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Research Article

EFFICACY AND SAFETY OF TENELIGLIPTIN AS ADD-ON THERAPY TO CONVENTIONAL THERAPY IN INDIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: Teneligliptin is a novel, highly selective dipeptidyl peptidase-4 inhibitor. The objective of the present study was to investigate the efficacy and safety of teneligliptin as add-on therapy in patients with type 2 diabetes mellitus (T2DM) who are inadequately controlled by conventional therapy (metformin/glimepiride) in India.

Methods: Clinical study protocol was approved by the Institutional Ethics Committee. T2DM patients (male/female) whose glycated hemoglobin (HbA1c) >7% were randomized to receive following group treatments, namely, Treatment A: Metformin/glimepiride plus add-on teneligliptin 20 mg and Treatment B: Metformin/glimepiride for 24 weeks. A pre-designed case report form was used to collect information from the prescribing physicians regarding the efficacy and safety of teneligliptin. Efficacy variables included change in plasma blood glucose (fasting and postprandial) and HbA1c from baseline to week 24. Treatment emergent adverse events were assessed.

Results: A total of 120 type 2 diabetes patients were analyzed. Teneligliptin as add-on therapy with metformin/glimepiride significantly reduced plasma glucose (HbA1c, fasting, and postprandial) concentration as compared to conventional therapy.

Conclusion: Add-on therapy with teneligliptin was found superior over conventional therapy in reducing plasma glucose concentration (fasting and postprandial) and HbA1c levels significantly in patients with T2DM. Further, it was found effective and well tolerated in Indian patients with T2DM who are inadequately controlled with conventional therapy.

Keywords: Teneligliptin, DDP-4 inhibitor, Glycated hemoglobin, Type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus, a chronic metabolic non-communicable disease has attained epidemic proportions worldwide [1]. Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia resulting from decreased insulin secretion from beta cells of pancreas and increased insulin resistance [2]. According to the International Diabetes Federation report, 2010 an estimated 50 million people were living with diabetes, and it increases to 87 million by the year 2030. India may be one of the fastest-growing countries with T2DM [3-5].

T2DM is a chronic disease which needs lifelong medical care and its treatment goal should be the prevention of short- and long-term complications, patient education, and support [6-7]. Although a number of oral antihyperglycemics agents are available, it is still difficult to maintain good glycemic control with the existing drugs and it cause significant problems like, lactic acidosis, gastrointestinal intolerance, weight gain, nausea, muscle weakness, etc [8,9]. Metformin and sulfonylureas are the most widely prescribed drugs in India due to their low cost and well-established safety and efficacy [10,11].

Dipeptidyl peptidase-4 (DPP-4) inhibitors work by increasing levels of active glucagon-like peptide-1 (GLP-1), thereby promoting insulin secretion and improving beta-cells sensitivity to glucose [7,12]. One meta-analysis report has suggested that DPP-4 inhibitors may be more potent in reducing glycated hemoglobin (HbA1c) levels in Asian T2DM patients than in non-Asian patients [13]. Teneligliptin consist J-shaped structure formed by five rings, out of four directly connected to DPP-4 enzyme which leads to enhance the potency and selectivity of the drug as compared to other gliptins [14-16]. Teneligliptin is metabolized and excreted through liver and kidney [17]. For the management of diabetes mellitus, treatment regimens should include complementary action that acts against associated multiple complication of T2DM [18,19].

DPP-4 inhibitor is expected to be safely used as a treatment for T2DM because it has no risk of hypoglycemia and/or weight gain which are reported in pre-existing diabetes therapies and no inconvenience related to dose adjustment depending on patient's condition. As there is no long term study conducted on add on therapy of teneligliptin, our study was designed to evaluate efficacy, safety, tolerability and affordability treatment for diabetic patients whose diabetes was inadequately controlled by conventional treatment (metformin/glimepiride) in India.

METHODS

Ethics approval

Before initiate the clinical study, the protocol, informed consent form, and essential documents were approved by the Institutional Ethics Committee; Safety, Health, and Welfare Ethics Committee registered under Drugs Controller General of India.

Study design and procedure

A prospective, open-label, randomized study was to assess the efficacy and safety of teneligliptin as add-on therapy of conventional treatment (metformin/glimepiride). The study was conducted at Jivraj Mehta Hospital and Bakeri Medical Research Centre, Ahmedabad, Gujarat, from December 2017 to December 2018.

Eligibility criteria

The study protocol was clearly defined for the patients and informed consent was obtained from all patients before participation. The study included male and female patients with T2DM, aged >18 years,

HbA1c levels of >7.0%, and body mass index of 20.0–35.0 kg/m^2 (both inclusive). The patients were excluded if they had serious disease such as kidney, liver, and cerebral stroke, history of severe heart disease or arrhythmias, taking DPP-4 inhibitor other than teneligliptin and on insulin therapy, pregnant, and history of alcohol and tobacco use.

Intervention

Eligible patients were randomized in 1:1 ratio to receive either metformin glimepiride plus add-on teneligliptin (Treatment A) or metformin/glimepiride only (Treatment B). Treatment for both the groups remained stable and it included: Teneligliptin 20 mg/day, metformin 500 mg/day, and glimepiride 2 mg/day for 24 weeks. The primary efficacy endpoint was the change in HbA1c from baseline to 24 weeks. Secondary efficacy endpoints include change in fasting plasma glucose (FBG) and post-prandial blood glucose (PPBG) from baseline to 24 weeks. During the clinical study period, we monitored possible adverse events (AEs), laboratory values, vital signs, and physical examination results. Safety was measured by recording AEs including symptomatic assessment by Naranjo causality scale for AE [20]. The incidence of AE in terms of number per patient was calculated based on the number of events, the number of patients and the total observation period.

Sample size and statistical analysis

The primary endpoint, difference in mean HbA1c from baseline to 24 weeks was assumed 0.5% and the standard deviation (SD) of 0.9% for each treatment group [21]. Based on a power of 80% and a Type I error rate of alpha = 0.05 (2-tailed), a sample size of at least 60 patients per group was required to detect a clinically significant difference between both the groups. Categorical data were presented as absolute number/percentage of patients, while quantitative data were presented as mean±SD. Within-group comparison was performed using paired *t*-test based on the distribution of data. An unpaired *t*-test was used to analyze the quantitative data for between-group comparisons. $p<0.05$ was considered as statistical significant difference. Data were calculated using GraphPad Prism version 5.0.

RESULTS

Of 171 screened patients, 130 eligible patients were randomized in this clinical study showing in consort diagram for flow of participants throughout the study (Fig. 1). Treatment A included 61 patients and Treatment B included 63 patients. Sixty patients in each group were analyzed as per sample analyzing plan. Both groups had similar demographic and clinical characteristic parameters at baseline (Table 1).

A consort diagram presented the disposition of the patients chart shown in Fig. 1.

Glycemic parameter

HbA1c level was found comparable in both the treatment groups at the baseline. However, there was a gradual reduction in HbA1c over

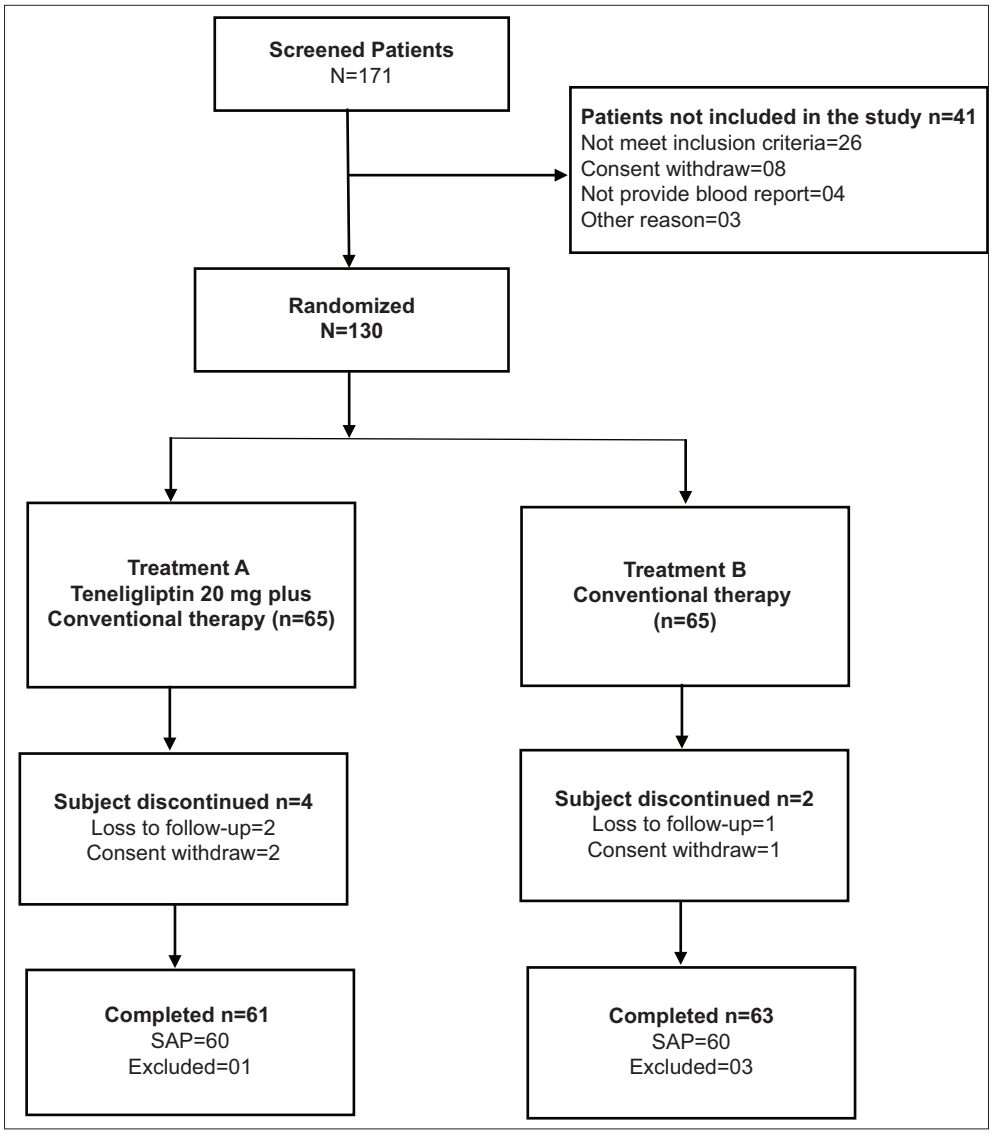

Fig. 1: Patient disposition chart

a period of 24 weeks in both the treatment groups. Between groups comparison showed significant reduction in HbA1c in Treatment A as compared to Treatment B. Blood glucose levels (FBG and PPBG) were comparable in both the treatment groups at the baseline. However, there was significant reduction in FBG and PPBG levels over a period of 24 weeks in both the treatment groups (Table 2).

Mean change indifference in blood glucose levels and HbA1c in both the treatment groups at the end of 24 weeks from the baseline was found statistically significant. The mean change of HbA1c in Treatment A was 1.20±0.50 and 0.76±0.32 in Treatment B. Change in HbA1c showing significantly decreased in the Treatment A group ($p<0.003$). Between groups comparison showed significant reduction in HbA1c in Treatment A as compared to treatment B (Fig. 2).

Mean change in FBG and PPBG levels were 41.08±35.02 and 54.11±35.77 in Treatment A and mean change in FBG and PPBG levels were 27.41±14.56 and 34.80±25.18 in Treatment B, respectively. The mean change in blood glucose (FBG and PPBG) levels significantly reduced in Treatment A as compared to Treatment B at the end of 24 weeks (Figs. 3 and 4).

Safety assessment

The incidence of AE was 45% (27/60 patients) in Treatment A group and 50% (30/60 patients) in Treatment B group (Table 3). Treatment A did not increase the incidence of AEs in comparison with Treatment B during the entire study period. There were no serious AEs or deaths

Table 1: Demographic and clinical characteristic

Patient characteristic	Treatment A (n=60)	Treatment B (n=60)
Gender (male/female)	30/30	34/26
Age (year)	50.73±12.08	49.81±14.29
Height (cm)	155.93±8.12	157.6±9.55
Body weight (kg)	62.43±9.11	62.55±8.18
BMI (kg/m^2)	25.79±4.01	25.35±4.00
Disease duration (year)	3.98±2.00	3.46±1.65

Description: Data are expressed as mean±SD. Treatment A: Conventional treatment plus add-on teneligliptin 20 mg and Treatment B: Conventional treatment (metformin/glimepiride), n: Number of patient, and BMI: Body mass index, SD: Standard deviation

Table 2: Mean change in blood glucose levels (fasting and post-prandial) and HbA1c from baseline to 24 weeks after study drug treatments

Parameters	Treatment A (n=60)	Treatment B (n=60)
HbA1c		
Baseline (HbA1c)	10.75±2.07	9.88±1.69
End of 24 weeks	9.55±1.94*	9.12±1.72
Change in HbA1c	1.20±0.50$^{@}$	0.76±0.32
FBG		
Baseline (FBG)	177.31±48.96	170.66±40.35
End of 24 weeks (FBG)	136.23±31.67*	143.25±36.11*
Change in fasting	41.08±35.02$^{\#}$	27.41±14.56
PPBG		
Baseline (PPBG)	258.41±53.74	246.43±58.30
End of 24 weeks (PPBG)	204.3±49.91*	211.62±51.96*
Change in post prandial	54.11±35.77$^{\$}$	34.80±25.18

Description: Treatment A: Conventional treatment plus add-on teneligliptin 20 mg and Treatment B: Conventional treatment. N: Number of patient, SD: Standard deviation. Values are expressed as mean±standard deviation. *p<0.05 from baseline by paired *t*-test (within-group comparison). $^{@}$: @ indicates change in HbA1c from the baseline to 24 weeks; $^{\#}$: # indicates change in FBG from the baseline to 24 weeks; $ $ indicates change in PPBG from the baseline to 24 weeks. Between groups comparison was done using unpaired *t*-test. FBG: Fasting blood glucose, PPBG: Post-prandial blood glucose, $HbA1_1c$: Glycated hemoglobin

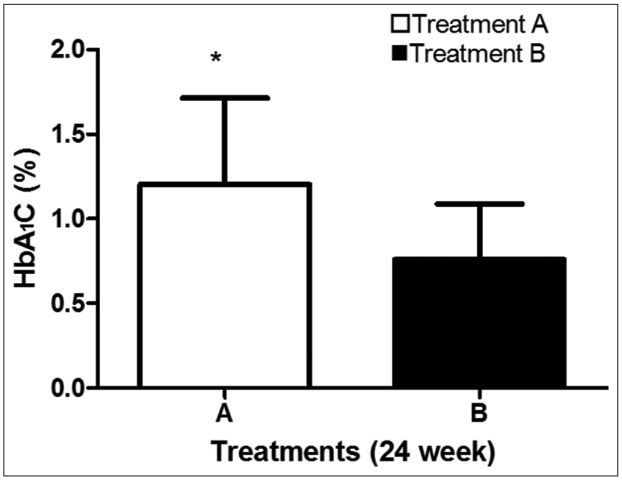

Fig. 2: Mean change in glycated hemoglobin level
Data were expressed as the Mean ± Standard deviation (n=60). *p<0.05 indicate change indicate change in HbA1c from baseline to 24 week by unpaired t test (between group comparison)

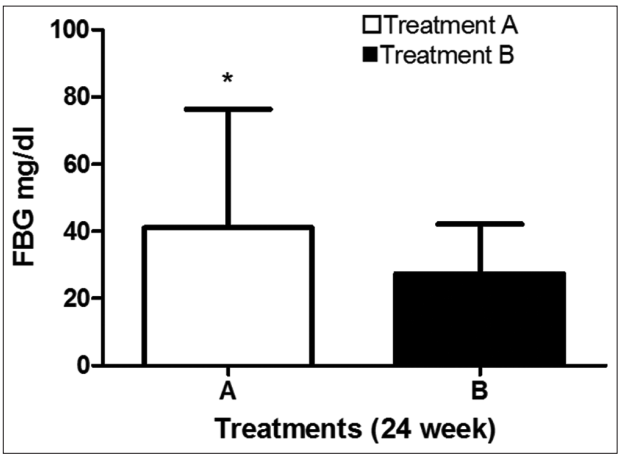

Fig. 3: Mean change in fasting blood glucose level
Data were expressed as the Mean ± Standard deviation (n=60). *p<0.005 indicate change indicate change in FBG from baseline to 24 weeks by unpaired t test (between group comparison)

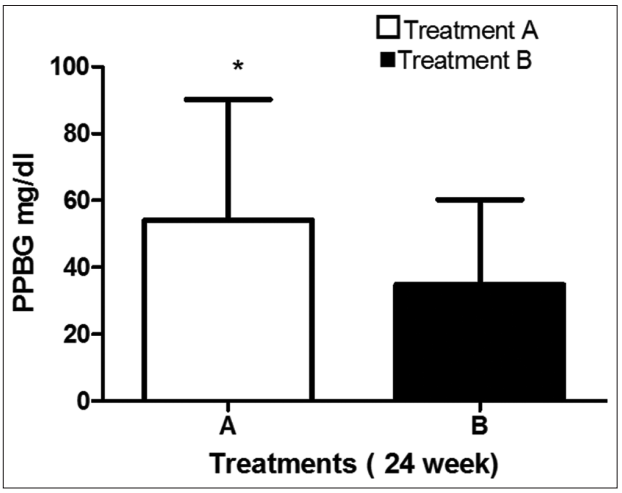

Fig. 4: Mean change in post-prandial blood glucose level
Data were expressed as the Mean ± Standard deviation (n=60). *p<0.05 indicate change indicate change in PPBG from baseline to 24 weeks by unpaired t test (between group comparison)

in either group. The incidence of hypoglycemia was similar in both groups (3.33%).

DISCUSSION

In the present study, we evaluated the efficacy and safety of newly developed DPP-4 inhibitor, teneligliptin in patients with T2DM whose glycemic parameters were inadequately controlled with conventional therapy. There is a need for effective add-on therapy like DPP-4 inhibitors besides existing standard therapy (metformin, glimepiride) to prevent uncontrolled diabetes and enhancing the efficacy of the treatment and reducing economic burden [22]. Although, International American Diabetes Association and local guideline recommended lifestyle management as the mainstay of treatment for T2DM; with metformin as the preferred initial oral antihyperglycemic agent in most of patients, there remains no consensus regarding which classes of agents to add as dual and triple therapy, if and when required [9-11,23]. Clinical trials have reported safety and efficacy of teneligliptin as DPP-4 inhibitors [24,25].

Despite the metformin is widely available in clinical practice, side effects such as GI and lactic acidosis are of major concern [11]. Teneligliptin is reported to improve glucose intolerance and synergistically increased plasma GLP-1 levels in Zucker diabetic fatty rats, a widely used genetic model of obese T2DM suggesting that teneligliptin might help in diabetes and obesity [26,27]. The present work clearly demonstrated that teneligliptin addition to glimepiride/metformin stable dose significantly reduced HbA1c level compared to conventional therapy at 24 weeks from the baseline. Kim MK *et al*., similar observation was reported to achieve <7 % of HbA1c with combination of metformin and teneligliptin at 16 week study [28].

Kadowaki T *et al*., reported teneligliptin in combination with glimepiride, teneligliptin significantly improved FBG at 12 weeks compared to add-on placebo group [29]. Teneligliptin also supressed fasting and postprandial glucagon. Teneligliptin-induced supression of glucagon could also be responsible for improved insulin sensitivity [30]. Gallwitz B and Haring HU, reported DPP-4 inhibitor and sulphonylurease accelerate insulin secretion in a coordinated manner via Epac2 [31]. The effect of teneligliptin on 2-h postprandial blood glucose and postprandial blood glucose AUC_{0-2h} was -42.9 and -54.03 respectively from the baseline to end of 16 week double blind placebo control study in Japanese patients with T2DM [21]. Further, we also observed gradual reduction in blood glucose levels (FBG and PPBG) in both the treatment groups at the end of 24 weeks.

The primary efficacy endpoint was the comparison of mean change in HbA1c form baseline to week 24 for both the treatment groups. HbA_1c level in blood are one of the key marker as well as widely accepted measure of overall, mid-term and long-term blood glucose control in T2DM [7]. We clearly demonstrate once daily dosage with teneligliptin (20 mg) resulted in statistically significant reductions in HbA1c at the end of 24 weeks of therapy. Our study results supported study teneligliptin add-on to insulin monotherapy in Japanese patients with type 2 diabetes mellitus for 16-week study which reduced HbA1c level and showing synergistic effect [21]. Kadowaki T, and Kondo K., reported teneligliptin plus pioglitazone significantly improved glycemic control (HbA1c, FBG, and PPBG) compared with placebo plus pioglitazone [30]. In our study, at the end of 24 weeks tenligliptin as add on treatment significantly reduction of HbA1c in patients with T2DM which might be possibly due to synergistic action.

Table 3: Summary of adverse events

AE	Treatment A n=60 (%)	Treatment B n=60 (%)	Score	Scale
Hypoglycemia	2 (3.33)	2 (3.33)	9	Definite
Constipation	5 (8.33)	4 (6.66)	9	Definite
Abdominal pain	5 (8.33)	3 (5.00)	5	Probable
Acidity	2 (3.33)	6 (1.00)	5	Probable
Tingling	1 (1.66)	3 (5.00)	5	Probable
Tiredness	2 (3.33)	2 (3.33)	4	Possible
Weakness	2 (3.33)	2 (3.33)	4	Possible
Pain	2 (3.33)	2 (3.33)	4	Possible
Headache	1 (1.66)	3 (5.00)	4	Possible
Dry skin	3 (5.00)	1 (1.66)	0	Doubtful
Itching	2 (3.33)	2 (3.33)	0	Doubtful
Total	27 (45)	30 (50)		

AE: Adverse event

Safety assessment

The clinical symptomatic assessment was done for AEs such as hypoglycemia and constipation which were considered as definite; abdominal pain, acidity, and tingling considered as probable; tiredness, weakness, pain, and headache considered as possible; and dry skin and itching considered as doubtful by Naranjo AE assessment scale. The incidence of hypoglycemic symptoms reported in terms of combination use of teneligliptin and oral antihyperglycemic agents was reported to be 10.1% in combination with sulfonylureas and 1.1% with metformin [32]. In the present study, the incidence of hypoglycemic symptoms was 3.33% in both groups. According to one meta-analysis, there was 50% chance of hypoglycemic symptoms when DPP-4 inhibitor was added to sulfonylurea, compared with placebo added to a sulfonylurea [33]. As per one meta-analysis of teneligliptin, the use of second-line therapy used with caution due to the risk of hypoglycemia, weight gain, and lower durability of glycemic response [24]. The selection of antidiabetic medications for combination therapy depends on the patient's characteristics, efficacy of initial medicine, and cardiovascular benefit [33]. Another network meta-analysis result suggested that DPP-4 inhibitors appear to be a tolerable option for patients with T2DM with low incidence of GI AE compared to other combinations [34].

The economic impact of T2DM is more vulnerable and visible in middle and lower income groups of the society and in a developing country like India. A combination therapy of metformin either with glimepiride or affordable DPP-4 inhibitor (Teneligliptin) or insulin should be initiated if ideal levels of HbA1c is not achieved after three-four months of treatment.

In the present study, the incidence of hypoglycemia was rare suggesting that teneligliptin did not increase the risk of hypoglycemia at 20 mg dose/day. Thus, the combination of the DPP-4 inhibitor with conventional therapy has been proposed as first or second-line therapy for T2DM as an alternative to the classical metformin-sulfonylurea combination therapy.

CONCLUSION

Our study demonstrated teneligliptin add-on therapy is well tolerated and effective in patients with T2DM. The addition of teneligliptin to glimepiride/metformin resulted in significant glycemic control and safety compared to glimepiride/metformin therapy alone.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest concerning this research article.

AUTHORS' CONTRIBUTIONS

The corresponding author has designed the work, data collection, analysis, and prepared manuscript. Both authors discussed and

provided critical feedback on manuscript. Both authors read and approved the final manuscript.

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