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Original Research Article

Effect of Teneligliptin supplementation as add on therapy to Metformin in Uncontrolled type 2 diabetes mellitus

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Abstract: Diabetes mellitus type 2 (DM) is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. Metformin is first line drug for diabetes mellitus due to its excellent safety and toleralability. Teneligliptin is newly approved drug for DM and having minimal side effects. Teneligliptin can be used either as monotherapy or add on therapy to metformin. Aim of the present study was to evaluate the effects of metformin and teneligliptin on HbA1c, fasting and postprandial blood glucose level at 12th, 24th week and to observe any side effect of drugs. This is case control study conducted at Department of General Medicine of a tertiary care centre. 100 adult patients (age >18 years) of type 2 DM were evaluated for possible inclusion in this study. All patients were randomly allotted into two groups. 50 patients were started with teneligliptin 20 mg/day along with metformin 1000 mg/day. 50 patients were started with placebo while continuing with metformin 1000 mg daily. Various parameters were measured at baseline, 12th week and 24th weeks. Total number of patients, mean age of patients and gender distribution were almost similar in both groups. Both group subjects had high FBS, PPBS and HbA1c at the start of study. After 24 weeks of treatment with teneligliptin and metformin, subjects had significant decrease in FBS, PPBS and HbA1c. There was no significant change in BMI, blood pressure and lipid parameters in both groups after study. All patients tolerated drugs well without any side effects. This study showed that teneligliptin can be an effective alternative to other drugs for add on therapy to the patients who are inadequately controlled with metformin alone.
Keywords: Diabetes mellitus, metformin, teneligliptin

INTRODUCTION

Diabetes mellitus type 2 (DM) is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2013 there were approximately 368 million people diagnosed with the disease compared to around 30 million in 1985 [1]. Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance [2]. Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue. In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood [3]. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion [2]. Metformin is the first-line medication for the treatment of type 2 diabetes [4], particularly in people who are overweight. Metformin is generally well tolerated. Common side effects include diarrhea, nausea and abdominal pain. It has a low risk of developing hypoglycemia. High blood lactic acid level is a concern if the drug is prescribed inappropriately and in overly large doses. It should not be used in those with significant liver disease or kidney problems. Metformin is in the biguanide class. Metformin decreases high blood sugar, primarily by suppressing liver glucose production (hepatic gluconeogenesis). In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by inducing the phosphorylation of

GLUT4 enhancer factor), decreases insulin-induced suppression of fatty acid oxidation [5], and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors. Inhibitors of dipeptidyl peptidase 4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemics that block DPP-4 (DPP-IV). Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP) [6], which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. Teneligliptin has unique J shaped or anchor locked domain structure because of which it has a potent inhibition of DPP 4 enzyme. Teneligliptin significantly controls glycemic parameters with safety. Some of the DPP-4 inhibitor drugs have gotten approval from the FDA to be used with metformin concomitantly with additive effect to increase glucagon-like peptide 1 (GLP-1) which also decrease hepatic glucose production [7]. Metformin is first line drug for diabetes mellitus due to its excellent safety and toleralability. Teneligliptin is newly approved drug for DM and having minimal side effects. Teneligliptin can be used either as monotherapy or add on therapy to metformin. This combination will have minimal risk of hypoglycemia and no weight gain. Aim of the present study was to evaluate the effects of metformin and teneligliptin on HbA1c, fasting and postprandial blood glucose level at 12^{th}, 24^{th} week and to observe any side effect of drugs.

MATERIAL AND METHODS

Study Design: This is case control study. Study Setup: This study is conducted at Department of General Medicine of a tertiary care centre. Study Duration: The duration of study was two years; November-2014 to October-2016.Sampling: Purposive sampling technique is used for selection of desired samples according to inclusion criterion. Sample Size: 100 adult patients (age >18 years) of type 2 DM were evaluated for possible inclusion in this study. Inclusion criteria: Male and female patients aged more than 18 years, inadequately controlled on metformin 1 gram alone, having HbA1c > 6.5, fasting blood sugar (FBS) >110 mg/dl, postprandial blood sugar (PPBS) > 180 mg/dl. Exclusion Criteria: Type 1 DM, acute illness, pregnancy, macrovascular diabetes complication, liver disease, thyroid disorder. Methods: After fulfilling these criteria, the patients were underwent thorough physical examination and underwent following investigations: complete blood count, FBS, PPBS, HbA1c, lipid profile, renal function test, liver function test, ECG. All patients were randomly allotted into two groups: Group A: 50 patients were started with teneligliptin 20 mg/day along with metformin 1000 mg/day. Group B: 50 patients were started with placebo while continuing with metformin 1000 mg daily. Dose adjustment of teneligliptin or metformin was not done at any time after randomization. No additional oral antdiabetic drug was added during study period. Patients were free to withdraw from the study at any point due to side effects, intolerability or unsatisfactory therapeutic response. Each patients attended medicine OPD every 2 weeks. Plasma glucose level (fasting and postprandial) was measured at each visit. HbA1c was measured at 12^{th} week and 24^{th} weeks. Complete blood count, lipid profile, renal function test, liver function test and ECG were repeated at the end of study. Ethical Consideration: Prior to conduct of the present study, the protocol of the study was submitted to ethical and scientific committee of hospital. After getting due approval from these two committees, the present study was initiated. Also prior to conduct of study related procedure / investigation, a voluntary written informed consent was taken from the patient /legally acceptable representative. Statistical Technique: Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables.

RESULTS

Total 100 diabetic subjects were included in this study. They were divided randomly into Group A taking teneligliptin 20 mg daily and Group B taking a placebo along with continuing metformin in both groups. Total number of patients, mean age of patients and gender distribution were almost similar in both groups. (table 1) Both group subjects had high FBS, PPBS and HbA1c at the start of study.(table 2) After 24 weeks of treatment with teneligliptin and metformin, subjects had significant decrease in FBS, PPBS and HbA1c.(table 3) There was no significant change in BMI, blood pressure and lipid parameters in both groups after study.(table 3). All patients tolerated drugs well without any side effects.

Table-1: Demographic measures and biochemical values of all subjects

Characteristics	Group A (Teneligliptin+Metformin)	Group B (Metformin alone)
Number	50	50
Gender % (Female)	60%	58%
Age (Mean ± SD)	49.2 ± 12.8 years	50.1 ± 11.9 years

Table-2: Pre-study characteristics of diabetic subjects

Characteristics	Group A (Teneligliptin+Metformin)	Group B (Metformin alone)	P value
BMI (Mean ±SD)	27.8 ±4.1 kg/m^2	28.2 ±3.9 kg/m^2	NS
History of Hypertension	45%	42%	NS
FBG (Mean ±SD)	149 ±28.4 mg/dl	152.4 ±19.8 mg/dl	NS
PPBG (Mean ±SD)	240.4 ±54.4 mg/dl	244.3 ±38.5 mg/dl	NS
HbA1c (Mean ±SD)	7.8 ±0.9	7.9 ±0.8	NS
LDL-C (Mean ±SD)	139 ±12.9 mg/dl	134 ±21.8 mg/dl	NS
HDL (Mean ±SD)	45.9 ±5.2 mg/dl	42.8 ±6.5 mg/dl	NS
Triglyceride (Mean ±SD)	189.8 ± 20.9 mg/dl	190.2 ±23.9	NS

BMI=Body mass index, NS= non significant

Table-3: Post-study (24 weeks) characteristics of diabetic subjects

Characteristics	Group A (Teneligliptin+Metformin)	Group B (Metformin alone)	P value
BMI (Mean ±SD)	27.8 ±4.1 kg/m^2	28.2 ±3.9 kg/m^2	NS
History of Hypertension	45%	42%	NS
FBG (Mean ±SD)	109 ±18.4 mg/dl	132.4 ±19.8 mg/dl	0.018
PPBG (Mean ±SD)	148.4 ±24.4 mg/dl	201.3 ±38.5 mg/dl	0.008
HbA1c (Mean ±SD)	6.1 ±0.5	7.8 ±0.8	0.001
LDL-C (Mean ±SD)	129 ±10.9 mg/dl	136 ±18.8 mg/dl	NS
HDL (Mean ±SD)	47.8±3.6 mg/dl	44.7 ±4.4 mg/dl	NS
Triglyceride (Mean ±SD)	187.8 ± 19.9 mg/dl	190.2 ±23.9	NS

DISCUSSION

This study was designed to compare the effects of metformin and teneligliptin in patients with type 2 DM. The study was started with 100 patients with type 2 DM who were taking metformin 1000 mg daily but were inadequately controlled with the monotherapy. They were divided randomly into Group A taking teneligliptin 20 mg daily and Group B taking a placebo along with continuing metformin in both groups. All patients completed study. There was considerable decrease in HbA1c, FBS and PPBS in Group A patients. There was no significant change in blood pressure, weight and other biochemical parameters in both groups after study.To assess blood glucose control over 24 hours and the safety of teneligliptin at 10 and 20 mg doses, a randomized, double-blind, placebo-controlled, parallel-group study was conducted at four locations in Japan.[8] Japanese patients with type 2 diabetes mellitus that was inadequately controlled with diet and exercise were eligible to participate in the study. Among the 99 patients who participated, 32 were treated with a placebo, 34 were treated with teneligliptin at a dose of 10 mg, and 33 were treated with teneligliptin at a dose of 20 mg before breakfast for 4 weeks. The results revealed that both teneligliptin-treated groups showed significantly smaller 2-hour postprandial glucose (PPG), 24-hour mean glucose (MG), and fasting plasma glucose (FPG) values than the placebo group when the values at week 4 were compared to the baseline values.

The corresponding LS means ± SE for teneligliptin (20 mg) versus the placebo were −38.1 ± 7.8, −28.6 ± 9.2, and −36.1 ± 7.5 mg/dL, respectively ($P < 0.001$, $P < 0.01$, and $P < 0.001$, respectively). Importantly, the postprandial blood glucose-lowering effects of teneligliptin administered before breakfast was sustained throughout the day, and the effects observed after dinner were similar to those observed after breakfast or lunch.The changes in the 24-hour MG level from baseline were −34.7 ± 3.9, −30.9 ± 4.0, and −5.4 ± 4.0 mg/dL in the groups receiving 10 and 20 mg of teneligliptin and the placebo groups, respectively. Therefore, the differences between the teneligliptin-treated and placebo groups were −29.3 ± 5.3 and −25.5 ± 5.3 mg/dL for teneligliptin at doses of 10 and 20 mg, respectively (LS mean ± SE). These findings

demonstrate that the 24-hour MG values significantly decreased in both teneligliptin-treated groups in comparison with the placebo group (both teneligliptin-treated groups, $P < 0.001$). In addition, when the 24–hour MG profiles were plotted, treatment with teneligliptin suppressed the increases in blood glucose levels over a 24-hour period in comparison with the effect of the placebo at week 4.The changes in the FPG values from baseline were −20.7 ± 2.7, −20.5 ± 2.8, and −6.9 ± 2.8 mg/dL in the 10 mg and 20 mg groups of teneligliptin and the placebo groups, respectively. These results indicate the differences between the teneligliptin-treated and placebo groups, which were −13.8 ± 4.0 and −13.6 ± 4.0 mg/dL for teneligliptin at doses of 10 and 20 mg, respectively (LS mean ± SE). The decreases in the FPG values with teneligliptin at doses of 10 and 20 mg (both, $P < 0.001$) were statistically significant, compared with the placebo. However, there were no significant differences in the 2-hour PPG values after each meal, as well as in the 24-hour MG or FPG values between the 10 and 20 mg teneligliptin groups. These results indicate that the once-daily administration of teneligliptin before breakfast improved blood glucose control, even at dinnertime. The incidence of adverse events (AEs) was not significantly different between the teneligliptin and placebo groups in the study conducted by Eto *et al.* Kadowaki and Kondo[9] conducted a double-blind placebo-controlled parallel-group study in 324 Japanese patients with type 2 diabetes randomized to receive different doses of teneligliptin or placebo once daily before breakfast for 12 weeks. The differences between the teneligliptin 10, 20, or 40 mg groups and the placebo group for the changes in HbA1c levels were −0.9 (LS mean; 95% CI: −1.0, −0.7), −0.9 (−1.1, −0.7), and −1.0 (−1.2, −0.9)%, respectively (all, $P < 0.001$). The respective LS means for FPG were −17.8 (−23.4, −12.1), −16.9 (−22.6, −11.2), and −20.0 (−25.7, −14.3) mg/dL (all, $P < 0.001$). These results indicate that treatment with teneligliptin for 12 weeks provided significant and clinically meaningful reduction in the levels of HbA1c and FPG across the dose range studied. Recently an Indian study by Suryawanshi et al, reported the results of a 16-week, multicentric, double-blind, placebo-controlled, Phase 3 studies of teneligliptin 20 mg daily in drug naive T2DM patients. This study (N = 237) reported a significant −0.55% glycated hemoglobin (HbA1c) reduction (placebo-subtracted) in teneligliptin arm ($P = 0.0043$) compared to control. While a significant reduction in 2 h postprandial glucose (PPG) (−25.8 mg/dl, $P = 0.0070$) versus placebo was observed, an insignificant reduction in fasting plasma glucose (FPG) was seen (−8.8 mg/dl, $P = 0.18$) in teneligliptin 20 mg arm. Similarly, higher percentage of patient achieved the target HbA1c of <7% in teneligliptin arm (43.4% vs. 27.3%, $P = 0.026$) compared to the control and "overall" the drug was well tolerated.[10] In TREAT-INDIA study, Data of 4305 patients was available for analysis. There was statistically significant improvement in mean HbA1c, FPG, and PPG with teneligliptin therapy. Means changes in HbA1c, FPG, and PPG were −1.37%±1.15%, 51.29±35.41 mg/dL, and 80.89±54.27 mg/dL, respectively. Subgroup analysis revealed that HbA1c (%) reduction with teneligliptin when used as monotherapy, add-on to metformin or add-on to metformin plus sulfonylureas combination, add-on to metformin plus alpha glucosidase inhibitor combination or add-on to insulin was 0.98±0.53, 1.07±0.83, 1.46±1.33, 1.43±0.80, and 1.55±1.05, respectively.[11]

CONCLUSION

This study showed that teneligliptin can be an effective alternative to other drugs for add on therapy to the patients who are inadequately controlled with metformin alone.

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