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Real-life experience with Dulaglutide: Analysis of clinical effectiveness to 24 months

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ABSTRACT

Objective: Dulaglutide is an agonist of "glucagon-like peptide type 1" receptors (arGLP1). The clinical efficacy of this molecule is based on reductions in glycosylated hemoglobin (HbA1c) and weight, data shown in the pivotal AWARD studies.

Methods: We propose a retrospective and multicenter study that allows evaluating the effectiveness of dulaglutide at 24 months after treatment began, under conditions of usual clinical practice, and comparing the results obtained with those that are reflected in the controlled trials.

Results: The results show a reduction in the HbA1c levels −1.4% at 6 M and this reduction were maintained throughout 12 M and 24 M ($p < 0.001$). Plasma glucose showed significant reductions around −30 mg / dL at 6 months ($p < 0.001$) that remained until the end of the follow-up at 12 and 24 M, respectively. The weight decreased significantly at 6 M ($p < 0.001$) but continued decreasing at 12 and 24 M, showing statistically significant differences (p: 0.001).

Conclusions: Our results are similar to those obtained in pivotal clinical trials and confirm these benefits in real life.

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1. Introduction

Dulaglutide is an agonist of "glucagon-like peptide type 1″ receptors (arGLP1) [1,2]. The "glucagon-like peptide type 1″ (GLP1) is an incretin hormone secreted by the "L" cells of the ileum that, through the pancreas, stimulates the secretion of insulin and suppresses the secretion of glucagon in relation to the intake. In addition, it delays gastric emptying and causes satiety due to its action in the hypothalamus [3,4] Dulaglutide was marketed in Spain in December 2015 under two forms of presentation: 0.75 mg and 1.5 mg, with a formulation that allows weekly administration, which favors a greater therapeutic adherence, compared to other molecules of daily administration [5].

The clinical efficacy of this molecule is based on reductions in glycosylated hemoglobin (HbA1c), weight with a high degree of security, data shown in the pivotal AWARD studies (Assessment of the Weekly Administration of LY2189265 in Diabetes) [6]. These studies had lasted between 6 months (M) and 12 M, except for the AWARD-5 [7] that lasted up to 24 M. The results showed a reduction in HbA1c from −0.70 to −1.48% and from −0.55 to −1.42%, for the dose of 1.5 mg and 0.75 mg, respectively. These results show a similar or greater efficacy compared to insulin and are more effective in reducing weight in patients undergoing treatment than those treated with insulin [6,8].

In AWARD-5 the efficacy of the two doses of dulaglutide versus sitagliptin was compared. At 24 M, reductions in HbA1c (mean and standard deviation [SD]) were −0.99 (0.06)%, −0.71 (0.07)% and −0.32 (0.06)% for dulaglutide 1.5 mg, dulaglutide 0.75 mg and sitagliptin, respectively ([$p < 0.001$] for both doses of dulaglutide versus sitagliptin). Weight reductions were greater with dulaglutide 1.5 mg ($p < 0.001$) and similar with 0.75 mg compared with sitagliptin (−2.88 [0.25], −2.39 [0.26] and −1.75 [0.25] kg, respectively). The most frequent adverse effects reported were: nausea, vomiting and diarrhea, ranging from 7% to 21% of patients. The incidence of treatment interruptions due to adverse reactions with dulaglutide was 5.1% for the presentation of 0.75 mg and 8.4% for the presentation of 1.5 mg, nausea was the most frequent cause, reported in the first 6 weeks [7].

There are few studies in real life with dulaglutide, and they are related to therapeutic compliance, most of these studies are of short duration (6 M–12 M) [5,9–12] or treat cost-effectiveness[13,14] We propose a retrospective and multicenter study that allows evaluating the effectiveness of dulaglutide (dose 1.5 mg) at 24 months after the start of treatment, under conditions of usual clinical practice, and comparing the results obtained with those that are reflected in the controlled trials.

2. Material and methods

We designed an observational, retrospective, multicenter study conducted in patients with type 2 diabetes mellitus (DM2) who had received treatment with dulaglutide for at least 24 M. The digital clinical histories of four health centers belonging to three health areas were analyzed: an Internal Medicine (MI) consultation of the San Carlos Clinical Hospital of Madrid; an MI consultation of the University Hospital of Salamanca and in two districts of the Huelva, Huelva-Costa and Condado-Campiña areas. We included patients older than 18 years with a diagnosis of DM2, treated with dulaglutide, weekly dose of 1.5 mg, during a period of at least 24 M between 2015 and 2018, according to the electronic prescribing and review of medical records programs. Patients who did not measure the variables were not included in the study.

The data were recorded: age, sex and antidiabetic treatment at the beginning. To measure the efficacy of the drug, the evolution of the following parameters was analyzed: basal plasma glucose, HbA1c and baseline weight at 6 M, 12 M and 24 M after prescription. The reasons for safety and tolerability were collected globally, as well as data on the causes that led to the withdrawal of the drug.

Statistical analysis: means and SD were calculated for quantitative variables and percentages for qualitative variables. The analysis of the evolution of the response variables at 6, 12 and 24 M was performed using the ANOVA for a repeated measures factor (time). The Greenhouse-Geisser adjustment was made when the sphericity assumption was not met. The Sidak test was used for multiple comparisons between times. The level of significance used was 0.05. The analyzes had been carried out with the statistical program IBM-SPSS version 25.

The study followed the ethical standards of each center that participated in the study

3. Results

Of the total of 207 patients with an active prescription at the beginning of the study, 28 patients were dropped because they did not meet selection criteria due to lack of any of the study variables. Therefore, the initial number of patients was 179 at the start of the study, although the number of patients who reached 24 M of treatment was 163 patients. During the follow-up period, there were 16 losses due to the following causes: 7 due to changes in the health area, 6 due to gastrointestinal side effects, 2 due to the desire for gestation, 1 due to unspecified causes.

The mean age of the subjects included in the study was 57.97 (10.01) and this corresponded to women (55.12%). More than 80% had received previous antidiabetic treatment, with metformin and insulin being the most frequent. The baseline values from which it started for were: plasma glucose: 178.57 (±65.79) mg/dL, HbA1c: 8.42 (±1.83)%, weight: 99.87 (±20.64) Kg. Table 1 shows the baseline characteristics of the patients at the start of treatment with dulaglutide.

HbA1c was significantly reduced by −1.4% at 6 M and this reduction was maintained throughout 12 M and 24 M ($p < 0.001$). Similarly, plasma glucose showed significant reductions around −30 mg/dL at 6 months ($p < 0.001$) that remained until the end of the follow-up at 12 and 24 M, respectively. The results of glycemic control and HbA1c should be attributed to treatment with dulaglutide and to

Table 1 – Patient demographic and clinical characteristics initiating treatment with dulaglutide. Values in mean and standard deviation (SD). DPP-4 Inhibitors: dipeptidyl peptidase-4 inhibitors; SGLT2 Inhibitors: sodium-glucose cotransporter 2 inhibitors. GF rate: glomerular filtrate rate.

Patients (n)	163
Age (years) (SD)	57.94 (±10.01)
Male/Female (%)	44.8/55.2
Creatinine (mg/dl) (SD)	0.83 (±0.24)
GF rate (mL/min/1.73 m^2) (SD)	105.05 (±35.49)
Initiating treatment, n (%)	
Metformin	139 (85.3%)
Sulfonylureas	34 (20.9%)
DPP-4 Inhibitors	55 (33.7%)
SGLT2 Inhibitors	49 (30.1%)
Insulin	85 (52.14%)
Antihyperglycemic drugs (without insulin), n (%)	
0	8 (4.90)
1	66 (40.49)
2	61 (37.42)
≥3	28 (17.17)
Glucose (mg/dl) (SD)	178.57 (±65.79)
HbA1c (%) (SD)	8.42 (±1.83)
Weight (kg) (SD)	99.87 (±20.64)

the adjustment of the other antidiabetic treatments that patients received, mots of them insulin, metformin. The weight decreased significantly at 6 M ($p < 0.001$) but continued decreasing at 12 and 24 M, showing statistically significant differences (p: 0.001). Table 2. Fig. 1.

4. Discussion

This study evaluates the effects of dulaglutide in HbA1c, glycemia and weight in patients with DM2 at 24 M under conditions of usual clinical practice, this fact generates limitations, given that there are some selection biases of patients. As mentioned in material and methods, the patients come from electronic prescribing and review of medical records programs, this fact makes facilitate to lose some data of patients that were not correctly registered. Although the patients collected present all the data required to assess the efficacy of the drug in real life in patients who are not subject to any other study, which allows comparing the results with similar studies. The results obtained show the efficacy in reduction of HbA1c, weight and glycemia in the periods of 6 M, 12 M and 24 M. These results are difficult to compare with other studies due to the time of evolution, shorter duration, or its design with the main objective being not clinical efficacy. Some of the studies carried out in real life, such as that of Mody et al.[11], show average decreases in HbA1c of −0.9% (95% CI, −1.08 to −0.73) at 6 M of treatment in 308 patients analyzed. The mean baseline HbA1c was 8.49 (1.70)%, which is similar to our study. However, our decrease in that same time was higher (−1.4%). In addition, in their study, the dropout rate is 37% (115 patients of the total), greater than ours (9%). In another study by the same author, Mody et al.[15], during 12 M, patients treated with dulaglutide experienced a greater statistically significant HbA1c reduction compared with liraglutide: −0.98% vs −0.77% based on very similar mean values: 8.78% for dulaglutide and 8.73% for liraglutide.

In another previous retrospective study of Unni et al,[12]. they compared cohorts of patients on weekly exenatide, dulaglutide and albiglutide. The cohort of dulaglutide starts from an initial mean HbA1c value: 8.5 (1.5)% presenting an average decrease in the 6 M: −0.5 (1.5)% ($p < 0.001$). In relation to the weight, they start from a mean value of 108.8 (25.7) Kg achieving a decrease of −2.7 (5.7) Kg ($p = 0.001$) at 6 M, with dulaglutide being the greatest reduction gotten.

In our setting, we found smaller studies in the number of patients and months of follow-up, in order to demonstrate

Table 2 – Parameters evolution after dulaglutide initiation: glucose, HbA1c and weight at initiating, 6 months (M), 12 M and 24 M.

	Basal		6 months		12 months		24 months		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Glucose (mg/dl)	178.0	65.44	144.0	51.08	134.97	43.36	141.98	50.78	<0.001
HbA1c (%)	8.57	1.89	7.15	1.10	7.07	1.14	7.13	1.19	<0.001
Weight (kg)	99.57	19.22	95.15	19.13	93.53	18.92	92.30	18.51	<0.001

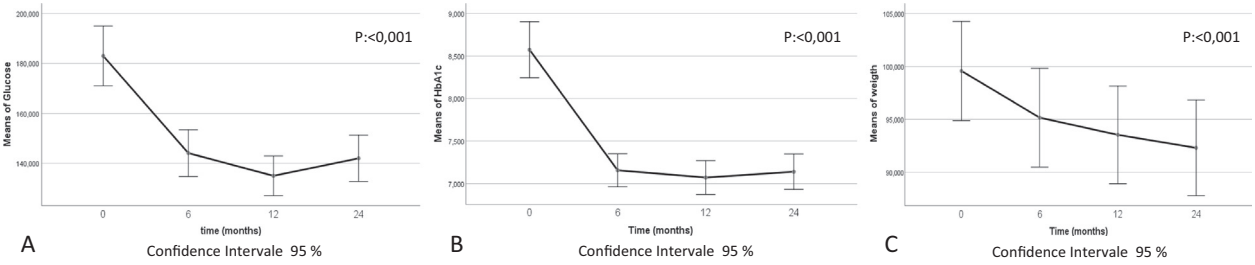

Fig. 1 – Evolution during 24 months of basal glycemia (A), glycosylated hemoglobin - HbA1c (B), weight (C).

the effectiveness of dulaglutide, although they are limited [16,17]. Our group presented a 12 M study with 135 patients with results similar to those shown in this article [18].

Regarding the results of our study, basal glucose experienced a significant decrease of about −35 mg/dL, maintaining a slight decrease, although not significant, both at 12 M and 24 M. On the other hand, HbA1c had ~~a~~ similar behavior, decreasing significantly at 6 M, persisting at 12 and 24 M (Fig. 1A and 1B).

However, the most striking decrease was in the weight (Fig. 1C), because at 6 M from the start of the treatment a significant reduction was achieved. But, in addition, the weight continued to decrease at 12 and 24 months, reaching significant reductions of −7 kg on average to 24 M of treatment. The decreases in the weight parameter obtained in our study are greater than those presented in the literature[2,3,8–14]. A possible explanation is found in the publication by Wasir et al [19] According to the authors, the effectiveness in reducing weight with dulaglutide would be a function of the basal weight values, a greater baseline mean weight of the population, greater reduction, and our cohort of patients will be higher weights than others that have been published.

The strongest strength of our study is that the results obtained with dulaglutide at 24 M in the pivotal controlled clinical trial, AWARD 5 [7], are confirmed for the first time with real-life data and with large sample size.

However, it is necessary to highlight some limitations of the present study: Due to its retrospective design, there are information from certain patients that was not recorded in the digital medical records, that does not allow us to evaluate other parameters within the evolution as they are the data of the intermediate controls, or the changes of other medications, in addition it is possible that not all the doctors reflected adverse effects of suitable form or withdrawal of drugs. That is why we focus the study on effectiveness criteria discarded from patients with incomplete data.

5. Conclusions

Dulaglutide is an arGLP1 of weekly administration that, in the cohort of patients with DM2 studied, demonstrates effectiveness in the reduction of basal plasma glucose, HbA1c and weight reaching statistical significance from 6 M and that remains at 24 M. The decrease in the weight variable is noteworthy. Our results are similar to those obtained in pivotal clinical trials and confirm these benefits in real life.

6. Transparency

The authors declare not have received funding for the study design, data collection and interpretation, manuscript preparation and the decision to publish this paper.

Declaration of Competing Interest

All authors declare no conflicts of interest

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