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ORIGINAL ARTICLE

Effectivity and security of vildagliptin as additional treatment for Type 2 diabetes mellitus in real-life conditions in Mexico. EDGE Study subanalysis

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Abstract

Background: *The multinational EDGE (Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin) study assessed the effectiveness and tolerability of vildagliptin versus other oral antihyperglycemic drugs (OAD) when added to monotherapy in patients in the real-world setting.* **Methods:** *Prospective, real-world observational study. The primary endpoint (PEP) was the proportion of patients achieving a reduction in HbA1c > 0.3% without peripheral edema, hypoglycemia, discontinuation, due to gastrointestinal event, or weight gain > 5%. The secondary endpoint (SEP) was the proportion of patient achieving HbA1c < 7% (at month 12), without proven hypoglycemia or weight gain (≥ 3%).* **Results:** *Of the 3,523 patients enrolled in Mexico, 2,847 were in the vildagliptin and 676 in the comparator cohort. The PEP was reached in 61.8 and 53.2% in the vildagliptin and comparator cohorts, respectively. The unadjusted odds ratio was 1.42 (95% CI: 1.19-1.68) in favor of vildagliptin. A similar advantage for vildagliptin-based therapies was seen for the SEP. The percentage was lower in the vildagliptin (n = 145; 5.0%) than in the comparator group (n = 95; 14.0%).* **Conclusion:** *Vildagliptin, added to a first-line OAD monotherapy, allows patients to reach target HbA1c without experiencing significant adverse events.* (Gac Med Mex. 2016;152:411-7)

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Introduction

As world population grows, there is an epidemic increase in non-transmittable diseases, out of which type 2 diabetes mellitus (DM2) is not an exception[1]. Currently, DM2 is the second most common cause of death in Mexico[2].

DM2 is a progressive disease and combined therapies are usually required to maintain good glycemic control and to prevent long-term complications[3]. Sulphonylureas (SU) are among the most widely used oral antihyperglycemic drugs (OADs), but usually they are associated with adverse events (AEs) such as hypoglycemia and weight gain[4]. Recent treatment guidelines suggest that effectiveness, tolerability, cost and patient preference should be considered when selecting an OAD. In any risk/benefit assessment for an individual patient, it is highly important to consider an OAD that improves glycemic control without increasing

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the risk for hypoglycemia and weight gain[5-7]. Vildagliptin is a potent dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control by increasing the response to glucose in alpha and beta cells, and has demonstrated a marked reduction in the risk for hypoglycemia in comparison with SU[8].

Treatment guidelines data usually stem from randomized, controlled clinical trials, which provide very useful information under controlled conditions, but limited data on a drug's effectiveness and tolerability under usual practice clinical conditions, owing to their strict inclusion and exclusion criteria. In contrast, in studies under *real-life* conditions, usually described as pragmatic studies, the benefits and risks of therapeutic agents are assessed in uncontrolled conditions where all possible factors affecting diabetes control can be considered[9-11].

The EDGE trial was an international study conducted under *real-life* conditions that assessed the effectiveness and tolerability of adding vildagliptin to other OAD in comparison with the combination of two OADs in patients with DM2 requiring treatment intensification to improve glycemic control.

In the EDGE study, Mexican investigators were at fourth place with regard to patients included in the study after India, Germany and Portugal, and for this reason, the authors of this article carried out a post hoc analysis in the population of Mexican patients.

Materials and methods

The EDGE trial was designed as a 1-year long prospective cohort study that included 45,868 patients from 2,957 centers in 27 countries in Europe, Central and South America, Asia and the Middle East. In Mexico, 3,821 patients were enrolled in 264 centers. To be eligible for the study, the patients had to be adults older than 18 years with DM2 and poor glycemic control with OAD monotherapy, either with SU, metformin, thiazolidinedione (TZD), meglitinide (glinide) or an α-glycosidase inhibitor (AGI), and in whom a second OAD was considered to be required to reach the glycemic goals. Exclusion criteria were: having started treatment with a DPP-4 inhibitor other than vildagliptin; having started treatment with any other incretin mimetic or analogue; use of 3 or more OADs at study start; use of insulin; change of OAD or OAD class at study start and prior to adding a new OAD; hypersensitivity to the study drug or to a drug of the same chemical class. Two comparative cohorts were considered for the study, with one comprised by the patients who received vildagliptin plus other OAD (vildagliptin/OAD) and the comparison cohort, where all other OAD combinations prescribed to the study population were included. Additional details on study design, assessments and data collection have been published elsewhere[12].

Effectiveness primary and secondary criteria

Primary effectiveness criterion was defined as the proportion of patients with response to the treatment (HbA1c reduction > 0.3% from baseline assessment to month 12) with no evidence of tolerability problems (peripheral edema, confirmed hypoglycemic event, study discontinuation due to GI event, or weight gain > 5%)[13]. Patients who could not be categorized as success or failure (e.g., HbA1c or body weight data missing at 12 months) were considered non-evaluable. Non-evaluable patients data were considered as failures in the disparity ratio (odds ratio, OR) calculation for success at reaching the effectiveness primary criterion. The primary effectiveness criterion analysis uses the per-protocol (PP) population. Data were censored when patients changed the assigned treatment. The secondary effectiveness criterion was the proportion of patients achieving HbA1c < 7% (at month 12) without confirmed hypoglycemia or weight gain (≥ 3%).

An AE was defined as the appearance or worsening of any sign, symptom or medical condition occurring after initiating the assigned OAD, even when the event was considered to be unrelated with exposure to the OAD. Medical conditions or diseases that were present prior to initiating the OADs were regarded as AEs only if they worsened after the start of the assigned OAD. Abnormal laboratory values or medical exams results were regarded as AEs only if they induced signs or symptoms that were deemed clinically significant or required treatment. Hypoglycemia was defined as symptoms consistent with hypoglycemia that resolved promptly after oral carbohydrate administration (including mild and severe events).

Primary and secondary criteria analysis

This post hoc analysis provides mainly descriptive statistics. Inferential analysis was used for primary and secondary effectiveness criteria. The probability of success was analyzed using a binary logistic regression model to calculate the odds ratio with 95% confidence intervals (CI). The odds ratio expresses the

Table 1. Baseline assessment patient demographic and clinical characteristics (intention-to-treat population)

	Vildagliptin/OAD cohort n = 2847	Comparison cohort n = 676	Total n = 3523
Age (years) mean (SD)	55.1 (12.46)	57.0 (11.69)	55.5 (12.34)
Gender			
Males n (%)	1358 (47.7)	306 (45.3)	1664 (47.2)
BMI (kg/m^2) mean (SD)	29.5 (5.27)	29.2 (5.04)	29.4 (5.23)
HbA1c (%) baseline mean (SD)	8.6 (1.72)	8.5 (1.65)	8.6 (1.71)
DM2 duration (years) mean (SD)	5.5 (6.04)	6.4 (5.64)	5.7 (5.98)

BMI: body mass index: OAD: oral antidiabetic drug; SD: standard deviation.

probability of success in favor of the vildagliptine or the comparative cohort, relative to the likelihood of success in favor of the comparison OADs. In this post hoc analysis, unadjusted odds ratio is provided. HbA1c change from baseline at the end of the study was adjusted for baseline medication using an ANCOVA model.

Role of the study funding source

The study sponsor and the steering committee had equal roles in the determination of the study design, preparation of the protocol and data interpretation. The sponsor was responsible for writing the protocol and for data collection and analysis. All the authors had final responsibility for the data, contents, and the decision to submit the manuscript for publication.

The EDGE study protocol was approved by local independent review committees and ethics committees.

Results

Patient populations and baseline characteristics

The population included in Mexico's centers was comprised by 3,821 patients who documented their informed consent, out of which 298 patients (229 in the vildagliptin cohort and 69 in the comparator cohort) were excluded due to inadequate source documents or problems in the quality and accuracy of data entry. The intention-to-treat (ITT) population, which was used for baseline demographics and safety analysis, was comprised by 2,847 subjects who received vildaglipin therapy added to the initially prescribed OAD (vildagliptin/OAD cohort) and 676 patients who received any other AOD added to the initially prescribed OAD (comparison cohort).

The PP population was a subset of the ITT population, and it was used for safety criteria analysis. The PP population included 3,464 patients for the effectiveness primary criterion (2,794 patients in the vildagliptin/OAD cohort and 670 in the comparator cohort) and 2,868 for the effectiveness secondary criterion (2,300 for vildagliptin/OAD, 568 for the comparator cohort).

Average age was 55.5 years (standard deviation [SD]: 12.3), body mass index was 29.4 kg/m^2 and DM2 average duration was 5.7 years (SD: 5.9). HbA1c average was similar in the vildagliptin and comparison groups, with 8.6% (SD: 1.7) and 8.5% (SD: 1.6), respectively (Table 1).

Table 2 reports the assigned therapies in the ITT population for each cohort according to the researcher physician's prescription. Of all patients included in the study, the majority were initially prescribed vildagliptin/metformin (64.49%); vildagliptin/SU (11.56%) or SU/metformin (11.25%). When the assigned combinations were grouped, the vildagliptin/OAD cohort was comprised by 2,845 patients (80.8%), who received either metformin/vildagliptin, SU/vildagliptin, TZD/vildagliptin, (AGI)/vildagliptin or meglitinide/vildagliptin. The comparative treatments cohort was comprised by 675 patients (19.2%) who received metformin/SU, metformin/TZD, SU/TZD, meglitinide/metformin, AGI/metformin, AGI/SU, meglitinide/TZD, AGI/TZD or meglitinide/SU.

Primary and secondary effectiveness criteria

Figure 1 reports the primary and secondary effectiveness criteria analyses. Among the vildagliptin-treated

Table 2. Assigned treatment (intention-to-treat population)

Vildagliptin/OAD cohort n = 2845		Comparison cohort n = 675	
Treatments	**n (%)**	**Treatments**	**n (%)**
Metformin/vildagliptin	2270 (79.8)	Metformin/SU	396 (58.6)
SU/vildagliptin	407 (14.3)	Metformin/TZD	140 (20.7)
TZD/vildagliptin	129 (4.5)	SU/TZD	81 (12.0)
AGI/vildagliptin	24 (0.8)	Meglitinide/metformin	28 (4.1)
Meglitinide/vildagliptin	15 (0.5)	AGI/metformin	13 (1.9)
		Meglitinide/TZD	4 (0.5)
		AGI/TZD	3 (0.4)
		Meglitinide/SU	2 (0.3)
		AGI/SU	8 (1.1)

AGI: alpha-glycosidase inhibitor; OAD: oral antidiabetic drug; SU: sulphonylurea; TZD: thiazolidinedione.

patients, 61.8% met the primary effectiveness criterion in comparison with 53.2% of those treated with comparators. A similar advantage for vildagliptin-based therapies was observed in the secondary effectiveness criterion.

Figure 2 depicts HbA1c changes in both cohorts, with higher reduction ($p < 0.001$) in HbA1c changes at 12 months in the vildagliptin-treated patients, –1.73% (95% CI: –1.77, –1.70%), than in comparator-treated patients, –1.54% (95% CI: –1.62, –1.46%) (analysis not previously specified in the protocol).

Safety analysis

The percentage of patients reporting AEs at any primary system organ class (SOC, according to MedDRA classification) was lower in the vilgagliptin/OAD cohort (n = 145, 5.0%) than in the comparison cohort (n = 95, 14.0%). Table 3 summarizes the AEs occurring during the study, listed by SOC.

Hepatobiliary disorders were reported in 3 vildagliptin/OAD-cohort patients (0.1%), in comparison with none in the comparison cohort. Hypoglycemia was reported by 4 patients (0.14%) in the vildagliptin/OAD and 9 patients (1.3%) in the comparison cohort, almost 10-fold higher than in the vildagliptin/OAD cohort.

Serious adverse events were reported in 10 patients (0.35%) of the vildagliptin/OAD cohort and 3 patients (0.45%) in the comparison cohort (data not shown).

Discussion

There is a scarcity of data from large studies conducted under *real-life* conditions complementing data from clinical trials about drug effectiveness and safety. The EDGE study results confirm the existence of clinical inertia, in spite of recent guidelines emphasizing on opportune glucose-reduction treatment intensification. In both cohorts, HbA1c baseline value was > 8.0%, suggesting that in Mexico's real-world practice patients have poor glycemic control for a considerable period of time before their treatment is intensified. Multiple factors contribute to optimal glycemic control, including access to health services and socio-cultural knowledge.

As in other countries and regions, there is a lack of data from studies in real-life conditions in Mexico. In fact, the only evidence relating the use of vildagliptin in Mexico stems from a randomized, controlled, crossover trial reported by González et al., which has demonstrated the effects of this DPP-4 inhibitor (in pharmacological treatment-naïve diabetic patients) on the control of glucose levels with no effects on insulin levels[14].

In this post hoc analysis, we found that when vildagliptin was added as a second agent, more than half the patients (61.8%) successfully met the primary efficacy criterion, which is comprised by an HbA1c > 0.3% decrease, without tolerability problems. In addition, 44.7% of patients who received vildagliptin

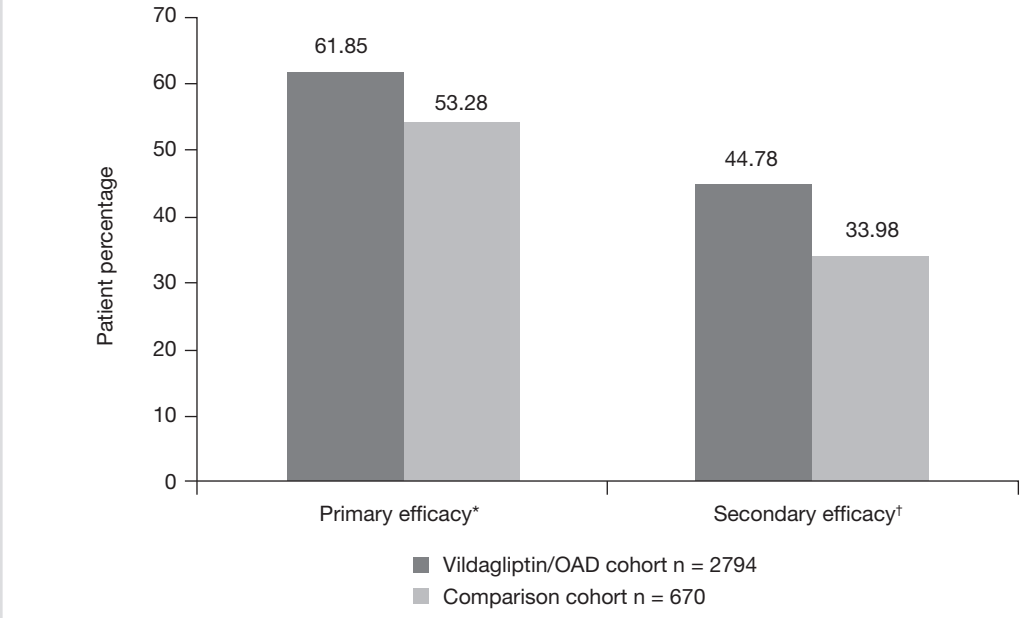

Figure 1. *Proportion of patients who met the primary and secondary effectiveness criteria (per-protocol population).*
**p < 0.001 for unadjusted odds ratio 1.42 (95% CI: 1.19-1.68) in favor of vildagliptin/OAD.*
**p < 0.001 for unadjusted odds ratio 1.57 (95% CI: 1.30-1.90) in favor of vildagliptin/OAD.*
Primary effectiveness criterion: proportion of patients experiencing a HbA1c decrease > 0.3%, without hypoglycemia, weight gain, gastrointestinal side effects or peripheral edema.
Secondary effectiveness criterion: proportion of patients reaching HbA1c levels < 7% by the end of the study, without confirmed hypoglycemic events or weight gain ≥ 3%, and with HbA1c > 7% at baseline measurement.

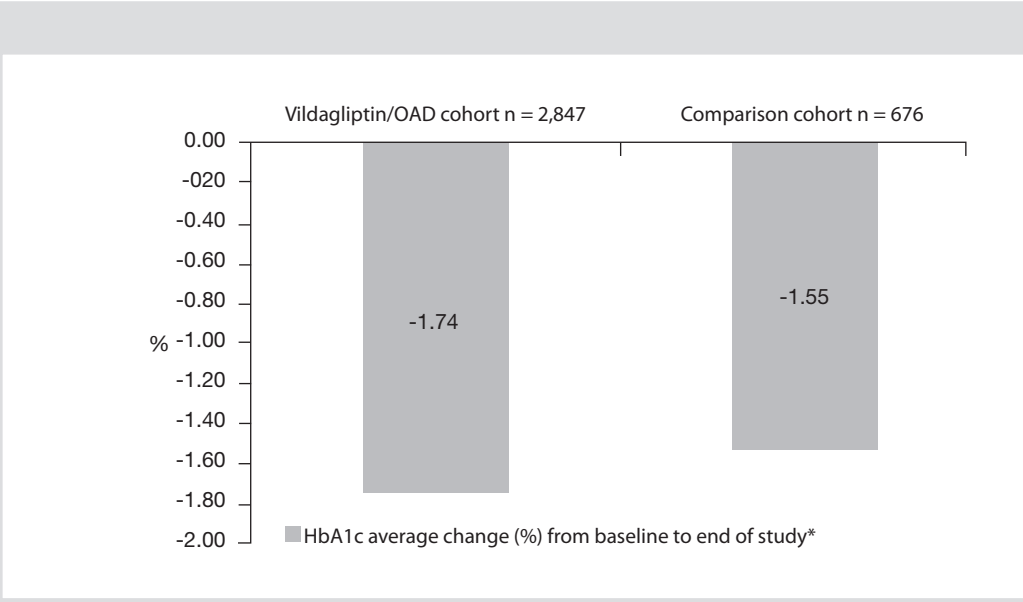

Figure 2. *HbA1c total reduction from baseline.*
**p > 0.001, calculated with an unadjusted ANCOVA method.*
Average HbA1c baseline measurement was 8.6% (SD: 1.72) in the vildagliptin/OAD cohort and 8.5% (SD: 1.65) in the comparison cohort. The difference between cohorts in HbA1c average change was –0.1939 (95% CI: -0.2787, -0.1093).

Table 3. Adverse events (AEs) according to primary system organ class and cohort (intention-to-treat population)

Primary system organ class (SOC)	Vildagliptin/ OAD cohort		Comparison cohort		Total	
	n = 2847		n = 676		n = 3523*	
Any SOC (general)	n = 145	5.09%	n = 95	14.05%	n = 240	6.81%
Blood and lymphatic system disorders	3	0.1	0	0	3	0.08
Cardiac disorders	2	0.07	2	0.29	4	0.11
Ear and labyrinth disorders	1	0.03	0	0	1	0.02
Eye disorders	1	0.03	1	0.14	2	0.05
Gastrointestinal disorders	19	0.66	11	1.62	30	0.85
General disorders and administration site conditions	8	0.28	6	0.88	14	0.39
Hepatobiliary disorders	3	0.1	0	0	3	0.08
Immune system disorders	1	0.03	0	0	1	0.02
Infections and infestations	42	1.47	27	3.99	69	1.95
Injury, poisoning and procedural complications	5	0.17	1	0.14	6	0.17
Metabolism and nutrition disorders	12	0.42	11	1.62	23	0.65
Musculoskeletal and connective tissue disorders	8	0.28	13	1.92	21	0.59
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2	0.07	1	0.14	3	0.08
Nervous system disorders	16	0.56	8	1.18	24	0.68
Pregnancy, puerperium and perinatal conditions	1	0.03	0	0	1	0.02
Psychiatric disorders	3	0.1	2	0.29	5	0.14
Renal and urinary disorders	5	0.17	3	0.44	8	0.22
Reproductive system and breast disorders	1	0.03	1	0.14	2	0.05
Respiratory, thoracic and mediastinal disorders	2	0.07	4	0.59	6	0.17
Skin and subcutaneous tissue disorders	1	0.03	1	0.14	2	0.05
Vascular disorders	9	0.31	3	0.44	12	0.34

*Total comprising also patients without initial double therapy.
EAs were coded according to MedDRA, version 14.0.
Primary SOCs are presented in alphabetical order.
One patient with an AE appearing several times within a cohort is counted only once in the AE category.
One patient with multiple AEs within a SOC is counted only once in the row for the corresponding cohort.
Patients who switched from fixed-dose vildagliptin/metformin to vildagliptin as double therapy complementary to metformin and vice versa were not counted as treatment switch.

reached HbA1c levels < 7% after 12 months of treatment, with no weight gain ≥ 3% or confirmed hypoglycemia.

Consistent with the results of a previous study[15,16], the rate of hypoglycemic events in the vildagliptin group was only 0.13%, thus confirming that vildagliptin safety profile in real-life conditions is favorable. However, total number of hypoglycemia events was low in both cohorts, which might be explained by events' under-reporting.

Main strengths of the EDGE study include its large sample size and the fact of being conducted under *real-life* conditions. However, these attributes might as well be limitations, since patients were recruited both in specialized centers and by doctors working at private practices and who are not used to fill data reports or to be supervised by clinical research associates.

AEs were reported using non-directed questionnaires every time the patient was contacted, which is

the most widely used method to identify AEs for new drugs in clinical practice[17]. However, a systematic review estimated that only 6% of EAs are reported to the national spontaneous report system[18]. These factors might explain the low AE rate observed in the EDGE study.

In spite of these limitations, SAEs appeared to be relatively balanced in both groups, including neoplasms and cardiac SAEs, which actually had a slightly higher prevalence in the comparison group. In the Mexican population, vildagliptin safety data relating the cardiovascular, pancreatic, hepatic and cutaneous systems were similar to those reported in previous randomized controlled vildagliptin clinical trials[19-21]. EGDE study design was open-label, which enabled doctors to select any drug they considered to be appropriate for their patients, just as in *real-life*. This, together with vildagliptin relative novelty at the time the study was conducted, might explain the unbalance observed between the cohort sizes.

The results of this study show evidence that in Mexico, under real-life conditions, adding vildagliptin to another OAD appears to be an efficacious and well-tolerated therapeutic option to improve the treatment in patients with sub-optimal glycemic control on a single OAD. In addition, in this subpopulation from Mexico, the patients who received vildagliptin added to the OAD for 12 months were more likely to experience clinically relevant HbA1c reductions without experiencing relevant tolerability problems such as hypoglycemia or weight gain with regard to the comparison group.

Conflicts of interest

Dr. Fabiola Mariñoes is an employee of Novartis PharmaAG, Mexico City, Mexico. The rest of authors have declared that there are no potential conflicts of interests to declare with regard to this scientific report.

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