International Journal of Research in Medical Sciences
Chatterjee AK. Int J Res Med Sci. 2018 Apr;6(4):1356-1361
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20181296

Original Research Article

Teneligliptin add on to monotherapy treatment in patients with type 2 diabetes

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Received: 31 January 2018
Accepted: 26 February 2018

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ABSTRACT

Background: In patient with type 2 diabetes (T2D) inadequately controlled on monotherapy, teneligliptin is efficacious and safe as add-on to treatment with oral antidiabetic drugs (OADs) or insulin. Data on efficacy of teneligliptin in Indian patients is relatively sparse. Aim of the study was to assess the efficacy of teneligliptin used as add-on treatment in patients inadequately controlled on monotherapy with OADs or insulin.
Methods: We retrospectively evaluated the electronic database at our endocrinology clinic from East India. Patients who were treated with teneligliptin (20 mg/day) as add-on to monotherapy with OADs or insulin were identified, and data analysed. Primary assessment parameters were change in glycosylated haemoglobin (HbA1c %), fasting plasma glucose (FPG, mg/dL) and post-prandial plasma glucose (PPG, mg/dL) over 12-week from the addition of teneligliptin. Paired t test and McNemar test applied to derive statistical significance of paired continuous and categorical variables respectively.
Results: In 88 patients, teneligliptin was used as add-on treatment in 77.3% and 22.7% patients receiving OAD and insulin as monotherapy respectively. Mean age of population was 48.3±15.1 years and 67% were males. From baseline to 12-weeks, there was significant change in HbA1c (9.6±2.1 to 8.4±1.2%, P<0.001), FPG (181.4±54.5 to 140.9±27.1 mg/dL, P<0.001) and PPG (273.7±75.6 to 201.1±47.7 mg/dL, P<0.001). Reduction in these glycemic parameters was significant in patients with teneligliptin as add-on to either OADs or insulin. Overall, 12.5% patients reached the target HbA1c of <7% after 12-week treatment (P=0.004).
Conclusions: In patients who are uncontrolled on monotherapy with either OADs or insulin, addition of teneligliptin resulted in significant reduction of HbA1c, FPG and PPG after 12-week treatment. This establishes usefulness of teneligliptin in Indian patients with T2D. A larger, randomized, comparative study with other gliptins is warranted.

Keywords: Blood glucose, Diabetes, HbA1c, Indian, Monotherapy, Teneligliptin

INTRODUCTION

Type 2 diabetes (T2D) is rapidly growing global epidemic. Recent estimates from International diabetes federation (IDF) suggest that 69.2 million people in India are diabetic and it is expected to rise to 123.5 million by 2040. Estimated number of patients with impaired glucose tolerance in India is 36.5 million.[1] With the rising prevalence of T2D, complications associated with uncontrolled hyperglycemia are on the rise. Recent survey from North India (n=5127) reports 8.3% were diabetic of which only 18% were known diabetic or were receiving any form of treatment. Among them, only 1/3rd had control of glycemia.[2] American Diabetes Association (ADA) guidelines recommend various treatments for T2D including oral antidiabetic drugs (OADs) and insulin in addition to diet and lifestyle therapy. Recently available dipeptidyl peptidase 4 inhibitors (DPP4i) are

recommended as second line treatment after metformin. However, guidelines also stated that patients centred approach is needed for selecting therapy. Insulin was recommended for those who do not achieve target glycemic levels with OADs.[3]

Teneligliptin was recently approved in India and is being used clinically. Teneligliptin has been approved in Japan as well as in Argentina for the management of T2D.[4] In monotherapy trials, teneligliptin was found to be effective in lowering HbA1c levels without hypoglycemia and weight gain.[5-7] Teneligliptin has also shown a significant glycemia lowering efficacy as add-on to metformin, glimepiride, pioglitazone and insulin.[8-11] From India, only few studies have evaluated efficacy of teneligliptin in clinical setting. TREAT-INDIA study involving 4305 T2D patients in real-world setting reported significant reduction in glycosylated haemoglobin, as well as in fasting and post-prandial plasma glucose levels. It was reported that teneligliptin as addition to insulin treatment was associated with highest reduction in HbA1c levels.[12] Given the relative lack of evidence on clinical effectiveness of teneligliptin in India, we performed a retrospective analysis teneligliptin as addition to monotherapy treatment in T2D.

METHODS

This study was retrospective analysis of patients with T2D at a private endocrine clinic in Eastern India. We screened our electronic database for 6-month period between June 2016 to December 2016 to identify T2D patients who were prescribed teneligliptin. We included patients who had glycosylated haemoglobin (HbA1c) level of >7% with monotherapy treatment and were prescribed with teneligliptin (20g/day) as add-on to monotherapy of either oral antidiabetic drug (OAD) or insulin for control of glycemia. Patients with chronic medical illness like hepatic insufficiency, end-stage renal disease, and malignancy were excluded. The study was conducted in accordance with ethical principles of Declaration of Helsinki.

From the database, patients' characteristics pertaining to demographic parameters like age, gender; glycemic parameters like HbA1c%, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG); renal function parameters like serum creatinine, estimated glomerular filtration rate (eGFR), albuminuria and hepatic enzymes like aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were acquired. Baseline was considered as values before the initiation of teneligliptin treatment. Efficacy outcome evaluated was change in glycemic parameters after 12-weeks of teneligliptin treatment. Additionally, we also sought for clinical safety of teneligliptin during 12-week treatment. As T2D management involves OADs and/or insulin, we assessed the efficacy outcome separately in patients who were being managed on monotherapy of OAD or insulin.

Statistical analysis

Microsoft office excel version 2010 was used for data assimilation. Statistical analysis was performed using statistical software for windows SPSS version 10. Data were presented as mean and standard deviation for continuous data and frequency and percentages for categorical data. Statistical significance was tested with paired-sample t test for continuous variables. Mean difference with 95% confidence interval was presented. McNemar test was used for paired categorical variables. P-value <0.05 was considered statistically significant.

RESULTS

From our database screened for six months, 505 patients were found to be prescribed with teneligliptin for management of T2D. Among these, teneligliptin was used as add-on to monotherapy treatment in 93 patients. Among them, follow-up data on glycemic parameters was not available for 5 patients and therefore, we included 88 patients in final analysis. Among 88 patients, 68 (77.3%) were receiving OAD and 20 (22.7%) were being managed with insulin treatment before addition of teneligliptin (Figure 1).

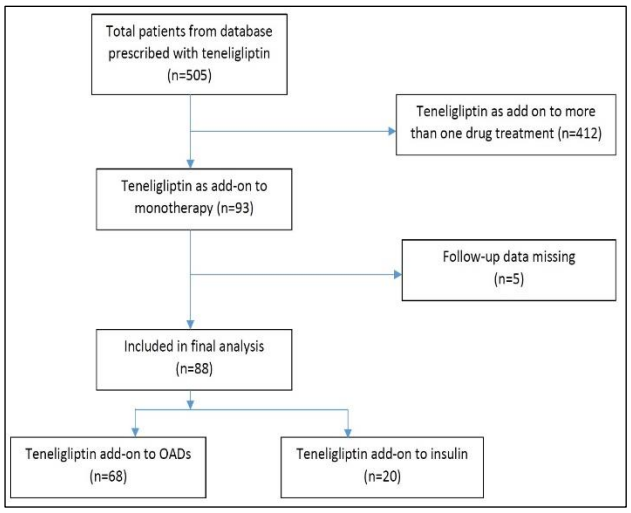

Figure 1: Study participants flow chart.

OADs prescribed to patients were metformin (n=38, 55.9%), sulphonylureas (n=23, 33.8%), and pioglitazone (n=7, 10.3%). Overall, mean age of the patients was 48.3±15.1 years and one-third were males. There was no difference in mean age of the patients who were treated with either OAD or insulin (P=0.168) and in distribution of males and females (p=0.446). Baseline characteristics of study population are summarized in Table 1. At baseline, mean HbA1c was 9.6±2.1%, mean FPG was 181.4±54.5mg/dL and mean PPG was 273.7±75.6mg/dL. Mean HbA1c did not differ significantly between patients treated with OAD or insulin but FPG (p=0.011) and PPG (p=0.005) were significantly greater in patients who were treated with insulin.

Table 1: Baseline characteristics of study population.

Characteristic	Total (n=88)	OADs (n=68)	Insulin (n=20)	P-value
Age				
Mean Age	48.3±15.1	49.5±14.5	44.2±16.7	0.168
Age groups				
≤50	48 (54.5)	36 (52.9)	12 (60.0)	0.674
51-75	38 (43.2)	30 (44.1)	8 (40.0)	
≥76	2 (2.3)	2 (2.9)	0	
Gender				
Male	59 (67.0)	47 (69.1)	12 (60.0)	0.446
Female	29 (33.0)	21 (30.9)	8 (40.0)	
Biochemistry				
HbA1c (%)	9.6±2.1	9.4±1.7	10.1±2.2	0.155
FPG (mg/dL)	181.4±54.5	173.5±46.9	208.4±69.8	0.011
PPG (mg/dL)	273.7±75.6	261.6±66.9	315.0±89.8	0.005
Serum creatinine (mg/dL)	0.95±0.15	0.94±0.16	0.95±0.15	0.782
eGFR (ml/min/1.73m^2)	95.6±20.4	95.0±19.4	97.5±23.6	0.639
Microalbuminuria	17 (19.8)	15 (22.4)	2 (10.5)	0.252
AST (U/L)	32.8±10.3	32.3±10.3	34.6±10.6	0.391
ALT (U/L)	42.0±14.4	41.8±15.0	42.7±12.4	0.804

HbA1c: glycosylated hemoglobin A1c, FPG: fasting plasma glucose, PPG: post-prandial plasma glucose, eGFR: estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase

Table 2: Glycaemia lowering efficacy in study population.

Parameter	Baseline (n=88)	12 weeks (n=88)	Mean Difference (95% CI)	P-value
HbA1c (%)	9.6±2.1	8.4±1.2	-1.2 (-0.9, -1.5)	<0.001
HbA1c≤7	0	11 (12.5)	-	0.004
FPG (mg/dL)	181.4±54.5	140.9±27.1	-40.5 (-30.8, -50.2)	<0.001
PPG (mg/dL)	273.7±75.6	201.1±47.7	-72.6 (-58.7, -86.4)	<0.001

HbA1c: glycosylated hemoglobin A1c, FPG: fasting plasma glucose, PPG: post-prandial plasma glucose

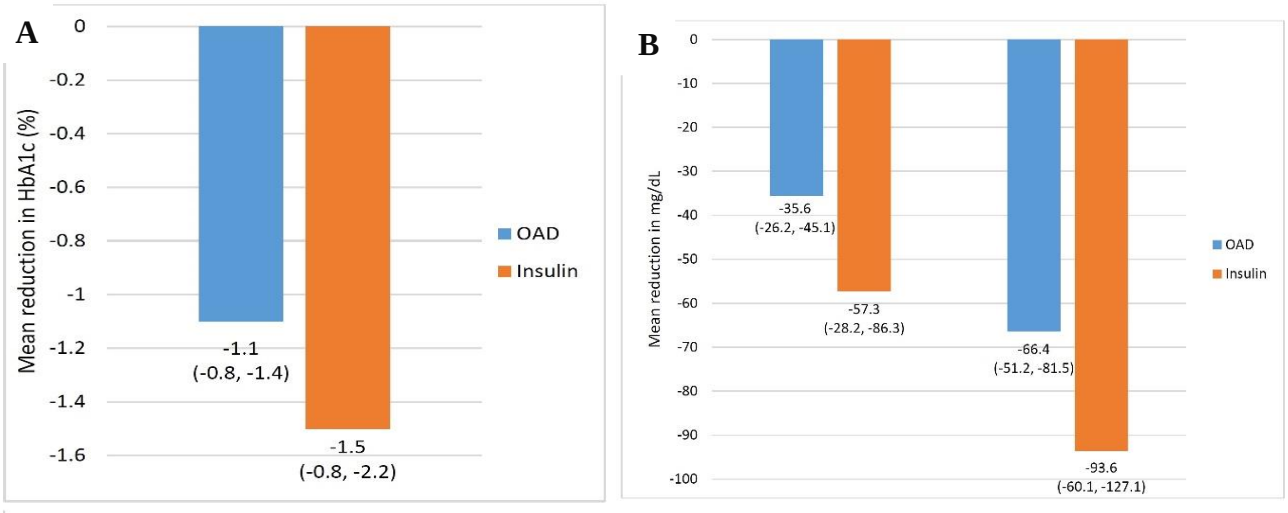

Figure 2: Reduction in hbA1c (A) and FPG and PPG (B) in two groups.

Glycemia lowering efficacy of teneligliptin as add on to monotherapy is shown in Table 2 and Figure 2 A and B. In overall study population, HbA1c was reduced significantly from baseline to 12-weeks (9.6±2.1 Vs 8.4±1.2%, P<0.001). Similarly, FPG (181.4±54.5 Vs 140.9±27.1mg/dL, P<0.001) and PPG (273.7±75.6 Vs 201.1±47.7mg/dL, P<0.001) reduction was significant from baseline to 12-week. In patients receiving OAD and insulin, significant reduction in glycemic parameters was

observed after addition of teneligliptin. Among patients who were treated with OAD and insulin, HbA1c was reduced by-1.1% (95% confidence interval (CI)-0.8, -1.4; P<0.001) and-1.5% (95% CI -0.8, -2.2; P<0.001) respectively. In FPG and PPG, significant (P<0.001 for both) reduction was observed in patients treated with OAD (-35.6mg/dL and -66.4mg/dL respectively) and insulin (-57.3mg/dL and -93.6mg/dL respectively). After 12-weeks of addition of teneligliptin, target HbA1c of 7% or below was achieved in 11 (12.5%) patients (P=0.004).

Table 3: Changes in renal and hepatic function parameters.

Parameter	Overall population			OAD + Teneligliptin			Insulin + Teneligliptin		
	Baseline (n=88)	12 weeks (n=86)	p-value	Baseline (n=68)	12 weeks (n=68)	p-value	Baseline (n=20)	12 weeks (n=18)	p-value
Serum creatinine (mg/dL)	0.95±0.15	0.95±0.15	0.421	0.94±0.16	0.96±0.15	0.394	0.95±0.15	0.95±0.14	0.928
eGFR (ml/min/1.73m^2)	95.6±20.4	85.6±21.0	<0.001	95.0±19.4	0.85±19.8	<0.001	97.5±23.6	88.2±25.5	0.036
eGFR<90	38 (43.2)	46 (53.5)	0.013	29 (42.6)	36 (54.5)	0.057	9 (45.0)	10 (55.6)	0.250
Micro-albuminuria	17 (19.8)	13 (15.1)	0.489	15 (22.4)	12 (17.6)	0.375	2 (10.5)	1 (5.6)	0.500
AST (U/L)	32.8±10.3	33.4±9.0	0.235	32.3±10.3	33.7±9.5	0.119	34.6±10.6	32.6±7.3	0.737
ALT (U/L)	42.0±14.4	40.0±11.8	0.131	41.8±15.0	41.0±12.5	0.449	42.7±12.4	36.9±8.4	0.052

eGFR: estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase

Table 3 describes changes in renal and hepatic function with teneligliptin treatment. In renal function, though there was no significant change in serum creatinine (P=0.421) and reduction in proportion of patients with microalbuminuria (19.8% at baseline to 15.1% at 12 weeks, P=0.489), eGFR reduced significantly from baseline to 12 weeks (95.6±20.4 Vs 85.6±21.0 ml/min/1.73m^2 respectively, p<0.001). Reduction in eGFR was also evident in patients who were treated with OADs (p<0.001) and insulin (p<0.036). Proportion of patients with eGFR <90 ml/min/1.73m^2 increased significantly (P=0.013) from 43.2% at baseline to 53.5% at 12 weeks. Increase in the eGFR in two groups was non-significant.

There were two cases of macroalbuminuria one in each group which did not reduce or reverse with addition of teneligliptin. Hepatic enzymes levels did not change significantly across groups during 12-week treatment. Clinically, teneligliptin was safe and there were no adverse effects reported with it. Complete laboratory safety assessments were not performed in any patient because of economic constraints.

DISCUSSION

Findings suggest that in patients with T2D who had inadequate control of glycemia with monotherapy, teneligliptin as add-on to existing treatment significantly reduced HbA1c, FPG and PPG at 12-weeks. Efficacy of teneligliptin in reducing glycemic burden as add-on to monotherapy has been shown in various studies. In a 16-week trial, Park et al, reported that teneligliptin 20 mg/day as add-on to metformin in comparison to placebo was associated with significant reduction in HbA1c (adjusted mean difference -0.90% Vs -0.12%, p<0.0001) and FPG (adjusted mean difference -1.10 mmol/L Vs 0.15mmol/L, p<0.0001).[8] In another placebo-controlled study, Kadowaki and Kondo, reported significant reduction of HbA1c and FPG with addition of teneligliptin to glimepiride monotherapy.[9] They observed maintenance of glycemic benefit over 52-weeks. Similar results were reported with pioglitazone as well.[10] Addition of teneligliptin to insulin monotherapy was effective in reducing glycemia burden. This was further supported by our finding of HbA1c goal of <7% was achieved in 12.5% patients (P<0.004). Addition of teneligliptin to insulin monotherapy was found to reduce HbA1c, FPG and PPG to a greater extent than addition to OADs (Figure 2 A and B).

This might be due to significantly higher levels of these glycemic parameters at baseline in patients who were treated with insulin. Jones et al, reported that baseline HbA1c is a major predictor of glycemic response.[13] They argued that studies should incorporate adjustment for baseline HbA1c to reduce the bias in studies assessing response to anti-hyperglycemic treatments. Teneligliptin addition to insulin was reported to significantly improve diurnal control of glycemia and reduction in glucose fluctuations in 24-hour period.[11] These evidences from clinical studies suggests that teneligliptin as add-on treatment to monotherapy treatment is effective in lowering glycemia levels irrespective of baseline antidiabetic medication.

Teneligliptin is a novel DPP4i in that it doesn't require dose reduction in patients with chronic kidney disease (CKD) including those with end stage renal disease (ESRD) and undergoing dialysis.[14] It has shown to improve blood glucose control in these patient population.[15] We observed no significant change in serum creatinine level after addition of teneligliptin but eGFR reduced significantly in overall population (p<0.001) and in patients who were treated with OAD (p<0.001) and

insulin (p=0.036). This contrasts to the observation of safety of teneligliptin in ESRD and hemodialysis cases. Previous studies have not reported significant changes in any laboratory parameters including eGFR with teneligliptin treatment.[7,8,10,11]

However, there was improvement in microalbuminuria in non-significant proportion of patients at 12-weeks. A case-control study by Sagara et al, in patients with T2D and CKD, teneligliptin treatment was not associated with significant change in eGFR or urinary albumin excretion after 24-weeks treatment.[16] The reduction eGFR in our study was possibly the worsening of existing CKD as there was significant increase in proportion of patients who had eGFR<90 ml/min/1.73m^2. This suggests monitoring of renal function is essential in T2D to understand the progression of existing disease in order to modify therapy. No effects on hepatic enzymes were noted.

The study was a retrospective analysis of available data. A prospective study would give better results in terms of efficacy. Small sample and short-duration are important limitations of our analysis. The observed reduction of 1.1% to 1.5% in HbA1c needs to be considered with caution as RCTs performed globally have shown HbA1c reduction of 0.7 to 1.0%. Differential analysis by baseline OAD can clarify the combination treatment with better efficacy. Comparative analysis by gender, obesity, renal function was not performed which would provide understanding of efficacy of teneligliptin in these subgroups. Detailed safety assessment was not possible as inadequate data was available for safety analysis. Above are the limitation of the study.

CONCLUSION

Teneligliptin as add-on in patients who have inadequate control with monotherapy resulted in significant lowering of HbA1c, fasting and postprandial plasma glucose levels over 12-weeks. Improvement in glycemic parameters was greater in patients who were treated with insulin than with OADs. This possibly was the result of greater baseline values in patients who were receiving insulin. Significant increase in eGFR probably reflected continuing renal dysfunction in existing CKD. Our study established and further confirmed the efficacy teneligliptin as add-on to monotherapy treatment in Indian patients with T2D.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Chatterjee Ak. Teneligliptin add on to monotherapy treatment in patients with type 2 diabetes. Int J Res Med Sci 2018;6:1356-1.