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EFFICACY AND SAFETY OF VILDAGLIPTIN AND TENELIGLIPTIN IN PATIENTS OF TYPE 2 DIABETS MELLITUS INADEQUATELY CONTROLLED ON STABLE DOSES OF METFORMIN

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ABSTRACT: This was a 24-week, randomized, open label study. Treatment-naive patients diagnosed with Type 2 diabetes mellitus were randomized into two groups, Group-1 (Vildagliptin 50 mg, twice dailyplus Metformin 500 mg, twice daily) and Group-2 (Teneligliptin 20 mg, once dailyplus Metformin 500 mg, twice daily). The primary objective was to compare fasting plasma blood glucose levels (FBG), 2-h post prandial blood glucose levels (2-h PPG) and HbA1c reduction from baseline in both the groups at the week 24 endpoint. From comparable baseline values HbA1c decreased in both treatment groups, to the greater extent with teneligliptin plus metformin combination therapy. Reductions in FPG were superior with teneligliptin plus metformin combination therapy [change from baseline -38.63 mg/dL] ($p>0.05$). Reductions in 2-h PPG were also superior with teneligliptin plus metformin combination therapy [change from baseline -37.85 mg/dL] ($p>0.05$). There was no incidence of hypoglycemia with either combination therapy. Efficacy and Safety of Teneligliptin over a period of 24 weeks was comparable to that of vildagliptin when given with stable doses of Metformin.

INTRODUCTION: Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [1]. Depending on the etiology of diabetes, factors contributing to hyperglycemia comprise reduced insulin secretion, decreased glucose utilization, and increased glucose production [2]. Globally, 425 million people are affected with diabetes and Type 2 diabetes (type 2 DM) is also increasingly seen in younger adults nowadays. India is heading towards being the diabetes capital of the world indicating that every fifth diabetic in the world is an Indian [3].

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Studies have shown that India has a potential epidemic of diabetes and by the year 2040, incidence of diabetes mellitus will increase [4]. The treatment goal for diabetes is usually individualized based on patient preferences and disease factors [5]. With the use of anti-diabetic agents in current therapeutic options, only 37% of the patients achieve a glycosylated hemoglobin (HbA1c) $\leq$7.0% [6].

Metformin is the first line therapy for type 2 DM but due to natural progression of the deterioration of beta cells additional therapies are often required to target various pathophysiological mechanisms. Sulfonylureas are the most common next therapeutic step when patients do not achieve or maintain glycemic control on metformin alone [7, 8], but they can cause hypoglycemia. Even the combination therapy may not be able to achieve glycemic control and insulin is often the subsequent choice.

Thiazolidinedione, which can be added to the therapy, may lead to edema and an increase in body weight. The risk of heart failure appears to be a class effect of the thiazolidinediones [9, 10].

Gliptins or dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of orally administered glucose lowering agents for Type 2 DM. These drugs can augment the effect of incretin hormones, glucose dependent insulinotropic polypeptide and Glucagon like peptide-1. Compared to the other oral hypoglycemic agents, gliptins possess several clinical advantages like a negligible risk of hypoglycemia and weight neutrality [11].

Vildagliptin is an effective and well tolerated DPP-4 inhibitor and addition of it in uncontrolled patients on metformin monotherapy is associated with a significant improvement in the control of HbA1c [12].

Teneligliptin is another novel, highly selective DPP-4 inhibitor with long half-life, approved in Japan (2012) and in Korea (2014) to treat patients of type 2 DM. It is characterized by a considerably rigid structure formed by five consecutive rings [13, 14]. Teneligliptin, 20mg/day as monotherapy and combination therapy in type 2 DM was shown to be effective in reducing HbA1c and fasting plasma glucose levels without any significant adverse events [15, 16]. However the efficacy and safety of teneligliptin demonstrated so far is based on researches done over a short time period. Teneligliptin is currently marketed in India with limited number of available clinical studies and data comparing the efficacy and safety of the various DPP-4 inhibitors are very few.

Therefore, the present study was designed to assess the efficacy and safety of vildagliptin and teneligliptin in patients of type 2 DM.

METHODS: The present study was conducted in the Department of Pharmacology and Rajiv Gandhi Centre for Diabetes and Endocrinology, JN Medical College and Hospital, AMU Aligarh on the patients of Type 2 DM attending the OPD from March 2016 to September 2017. This was a randomized, prospective, open labelled and parallel group study. Eligible patients were randomized into two groups (Group 1 and Group 2) according to the table generated by random allocation software. The randomization was generated having 20 patients in each block.

Ethical clearance for the study protocol was obtained from the Institutional Ethics Committee (IEC) of J.N. Medical College and Hospital, AMU, Aligarh on 02.02.2016(D. No: 2249/FM).

The study was also registered with Clinical Trial Registry of India (CTRI/2017/02/007766).

Patients with type 2 DM having inadequate glycemic control on Metformin 500 mg twice daily were selected for the study. Patients on other oral antidiabetic agents and significant systemic illness were excluded from the study.

Informed and written consent was obtained from all patients before enrolling them in the study.

Diagnosis of diabetes was made according to criteria for the diagnosis of diabetes mellitus of American Diabetes Association, 2017 [17].

The patients were divided into two groups:

Group1: Vildagliptin (50 mg, twice a day) was administered as add-on therapy to all the patients of Group1 (n = 21) who were already receiving Metformin (500mg) twice a day

Group 2: Teneligliptin (20 mg, once a day**)** was administered as add-on therapy to all the patients of Group 2 (n = 19) who were already receiving Metformin (500 mg) twice a day.

The patients of all groups were followed up at 6, 12, 18 and 24 weeks. They were also advised to consult the endocrinologist / treating physician / investigator for any queries or adverse effect of medicines if occurring during the treatment period. All the patients were recommended to take diabetic diet as advised by the registered dietician of the hospital.

HbA1c, FPG, 2-h PPG, Complete blood count, Renal Function Test, Urine- Routine/Microscopic, Liver Function Test, Lipid Profile, C-reactive proteins and other investigations (as and when indicated) were done. The efficacy of vildagliptin and teneligliptin, was compared by measuring the Fasting Plasma Glucose: 0 (baseline values), 6, 12,

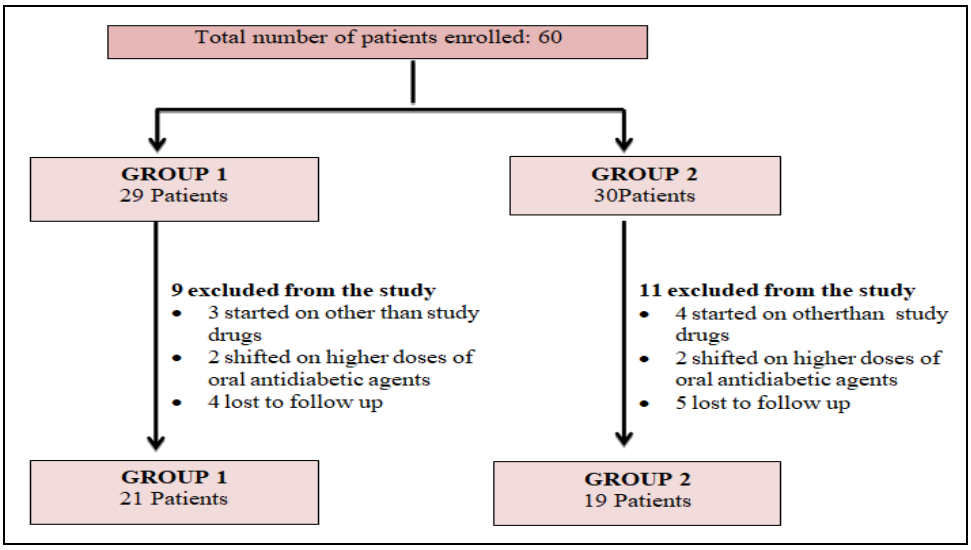
18 and 24 weeks; 2 h Post Prandial Plasma Glucose: 0, 6, 12, 18 and 24 weeks; Glycosylated Hemoglobin: 0, 12 and 24 weeks.

Safety assessment was done using Naranjo's Adverse Drug Reaction Probability Scale [18]. Severity of the reaction was assessed using Adverse Drug Reaction Severity Assessment Scale, Modified Hartwig and Siegel [19].

Statistical Analysis: For descriptive statistics; frequency, percentage, mean ± standard deviation, graph and pie charts were used to present the study results. Intra and inter-group analysis of the two groups was done using repeated measure ANOVA (RM-ANOVA). P<0.05 was considered as statistically significant. Statistical analysis was done using Statistical Package for Social Sciences (SPSS-23) software and charts were prepared using Microsoft Excel 2013.

OBSERVATIONS AND RESULT: A total of 60 patients were enrolled, 30 patients in each (Group 1 and Group 2) and finally 21 patients of group 1 and 19 patients of group 2 were analyzed.

Flow Chart Showing the Distribution of Patients in the Study:



The age of patients varies from 25 years to 75 years. The mean BMI of patients in Group1 and Group 2 was 27.87 ± 3.07 and 27.75 ± 3.75 kg/m^2 respectively.

Five patients of Group-1 and three patients of Group-2 were also receiving Aspirin (75 mg) once a day. Four patients of Group-1 and three patients of Group-2 were on Telmisartan (40 mg - 80 mg). Two patients in Group-1 and three patients in Group-2 were on metoprolol (12.5-50 mg) once a day.

Efficacy Outcomes: The mean values of fasting plasma glucose (FPG) at 0 week (baseline) in Group 1 and Group 2 were statistically insignificant (p>0.05). The reduction in mean values of FPG, when compared to baseline, was significant, at all times points (at 6, 12, 18 and 24 weeks) within the groups (p < 0.001). However, the reduction in FPG in Group-1 and Group-2 at 6, 12, 18 and 24 weeks when compared with baseline values of two groups were found to be statistically insignificant (p>0.05) **Table 1**.

TABLE 1: MEAN FASTING PLASMA GLUCOSE (FBG) LEVELS

Groups	Baseline (mg/dL) Mean ± SD	6 weeks (mg/dL) Mean ± SD	12 weeks (mg/dL) Mean ± SD	18 weeks (mg/dL) Mean ± SD	24 weeks (mg/dL) Mean ± SD	Percentage Reduction	Intragroup comparison	Intergroup comparison
Group 1 (n= 21)	124.28 ±46.64	116.00 ±36.29	109.71 ±31.48	105.38 ±25.49	94.14 ±18.52	24.25	p< 0.001	p> 0.05
Group 2 (n= 19)	131.73 ±30.95	114.00 ±27.13	106.36 ±23.53	102.31 ±22.24	93.10 ±15.35	29.32	p< 0.001	p> 0.05

Values are expressed as Mean ± SD; Intragroup comparison shows highly significant values (p<0.001) at all-time points when compared to baseline value of respective group. Values were not significant (p>0.05) in intergroup comparison.

The mean values of 2 hours 2-h PPG at 0 week (baseline) in Group 1 and Group 2 were statistically insignificant (p>0.05). The reduction in mean values of 2-h PPG, when compared to baseline, was significant, at all times points (at 6, 12, 18 and 24 weeks) within the groups (p<0.001). However, the reduction in PPG in Group-1 and Group-2 at 6, 12, 18 and 24 weeks when compared with baseline values of two groups (Group 1 and Group 2) was found to be statistically insignificant (p>0.05) **Table 2**.

TABLE 2: MEAN 2 HOURS POST PRANDIAL PLASMA GLUCOSE (2 h PPG) LEVELS

Groups	Baseline (mg/dL) Mean ± SD	6 weeks (mg/dL) Mean ± SD	12 weeks (mg/dL) Mean ± SD	18 weeks (mg/dL) Mean ± SD	24 weeks (mg/dL) Mean ± SD	Percentage Reduction	Intragroup comparison	Intergroup comparison
Group 1 (n=21)	183.85 ±56.79	175.14 ±36.27	163.71 ±40.99	171.61 ±29.24	150.23 ±33.44	18.28	p<0.001	p>0.05
Group 2 (n=19)	188.21 ±52.15	179.73 ±33.33	168.63 ±34.75	161.05 ±24.12	150.36 ±25.60	20.11	p< 0.001	p > 0.05

Values are expressed as Mean ± SD; Intragroup comparison shows highly significant values (p<0.001) at all-time points when compared to baseline value of respective group. Values were not significant (p>0.05) in intergroup comparison.

The values of HbA1c at 0 week (baseline) in Group-1 and Group-2 were statistically insignificant (p>0.05). The reduction in mean values of HbA1c, when compared to baseline, was significant, at all times points (at 12 weeks and 24 weeks) within the groups (p<0.001). However, the reduction in HbA1c in Group 1 and Group 2 at 12 and 24 weeks was found to be statistically insignificant (p>0.05) **Table 3**.

TABLE 3: MEAN GLYCOSYLATED HEMOGLOBIN (HbA1c) LEVELS

Groups	Baseline (%) Mean ± SD	12 weeks (%) Mean ± SD	24 weeks (%) Mean ± SD	Percentage reduction at 24wks	Intragroup comparison	Intergroup comparison
Group 1 (n=21)	7.80 ± 1.22	7.21 ± 0.99	6.63 ± 0.68	15.00%	p< 0.001	p> 0.05
Group 2 (n=19)	7.63 ± 1.12	6.92 ± 1.11	6.42 ± 0.84	15.86%	p< 0.001	p> 0.05

Values are expressed as Mean ± SD; Intragroup comparison shows highly significant values (p<0.001) at all-time points when compared to baseline value of respective group. Values are not significant (p>0.05) in intergroup comparison.

Safety Assessment: In Group 1, five patients experienced adverse events and in Group 2, six patients experienced adverse events. The most commonly observed adverse event was nausea, followed by headache. Other adverse events observed were vomiting and change in bowel habit.

No adverse events in patients of any group who have completed study required discontinuation of therapy. The adverse events were mild to moderate in severity in all of the cases. On Naranjo's ADR Probability Scale [18], the events were possible in 2 cases and probable in 2 cases in Group 1, while possible in 3cases and probable in 2 cases in Group 2.

DISCUSSION: Metformin, the first line therapy for type 2 DM has been shown to delay the progression of diabetes patients by decreasing hepatic glucose synthesis and sensitizing peripheral tissues to insulin [20]. However, the use of metformin may cause gastrointestinal disturbances, including diarrhea and nausea in almost 30% of patients [21, 22]. Sulfonylureas often added to metfomin may cause hypoglycemia [23].

Gliptin when administered to patients inadequately controlled with metformin cause a considerable improvement in HbA1c (0.50–0.75%) with twice the number of patients achieving an HbA1c of <7% compared to metformin alone [24].

For patients with HbA1c between 7-8% while on metformin therapy if a gliptin is added to already existing dose of metformin rather than increasing the dose of metformin, the HbA1c reduction is greater than up-titrating the dose of metformin [25]. Vildagliptin when added to metformin in patients with type 2 DM, the improvement in beta cell function, post-meal insulin sensitivity with lowering the levels of HbA1c and fasting plasma glucose significantly has been seen [26].

In the present study, vildagliptin (50 mg, twice a day) and teneligliptin (20 mg, once a day) were added in patients with type 2 DM inadequately controlled on stable doses of metformin (500 mg twice a day). Results showed a change in mean HbA1c-1.17% from the baseline in the Group 1 and -1.21% in Group 2 **Table 3** at 24 weeks of study period. The vildagliptin as an add-on therapy with metformin have lower incidence of hypoglycemia compared to sulfonylurea group [27, 28].

Our study results showed adverse events similar in profile to the previous studies with no episode of hypoglycemia reported in either of the groups receiving vildagliptin or teneligliptin. The reduction in HbA1c, FPG, 2-h PPG was greater in the group receiving teneligliptin. This may be explained by the structural advantage of teneligliptin, which binds to the S2 extensive subsites *via* an 'anchor lock domain', and this interaction may be related to the increased strength of inhibition, the residual time for binding to DPP-4, and the long duration of action *in-vivo* [13].

Kutoh E *et al*., (2014) reported in 12-week study, a significant change in HbA1c (-1.96%) and fasting blood glucose (-44mg/dL) after administration of teneligliptin [16]. We observed in the present study that at 12-week, the change in HbA1c levels from baseline values in vildagliptin and teneligliptin were 0.59% and 1.17% respectively. The reduction in Post Prandial Plasma Glucose at 2 h in Vildagliptin was 33.62 mg/dl and in Teneligliptin group was 37.85 respectively. Kim MK *et al*., (2015) in 16-week study where teneligliptin (20 mg, OD), as add on therapy to stable doses of metformin (>1000mg/day) improved HbA1c (-0.78%) and Fasting plasma glucose (-22.42mg/dl) in Korean patients with type 2 DM.

Teneligliptin has a pharmacokinetic advantage of a longer half-life of 24.2 h and causes more than 90% inhibition of the DPP-4 activity even after a period of 24 h, which favors once a day regimen for this drug [14, 29].

In present study, lipid profile, liver function tests (Serum bilirubin, AST, ALP) and renal function tests (Blood urea, serum creatinine) showed no significant change over 24 weeks in either group with stable doses of metformin.

Kadowaki K *et al*., (2015) reported that teneligliptin alone and in combination with sulfonylureas, metformin, the incidence of adverse events was similar in all groups except the combination with a sulfonylurea [28]. There have been studies comparing gliptins to other classes of antidiabetic agents, but studies showing a comparison between the gliptins are very few. There are structural differences among the various gliptins and also in the manner they bind to the enzyme, DPP-4. These differences might be significant in terms of efficacy and safety.

CONCLUSION: Teneligliptin showed a reduction of mean HbA1c over a period of 24 weeks, which was comparable to that of vildagliptin when given with stable doses of metformin. Teneligliptin has a longer half-life and is administered once daily as compared to vildagliptin, which is administered twice daily. Patients in both the groups showed similar tolerability profile with no significant adverse event requiring a change in therapy. They cause lesser episodes of hypoglycemia and are weight neutral. However, long term safety and efficacy studies of Teneligliptin need to be done to establish its beneficial role in the management of type 2 DM.

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