Original research

Effectiveness of vildagliptin versus other oral antidiabetes drugs as add-on to sulphonylurea monotherapy: Post hoc analysis from the EDGE study

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A B S T R A C T
Aim: In this post hoc analysis of the EDGE study, we assessed the effectiveness and safety of vildagliptin versus other oral antidiabetes drugs (OADs) as add-on to first-line sulphonylurea (SU) therapy in patients who did not receive metformin in a real-life setting.

Methods: The primary endpoint was odds of achieving an HbA1c reduction of >0.3% without tolerability issues. Secondary endpoint was odds of achieving HbA1c <7.0% without hypoglycaemia or weight gain. Changes in HbA1c, body weight; and safety were also assessed.

Results: 2936 patients received vildagliptin and 820 received comparator OADs (any α-Gl, TZD, glinide) as add-on to first-line SU therapy. Overall, the mean age, disease duration, HbA1c, and BMI at baseline were 57.1 years, 6.3 years, 8.5%, and 27.7 kg/m2, respectively. The odds ratios for achieving primary and secondary endpoints were 1.6 (95% CI: 1.36, 1.86; p < 0.0001) and 1.8 (1.45, 2.21; p < 0.0001), respectively, in favour of vildagliptin. The between-treatment differences (vildagliptin vs. comparator OAD) for the mean change in HbA1c and body weight were −0.2 ± 0.04% (p < 0.0001) and −0.8 ± 0.16 kg (p < 0.0001), respectively. Overall, the incidence of adverse events was low (vildagliptin, 7% vs. comparator, 8.2%) in both groups. Similar results were observed in a subset of patients enrolled from India and patients who received TZDs as a comparator OAD.

Conclusion: Under real-life settings, vildagliptin as add-on to SU monotherapy showed better glycaemic response without tolerability issues compared with other OADs.

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1. Introduction

Guidelines for management of type 2 diabetes mellitus (T2DM) recommend metformin as the first-line treatment unless contraindicated, followed by a stepwise intensification with other oral antidiabetes drugs (OADs) aimed at maintaining glycated haemoglobin (HbA1c) levels $<7.0\%$ [1,2]. In patients who are intolerant (gastrointestinal [GI] disturbances) or contraindicated (renal impairment, congestive heart failure) to metformin, sulphonylureas (SUs) are often still the preferred first-line treatment option [3]. Additionally, in countries such as India, SUs are frequently prescribed as first-line treatment due to their efficacy and low economic burden, particularly in lean patients [4].

Although SUs have good initial efficacy in recently diagnosed patients, they are often associated with higher rate of secondary failure [5], which eventually leads to addition of other OADs to maintain glycaemic control. Several OADs other than metformin, such as $\alpha$-glucosidase inhibitors (a-GI), glinides, thiazolidinediones (TZDs), dipeptidyl peptidase (DPP)-4 inhibitors, or sodium-glucose cotransporter (SGLT)-2 inhibitors, are now available for use as add-on. However, an add-on should be selected considering patient's characteristics (clinical profile, co-morbidities, and personal preferences) and safety profile (hypoglycaemia and weight gain) of various OADs. New therapeutic drug classes such as DPP-4 inhibitors could offer solutions for some of the challenges physicians face in clinical practice while intensifying treatment. The combination therapy of a SU (increases insulin secretion) and a DPP-4 inhibitor (increases insulin secretion and modulates glucagon secretion in a glucose-dependent manner) targets multiple pathophysiological defects of T2DM [6–8]. In addition, DPP-4 inhibitors by themselves do not increase the risk of hypoglycaemia [7,9].

The Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEnformin (EDGE) study was a large, 1-year, real-life, observational study, which assessed the effectiveness and safety of adding a DPP-4 inhibitor (vildagliptin) vs. other OADs (metformin; any SU, TZD, $\alpha$-GI or glinide) in 45,868 patients with T2DM inadequately controlled on monotherapy [10]. Physician could prescribe any add-on agent to failing monotherapy and accordingly patients were assigned to vildagliptin cohort or other OAD cohort. As expected, majority (approximately 82%) of the patients enrolled in the EDGE study were on first-line therapy with metformin. The overall results (vildagliptin + first-line therapy vs. other OADs + first-line therapy) and results of the sub analysis (vildagliptin + metformin vs. SU + metformin) are already published [10,11]. However, to date, limited evidence is available to guide physicians’ choice of a second-line OAD after SU monotherapy failure in patients who cannot receive metformin. Therefore, it is of clinical importance to investigate the effectiveness and safety of various OADs as add-on to SU monotherapy.

The pragmatic design of the EDGE study and the large enrolled population at the time when DPP-4 inhibitors were launched as a new therapeutic alternative offered an unique opportunity to explore the real-world effectiveness and safety of a DPP-4 inhibitor vs. comparator OADs (any $\alpha$-GI, TZD, glinide) in patients failing on SU monotherapy and who did not receive metformin. The current exploratory post hoc analysis included the overall EDGE population and patients enrolled from India.

2. Methods

2.1. Study design and patients

EDGE was a 1-year, prospective, observational study conducted in 27 countries. The study design and patient inclusion/exclusion criteria are extensively described elsewhere [10]. In brief, patients aged $>18$ years who were inadequately controlled on OAD monotherapy and were prescribed an additional OAD by their physician were included in the study. The choice of add-on therapy was at the physician’s discretion. To avoid bias in the selection of second OAD, enrolment was confirmed after the patients were prescribed the add-on therapy. All the patients provided consent for data collection. Patients were assigned to one of two groups: DPP-4 inhibitor (vildagliptin) or comparator (metformin; any SU, TZD, glinide or $\alpha$-GI). This exploratory analysis included patients (overall and India) inadequately controlled on SU monotherapy and who were prescribed an add-on OAD other than metformin. Data were collected at baseline and at any point during the 1-year observation period, with a compulsory visit at month 12.

2.2. Study assessments

The primary effectiveness endpoint of this post hoc analysis, as in the original protocol, was the proportion of patients achieving a clinically relevant reduction in HbA1c, defined as a drop of $>0.3\%$, without any tolerability findings (hypoglycaemia, discontinuation due to GI side effects, peripheral oedema or weight gain $\geq 5\%$). The secondary effectiveness endpoint was the composite of glycaemic response, defined as achieving HbA1c $<7.0\%$, without hypoglycaemia or weight gain $\geq 3\%$. Changes in HbA1c and body weight from baseline to the end of the 12-month observation period were also assessed. Safety assessments included recording incidence and severity of all adverse events (AEs) as well as their relationship to the treatment.

2.3. Statistical analysis

All analyses were conducted for the intention-to-treat population, which included patients who received at least one dose of the new add-on agent. Baseline and safety data were descriptively summarised for both groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression models for the primary and secondary effectiveness endpoints. The OR expresses odds in favour of success (patients achieving endpoints) with vildagliptin relative to comparators. As this analysis was not prespecified in the protocol, only unadjusted ORs are presented. Changes in HbA1c and body weight were analysed using analysis of covariance (ANCOVA) model and were adjusted for covariates (treatment arm and the respective baseline clinical characteristics). Approximately 40% of patients included in this post hoc
patients enrolled in the EDGE study on prior treatment with SU monotherapy or glinide. SUs, sulphonylureas; TZDs, thiazolidinediones.

*Patients enrolled in the EDGE study on prior treatment with SU monotherapy or α-GI, α-glucosidase inhibitor; OAD, oral antidiabetes drug; SU, sulphonylurea; TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus.

**Fig. 1 – Flow chart depicting patient disposition.**

analysis were enrolled from India and >65% in the comparator arm were on TZDs, and thus, as part of sensitivity analyses, all the statistical analyses were also performed in both Indian and TZD subsets. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Patient disposition and baseline demographics

Of the 45,868 patients enrolled worldwide, 3756 (n = 1554; Indian subset) were receiving SU monotherapy. Upon treatment intensification, 2936 patients received vildagliptin (n = 1252; Indian subset) and 820 (n = 302; Indian subset) received comparators as add-on. The most widely prescribed add-on to SU monotherapy in the comparator group was TZD (n = 536) (Fig. 1). Patient demographics and baseline characteristics are summarised in Table 1. In general, patients from India (53.3 ± 9.76 years) were younger than the overall population (57.1 ± 11.5 years), had been diagnosed with T2DM in their late 40’s vs. early 50’s (disease duration: 5.5 ± 4.87 vs. 6.3 ± 5.51 years), had lower BMI (26.3 ± 4.01 vs. 27.7 ± 4.59 kg/m²), and had higher baseline HbA1c (8.7 ± 1.16% vs. 8.5 ± 1.38%).

3.2. Overall results

The ORs for achieving the primary and secondary effectiveness endpoints are presented in Table 2. A higher proportion of patients in the vildagliptin group vs. the comparator group (59.8% vs. 48.3%) achieved HbA1c reduction of >0.3% without any predefined tolerability issues. The unadjusted OR was 1.6 (95% CI: 1.36, 1.86; p < 0.0001) in favour of the vildagliptin group. The OR was 1.5 (95% CI: 1.21, 1.75; p < 0.0001) for the vildagliptin group compared with the patients who were prescribed TZDs. Moreover, 28.7% and 18.4% of patients in the vildagliptin and comparator groups, respectively, reached the clinically relevant composite endpoint of HbA1c <7.0%, without hypoglycaemia or weight gain ≥3% [OR 1.8 (95% CI: 1.45, 2.21; p < 0.0001)]. The corresponding OR vs. patients who were prescribed TZD was 1.7 (95% CI: 1.35, 2.20; p < 0.0001). After 1 year of treatment, the adjusted mean reduction in HbA1c was −1.4% for the vildagliptin group and −1.2% for the comparator group, with a mean between-group difference of −0.2% (p < 0.0001). The adjusted mean body weight reduction was higher in the vildagliptin group (−1.1 kg) than in the comparator group (−0.3 kg), with a between-treatment difference of −0.8 kg (p < 0.0001) (Fig. 2). The between-treatment difference in weight change vs. TZDs was −1.4 kg (p < 0.0001).

The incidence of total AEs was low in general; the incidence was lower in the vildagliptin group compared with the comparator group (vildagliptin: 7.0%, n = 204; comparator: 8.2%, n = 67). The incidence of AEs in patients who were prescribed TZDs was 5.2% (n = 43). AEs that occurred during the study in >0.5% of patients, listed by primary system organ class (SOC), are summarised in Table 3. The most commonly reported AEs by primary SOC in both groups were GI disorders, infections and infestations. The overall incidence of hypogly-
Table 2 – Proportion of patients achieving primary and secondary effectiveness endpoints in the overall population and the Indian subset.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Indian subset</th>
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<tbody>
<tr>
<td></td>
<td>SU+vildagliptin</td>
<td>SU+comparator</td>
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<tr>
<td></td>
<td>n = 2936</td>
<td>n = 820</td>
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<tr>
<td>Primary effectiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>endpoint (HbA1c drop</td>
<td>Success,( n (%))</td>
<td>Success,( n (%))</td>
</tr>
<tr>
<td>of &gt;0.3% without any</td>
<td>1755 (59.8)</td>
<td>813 (64.9)</td>
</tr>
<tr>
<td>tolerability issues(^b))</td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted OR(^c)</td>
<td>1.59 (1.36, 1.86; (p &lt; 0.0001))</td>
<td>1.38 (1.07, 1.78; (p = 0.0134))</td>
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<tr>
<td>Secondary effectiveness</td>
<td></td>
<td></td>
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<tr>
<td>endpoint(^e) (HbA1c</td>
<td>Success,( n (%))</td>
<td>Success,( n (%))</td>
</tr>
<tr>
<td>&lt;7.0% without</td>
<td>744 (28.7)</td>
<td>235 (20.5)</td>
</tr>
<tr>
<td>hypoglycaemia or ≥3%</td>
<td>Unadjusted OR(^c) (95% CI; (p )</td>
<td>1.79 (1.45, 2.21; (p &lt; 0.0001))</td>
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<td>weight gain)</td>
<td>value)</td>
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<td>Comparator includes any</td>
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<td>TZD, (\alpha)-GI or glinide.</td>
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<td>Tolerability issues: hypoglycaemia, weight gain (≥5%), peripheral oedema, discontinuation due to gastrointestinal events.</td>
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<td>Patients with missing endpoint values of HbA1c or weight (non-evaluable) were considered as failures for calculating OR.</td>
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<tr>
<td>Patients achieving endpoint.</td>
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<td>Comparator includes any</td>
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<td>TZD, (\alpha)-GI, alpha glucosidase inhibitors; OR, odds ratio; SU sulphonylurea; TZD, thiazolidinedione.</td>
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Fig. 2 – Adjusted mean change in HbA1c (A and B) and body weight (C and D) from baseline to endpoint (intention-to-treat population).
caemic events was low: 0.9% (n = 27) in the vildagliptin group and 1.2% (n = 10) in the comparator group. The incidence of severe hypoglycaemia was 0.2% (n = 6) and 0.4% (n = 3) in the vildagliptin and comparator groups, respectively. The incidences of hypoglycaemia and severe hypoglycaemia were 1.5% (n = 8) and 0.6% (n = 3), respectively in patients who received TZDs.

3.3. **Indian subset**

Similar to the results in the overall population, vildagliptin showed a better treatment response for both primary and secondary effectiveness endpoints in patients enrolled in India. Overall, 64.9% of patients in the vildagliptin group and 57.3% in the comparator group achieved an HbA1c reduction of >0.3% without any predefined tolerability issues, resulting in an OR of 1.4 (95% CI: 1.07, 1.78; p = 0.0134) in favour of vildagliptin. The OR was 1.6 (95% CI: 1.17, 2.10; p = 0.0027) in favour of vildagliptin compared with that in patients who were prescribed TZDs. The composite endpoint of HbA1c <7.0% without hypoglycaemia or weight gain was achieved by 20.5% and 11.6% of patients in the vildagliptin and comparator groups, respectively. The OR was 2.0 (95% CI: 1.32, 2.94; p < 0.0009) in favour of vildagliptin, the corresponding OR was 2.3 (95% CI: 1.40, 3.76; p < 0.0010) vs. the patients who were on TZDs. The adjusted mean reduction in HbA1c was higher for the vildagliptin group (−1.4%) compared with that for the comparator group (−1.2%) with a statistically significant between-treatment difference (−0.3%; p < 0.0001). The change in body weight after 1 year of treatment was −0.7 kg in the vildagliptin group and +0.5 kg in the comparator group (between-treatment difference, −1.2 kg; p < 0.0001) [Fig. 2]. The between-treatment difference in weight change vs. TZDs was −1.4 kg (p < 0.0001).

The incidence of total AEs was 5.5% (n = 69) and 10.3% (n = 31) in the vildagliptin and comparator groups, respectively. The incidence of total AEs in patients who were prescribed TZDs was 6.0% (n = 18). The incidence of hypoglycaemia was two-fold higher in the comparator group (2.3%, n = 7) compared with vildagliptin group (1.1%, n = 14); incidence of severe hypoglycaemia was 0.4% (n = 5) in the vildagliptin group and 1.0% (n = 3) in the comparator group. The incidences of hypoglycaemia and severe hypoglycaemia were 2.3% (n = 5) and 1.4% (n = 3), respectively, in patients who received TZDs.

4. **Discussion**

For patients on SU monotherapy, in whom metformin is contraindicated, there are no (or only limited) specific recommendations for the optimal second-line agent. Early treatment intensification in patients with first-line SU is warranted to prevent further deterioration of glycaemic control, as SUs are associated with higher rate of secondary failure, and several patients are diagnosed at a younger age (in countries such as India). This exploratory post hoc analysis of the EDGE study provides new insights into the treatment of patients with T2DM inadequately controlled on SU monotherapy.

The results of this post hoc analysis showed that the mean HbA1c at the time of adding the second OAD was high in both the overall population (8.5%) and the Indian subset (8.7%), reflecting insufficient glycaemic control. There seems to be a delay in treatment intensification with second OAD, despite the longer T2DM duration (≥6 years) and high baseline HbA1c, suggesting the presence of clinical inertia. In addition, intensification of the failing SU therapy was delayed even further compared with the overall EDGE data. Prospective work targeted at educating physicians and patients regarding early treatment intensification might help improve overall outcomes [12].

Apart from vildagliptin, the most widely prescribed OAD as an add-on to SU monotherapy was TZD, particularly in India. This is logical, as TZDs act by improving insulin resistance [13], complementing the effect of SUs. However, this combination is associated with adverse effects like weight gain and fluid retention [14]. Additionally, caution is suggested when prescribing TZDs to patients with congestive heart failure [15].

After 1 year of treatment, a significantly higher proportion (~50%) of patients achieved a clinically meaningful HbA1c reduction of >0.3% without any tolerability issues with addition of vildagliptin. This highlights the importance of timely...
Reported outcomes for patients with first-line SU monotherapy, addition to SU and DPP-4 inhibitors, and none of the studies has been either receiving or received treatment with metformin in clinical practice, eventually benefiting patients on SU monotherapy with limited options for intensification. Based on the nature of the study, some missing HbA1c and weight data and underreporting of AEs (patients were encouraged to report AEs voluntarily) might have affected the overall findings. Several studies have evaluated the efficacy and safety of DPP-4 inhibitors as add-on to SU under randomised and real-life settings [16–18]. However, most of the patients enrolled were either receiving or received treatment with metformin in addition to SU and DPP-4 inhibitor and, none of the studies has reported outcomes for patients with first-line SU monotherapy for whom metformin is not an option.

Interpretation of the results of this post hoc analysis should consider its limitations. The EDGE study was conducted at a time when DPP-4 inhibitors were being launched and was designed to assess the effectiveness and safety of vildagliptin compared with other OADs (except SGLT-2 inhibitors which were not yet approved) under real-life settings. The information regarding duration or therapeutic doses of the SU therapy were lacking, but based on the baseline HbA1c levels reported, patients might have been on SUs for a long time and some may have even developed resistance to SU-induced hyperglycaemia. As this was a secondary analysis and not pre-specified in the protocol, the results were not adjusted for potential baseline and demographic confounders. The young age at diagnosis, low BMI and high baseline HbA1c of the patients enrolled from India are characteristics of Latent Autoimmune Diabetes in Adults (LADA), however, glutamic acid decarboxylase (GAD) autoantibodies were not measured in this real-life study to confirm the presence of LADA. Owing to the real-life nature of the study, some missing HbA1c and weight data and underreporting of AEs (patients were encouraged to report AEs voluntarily) might have affected the overall findings.

In general, vildagliptin in comparison with comparators was well tolerated, with an overall low incidence of AEs (7.0% vs. 8.2%) and hyperglycaemia (0.9% vs. 1.2%). Patients enrolled from India were younger, had lower BMI and higher baseline HbA1c when compared with the overall population. A higher proportion of patients from India in the vildagliptin and comparator groups achieved HbA1c reduction >0.3% without any tolerability issues when compared with the overall group. On the contrary, a lower proportion of patients from India reached HbA1c <7.0% without any tolerability issues. The differences in the results may be possibly driven by high HbA1c in the Indian subset. The incidence of AEs was low in general and similar across the Indian and overall population.

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In general, this report and any such future reports on optimisation and intensification of the failing first-line SU monotherapy may contribute towards an evidence-based clinical practice, eventually benefiting patients on SU monotherapy with limited options for intensification.

5. Conclusions

In people with T2DM failing on SU monotherapy, vildagliptin as an add-on therapy resulted in a higher proportion of patients achieving clinically relevant HbA1c reductions without tolerability issues compared with other OADs. These data support the use of DPP-4 inhibitors such as vildagliptin in patients who require intensification of existing SU therapy and in whom metformin is contraindicated or not tolerated.

Conflict of interest

This study was funded by Novartis Pharma AG. KMPK and UP have no specific conflict of interest relevant to the study. HB has received honoraria for lectures and advisory boards from all major diabetes companies, including Novartis, but has no specific conflict of interest relevant to the study. AG is an employee of Novartis Healthcare Private Limited. PMP has served on advisory panels for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca, Pfizer, Johnson and Johnson, Boehringer Ingelheim, Hanmi and Mannkind, and Katholieke Universiteit Leuven, which has received research support from Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Roche, Abbott, and Novartis; and also serves or has served on speakers bureaus for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Astra Zeneca, and Novartis.

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