

Research Article



A Comparative Study to Evaluate the Efficacy and Safety of Vildagliptin as an Add-on Therapy to a Low-Dose Metformin vs an Uptitration of Metformin in Type 2 DM Patients

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ABSTRACT

Gliptins act by prolonging action of gut hormone; Incretins which release insulin in glucose dependent manner do not cause hypoglycemia seen frequently with Sulfonyl urea's and exogenous Insulin. This study was conducted to evaluate the efficacy and safety of addition of Vildagliptin to low-dose Metformin and compare it to an up titration of Metformin in type 2DM patients. Total 73 eligible patients were randomized into 2 groups to receive combination of Vildagliptin+ Metformin (50+500mg) BD or only Metformin 1000 mg BD for 12 weeks. The primary endpoint was baseline to endpoint HbA1c reduction. The mean changes of different parameters from baseline to end point were compared by analysis of covariance and Student t-test at 5% level of significance. After 12 weeks, mean reduction in HbA1c in combination and only Metformin group was -0.58 ± 0.67 and -0.13 ± 0.67 respectively. Reduction was statistically significant in combination group ($p < 0.001$). Reduction in FBS and PPBS was -52.13 ± 45.11 and -76.93 ± 66.55 in combination and -18.93 ± 50.95 , -33.5 ± 73.73 in only Metformin group and the comparative mean reduction between group was significantly greater in combination group than only Metformin group ($P < 0.01$). There was no statistically significant reduction seen in body weight and lipid profile for both groups. Gastrointestinal adverse events were more in Metformin group (28.0%). In patients with T2DM inadequately controlled with Metformin up to 1000 mg daily, the addition of Vildagliptin 100 mg daily achieved significant reduction in HbA1c, FBS and PPBS with fewer GI events and no weight gain.

Keywords: HbA1c, Metformin, T2DM, Vildagliptin.

INTRODUCTION

Diabetes mellitus is considered as the number one killer among all chronic diseases. During the last fifteen years the prevalence of type 2 diabetes has increased by five folds worldwide. There are about 200 million people around the world who are suffering from type 2 diabetes and the number is expected to reach 300 million cases by the year 2025.¹

India shelters the most number of people with diabetes mellitus worldwide. From 31 million in the year 2000, the number of persons with diabetes mellitus in India would register a 2.5 fold increase over the next 30 years so as to reach an alarming level of estimated 80 million by the year 2030.²

Although different classes of Oral Hypoglycemic Agents are now available that target the different pathophysiologic factors contributing to T2DM, hypoglycemia is very common problem with medications that raise insulin levels independently of blood glucose, such as oral insulin secretagogues (sulfonylureas and glinides) and exogenous insulin.³

Vildagliptin is a Dipeptidyl peptidase 4 inhibitor which acts by prolonging the action of gut hormones called Incretins (Glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, GIP) by inhibiting its degradation by enzyme DPP-4. The effect of incretins i.e. GLP-1 on insulin secretion depends on the plasma glucose concentration, with a greater insulin secretory effect at

higher glucose level and minimal effect at euglycemic levels. This mechanism suggests that drugs that boost GLP-1 activity should not cause hypoglycemia.⁴

Metformin is the gold standard first-line treatment for type 2 diabetes mellitus (T2DM).⁵ This recommendation is based on its therapeutic efficacy, a relatively low incidence of hypoglycemia and no weight gain. Mechanistic studies have suggested that DPP-4 inhibitors such as Vildagliptin may be particularly effective when used in combination with Metformin because of a synergistic effect.⁶ The effect of Vildagliptin to increase plasma levels of intact glucagon-like peptide-1 (GLP-1) was enhanced in patients receiving concomitant Metformin while there was no evidence of any effect of Metformin on plasma DPP-4 activity or on GLP-1 or GIP in the absence of vildagliptin.⁷

So combination therapy of Metformin and DPP-4 inhibitors is supposed to be one of the best treatments available for type 2 DM.

So the aim of the present study was to assess the efficacy and safety of the addition of Vildagliptin (100 mg qd) to low-dose Metformin (500 mg bid) with that of an upward titration of Metformin in patients with T2DM with inadequate glycemic control on Metformin monotherapy.

MATERIALS AND METHODS

This was a single center, open-label, randomized parallel group study conducted at the Rajarajeswari Medical



College and Hospital, Bangalore. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from the participants. Inclusion criteria for the study was patients with age more than 18 years of either sex, glycosylated hemoglobin > 6.5 %, Fasting plasma glucose (FPG) < 270 mg/dL and also patients who received metformin 1000 mg daily for at least 2 month prior to screening with inadequate glycaemic control.

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, evidence of significant diabetic complications, acute infections, myocardial infarction, unstable angina, congestive heart failure, renal and hepatic dysfunction, pregnant and lactating women, patients on chronic insulin treatment within the past 6 months and/or any oral antidiabetic drug other than Metformin within 3 months prior to visit 1; chronic oral or parenteral corticosteroid treatment within 8 wk prior to visit 1; treatment with growth hormone or similar drugs.

A patient's treatment was discontinued if one or more of the following event occurred: unsatisfactory therapeutic effect defined as FPG > 270 mg/dL after 4 week of treatment, occurrence of an adverse event (AE) including frequent hypoglycemia (i.e. > 3 hypoglycemic events per wk).

Eligible patients were randomized into two groups according to the treatment they received. First group received combination of Metformin 500 mg and Vildagliptin 50 mg twice daily and second group only Metformin 1000 mg twice daily.

The blood glucose level, both fasting and postprandial, glycosylated hemoglobin, lipid profile and BMI were recorded at the initial visit. Then FPG and PPG were monitored regularly at every month. The HbA1C and lipid profile were examined after 3 months of treatment. The glycosylated hemoglobin determination was carried out by using BIORAD Micromat II HbA1C instrument, while FPG, PPG and Lipid profile were determined by using Microplate reader.

If the patients were unable to tolerate the study drug due to GI symptoms following the up-titration, Metformin could be reduced by one tablet (500 mg) until the GI symptoms had improved. The dose had to be then restored gradually over 1-2 weeks based on the patient's ability to tolerate the study drug.

Efficacy and safety evaluations

The primary efficacy variable was the change in HbA1C from baseline to 3 months. Secondary efficacy outcomes included changes in FPG, 2-h PPG and fasting lipid profile levels, change in BMI from baseline to 3 months after randomization of the patients. Safety outcomes included adverse events, particularly hypoglycaemic symptoms and GI symptoms.

Statistical analysis

Results were presented as mean \pm standard deviation (SD). The analysis of different parameters was carried out by using appropriate test. Within groups, comparisons were made by using paired two-tailed t tests and between groups; comparisons were analyzed by using one way ANOVA test. p value below 0.05 was considered as statistically significant.

RESULTS

A total of 73 patients were screened and randomized into the two treatment groups, (Vildagliptin / Metformin group – 36 patients and only Metformin group – 37 patients).

Out of 73 patients, 58.2% of patients were male while 41.8% of patients were female. The baseline characteristics of all patients at randomization are summarized in table 1.

Table 1: The baseline characteristics of all patients at randomization

	Vildagliptin + Metformin	Only Metformin
No of patients at randomization	36	37
Age (yrs)	49.95 \pm 2.032	48.27 \pm 2.902
HbA1c (%)	8.38 \pm 0.63	8.21 \pm 0.62
FPG (mg/dl)	198.26 \pm 16.62	193.52 \pm 16.98
PPG (mg/dl)	298.08 \pm 13.58	301.70 \pm 7.75
Total Cholesterol (mg/dl)	222.14 \pm 16.19	221.34 \pm 16.5
Serum Triglyceride mg/dl)	222.3 \pm 17.8	230.5 \pm 17.2
HDL (mg/dl)	43.7 \pm 3.67	40.3 \pm 2.72
LDL (mg/dl)	124.4 \pm 10.80	129.6 \pm 10.23
BMI (Kg/m ²)	31.47 \pm 1.49	31.28 \pm 1.50

Out of 36 patients in Vildagliptin + Metformin group, 36 (100.0%) patients completed the study; Whereas out of 37 patients in only Metformin group 34 (91.8 %) patients completed the study. 3 patients in only Metformin group withdrew from the study because of severe GI intolerance.

Glycemic Control

Glycosylated Hemoglobin

After 12 weeks of therapy mean reduction in HbA1c in Vildagliptin-Metformin group and only Metformin group was - 0.58 \pm 0.67 and - 0.13 \pm 0.67 respectively and statistically significant reduction was seen only in Vildagliptin -Metformin group (p<0.001). [table2].

FPG and PPG

The FPG and PPG values were found to be reduced by - 76.93 \pm 66.55 and -52.13 \pm 45.11 mg/dl respectively for Vildagliptin-Metformin group and -18.93 \pm 50.95 and - 33.5 \pm 73.73 mg/dl respectively for only Metformin group.

The statistically significant reductions in the FBS and PPBS were found in both groups [Table 2]. But the comparative reduction in FBS and PPBS in the Vildagliptin-Metformin group was significantly greater than only Metformin group ($P < 0.01$).

Lipid profile

There was no statistically significant result found in terms of mean reduction in TC, TG and LDL for both the groups [Table 2]. Mean increase in HDL concentration was also not found to be statistically significant for both groups.

BMI

Mean reduction in BMI was also not found to be statistically significant for both groups, although it proved the weight neutral property of Vildagliptin and Metformin.

Safety and Tolerability

There was no serious adverse event reported during the study period, though 3 patients from only Metformin group withdrew from the study because of GI adverse effect (diarrhea, nausea and abdominal pain) and switched over to other medications. The common side effects noted are mentioned in Table 3.

Table 2: Showing means changes in different parameters from baseline value. Results are presented as mean \pm SD; $p < 0.05$ was considered statistically significant.

Parameters	Group I (Vildagliptin + Metformin) Mean reduction after 12 week	p value for intra-group comparison for (Vildagliptin + Metformin) group	Group II Only Metformin Mean reduction after 12 week	p value for intra-group comparison of Metformin group	p value of Intergroup Comparison between Group I & group II
HbA1c (%)	- 0.58 \pm 0.67	< 0.001	- 0.13 \pm 0.67	>0.05	< 0.01
FPG (mg/dl)	-52.13 \pm 45.11	< 0.001	-18.93 \pm 50.95	< 0.05	< 0.01
PPG (mg/dl)	- 76.93 \pm 66.55	< 0.001	-33.5 \pm 73.73	< 0.05	< 0.01
Total Cholesterol (mg/dl)	-1.17 \pm 12.09	>0.05	-1.06 \pm 11.21	>0.05	>0.05
Serum Triglyceride (mg/dl)	-9.7 \pm 39.6	>0.05	-4.9 \pm 24.7	>0.05	>0.05
HDL (mg/dl)	0.9 \pm 3.5	>0.05	0.8 \pm 4.8	>0.05	>0.05
LDL (mg/dl)	-5.9 \pm 23.7	>0.05	-3.1 \pm 11.5	>0.05	>0.05
BMI (Kg/m ²)	-0.18 \pm 0.82	>0.05	-0.17 \pm 0.73	>0.05	>0.05

Table 3: The common side effects noted

Side effects	Vildagliptin-metformin group N (%)	Only metformin group N (%)
Diarrhea	2 (5.55%)	8 (23.5%)
Headache	4 (11.11%)	9 (26.4%)
Nasopharyngitis	2 (5.55%)	0 (0)
Flatulence	2 (5.55%)	12 (35.2%)
Abdominal pain	3 (8.3%)	10 (29.4%)
Upper respiratory tract infection	3 (8.3%)	0 (0)
Hypoglycaemia	0 (0)	2 (5.8%)
Dyspepsia	3 (8.3%)	11 (32.3%)

DISCUSSION

Vildagliptin, a Dipeptidyl peptidase-4 inhibitors is a relatively new class of drugs for the treatment of type 2 diabetes which act by prolonging the action of Incretins.⁸ These agents work in a unique way to improve insulin secretion from the beta cells of the pancreas in response to an increase in blood sugar and simultaneously decrease glucagon output from the alpha-cells which results in decreased hepatic gluconeogenesis.

T2DM is a disease associated with a progressive decline in β -cell function. Unlike many other antihyperglycemic medications, Vildagliptin improves glycemic control through physiological mechanisms that result in an attenuation of β -cell decline.⁹⁻¹³

Vildagliptin is particularly useful in combination with Metformin because of the synergistic effect. In a previous study, it was found that combination of Vildagliptin with low-dose Metformin achieved superior efficacy to high doses of Metformin without any associated GI tolerability issues.¹⁴ So the present study was designed to compare the benefits of more aggressive treatment by either escalating the dose of Metformin from 1 gm to 2 gm per day or by adding Vildagliptin (100 mg /day) to a lower dose of Metformin (1000 mg / day) in patients with inadequate glycemic control with Metformin 1000 mg /day therapy. The data showed that an addition of Vildagliptin to a low-dose



Metformin provided larger reductions in HbA1c. Our study also supported the finding of one other study.⁶

Hypoglycemia is a most common problem with medications (i.e. Sulfonyl ureas ,exogenous insulin) that raise insulin levels independently of blood glucose and has long been known as a risk factor for cardiac arrhythmia¹⁵ cardiac ischemia^{16,17} and prothrombotic changes.¹⁸ An observational study by the UK Hypoglycaemia Study Group found that the prevalence of severe hypoglycemia was significantly increased in T2DM patients treated with insulin for >5 years.¹⁹ Again In another observational study conducted in France found that patients treated with a combination of Metformin and sulfonylurea reported severe hypoglycemia over 6 months.²⁰ But Drugs like Vildagliptin has unique mechanism of action which contribute to its superior efficacy with very low hypoglycemic potential. Basically it enhances alpha cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia thereby has very less potential for causing hypoglycaemia.²¹ This was supported by one phase 3 study where it was found that 1-year treatment with Vildagliptin resulted in a significant HbA1c reduction without any hypoglycemic event.²² Another study showed the same effect²³ In our study also we found that there was not a single hypoglycaemic event occurred in Vildagliptin-Metformin group.

Another advantage of Vildagliptin is the weight neutral property even on long term use.

The Potential advantages of DPP-4 inhibitors over Thiazides (TZD) include a neutral effect on body weight and better tolerability profile, without fluid retention, peripheral edema and cardiovascular adverse events.²⁴⁻²⁸ In one study, it was found that when Vildagliptin added to Metformin showed similar efficacy to that of Pioglitazone–Metformin group, but significant increase in body weight was found only Pioglitazone group.²⁹ Studies by Scheen³⁰ and Del Prato³¹ also proved the similar weight neutral property of Vildagliptin. The present study also showed that GI events (diarrhea, nausea and abdominal pain) were less frequent in patients receiving Vildagliptin– Metformin group than only Metformin group. This is important since in clinical practice, Metformin is uptitrated up to 2-3 g daily with many patients having GI AEs, which may lead to low compliance and treatment discontinuation. A dose-related incidence of GI adverse effects with Metformin has been reported by some studies.³² The main limitations of our study were small sample size and single centered study. So in future we expect a large multicenter study to prove the efficacy and safety of this novel drug combination of Vildagliptin and Metformin.

CONCLUSION

The novel combination of Vildagliptin and Metformin is supposed to be one of the best approaches for the treatment of type II DM. The results of our study

demonstrated that patients with T2DM with inadequate glycaemic control with Metformin up to 1000 mg daily, the addition of Vildagliptin 100 mg daily achieved larger HbA1c reduction with fewer GI events. These data suggest that an early addition of Vildagliptin to submaximal doses of Metformin has the potential to offer benefits over up titration of Metformin with superior efficacy, lower incidence of GI AE, no increase in the hypoglycemic event rate and no weight gain.

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