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Original Research Article

Effect of teneligliptin vs metformin on glycemic control in Indian patients with newly-diagnosed, drug-naïve type 2 diabetes mellitus: a 12-week randomized comparative clinical study

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ABSTRACT

Background: This comparative study was done to evaluate the change from baseline in HbA1c levels with teneligliptin vs. metformin treatments at week 12 among recently diagnosed type 2 DM patients attending Medicine OPD of Dr. B. C. Roy Hospital, Haldia, West Bengal (a tertiary care teaching hospital).
Methods: In this prospective parallel group clinical study patients were divided into two groups. Group A patients were on metformin monotherapy therapy and Group B patients were on teneligliptin monotherapy. Data of 40 patients (20 patients in each group) were available for analysis in the present study. Secondary endpoints included changes from baseline FPG and 2h-PPG values at 12 weeks were evaluated. Safety and tolerability were assessed by the incidence of adverse events (AEs) throughout the study period.
Results: The mean age of patients was 50.05±12.35 years and out of the entire patient population 70% were males and 30% were females. At the end of 12 weeks or 3 months of metformin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 0.52%, 16.2mg/dL, and 36.8mg/dL, respectively, and 37.75% of patients achieved the HbA1c target of <7%. At the end of 12 weeks or 3 months of teneligliptin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 0.60%, 19.4mg/dL, and 49.8mg/dL, respectively (Table 2), and 40% of patients achieved the HbA1c target of <7%.
Conclusions: Teneligliptin, a DPP4 inhibitor reduced HbA1C significantly compared with monotherapy of metformin in treatment naive patients at week 12. It also reduced FBG and 2-h PPBG as compared with metformin at week 12.

Keywords: Clinical study, DPP-4 inhibitor, Efficacy, HbA1C, Metformin, Oral antidiabetic drugs, Teneligliptin, Type 2 diabetes

INTRODUCTION

Diabetes is one of the most challenging health problems of the 21st century. It is estimated that by 2040, some 642 million people, or one adult in 10, will have diabetes. This equates to almost 10 million new cases per year. As per the International Diabetes Federation (IDF) 2015 report, India is harbouring 69.2 million diabetes patients, second only to China (109.6 million). If the current trends continue, by 2040 India will have about 123.5 million patients with diabetes.[1] Metformin has been found to be useful in the prevention of development of diabetes in

many large, well-powered trials. It helps in maintaining diet-induced weight loss and lowers fasting plasma insulin concentrations, total and low density lipoprotein-cholesterol, and free fatty acids. These effects make metformin a first-line agent for the prevention of type 2 diabetes as recommended by the ADA. However, most patients require a combined therapy to reach and/or maintain targets of glucose control. Many patients with T2DM remain inadequately managed, which results in progressively declining glycemic control.[2] Oral antidiabetic drugs (OADs) present multiple drawbacks such as treatment-limiting adverse effects, including hypoglycemia, gastrointestinal (GI) disorders, edema, and weight gain.[3] Dipeptidyl peptidase 4 (DPP-4) inhibitor is a relatively new class of antihyperglycemic agents that are now recommended as second- or first-line agents in treatment of diabetes by guidelines like American Diabetes Association (ADA) 2016 and American Association of Clinical Endocrinologists and American College of Endocrinology 2016.[4-6]

DPP-4 inhibitors control fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels through selective inhibition of DPP-4, resulting in increased plasma concentrations of active glucagon-like peptide-1. DPP-4 inhibitors unlike sulfonylureas, meglitinides, or insulin are weight neutral and no risk of hypoglycaemia.[7,8] Teneligliptin is a novel DPP-4 inhibitor, having a unique chemical structure which is characterized by five consecutive rings (J-shaped), which might account for its unique potency and half-life time.[8] It was introduced in India in May 2015 and is available at almost one quarter to one fifth of the cost of other DPP-4 inhibitors (namely sitagliptin, vildagliptin, saxagliptin, and linagliptin). In a very short span of time (8-9 months) teneligliptin has become the most widely prescribed DPP-4 inhibitor in India.[9] Efficacy and safety of teneligliptin has been established in Japanese, Chinese and Korean populations in several randomized controlled trials with limited sample size.[7,10,11]

Several large studies from Asia and other continents have demonstrated clinically meaningful improvements in glycemic control, enhanced b-cell function, and a good safety profile of linagliptin 5 mg alone or in combination with other OADs.[12-16] Till date in India the only few data are available regarding safety and efficacy of monotherapy in type 2 DM patient.[6,17] Metformin mainly decreases FPG, while DPP-4 mainly inhibits PPG.[18] Therefore, DPP-4 inhibitors could be more efficient in Indian patients consuming a traditional Indian diet. However, there is a lack of data about teneligliptin monotherapy in Indian patients' especially eastern part of India with newly diagnosed T2DM. Therefore, this randomized, open labeled, parallel-group trial was carried out under active guidance of treating physicians and guide to examine the efficacy and safety of teneligliptin as initial therapy in treatment naïve Indian patients with newly-diagnosed T2DM.

METHODS

A randomized, open label, parallel-group clinical study was carried out under active guidance of treating physicians and guide to examine the efficacy and safety of teneligliptin as initial therapy in treatment-naïve Indian patients with newly-diagnosed T2DM in the Outpatient Department of Medicine, in Dr B C Roy Hospital associated with ICARE Institute of Medical Sciences and Research, Haldia, West Bengal for 3 months in 2017. Permission from the Institutional Ethics Committee was obtained before starting research work. Subjects and their accompanying family members were interviewed by pre-structured questionnaire. All decisions relating to management of the patient including drugs and investigations was taken by the treating physician only. Investigator did not interfere in the management of patient and only observed the proceedings.

Inclusion criteria

- Type 2 diabetes mellitus patients aged ≥18 to ≤65 years inclusive of either sex
- Patient with inadequate glycaemic control (glycosylated haemoglobin (HbA1c) >7% to ≤8.5%) with diet and exercise therapy alone and treatment naive.
- Patient with ability to understand and provide written informed consent form, which must have been obtained prior to screening.

Exclusion criteria

- Patients with type 1 diabetes, secondary diabetes, acute complications of diabetes,
- Pregnant or lactating women,
- Patients with known hypersensitivity to any of the components of the formulation,
- Known cases of diabetic nephropathy, diabetic ketoacidosis, diabetic coma, hyperglycemia hyperosmolar state, retinopathy, neuropathy,
- Patients with hypertensive emergencies, unstable coronary heart disease, acute myocardial infarction, acute left ventricular failure, advanced kidney or liver failure, and cerebral stroke, severe infection etc. or any other medical illness that may affect patient safety or difficult to evaluate the efficacy of the product.
- Patients receiving treatment with systemic corticosteroids.
- Subjects not agreeing to participate.

All patients were treatment-naïve before enrolment except for diet and physical exercise therapy. Recently diagnosed Type 2 DM patients attending Medicine OPD at Dr. B C Roy Hospital, Haldia, West Bengal, India.

A sample size of 40 randomized Type 2 DM patients (20 subjects in each group), assuming a 15% drop-out rate will be studied because time and facility constraints. This

will provide 80% power to detect a mean difference of 0.7% [standard deviation (SD) of 0.8%] in the change from baseline in HbA1c levels between the teneligliptin and metformin groups at week 12, at a 2-sided significance level of 0.05. It was a randomized, open label, comparative study. Randomization was done by using a computer-generated random sequence and sealed envelopes prepared in advance. The total study duration for each subject will be 12 weeks. The efficacy and tolerability of the treatment was assessed at 6 and 12 weeks. Patients will be continuously advised on lifestyle modification.

investigational product (s), dose, and mode of administration

Investigational Product: Teneligliptin, Dosage form: Tablets, Dosage: 20mg.

Dosage Frequency

One tablet to be taken orally once daily before breakfast every morning. In case patients were not controlled on 20mg Teneligliptin, dose may be uptitrated to 40mg daily. The 40mg dose was administered as two 20mg tablets taken orally once daily before breakfast every morning. Mode of administration: Oral.

Comparator: Metformin, oral dosage form, 500mg tablet orally initially OD, then BD if not controlled. HbA1c, FPG and PPG levels was assessed at each visit. At 0, 6, and 12 weeks; tests evaluating liver functions, blood lipid profiles, blood amylase was performed at 0 and 12 weeks.

RESULTS

Of the 76 subjects screened, 49 eligible subjects were randomized to treatment as follows: 25 received teneligliptin and 24 received metformin monotherapy. In total, 40 subjects (81.63%), 20 in each group completed 12 weeks of treatment. Our analysis set consisted of 40 subjects for whom baseline and post-baseline values of the primary efficacy endpoint were available. In this prospective parallel group clinical study patients were divided into two groups. Group A patients were on metformin monotherapy therapy and Group B patients were on teneligliptin monotherapy.

Table 1: Demographic, clinical and laboratory characteristics of the study participants.

Patients characteristics	Group A [metformin monotherapy therapy] N (Percentage)	Group B [teneligliptin monotherapy]	P Value
Number of patients	20	20	-
Gender			
Male	13 (65%)	14 (70%)	-
Female	7(35%)	6 (30%)	
Age			
≤60 years	13 (65%)	15 (75%)	-
>60 years	7 (35%)	5(25%)	
Age [Mean±SD]	50.4±12.8 years	49.7±11.9 years	0.8588 [95% CI -8.6113 to 7.2113]
BMI (Mean ±SD)	27.2±4.4 kg/m^2	26.9±3.8 kg/m^2	0.8187 [[95% CI-2.9317 to 2.3317]
FBG (Mean ±SD)	164±29.4 mg/dl	168.8±25.8 mg/dl	0.5864 [95% CI-12.9062 to 22.5062]
PPBG (Mean ±SD)	244.4±32.4 mg/dl	247.3±35.5 mg/dl	0.7887 [95% CI-18.8564 to 24.6564]
HbA1c (Mean ±SD)	7.58±0.85	7.65±0.78	0.7876 [95% CI-0.4522 to 0.5922]
LDL- C (Mean ±SD)	132±39.7 mg/dl	141±48.8 mg/dl	0.5261 [95% CI-19.4769 to 37.4769]
HDL (Mean ±SD)	42.8±6.5 mg/dl	45.9±5.2 mg/dl	0.1040 [95% CI-0.6680 to 6.8680]
Triglyceride (Mean ±SD)	190.8±33.9 mg/dl	189.8±30.7 mg/dl	0.9226 [95% CI-21.7028 to 19.7028]
Serum amylase	82±45 U/L	77±28 U/L	0.6755 [95% CI-28.9914 to 18.9914]
Alanine aminotransferase	37±16 U/L	32±12 U/L	0.2706 [95% CI-14.0534 to 4.0534]
Alkaline phosphatase	62±29 U/L	67±23 U/L	0.5494 [95% CI-11.7548 to 21.7548]
Presence of comorbidities			
Hypertension	6 (30%)	7 (35%)	-
Dyslipidemia	5 (25%)	7 (35%)	
CV events	2 (10%)	3 (15%)	
Active hepatic disease	1 (5%)	0	
Active renal disease	0	0	

Table 1 shows the baseline demographic and clinical characteristics of the study participants. Total number of patients, mean age of patients and gender distribution were almost similar in both groups. The groups were not significantly different with respect to demographic or clinical characteristics. The mean age of patients was 50.05±12.35 years and out of the entire patient population 70% were males and 30% were females. Almost 59% (n=40) of patients had comorbid conditions, and hypertension (32.5%), and dyslipidemia (30%) being the most common (Table 1).

The glycaemic efficacy was assessed by analysing the mean changes in the values of FBG, PPBG and HbA1c from start of therapy to the end of 12 weeks study period. The mean baseline HbA1c value was 7.65% in the teneligliptin group and 7.58% in the metformin group (Table 1). The mean baseline FBS value was 168.8 mg/dl in the teneligliptin group and 164 mg/dl in the metformin group.

At the end of 12 weeks or 3 months of metformin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 0.52%, 16.2mg/dL, and 36.8mg/dL, respectively (Table 2), and 37.75% of patients achieved the HbA1c target of <7%. At the end of 12 weeks or 3 months of teneligliptin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 0.60%, 19.4mg/dL, and 49.8mg/dL, respectively (Table 2), and 40% of patients achieved the HbA1c target of <7%. Significant reduction in HbA1c by 0.60% was seen in patients receiving teneligliptin monotherapy but no significant reduction in HbA1c metformin, monotherapy (Table 2). In patients receiving teneligliptin monotherapy, 35.48% of patients achieved HbA1c target of <7%. The mean changes from baseline FBG values were -19.4 mg/dl for the teneligliptin group compared with -16.2 mg/dl for the metformin group (p=0.0840), but not significant in between groups. A greater decrease in PPBG (-49.8 mg/dl) was observed in the group B (teneligliptin) compared with the metformin group A at 6 week [p<0.05] and throughout the randomized treatment period. A greater decrease in HbA1c (0.60%) was observed in the group B (teneligliptin) compared with the metformin group A at 12 week [-0.052%] [p=0.0943] and throughout the randomized treatment period. A significantly greater proportion of patients achieved a therapeutic glycemic response (HbA1C<7%) with group B teneligliptin than group A metfomin (40% vs 30%, respectively; p=0.0943) (Table 2).

Table 2: Changes of glycemic parameters with metformin vs teneligliptin.

Parameter	Treatment Group	Baseline values	Changes upto end of treatment period 6 weeks	Changes upto end of treatment period 12 weeks	Change from baseline	P Value
FBG [mg/dl] (Mean ±SD)	Group A [Met] n=20	164 ±29.4	139.7±27.5	147.8±25.5	-16.2	0.0704 [95% CI -33.8169 to 1.4169]
	Group B [Lina] N=20	168.8±25.8	141.2±24.7	149.4±26.5	-19.4	0.0243* [95% CI -36.1419 to -2.6581]
PPBG [mg/dl] (Mean ±SD)	A	244.4±32.4	224.4±37.4	207.6±33.5	-36.8	0.0011** [95% CI -57.8965 to -15.7035]
	B	247.3±35.5	214.5±32.5	197.5±33.6	-49.8	0.0001** [95% CI -71.9262 to -27.6738]
HbA1c (Mean ±SD)	A	7.58±0.85	7.24±0.79	7.06±0.93	-0.52	0.0727 [95% CI -1.0903 to 0.0503]
	B	7.65±0.78	7.25±0.83	7.05±0.85	-0.60	0.0255* [95% CI -1.1222 to -0.0778]

Paired Student's t-test was used to compare the changes of the indicated parameters before and after treatment. The results are expressed as the mean ± SD. *P value <0.05, ** P value <0.001

Mean serum LDL level was greater reduced (-18.2mg/dl) in teneligliptin group than metformin group (-6.5mg/dl) [p value <0.05]. HDL level was slightly increased in both the groups and greater in teneligliptin group. Mean serum triglycerides level was greater reduced (-18.6mg/dl) in teneligliptin group than metformin group (-11.9mg/dl) but the differences are not significant (Table 3).

The incidence of adverse reactions was 30% (6 of 20 subjects) in the metformin group and 15% (3 of 20 subjects) in the teneligliptin group. The abdominal distension or flatulence was observed more in metformin group [A], whereas constipation one case [5%] was noticed with teneligliptin therapy (Table 4). Mild hypoglycaemia (10%) was observed in Group B, whereas no hypoglycaemia was noticed in Group A. No serious adverse events or drug-related adverse events leading to discontinuation were observed in either of the group. Resting 12-lead ECG was not done in either of the group to see particularly relevant variability.

Table 3: Changes of non-glycemic parameters with metformin vs teneligliptin.

Parameter	Treatment Group	Baseline values	Changes upto end of treatment period 12 weeks	Change from baseline	P Value
LDL- C mg/dl (Mean ±SD)	Group A [Met] N=20	132±39.7	125.5±35.8	-6.5 [95% CI -45.5528 to 11.1828]	0.5898
	Group B [Lina] N=20	141±48.8	122.8±42.7	-18.2 [95% CI -47.5528 to 11.1528]	0.2171
HDL mg/dl (Mean ±SD)	A	42.8±6.5	44.3±6.2	1.5 [95% CI -2.5662 to 5.5662]	0.4598
	B	45.9±5.2	49.1±6.3	3.2 [95% CI -0.4978 to 6.8978]	0.0879
Triglyceride mg/dl (Mean ±SD)	A	190.8±33.9	178.9±37.5	-11.9 [95% CI -94.3235 to 70.5235]	0.7717
	B	189.8±30.7	171.2±29.6	-18.6 [95% CI -37.9043 to 0.7043]	0.0585*
Serum amylase U/L (Mean ±SD)	A	82±45.5	77±39.5	-5 [95% CI -32.2749 to 22.2749]	0.7126
	B	77±28	69±26.6	-8 [95% CI -25.4824 to 9.4824]	0.3601
Alanine aminotransferase U/L (Mean ±SD)	A	37±16	34.6±17.5	-2.4 [95% CI -13.1336 to 8.3336]	0.6534
	B	32±12	29±11.8	-3 [95% CI -10.6183 to 4.6183]	0.4303
Alkaline phosphatase U/L (Mean ±SD)	A	62±29	58±32	-4 [95% CI -23.5488 to 15.5488]	0.6810
	B	67±23	56±25.5	-11 [95% CI -26.5447 to 4.5447]	0.1602

Paired Student's t-test was used to compare the changes of the indicated parameters before and after treatment. The results are expressed as the mean ± SD. Note: Values are presented as mean ± standard deviation. *P value <0.05, ** P value <0.001

DISCUSSION

This was the first 12-week, randomized, open labelled, parallel group study on the efficacy and safety of teneligliptin and which was compared with standard metformin monotherapy as initial pharmacotherapeutic option for T2DM. In monotherapy study, adverse drug reactions (ADRs) and AEs occurred in ≥5% of patients in any group were nasopharyngitis, positive urine ketone body, urine glucose, and urinary protein.[19] All ADRs were categorized as mild in intensity by the investigator. In phase 3 add-on to glimepiride study, the incidence rates of serious AEs were similar in both groups at week 12.[20] In Phase 3 add-on to pioglitazone, specific AEs occurred in >5% and included nasopharyngitis and peripheral edema.[21] Hypoglycemia was reported in two patients (10%) in the teneligliptin group at week 12. In the pooled 52 weeks safety analysis, treatment-related hypoglycemia occurred with an overall incidence of 3.4% in teneligliptin recipients, with all episodes of mild intensity. The incidence of hypoglycemia was numerically higher in the teneligliptin plus SU (10.1%) and teneligliptin plus glinide (5.0%) groups than in the teneligliptin monotherapy (2.5%), teneligliptin plus biguanide (1.1%), or teneligliptin plus α-glucosidase inhibitor (1.3%) groups.[22] The incidence of adverse events (AEs) was not significantly different between the teneligliptin and placebo groups in the study conducted by Eto et al.[23] None of the patients in the present study in any of the groups experienced moderate to severe hypoglycemic symptoms or serious AEs.

Effects of teneligliptin on lipid profiles

The lipid profile is an important determinant of cardiovascular risk in type 2 diabetes. It can affect antidiabetic therapy and is important in the clinical management of patients with type 2 diabetes.[24,25] Meta-analyses suggested a potential beneficial effect of DPP-4 inhibitors on cholesterol, which could contribute to a reduction in cardiovascular risk.[24,26] The administration of several DPP-4 inhibitors reduces postprandial triglyceride levels in humans, mice, and hamsters; however, its effects on postprandial free fatty acid levels are a matter of debate.[27,28] GLP-1 inhibits the secretion of gastric lipase and reduces intestinal triglyceride absorption and apo B and apo A-IV production, and insulin suppresses lipolysis in adipose tissue, resulting in a reduction of the plasma free fatty acid levels; therefore, the study speculated that the reduction in triglyceride and

free fatty acid levels could be a consequence of the elevation of active GLP-1 and insulin levels.[29-31]

Table 4: Adverse events (safety analysis).

Parameter	Treatment Group	Percentage/ Mean ±SD
Hypogycemia [mild]	A	0
	B	2 [10%]
Hypogycemia [moderate]	A	
	B	0
Hypogycemia [severe]	A	0
	B	
Abdominal distension/ flatulence	A	5 [25%]
	B	0
Diarrhoea	A	01 [5%]
	B	0
Constipation	A	0
	B	1 [5%]
Nasopharyngitis	A	
	B	0
Hypotension	A	
	B	0
Duodenitis	A	
	B	0
Increased liver enzymes	A	
	B	0
Weight gain	A	-0.64±0.39 kg
	B	+0.29±0.11 kg
Drug-related adverse events	A	06 [30%]
	B	3 [15%]
Serious adverse event	A	0
	B	
Serious drug-related adverse events	A	0
	B	
Adverse events leading to discontinuation	A	0
	B	
Drug-related adverse events leading to discontinuation	A	0
	B	
Death	A	0
	B	

Influence on body weight

Studies on the effect of DPP-4 inhibitors on body weight demonstrated variable results; however, these results were generally considered to be neutral.[32,33] The mean body weight change of the patients at week 12 (mean ± SD) was +0.29±0.11kg, which indicated that the effect of teneligliptin on body weight was neutral, whereas metformin group observed weight loss.

The limitations of this study are that the number of the subjects is small and the study duration is short. However, one can assume that the observed changes were caused exclusively by teneligliptin based on the design of the study (monotherapy with drug naive patients). Further randomized, double-blind, placebo-controlled longer period study with increased number of subjects will be necessary to strengthen the finding in this study.

CONCLUSION

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Teneligliptin, a DPP4 inhibitor reduced HbA1C significantly compared with monotherapy of metformin in treatment naive patients at week 12. Teneligliptin also reduced FBG and 2-h PPBG as compared with metformin at week 12. There is significant elevation of serum HDL-cholesterol as compared metformin. There is a tendency of reduction of the serum triglyceride level. So, teneligliptin improves serum lipid profile which is very important in T2DM patients with dyslipidemia. It is a unique J-shape structure leads to potent inhibition of DPP4 enzyme and long lasting action for 24 hours. It offers lower incidence of hypoglycaemia on proper dose titration and shows weight neutral effect. Therefore, teneligliptin was generally well tolerated.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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