Original Article

Effectiveness, Safety and Tolerability of Vildagliptin with or without Metformin in Bangladeshi Patients with Type 2 Diabetes Mellitus: Results from Real-Life Observational Study

Latif ZA[a], Pathan MF[b], Uddin MF[c], Hasanat MA[d], Ashrafuzzaman SM[e], Ali TM[f], Rahman MM[g]

Abstract

Background: *Type 2 diabetes mellitus (T2DM) is a progressive disease which needs prolonged management with anti-diabetic drugs. The purpose of the present study was to assess effectiveness, safety and tolerability of treatment by vildagliptin alone or with the combination of vildagliptin and metformin in T2DM patients in a real-world setting.*

Methods: *This non-interventional, prospective, multi-center study was conducted in several hospitals in Bangladesh from 15th September 2010 to 12th June 2012. Both male and female patients, aged ≥18 years with an established diagnosis of T2DM, who had been prescribed vildagliptin or vildagliptin added to metformin free-dose or single-pill combination according to local prescribing information and who consented to data collection, were eligible for inclusion in the study. During the observational period of 24±6 weeks, data from three routine clinic visits were recorded; i.e. the baseline visit (Day 1), visit 2 (week 12±4 weeks) and a final visit (visit 3) at the end of the study (week 24±6 weeks).*

Result: *A total number of 510 patients were enrolled in this study of which 468 patients were analyzed for the study and the remaining 42 patients were lost to follow up. Patients in vildagliptin group were treated with vildagliptin as monotherapy which was received by 101 patients; however, patients in vildagliptin/metformin group received the combination of vildagliptin and metformin which was in 367 cases. In vildagliptin group, the mean HbA1c was reduced from baseline (8.50±1.02 %) to 24 week (7.19±0.74%) (p<0.0001). Similarly, in vildagliptin group the mean HbA1c at week 12 (7.76±0.96 %) was lower vs. baseline (8.50±1.02 %) (p<0.0001). In vildagliptin and metformin combination group, the mean HbA1c at week 24 (7.02±0.66%) was lower vs. baseline (8.55±0.75%) (p<0.0001). There were no deaths and no serious adverse effects. None of the patients reported any hypoglycemic event.*

Conclusion: *In conclusion vildagliptin treating T2DM patients with or without metformin is associated with a significant and clinically relevant improvement in glycaemic control. Furthermore, vildagliptin treatment is generally well tolerated.*

Keywords: *efficacy; metformin; safety; type 2 diabetes mellitus; vildagliptin.*

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Author Informations

a. Prof. Zafar Ahmed Latif, Professor of Endocrinology and Director, BIRDEM Academy, BIRDEM General Hospital, Bangladesh.

b. Prof. Md. Faruque Pathan, Professor and Head, Department of Endocrinology, BIRDEM General Hospital, Bangladesh.

c. Prof. Md. Farid Uddin, Professor, Department of Endocrinology, BSMMU, Bangladesh.

d. Prof. M A Hasanat, Professor and Chairman, Department of Endocrinology, BSMMU, Bangladesh.

e. Dr. S M Ashrafuzzaman, Associate Professor, Department of Endocrinology, BIRDEM General Hospital, Bangladesh.

f. Dr. Tanvir Mobarak Ali, Chief Scientific Officer, Novartis (Bangladesh) Limited.

g. Dr. Md. Mahfuzur Rahman, Medical Advisor, Novartis (Bangladesh) Limited.

Address of correspondence: Prof. Zafar Ahmed Latif, Professor of Endocrinology and Director, BIRDEM Academy, BIRDEM General Hospital, 122, Kazi Nazrul Islam Avenue, Shahbagh, Dhaka-1000, Bangladesh. Email: zafaralatif2011@yahoo.com

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Introduction

Type 2 diabetes mellitus (T2DM) patients number is increasing due to population growth, aging, urbanization and increasing prevalence of obesity and physical inactivity.[1] The total number of people with diabetes is projected to rise from more than 371 million in 2012 to half a billion (552 million) in 2030 globally and posing a major burden on world health.[2] In Bangladesh, the projected number of diabetes cases in 2030 is expected to be approximately 16,837 lakhs.[3]

The management of T2DM primarily targets the treatment of hyperglycemia through oral anti-diabetic drugs (OADs) with or without insulin therapy.[4] Therefore the uses of OADs are the main choice for the treating T2 DM patients. OADs like secretagogues trigger insulin release or production from the pancreatic β cells, sensitizers either reduce the hepatic glucose

output (metformin) or enhance insulin sensitivity, retard glucose uptake from the gastrointestinal tract.[5] Though the existing OAD monotherapy provide short-term glycemic control, they are often associated with adverse effects like weight gain, hypoglycemia, gastrointestinal disturbances and edema, thereby limiting their tolerability.[6] Vildagliptin is an agent of a new class of OADs which improves glycemic control by elevating levels of glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide through inhibition of dipeptidyl peptidase 4 (DPP-4).[7]

Vildagliptin and the combination of vildagliptin and metformin are authorized for use in the treatment of T2DM in most countries in region of Asia-Pacific, Middle-East and African countries and many other countries worldwide.[5] Although the efficacy and safety profile of vildagliptin and combination of vildagliptin and metformin in randomized controlled trials (RCTs) are well established[8-10], demonstration of its true clinical effectiveness in routine clinical practice is limited. In this context the lack of data regarding this issue, has directed for doing this study. Furthermore T2DM is going to be one of the main crises in the health sectors. Thus use of OADs has given the uplifting the burden of the costing of insulin. Therefore, the purpose of this observational study was to evaluate the effectiveness, safety and tolerability of treatment with vildagliptin or combination of vildagliptin with metformin in T2DM patients in a real-world setting.

Methods

The study was a multicentre, post-authorization, non-interventional, prospective study that pooled data for analysis from GUARD (vildaGliptin clinical Use in the reAl woRlD) study, conducted in Asia, the Middle-East, Central America and Africa, according to one umbrella protocol. This study was conducted in several hospitals in Bangladesh from 15th September 2010 to 12th June 2012 for a period of one year and nine months. The study complied with all required guidelines, local regulations and the Declaration of Helsinki. Both male and female outpatients with T2DM in the age group of ≥18 years who had been prescribed vildagliptin (Galvus) or vildagliptin (Galvus) added to metformin (open label) in free-dose or single pill combination according to local prescribing information and who had given consent to participate in this study, were included as study population. Data originating from assessments and evaluations performed according to the physician's routine practice and standard care was recorded. During the observational period of 24 ± 6 weeks, data from three routine patient visits were recorded: the baseline visit (Day 1), Visit 2 (12 ± 4 weeks) and a final visit (Visit 3) at study end (24 ± 6 weeks). The primary effectiveness endpoint was change in mean glycated haemoglobin (HbA1c) concentration from baseline to final visit at 24 ± 6 weeks. Key secondary endpoints included the proportion of patients reaching a target HbA1c of ≤6.5 and ≤7.0% at week 24, changes in body weight and body mass index (BMI) from baseline to week 24, and the number of patients experiencing a hypoglycaemic event. Safety and tolerability were also assessed by recording and evaluating adverse effects (AEs) and serious AEs (SAEs). Assessment of whether AEs/SAEs were considered to be related or unrelated to the medication of interest was carried out by the treating physician. Supportive analyses of covariance were performed to assess the change from baseline HbA1c in relation to different patient subgroups, categorized according to baseline HbA1c, patient age and obesity status. No diagnostic or monitoring procedures additional to standard care and routine practice were applied to the patients, and epidemiological methods were used for the analysis of collected data. The statistical tables and listings were generated using SAS® version 9.2. Summary statistics for quantitative variables included the number of observations, mean, standard deviation, median, minimum, and maximum, and for qualitative variables included number and percentage of patients in frequency tables. The primary effectiveness variable was the status effect of vildagliptin as monotherapy or in addition to metformin on change from baseline in HbA1c after 24 weeks treatment. The two-sided 95% confidence interval for the estimated difference was presented. A p-value less than 0.05 indicated that the mean change from baseline in HbA1c in the treatment group was significantly different from zero.

Results

A total number of 510 patients were enrolled in this study, of which 42 patients were excluded from the analyses due to lost to follow up. Therefore total 468 patients were analyzed in this study of which 101 patients in the vildagliptin group and 367 patients in combination of vildagliptin and metformin group. Of

these, 438 (93.6%) patients completed the study while 30 (6.4%) patients discontinued. The primary reasons for discontinuation were lost to follow-up [28 (6.0 %)], AEs and withdrawal of consent [1 (0.2%) each]. Fourteen patients in the monotherapy group were also treated with other oral anti-diabetic medications. The mean age of patients was 47.1 ± 8.40 years and majority [455 (97.2 %)] were less than 65 years of age. There were 274 (58.5%) male and 194 (41.5%) female patients. The mean BMI of the patients was 26.3 ± 3.84 kg/m^2 and majority [314 (67.1%)] had BMI < 30 kg/m^2. The mean Baseline HbA1c was 8.50 ± 0.81 % and for majority [273 (58.3 %)] of the patients HbA1c was in the range of >8% to 9%, for 120 (25.6%) in the range of ≤ 8%, 36 (7.7%) in the range of >9% to 10% and 21 (4.5%) had baseline HbA1c >10% (Table-I).

Table-I. Demographic and Baseline Characteristics

Variable Statistic	Group A (V) (N=101)	Group B (V+M) (N=367)	Total (N=468)
Age group			
Mean (SD)	45.6 (±8.72)	47.5 (±8.27)	47.1 (±8.40)
Sex, n (%)			
Male	60 (59.4)	214 (58.3)	274 (58.5)
Female	41 (40.6)	153 (41.7)	194 (41.5)
HbA1c group, n (%)			
Baseline Mean (SD)	8.50 (±1.02)	8.60 (±0.75)	8.50 (±0.81)
HbA1c ≤ 8%	32 (31.7)	88 (24.0)	120 (25.6)
HbA1c > 8% – 9%	52 (51.5)	221 (60.2)	273 (58.3)
HbA1c > 9% – 10%	7 (6.9)	29 (7.9)	36 (7.7)
HbA1c > 10%	7 (6.9)	14 (3.8)	21 (4.5)
Weight, kilograms			
Mean (SD)	68.1 (±9.19)	68.8 (±10.87)	68.6 (±10.56)
BMI group, n (%)			
BMI < 30 kg/m^2	67 (66.3)	247 (67.3)	314 (67.1)
BMI ≥ 30 kg/m^2	10 (9.9)	58 (15.8)	68 (14.5)
Mean (SD) kg/m^2	25.5 (±3.48)	26.5 (±3.90)	26.3 (±3.84)
Duration of T2DM, yrs			
Mean (SD)	1.2 (±2.53)	3.9 (±4.50)	3.4 (±4.30)

[1]Prior to study start; BMI= Body mass index; SD= Standard deviation; T2, DM= Type 2 diabetes mellitus; V=Vildagliptin; V+M=Vildagliptin+Metformin

In vildagliptin + metformin group, the mean HbA1c at week 24 (7.02 ± 0.66 %) was lower than baseline (8.55 ± 0.75%), and the change was statistically significant ($p < 0.0001$). In vildagliptin group, there was a significant ($p < 0.0001$) reduction from baseline to week 24 in HbA1c values (Table-II).

Table II. Change from Baseline in HbA1c Results in 24th Week [Mean (±SD)]

Primary Efficacy Variable: HbA1c	Group A (V)	Group B (V+M)	Total
Baseline	8.50±1.02	8.55±0.75	8.54±0.81
Week 24 (LOCF)	7.19±0.74	7.02±0.66	7.06±0.68
P value	<0.0001	<0.0001	<0.0001

Baseline= Week 0; if week 24 assessment was missing, the last post baseline observation was carried forward; LOCF=Last observation carried forward; SD= Standard deviation; V=Vildagliptin; V+M=Vildagliptin+Metformin

In vildagliptin group, there were 17 (16.8 %) patients who reached the HbA1c target value of ≤ 6.5% and 45 (44.6 %) patients who reached the HbA1c target value of ≤ 7.0 %. In vildagliptin + metformin group, there were 77 (21.0 %) patients who reached the HbA1c target value of ≤ 6.5% and 198 (54.0 %) patients who reached the HbA1c target value of ≤ 7.0 % (Table III).

Table III. Number (%) of Patients Reaching HbA1c Targets after 24 Weeks of Treatment

HbA1c	Group A (V) (N=101)	Group B (V+M) (N=367)	Total (N=468)
< 6.5%, n (%)	17 (16.8)	77 (21.0)	94 (20.1)
< 7.0%, n (%)	45 (44.6)	198(54.0)	243 (51.9)

There were no patients with AEs. There were no deaths and no SAEs. There was 1(0.3%) patient who discontinued due to an AE; however the AE was categorized as non-serious. None of the patients reported any hypoglycemic events (Table IV).

At week 24, in vildagliptin group, mean (SE) body weight change (kg) and BMI (kg/m^2) reduction were -1.98 (0.36) and -0.71 (0.13) respectively, both of which were statistically significant (P-value < 0.0001). For vildagliptin+metformin group also the mean (SE) body weight change (kg) and BMI (kg/m^2) reduction [-1.78 (0.17) and -0.64 (0.08) respectively] were statistically significant (P-value < 0.0001).

Table-IV. Patients with Death, Serious Adverse Events, or Adverse Events Leading to Medication of Interest Discontinuation

Outcomes	Group A (N=101)	Group B (N=367)	Total (N=468)
Deaths, n (%)	0 (0)	0 (0)	0 (0)
SAEs, n (%)	0 (0)	0 (0)	0 (0)
Discontinued	0 (0)	1 (0.3)	1 (0.2)
Due to SAE, n (%)	0 (0)	0 (0)	0 (0)
Due to AE, n (%)	0 (0)	1 (0.3)	1 (0.2)
Hypoglycaemia	0 (0)	0 (0)	0 (0)

*SAE= Serious Adverse Event

Discussion

The combination of vildagliptin and metformin as prescribed in free-dose or combination in different studies have shown significant reduction of blood sugar as well as HbA1c.[11-12] Several RCTs carried out to see the safety, efficacy and tolerability of vildagliptin.[8-10] However an advantage of observational studies is the access to large, diverse groups of patients who better represent the population to which a drug is prescribed, and safety and effectiveness data collected from these studies are valuable in clinical practice. Vildagliptin and the combination of vildagliptin and metformin are authorized for use in the treatment of T2DM in many countries worldwide.[5]

In this study the results showed that there was a significant change from baseline in HbA1c after 24 weeks treatment with vildagliptin as monotherapy and vildagliptin and metformin combination therapy ($p< 0.0001$). The mean change from baseline in HbA1c after 24 weeks treatment with vildagliptin alone and vildagliptin with metformin was similar to that reported in various RCTs for vildagliptin[8-10] and vildagliptin +metformin.[13-15] These findings support the results from RCTs, where the magnitude of HbA1c reductions with vildagliptin[16] and vildagliptin+metformin was greater in patients with higher baseline HbA1c.[17] Approximately, 16.8% patients reached the HbA1c target value of ≤6.5% and 44.6% patients reached the HbA1c target value of ≤7% with vildagliptin as monotherapy suggesting a good glycemic control in 24 weeks. Similarly, 21.0% patients reached the HbA1c target value of ≤6.5% and 54.0% patients reached the HbA1c target value of ≤7% with combination of vildagliptin and metformin, again suggesting a good glycemic control in 24 weeks. There was a significant change from baseline body weight and BMI after 24 weeks of vildagliptin as well as combination of vildagliptin and metformin. Reduction in weight was also observed in few trials with vildagliptin as monotherapy.[18]

There were no discontinuations due to unsatisfactory effectiveness or need for an additional OAD or insulin, which is in-line with data from RCTs.[15] Investigator assessment scores for vildagliptin and combination of vildagliptin and metformin were good to very good for effectiveness, tolerability, and compliance, and the decision to continue the treatment with vildagliptin or vildagliptin and metformin was made for most (96.2%) of the patients in the study in the study population. There were no deaths and no SAEs in either of the treatment groups, and one patient discontinued due to AE in vildagliptin + metformin group. None of the patients reported any hypoglycemic events. These results are similar to that obtained in RCTs.[15-17] Vildagliptin and combination of vildagliptin and metformin were both well tolerated, and there were no patients who reported SAE. It is interesting to get the result which is statistically significant. In Bangladesh, so far this type of study has not been performed to evaluate effectiveness of vildagliptin alone or with the combination of metformin.

In vildagliptin and metformin combination group, the within treatment comparison for change from baseline to week 24 in HbA1c for Full Analysis Set (FAS) showed a significant ($p< 0.0001$) reduction from baseline to week 24, and baseline HbA1c, BMI group, and gender had a significant impact on the change in HbA1c from baseline to week 24 ($P = 0.000$, $P = 0.043$, and $p=0.045$, respectively) while age group did not affect the results significantly. In vildagliptin and metformin combination group, there were 77 (21.0%) patients who reached the HbA1c target value of ≤6.5% and 198 (54.0%) patients who reached the HbA1c target value of ≤7%. In vildagliptin group, the change from baseline in body weight was statistically significant ($P < 0.0001$), and significant covariates were BMI group ($P = 0.014$). The change from baseline in BMI after 24 weeks of treatment was also statistically significant ($P < 0.0001$), and BMI group ($P = 0.006$), were significant covariates. In vildagliptin and metformin

combination group, the change from baseline in body weight was statistically significant (P< 0.0001), and significant covariates was BMI group (P = 0.000). The change from baseline in BMI after 24 weeks of treatment was also statistically significant (P < 0.0001), and BMI group (P = 0.000) was significant covariate. There were no patients who discontinued due to unsatisfactory effectiveness or who needed additional OAD or insulin in FAS. The results confirm the effectiveness, safety, and tolerability data for vildagliptin and combination of vildagliptin and metformin demonstrated in RCTs. This is relevant as observational studies assess the effectiveness of a drug previously documented to be efficacious in controlled environment in a real-world setting. Therefore, it provides information on how a drug works in daily practice, under ordinary and variable conditions, prescribed by physicians with varying degrees of knowledge and expertise, to treat a variety of eligible patients. The result demonstrated that vildagliptin as monotherapy, and in combination with metformin was effective in large, diverse group of patients representing the population to which the drug is prescribed. The safety and effectiveness data collected from this study is hence valuable for clinical practice. There were several patients who had to be excluded from analysis as data was incomplete or missing for these patients. Despite these limitations this data provides a real-world experience with respect to effectiveness, safety and tolerability of vildagliptin as monotherapy, and also in combination with metformin.

Conclusion

Vildagliptin treatment with or without metformin provided consistent, clinically relevant improvements in glycaemic control, regardless of baseline HbA1c, obesity status and age, and was well tolerated in routine clinical practice.

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