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Original Article

Efficacy of Teneligliptin as Add-on Therapy in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Real-World Experience

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) with chronic kidney disease (CKD) is dreadful combination necessitating adequate glycemic control to prevent further complications. Teneligliptin is found to be renal friendly antidiabetic agent which can provide effective glycemic control.

Objective: The objective of this study was to determine the efficacy of teneligliptin as add-on to existing therapy in patients of T2DM with CKD.

Materials and Methods: This was a retrospective study where patients with T2DM and CKD who received teneligliptin were included in the study. Changes in glycemic parameters such as hemoglobin A1c (HbA1c) (%), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) and change in estimated glomerular filtration rate (eGFR) were analyzed.

Results: In total, 66 patients were included in analysis. Mean age was 57.7 ± 14.0 years and 60.6% were males. Baseline HbA1c, FPG, and PPG levels were 7.8 ± 0.7%, 128.0 ± 25.5 mg/dl, and 214.0 ± 55.9 mg/dl, respectively. There was a significant reduction in HbA1c at 3 and 6 months (mean difference from baseline: −0.9 ± 0.5 and −1.2 ± 0.5 respectively, $P < 0.001$ for both). Similarly, mean change in FPG (−28.4 ± 20.9 and −29.9 ± 24.3 mg/dl, respectively) and PPG (−70.5 ± 49.2 and −97.0 ± 60.7 mg/dl, respectively) was also significant ($P < 0.001$ for all comparisons). The change in eGFR was significant at 3 months ($P = 0.049$) and 6 months ($P = 0.014$).

Conclusion: Teneligliptin is effective in reducing glycemic burden in patients with T2DM and CKD and can be considered as be considered among first choices for glycemic control in patients with renal impairment.

Key words: Estimated glomerular filtration rate, Hemoglobin A1c, Renal failure, Teneligliptin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is rapidly growing epidemic in India. It is well known that the level of glycemia is associated with complications of T2DM. Nephropathy is a major microvascular complication of T2DM. A recent study from India reported nephropathy in 43% of newly diagnosed T2DM cases.[1] Decline in renal function in T2DM demands careful selection of renal-friendly agents. Among various gliptins, teneligliptin is being used widely in India setting since its approval in 2015.[2] Teneligliptin kinetics are not altered with any degree of renal dysfunction and therefore make it a suitable agent for T2DM management in chronic kidney disease (CKD) at all stages.[3] Glycemia lowering efficacy of teneligliptin as add-on treatment to monotherapy and dual or triple drug therapy is already proven.[4]

With teneligliptin use in CKD, there are relatively scarce clinical studies in Indian setting. A study from Mumbai, India, reported a significant glycemia lowering efficacy

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of teneligliptin in CKD patients at 12 and 24 weeks.[5] However, the study consisted of small sample. Therefore, more studies are necessary for assessing teneligliptin efficacy and safety in CKD patients with T2DM. We report here the experience of using teneligliptin in CKD patients in our hospital setting.

MATERIALS AND METHODS

Study Setting

This study was conducted at a diabetology clinic from Central India. This clinic provides all the services in the field of medicine and diabetology. Patients with T2DM are among the most frequently visiting patients in this clinic.

Study Design

This was a single-center, retrospective, observational study where data from patient records were analyzed.

Study Population

Adult (>18 years of age) patients of T2DM with CKD in all stages who were prescribed teneligliptin in addition to their existing therapy were included for analysis. CKD was already diagnosed in these cases based on estimated glomerular filtration rate (eGFR) and/or presence or absence of microalbuminuria. Patients were included in analysis irrespective of their hemodialysis status.

Study Objective

The objective of this study was to determine the efficacy of teneligliptin in patients of T2DM with CKD at 3 and 6 months after initiation of teneligliptin. The efficacy parameters analyzed were hemoglobin A1c (HbA1c, (%), fasting plasma glucose (FPG, mg/dl), and postprandial plasma glucose (PPG, mg/dl).

Data Collection

Data from patients' records over 1-year period between April 2017 and March 2018 were collected in a pre-defined structured pro forma. Data on demographic parameters such as age, sex, and presence of different comorbid conditions were noted. Details of T2DM such as duration, current treatment, levels of HbA1c, FPG, and PPG were also noted. Available values of eGFR were identified and recorded. The details were assessed at baseline (at the time of start of treatment), after 3 months, and after 6 months of teneligliptin treatment. All the investigations were performed at a single laboratory. In all the patients, eGFR estimation was done as per the CKD Epidemiology Collaboration (CKD-EPI) equation.

Statistical Analysis

The data were entered into Microsoft Excel sheet and were analyzed with the same. Categorical variables were presented as frequency and percentages. Continuous variables were presented as mean and standard deviation. Student *t*-test was applied to identify the change in HbA1c, FPG, PPG, and eGFR from baseline to 3 and 6 months. Percentage of patients achieving target HbA1c <7% was assessed at 3 and 6 months. $P < 0.05$ was considered to be statistically significant.

RESULTS

There were a total of 66 patients included in the analysis. Mean age of the patients was 57.7 ± 14.0 years and 60.6% were males. Hypertension (62.1%) was the most frequent comorbid condition observed in study patients. Mean duration of T2DM was 11.0 ± 7.8 years. Among antidiabetic drugs, sulfonylureas (glimepiride - 60.6% and gliclazide - 16.2%) and metformin (48.5%) were commonly prescribed. The baseline characteristics are shown in Table 1.

Table 2 describes the changes in glycemic parameters. At baseline, mean HbA1c level was 7.8 ± 0.7%. There was a significant reduction in HbA1c at 3 months (6.9 ± 0.5%, mean difference: −0.9 ± 0.5%, $P < 0.001$) and further reduction was seen at 6 months (6.6 ± 0.4%, mean difference: −1.2 ± 0.5%, $P < 0.001$). As there was loss of data at 6 months, we analyzed the FPG and PPG change considering the baseline of evaluable patients. At 3 months, FPG reduced from 128.0 ± 25.5 mg/dl at baseline to 99.6 ± 9.2 mg/dl at 3 months (mean difference:

Table 1: Baseline characteristics

Characteristics	Observation (*n*=66)
Age (years)	
Mean±SD	57.7±14.0
Age groups	
≤50	24 (36.4)
51–60	15 (22.7)
61–70	16 (24.2)
>70	11 (16.7)
Gender	
Males	40 (60.6)
Females	26 (39.4)
Comorbidities	
Hypertension	41 (62.1)
Dyslipidemia	8 (12.1)
Ischemic heart disease	4 (6.1)
Cerebrovascular disease	3 (4.5)
Duration of diabetes (years)	11.0±7.8
Antidiabetic medications	
Metformin	32 (48.5)
Glimepiride	40 (60.6)
Gliclazide	11 (16.2)
Alpha-glucosidase inhibitors	19 (28.7)
Insulin	8 (12.1)
Pioglitazone	4 (6.1)
Hemodialysis	2 (3.0)

Data presented as frequency (%) and mean±SD

Table 2: Change in glycemic parameters

Parameter	Baseline (*n*=66)	3 months (*n*=66)	Baseline (*n*=27)	6 months (*n*=27)
HbA1c (%)				
Mean±SD	7.8±0.7	6.9±0.5	7.8±0.7	6.6±0.4
Change from baseline		−0.9±0.5*		−1.2±0.5*
FPG (mg/dL)				
Mean±SD	128.0±25.5	99.6±9.2	126.5±24.2	96.6±5.0
Change from baseline		−28.4±20*		−29.9±24.3*
PPG (mg/dL)				
Mean±SD	214.0±55.9	143.5±24.5	236.8±57.6	139.8±13.8
Change from baseline		−70.5±49.2*		−97.0±60.7*

FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, SD: Standard deviation. *P<0.001

Table 3: Change in eGFR

eGFR	Values		
	Baseline	3 months (*n*=57)	6 months (*n*=22)
Baseline of patients assessed at 3 months	80.4±25.3	81.1±24.7	-
Baseline of patients assessed at 6 months	77.3±25.6	-	79.3±24.8
Change from baseline		0.70 (P=0.049)	2.0 (P<0.014)

Data presented as mean±SD

−28.4 ± 20.9 mg/dl, $P < 0.001$) and from 126.5 ± 24.2 mg/dl to 96.6 ± 5.0 mg/dl at 6 months (mean difference: −29.9 ± 24.3 mg/dl, $P < 0.001$). Reduction in PPG was also significant at 3 months (mean difference: −70.5 ± 49.2 mg/dl, $P < 0.001$) and 6 months (mean difference: −97.0 ± 60.7 mg/dl, $P < 0.001$) follow-up. At baseline, only 7.6% of patients had HbA1c <7%. After addition of teneligliptin, proportion of patients achieving HbA1c <7% increased to 57.6% at 3 months and further to 73.1% at 6 months [Figure 1].

Table 3 describes the changes in eGFR levels. There was mild but significant increment in eGFR at 3 months (mean change: 0.70 ml/min/1.73m^2, $P = 0.049$) as well as at 6 months (mean change: 2.0 ml/min/1.73m^2, $P < 0.014$).

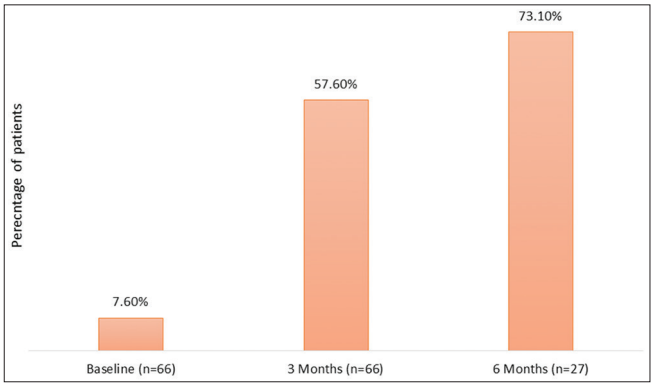

Figure 1: Proportion of patients with target hemoglobin A1c (<7%)

DISCUSSION

T2DM is a major etiological factor for kidney disease. Most of the antidiabetic agents have restrictions for their use if eGFR falls to <30 ml/min/1.73m^2. Teneligliptin, on the other hand, does not require dose adjustment even in end-stage renal disease.[3] Addition of teneligliptin in our study was found to provide a significant reduction in HbA1c, FPG, and PPG. Mean reduction of HbA1c was −0.9% at 3 months and −1.2% at 6 months after addition of teneligliptin. A study from Shah in CKD patients with T2DM (n = 37) reported HbA1c reduction of 0.48% (P = 0.001) and 1.0% (P = 0.001) at 3 and 6 months, respectively.[5] Reduction in FPG and PPG also significant confirming teneligliptin efficacy in all three glycemic parameters. Another evaluation from Otsuki *et al.* reported that teneligliptin is efficacious in lowering glucose levels significantly even in patients on hemodialysis (HD) and it was seen in patients started newly on teneligliptin or switched from voglibose or vildagliptin. Reduction in HbA1c was 0.3–0.8% at 24 weeks after initiating teneligliptin.[6] Wada *et al.* also reported similar finding with significant glycemia lowering efficacy of teneligliptin in patients on HD.[7] A large, post-marketing surveillance study from Japan also confirmed the efficacy of teneligliptin in providing significant HbA1c reduction at 1 year (−0.68 –−0.85% across different eGFR groups after adjusting for baseline HbA1c) and 2 years (−0.71–−0.85% across different eGFR groups after adjusting for baseline HbA1c).[8] Teneligliptin was used as an add-on to therapy with various antidiabetic agents as shown in Table 1. This suggests that the addition of teneligliptin is helpful in lowering glycemic burden in CKD patients. Teneligliptin has shown to lower insulin dosage and reduce hypoglycemic events in patients on HD treated with insulin.[9] These evidence strongly point out that teneligliptin should be

considered from the early phase of renal insufficiency in patients with T2DM.

When considering target HbA1c in patients of T2DM with renal impairment, individualized target levels are advised considering overall health of the patient.[10] An observational study in patients of CKD without dialysis showed U-shaped relationship of HbA1c with mortality. HbA1c of >9.0% and <6.5% showed increased mortality.[11] This suggests that individualized target should be considered. We observed that, after the addition of teneligliptin, HbA1c target of <7% was achieved among 57.6% and 73.1% of patients assessed at 3 and 6 months, respectively. Although the target HbA1c values are unclear in patients of CKD with or without dialysis, a general target of <7% might be helpful in reducing other potential microvascular and macrovascular complications of T2DM.[10]

The renal function as assessed by eGFR showed significant improvement at 3 and 6 months. Although teneligliptin has no effect on eGFR, the positive change observed is probably secondary to the improvement in glycemic burden. Shah also reported a significant improvement in eGFR from 53.35 ± 4.24 ml/min/1.73m^2 to 55.08 ± 4.19 and 57.95 ± 4.36 ml/min/1.73m^2 at 3 and 6 months, respectively ($P = 0.001$ for both comparisons).[5] However, evidence from post-marketing surveillance study from Haneda *et al.* reported relatively stable eGFR levels over 1 and 2 years with no significant change after initiating teneligliptin.[8] Another evaluation reported no significant difference in eGFR change when compared to sitagliptin at 24 weeks. However, teneligliptin and not sitagliptin improved endothelial function and reduced renal and vascular oxidative stress.[12] These findings suggest that teneligliptin can be among the first choices for glycemic control in T2DM with renal impairment.

Limitations

The study was limited by retrospective design, small sample size, and missing data on follow-up. Assessment of microalbuminuria may have provided more insights into the understanding of preservation or reversal of renal impairment. Detailed analysis of glycemia lowering efficacy according to different eGFR levels was not possible due to the loss of data on follow-up visits. A comparative analysis among different drug combinations and with other gliptins can further provide a better understanding of drug combinations for achieving optimal glycemic lowering in renal impairment.

CONCLUSION

Our retrospective analysis in patients of T2DM with CKD suggests that teneligliptin effectively provides a reduction in HbA1c as well as fasting and post-prandial glucose. The renal function during teneligliptin treatment improved over 6-month period possible due to improvement in glycemic burden. Teneligliptin can, thus, be considered among the first-choice treatments for T2DM with any degree of renal impairment.

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