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RESEARCH ARTICLE

Comparison of efficacy and safety of vildagliptin 50 mg tablet twice daily and vildagliptin 100 mg sustained release once daily tablet on top of metformin in Indian patients with Type 2 diabetes mellitus: A randomized, open label, Phase IV parallel group, clinical trial

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is mainly due to multifactorial of which insulin resistance and deficiency in the incretion are two important pathophysiological factors. Vildagliptin, an oral hypoglycemic agent, acts by inhibiting dipeptidyl peptidase-4 enzyme, often uses as a first line drug along with metformin to enhance outcome. **Aim and Objective:** The aim of this study was to compare the effectiveness and safety of vildagliptin 50 mg twice daily dose with vildagliptin 100 mg sustained release tablet (SR) once daily in Type 2 DM patients and uncontrolled with metformin monotherapy. **Materials and Methods:** Adult patients with Type 2 DM fulfilling the inclusion criteria were randomized in two groups. Group 1 patient received metformin 1000 mg/day in two divided dose and tablet vildagliptin 50 mg 2 times daily, while Group 2 patients received metformin 1000 mg/day in two divided dose along with vildagliptin 100 mg SR once daily. Fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and glycated hemoglobin (HbA1C), were measured at baseline, on week 4, week 8, and week 12 visits. Liver function test (SGOT), SGPT, Serum Bilirubin), kidney function test electrolytes, serum urea, serum creatinine), and body weight also measured in first visit and in 12th week. **Results:** HbA1C, FPG, and PPPG all three decreased equally at 12 week from their respective baseline values ($P < 0.05$) in both groups. There is no statistically significant alteration of liver enzymes and in serum bilirubin level from baseline to 12th week in both groups. **Conclusion:** Vildagliptin 100 mg SR once daily dose is equally effective and safe as 50 mg twice daily dose in terms of reducing HbA1C, FPG, and PPPG when it is used along with metformin 1000 mg.

KEY WORDS: Vildagliptin; Type 2 Diabetes Mellitus; Efficacy

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INTRODUCTION

Diabetes mellitus (DM) is characterized by persistent hyperglycemia and alteration of metabolism of carbohydrate, fat, and protein occurs due to deficiency of insulin (Type 1) or insensitivity of the target tissues to insulin (Type 2).[1] Deficiency of uncertain is also a major

determinant in Type 2 DM. Appropriately administered oral medication can help patients to achieve target glycemic level over a period of time. OAD drugs have their limitations. Issues related to safety and tolerability, notably weight gain, often limit their optimal application.[2] In spite of growing therapeutic armamentarium, lifestyle modifications and exercise remain the mainstay of the management of Type 2 DM. Initial treatment regimen of Type 2 DM focused on metformin monotherapy. However, evidence suggest beneficial role of early combination therapy not only in patients with higher glycated hemoglobin (HbA1C) levels but also with lower HbA1C levels.[3] Intensification of metformin monotherapy with increased doses has shown improved glycemic control, but it is coupled with increased incidence of gastrointestinal adverse drug reactions leading to decreased patient compliance. Hence, the limitations of step-wise increment of doses during monotherapy with metformin warrant new treatment strategies. Early use of combination therapy before the decrease of responsiveness of metformin monotherapy can proved to be an effective approach.[4]

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that increases responsiveness of alpha (α) and beta (β) cells without increasing the risks of hypoglycemia or promoting weight loss. Vildagliptin appears to offer improved benefit risk profile over traditional drugs. Evidence suggests that vildagliptin increases plasma insulin level, decreases plasma glucagon level, and suppresses endogenous glucose production. Thus, it offers robust control against hyperglycemia.[5] Various clinical trials have proved that combination therapy with vildagliptin and metformin provides superior glycemic control in a dose dependent manner compared to metformin monotherapy.[3,5] It has been also reported that vildagliptin effective and well tolerated in drug naïve patients with Type 2 DM. Evidence also suggests that 100 mg vildagliptin provides similar clinical benefit whether given as single dose or in two divided doses.[6] However, there are no data available on comparison of efficacy and safety of 100 mg single dose vildagliptin with 100 mg vildagliptin in two divided dose in Indian patients with Type 2 DM. Against this backdrop, the present study was conducted to compare efficacy and safety of viladagliptin 50 mg twice daily and metformin combination therapy with vildagliptin 100 mg sustained release tablet (SR) once daily and metformin combination therapy in Indian patients with Type 2 DM.

MATERIALS AND METHODS

It was a prospective, randomized, open-labeled, parallel group Phase IV, and clinical trial. The study commenced after approval of the Institutional Ethics Committee and was conducted according to National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017 of ICMR and the Declaration of Helsinki. Patients were recruited in the diabetes outpatient department under the department of endocrinology of a tertiary care teaching hospital and the study was conducted between November 2021 and February 2022. The data were analyzed and archived in the department of pharmacology. The study was registered under Clinical Trials Registry-India (Registration Number-CTRI/2021/10/037574).

The power of the study was set at 80%, $\alpha = 0.05$, expected standard deviation = 10%. The difference of mean was considered 10% and the true mean difference between two treatment group was set as zero. With these data, the number of patients in each group was 17. Considering a 10% drop out rate, the target recruitment was set at 19 patients in each group. The sample size was calculated using primer of biostatistics software (version 5.0) (Appleton and Lange, New York, USA.).

Adult patients of either gender, aged between 18 and 60 years, and newly diagnosed cases of Type 2 DM (as per per American Diabetes Association [ADA] guidelines)[7] with HbA1C $\geq$6.5 and $\leq$8 were recruited in the study. Patients with fasting plasma glucose (FPG) >250 mg/dl, postprandial plasma glucose (PPPG) >350 mg/dl, pregnant or lactating women, comorbid cardiovascular, renal and psychiatric complications, and coadministration of drugs that were likely to interact with metformin or vildagliptin were excluded from the study.

Patients fulfilling the selection criteria were randomly distributed in two different groups. Randomization was done by coin toss. Patients in Group A received metformin SR (USV limited, Mumbai, Maharashtra India) 500 mg twice daily after food plus vildagliptin (USV limited, Mumbai, Maharashtra India) 50 mg twice daily after food. Patients in Group B received metformin SR (USV limited, Mumbai, Maharashtra India) 500 mg twice daily after food plus vildagliptin (USV limited, Mumbai, Maharastra India) 100 mg SR once daily after lunch. The study drugs were dispensed thrice, once at baseline visit for 4 weeks and subsequently at the first and second follow-up visits for 4 weeks. Patients were asked to take their study medications as per the standard treatment guidelines.

Clinical (body weight) and biochemical examinations were done at baseline (day 0) and at subsequent follow-up visits on weeks 4, 8, and 12. HbA1C was estimated at baseline and at the end of treatment (week 12). Compliance was assessed by pill count at each follow-up visit and at the end of study. Adherence was assessed by Medication Adherence Report Scale. Patients with increasing plasma glucose levels or worsening clinical conditions were withdrawn from the study. All patients were advised to stop consumption of alcohol and smoking throughout the study period. We monitored the patients continuously for any adverse event (AE). Causality analysis of AE was done as per the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria.[8]

Statistical Analysis

Data were collected, checked for completeness, and analyzed statistically. Modified intention to treat principle was adopted

to analyze the data. Patients who reported for at least one post-baseline visit were included for analysis. Safety analysis was done for all enrolled patients. Baseline demographic profile and other categorical data were analyzed by Chi-square test. Numerical data were analyzed by repeated measures analysis of variance and paired *t*-test for intra-group comparison and by unpaired *t*-test for inter-group comparison. *Post hoc* analysis was done by Tukey's honestly significant difference test. $P < 0.05$ was considered to be statistically significant.

RESULTS

The present randomized, open label, and Phase IV parallel group study included 120 patients. Participant on fulfilling the selection criteria was enrolled and randomized to either vildagliptin 50 mg twice daily arm (Group 1) or vildagliptin 100 mg SR preparation once daily (Group 2). Both arms also received tablet metformin 500 mg in twice daily dosing (Hospital supply medicine-manufactured by Apple Pharmaceuticals Pvt. Ltd., Uttarakhand Batch No-MSR-1903, Mfg-12/2020-Exp 11/2022). Two participants from Groups 1 and 3 participants from Group 2 discontinued their visits from 8th week and, hence, were considered dropouts. The final analysis thus includes 58 participants in Group 1 and 57 participant in group 2 [Figure 1]. Sex ratio was observed to be 3:1 (Male: Female). Information on smoking and alcohol intake details was obtained.

The groups were matched for baseline glycemic indices (HbA1C%, FBG, PPBG) and body weight. No significant difference was observed between the groups [Table 1]. Treatment with vildagliptin 50 mg twice daily or 100 mg SR formulation once daily, showed significant decrease in HbA1C%, FBG, and PPBG levels from their respective baseline values for both groups ($P < 0.05$) [Tables 2 and 3]. However intergroup comparison showed no significant changes in glycemic indices at 12th week [Table 4]. In both arms, there was a statistically significant weight loss at the end of 12th week compared to the baseline values, when compare baseline body weight to body weight at 12th week. However, since metformin can also cause reduction in body weight, so from this study, we cannot specifically comment if the body weight reduction is due to vildagliptin or metformin or by its combined effect. However, this finding at least affirms the weight neutrality of vildagliptin whether given as 50 mg twice daily or 100 mg SR dose. Liver enzymes did not show any statistically significant changes at the end of 12th week in either of the intervention groups. This reassures the safety of SR100 mg vildagliptin given once daily so far as alteration in liver enzyme parameter is concerned [Tables 5 and 6].

Safety analysis was carried out for all randomized patients and no major AEs were noted. Only mild headache was noted in three patients from Group 2 in the initial period of therapy, which subsided within a week. No patients were withdrawn from the study due to safety concerns. As Per WHO-UMC causality assessment criteria, the three reported AEs were under "possible" category. No episode of hypoglycemia occurred during the study time.

DISCUSSION

Type 2 DM is increasing worldwide as a lifestyle disease. It is not only a disease of increasing blood sugar, but also it can harm heart, kidney, brain, and eye even feet. Beside insulin,

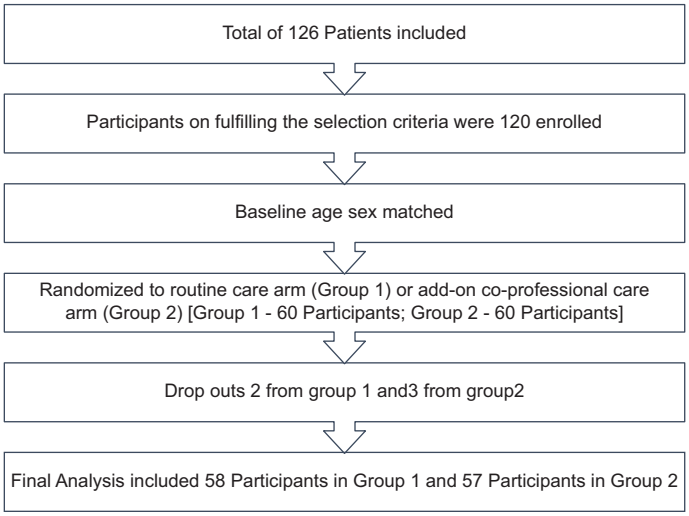

Figure 1: The consort flowcharts

Table 1: Baseline parameters

Parameter	Group 1	Group 2	*P*-value
HbA1C (in %)	9.13±1.74	9.49±1.19	0.664
FBG (in mg/dl)	193.6±32.7	203.68±38.18	0.123
PPBG (in mg/dl)	314.10±68.48	314.85±62.06	0.95
Body Weight (in kg)	65±5.9	63.83±8.23	0.37

HbA1C: Glycated hemoglobin, FBG: Fasting Plasma Glucose, PPBG: Postprandial plasma glucose

Table 2: Effect of vildagliptin 50 mg twice daily

Parameters	Baseline	Week 12	*P*-value
HbA1C (in %)	9.17±0.954	6.641±0.476	0.001
FBG (in mg/dl)	194.76±32.65	116.0±21.64	0.001
PPBG (in mg/dl)	317.09±67.69	162.09±12.40	0.001
Body Weight (in kg)	64.9±5.96	63.64±5.87	0.05

HbA1C: Glycated hemoglobin, FBG: Fasting Plasma Glucose, PPBG: Post prandial plasma glucose

Table 3: Effect of vildagliptin 100 mg sustained release tablets once daily

Parameters	Baseline	Week 12	*P*-value
HbA1C (in %)	9.023±1.069	6.5±0.45	0.001
FBG (in mg/dl)	203.68±38.18	115.84±12.91	0.001
PPBG (in mg/dl)	311.95±62.34	157.51±14.22	0.001
Body Weight (in kg)	64.04±8.34	63.16±8.24	0.04

HbA1C: Glycated hemoglobin, FBG: Fasting Plasma Glucose, PPBG: Postprandial plasma glucose

Table 4: Intergroup Comparison

Parameters	Group 1(V50)	Group 2 (V 100)	*P*-value
HbA1C (in %)	6.64±0.47	6.5±0.45	0.115
FBG (in mg/dl)	116.0±21.64	117.12±10.68	0.72
PPBG (in mg/dl)	162.09±12.40	57.85±14.10	0.08
Body Weight (in kg)	63.64±5.87	63.27±8.1	0.11

HbA1C: Glycated hemoglobin, FBG: Fasting Plasma Glucose, PPBG: Postprandial plasma glucose

Table 5: Effect of vildagliptin 50 on bilirubin, SGPT, and SGOT

Parameter	Baseline	Week 12	*P*-value
Bilirubin (in mg/dL)	0.64±0.23	0.62±0.3	0.196
SGOT (in U/L)	56±10.75	55.92±10.79	0.095
SGPT (in U/L)	51.5±6.13	52±6.18	0.832

Table 6: Effect of vildagliptin 100 on bilirubin, SGPT, and SGOT

Parameter	Baseline	Week 12	*P*-value
Bilirubin (in mg/dL)	0.74 ± 0.170	0.75 ± 0.75	0.195
SGOT (in U/L)	53.98 ± 7.1	53.84 ± 7.3	0.911
SGPT (in U/L)	53.53 ± 7.5	53.45 ± 7.7	0.388

there are several oral antidiabetic agents available starting from biguanides and sulfonylurea to DPP4 inhibitor and very recently SGLT2 inhibitor. All have some advantages and disadvantages. As per guidelines (ADA 2021), Type 2 diabetes patient whom HbA1C ranges between 6.5 and 9 can be treated by two antidiabetic drugs along with lifestyle modification. Vildagliptin is a DPP4 Inhibitor. It increases intact GLP1 level both after meal and fasting state. It also stimulates insulin secretion and inhibit glucagon release. It improves insulin sensitization and prevent hepatic glucogenesis. All this action helps to decrease blood sugar level both FPG and PPPG. Previously, vildagliptin is available in 50 mg dose and patient has to take it twice daily which was little bit troublesome to patient particularly in view of adherence. Hence, there is always a need for a new dosages form which improves patient adherence. Data from our studies suggest that this new 100 mg SR formulation is equally effective as 50 mg twice daily tablets in terms of efficacy that is reducing HbA1C, FBG, and PPBG.

Safety analysis of our study shows that both vildagliptin 100 mg SR preparation and vildagliptin 50 mg tablets are equally safe in term of liver enzyme increasing. None of our patients are withdrawn from the study.

However, the study had certain limitations. The duration of study was relatively short and sample size was also limited due to logistic problems. Moreover, the COVID-19 pandemic also limited patients' visit to the hospital facility. We hope to overcome these limitations in future research to evaluate the efficacy and safety of this new promising agent.

CONCLUSION

The result of this randomized, open label, Phase 4, and clinical trial showed that 100 mg SR vildagliptin daily tablets once daily dose along with 1000 mg metformin in two divided dose is equally effective as 50 mg twice daily vildagliptin along with 1000 mg metformin in two divided doses in terms of reducing HbA1C, FBG, and PPBG. Both the drugs are equally safe in the parameter of changes in liver enzymes (SGOT and SGPT) and serum bilirubin.

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