.4 kg across a number of 15 real-world studies including patients treated with Dulaglutide followed over periods ranging from 3 to 12 months [19]. Also, two retrospective clinical studies reported a significant reduction of −2.9 kg [20] and −2.05 kg [23] in bodyweight after 6 months of Dulaglutide treatment. Different outcomes in terms of bodyweight changes could be explained by the different previous treatments used by patients when Dulaglutide was initiated. The mechanisms involved in the decrease of bodyweight with Dulaglutide and other GLP-1 receptor agonists are a delay in gastric emptying, reduced appetite, increased satiety, and thus reduced food consumption and caloric intake [5].

Another finding of the present analysis is the reduction in total insulin requirement after Dulaglutide

treatment initiation. A percentage of 70% of patients included in the study were treated with insulin. We found lower insulin dose per bodyweight at both 6 months and 12 months intervals, but the statistical significance was reached only at 6 months. When evaluating the total insulin dose, we observed a significant reduction at 6 and 12 months compared to baseline. Data from the AWARD-9 clinical trial indicate that the increase from baseline in mean basal insulin dose was significantly smaller with Dulaglutide added to basal insulin compared to basal insulin alone [10]. A retrospective study investigating the effect of Dulaglutide as an add-on to insulin therapy in a real-world clinical setting reported a significant reduction in total daily insulin dose of −11.67 IU after 6 months [23]. It should be taken into account that 72% and 65% of patients did not achieve an optimal glycemic control at 6 months and 12 months, respectively; thus, a reduction in insulin dose was less likely to occur even after Dulaglutide initiation.

This study has several limitations. The constraints consist mainly of the small sample size and the inhomogeneity of the antihyperglycemic treatment administered to patients before and after the Dulaglutide 1.5 mg therapy initiation. During the follow-up period, one patient was newly initiated on Dapagliflozin, one patient was switched from Gliclazide to Dapagliflozin and two patients were newly initiated on insulin therapy. Due to the SARS-CoV2 pandemic and traffic restrictions applied to reduce the incidence of cases, some follow-up visits were conducted over the phone. Thus, bodyweight and fasting glycemia were verbally communicated by the patient to the attending physician. As research directions for the future, we would propose a study on a larger population sample with a broader homogeneity in treatment regimens.

Conclusions

Our real-world clinical data demonstrate that once-weekly Dulaglutide 1.5 mg significantly improved glycemic and bodyweight control at 6 and 12 months after treatment initiation in patients with type 2 diabetes that was inadequately controlled by previous treatment.

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