ORIGINAL ARTICLE

A ProspectIve, OpeN-Label, Randomized Study Comparing EffIcacy and Safety of Teneligliptin VErsus Sitagliptin in Indian Patients with Inadequately Controlled Type 2 Diabetes Mellitus: INSITES Study

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Abstract

Background: Teneligliptin is widely prescribed dipeptidyl peptidase-4 inhibitor (DPP-4i) in India because of its economical pricing. However, there is no head-to-head trial comparing teneligliptin with any other DPP-4i in Indian setting. We evaluated the efficacy and safety of teneligliptin versus sitagliptin as add-on to metformin and/or sulfonylureas in patients with type 2 diabetes mellitus (T2DM).

Methods: This prospective, open-label, randomized, active-controlled study enrolled 76 patients (1:1) at 2 centres. Patients received teneligliptin 20 mg or sitagliptin 100 mg orally once daily for 12 weeks as add-on to ongoing metformin or sulfonylurea therapy. Primary endpoint was mean change in glycosylated hemoglobin (HbA1c) from baseline at week 12.

Results: Both arms were comparable (p>0.05) at baseline in terms of age, gender, metformin daily dose, sulfonylurea use, HbA1c, fasting and postprandial blood glucose (FBG and PPBG). At the end of 12 weeks, statistically significant reductions were observed in both teneligliptin and sitagliptin arms in HbA1c (–1.19 ± 1.16% p<0.0001 and -0.92 ± 0.95%, p<0.0001), in FBG (-28.3 ± 63.0 mg/dL, p= 0.01 and -22.9 ± 47.4 mg/dL, p=0.006) and PPBG (-41.3 ± 85.4 mg/dL, p=0.006 and -54.7 ± 85.6 mg/dL, p=0.0005). The reductions in all glycemic parameters were similar between the arms. Both gliptins were well-tolerated with no difference in the number of adverse events. There was no change in QT/QTc intervals or other ECG parameters at week 12 in both arms. In post-hoc comparison, percentage of patients achieving target HbA1c <7% (as per American Diabetes Association guidelines) at week 12 favored teneligliptin arm over sitagliptin arm (33.3% vs. 19.4% patients).

Conclusion: Teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, FBG and PPBG values significantly within 12 weeks of treatment. Both gliptins were found to be safe and well-tolerated in Indian patients with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) had a global prevalence of 9.09% in 2017.[1] In India, 8.8% of the adult population had diabetes in 2017; if the current trend continues, prevalence in India will increase to about 12.1% by 2040.[1] Uncontrolled glycemia and reduced insulin sensitivity increases the risk of macrovascular and microvascular complications, including cardiovascular disease, renal disease and retinopathy.[2-4] More than half of Indian patients fail to achieve the target glycemic control (glycosylated hemoglobin [HbA1c] <7%) recommended by most guidelines.[5,6] The natural history of progressive decline in β-cell function limits the long-term use of metformin monotherapy. Hence, combination therapy with other oral anti-diabetic agents (OADs) is recommended for achieving and maintaining optimum glycemic control after failure of metformin monotherapy.[7,8]

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are a promising class of OADs, which inhibit the endogenous glucagon-like peptide-1 (GLP-1) metabolism and thereby increase GLP-1 level in the physiological range. They act by regulating insulin and glucagon secretion. DPP-4i unlike sulfonylureas, meglitinides, or insulin are weight neutral.[9] DPP-4i with metformin is associated with a lower risk of severe hypoglycemia, cardiovascular events, and all-cause mortality compared with metformin plus sulphonylurea.[10] A recent study reported improvement of long-term survival in diabetic patients after first acute myocardial infarction, regardless of gender with use of DPP-4i.[11] In a propensity score-matched T2DM patients (n=321,606), use of DPP-4i was associated with a reduced risk of heart failure hospitalization compared to GLP-1 agonists.[12] The international guidelines advocate the use of DPP-4i as first line or second line agents in the treatment of T2DM.[13] The Research Society for the Study of Diabetes in India (RSSDI) also advises the use of DPP-4i in patients who are non-responsive or contraindicated to metformin.[14]

Teneligliptin is a novel DPP-4i and has a unique J structure characterized by five consecutive rings; the interaction occurs between the phenyl ring on the pyrazole of teneligliptin and the S2 extensive subsite of DPP-4 enzyme. These unique properties

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Received: 17.04.2019; Accepted: 13.07.2019

and the 24 hours plasma half-life produces a potent, selective and long-lasting glucose-lowering effect.[15] The pharmacokinetic properties, and the elimination route differs among DPP-4i and these differences are related to the need for dose adjustments in patients with renal or hepatic dysfunctions. However, present evidence suggests that linagliptin[16] and teneligliptin[17] can be used safely without dose adjustments in patients with renal impairment, including End Stage Renal Disease.

Teneligliptin was extensively evaluated for efficacy, safety and tolerability in Japanese and Korean patients with T2DM. A pooled analysis of two phase III trials has shown that teneligliptin as monotherapy or combination therapy has similar adverse event (AE) profile with lesser risk of hypoglycemia as compared to sulfonylurea for as long as 52 weeks.[18] Teneligliptin monotherapy significantly reduced HbA1c by -0.94% in a 24-week placebo-controlled trial in Korea.[19] Teneligliptin improved first phase of insulin secretion thus decreasing post meal glucose excursions in a 12-week study in drug-naive Japanese patients.[20] Patients with mild, moderate, severe or end-stage renal diseases have been shown to tolerate teneligliptin, and dialysis did not affect the drug's efficacy or safety.[21] Recently, a post-marketing surveillance reported long-term safety of teneligliptin in T2DM patients with any stage of renal impairment.[22] Moreover, no dose adjustment was required in hepatic impairment as the drug concentration was within FDA cut-off.[23]

Sitagliptin is the first molecule launched in the class of DPP-4i. Sitagliptin monotherapy for 18 weeks was shown to significantly lower HbA1c as compared to placebo in Indian, Chinese and Korean patients.[24] In a real world study, addition of sitagliptin was effective in lowering HbA1c by about 1% in patients who failed on sulfonylurea/ metformin.[25] Teneligliptin has been introduced in India as an affordable and efficacious alternative gliptin. Teneligliptin can reduce the average pharmacotherapy cost by about 80% in India when compared to other DPP-4i.[26] It was approved in India in 2015 based on data from a phase III clinical trial. Several individual studies have evaluated its efficacy and safety in Indian patients. However, no head-to-head trial has compared teneligliptin with any other DPP-4i in Indian setting. We conducted this study to evaluate the efficacy and safety of teneligliptin versus sitagliptin as an add-on to metformin and/or sulfonylureas in adult Indian patients with T2DM.

Methodology

After obtaining approval from the Institutional Review Board of Madras Diabetes Research Foundation each, the study was conducted in compliance with the protocol and all applicable regulatory guidelines. Written informed consent was obtained from all patients prior to study participation. All study related data were recorded in a structured Case Record Form.

Study Population

Male and female patients aged 18-65 years with uncontrolled T2DM (HbA1c >7.5% and <10.0%) who were on a stable dose of metformin alone/ metformin plus sulfonylurea for past 4 weeks were included in the study. Patients with T1DM; history of hypersensitivity to study medication or its ingredients, any insulin use in past 6 weeks; history of administration of any other OADs except for metformin or sulphonylurea in past 4 weeks; history of serious infection/ surgical procedure/ severe trauma in past 4 weeks or planned surgery during the study period; history of repeated episodes of hypoglycemia or hyperglycemic events like hyperosmolar coma; history of concomitant medications such as corticosteroids, anti-epileptics, antipsychotics, and antiretroviral therapy; likely to go for ritual fasting or travel for longer duration; history or evidence of significant cardiovascular disorder such as heart failure, myocardial infarction or any conduction abnormality on electrocardiography (ECG) e.g. QT prolongation, arrhythmias; history or evidence of any significant hepatic, renal, gastro-intestinal, neurological or other endocrine disorder; history or risk of acute pancreatitis, chronic alcoholism or drug abuse; pregnant or lactating women were excluded. During study conduct, patients were planned to be withdrawn prematurely if blood glucose control worsened (fasting blood glucose [FBG] >180 mg/dL) and patient required additional anti-diabetic medication(s).

Study Design and Treatment

This was a prospective, randomized, open-label, active-controlled trial conducted at 2 sites in Chennai (Madras Diabetes Research Foundation (MDRF), Gopalapuram, Chennai and Dr Mohan's Diabetes Specialties Centre, Tambaram, Chennai between November 2017 and October 2018. Patients were randomly assigned (1:1) on day 1 to receive either Teneligliptin (INOGLA® 20 mg marketed by Wockhardt Ltd.) or Sitagliptin (JANUVIA® 100 mg marketed by MSD Pharmaceuticals Pvt. Ltd.) once daily orally along with stable dose of metformin. The patients were instructed to bring all unused study drugs and empty blister packages to assess treatment compliance during scheduled follow-ups at week 6 and 12.

Study endpoints and assessment

The primary outcome measure was mean change in HbA1c from baseline at week 12. The secondary outcome measures included changes in FBG and postprandial blood glucose (PPBG) levels from baseline at week 6 and 12, and change in lipid profile from baseline at week 12. The safety endpoints included recording of type, incidence, severity, timing, seriousness, and relatedness of all AEs, adverse drug reactions, and serious adverse events (SAE). The ECG parameters examined included heart rate (HR), PR interval, QT interval and QT interval after correction for the change in HR (QTc) at week 6 and 12. Prolonged QTc was defined as any value above the cut-off point of 450 milliseconds (ms).

Baseline assessment included demographics, significant medical and surgical history, vital signs, anti-diabetic therapy, concomitant medications and a thorough physical examination. Investigations included HbA1c, FBG, PPBG, lipid profile, hemogram, SGOT (aspartate aminotransferase), SGPT (alanine aminotransferase), creatinine, amylase, lipase and ECG. At week 6, FBG, PPBG, and ECG were repeated. At week 12, patients underwent blood investigations (HbA1c, FBG, PPBG, lipid profile, hemogram, SGOT, SGPT and creatinine) along with ECG.

Statistical analyses

The study was planned to enroll 76 patients with T2DM considering maximum drop-out rate of 20% to get

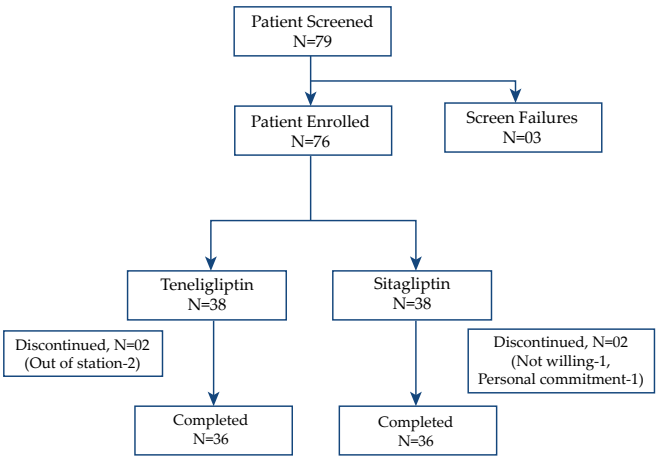


Fig. 1: Patient disposition (all randomized patients)

Table 1: Baseline characteristics of study groups

		Total (n=76)	Teneligliptin (n=38)	Sitagliptin (n=38)	p-value
Age (years), Mean (SD)		49.4 (9.49)	48.7 (9.46)	50.2 (9.58)	0.5020
Female, n (%)		39 (51.3)	22 (57.9)	17 (44.7)	0.5177
Male, n (%)		37 (48.7)	16 (42.1)	21 (55.3)	
Weight (kg), Mean (SD)		68.7 (14.41)	70.4 (16.14)	66.9 (12.43)	0.3029
BMI (kg/m²), Mean (SD)		27.5 (4.61)	28.6 (5.20)	26.3 (3.65)	0.0287
Metformin Daily Dose (mg), Mean (SD)		1104.6 (257.4)	1136.8 (308.8)	1072.4 (192.0)	0.2786
Sulfonylurea	No, n (%)	13 (17.1)	8 (21.1)	5 (13.2)	0.6660
	Yes, n (%)	63 (82.9)	30 (78.9)	33 (86.8)	
FBG (mg/dL), Mean (SD)		174.2 (44.1)	177.8 (48.7)	170.6 (39.3)	0.4814
PPBG (mg/dL), Mean (SD)		284.5 (79.0)	286.0 (86.6)	283.0 (71.8)	0.8684
HbA1c (g%), Mean (SD)		8.7 (0.74)	8.8 (0.76)	8.7 (0.71)	0.3301

BMI: body mass index; FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin; PPBG: post-prandial blood glucose; SD: Standard deviation; Percentages are calculated based on total number of subjects in the respective treatment arm; n = Number of subjects in respective categories; N = Total number of subjects in the respective treatment arm/safety population; p-value compared the treatment groups using chi-square/fisher's exact test for categorical parameters and independent t-test for continuous variables.

at least 60 analyzable patients. The intention-to-treat (ITT) population included all randomized patients who received at least one dose of study medication and had at least one post-baseline follow-up visit. All the randomized patients who consumed at least one dose of study medication were considered for safety analysis. The patients who required withdrawal due to worsening of blood glucose control after 6 weeks were considered as non-responders and included in the per protocol (PP) analysis.

Demographic data such as age, gender, weight, height, body mass index (BMI) were summarized using descriptive statistics. Baseline characteristics of both arms were compared using appropriate statistical tests. Summary statistics for quantitative variables included the number of observations (n), arithmetic mean, standard deviation (SD). Primary and secondary quantitative variables (FBG, PPBG, HbA1c and lipid profile) for changes across time (baseline to week 6 and 12) were analyzed using paired t-test at 5% level of significance with two-sided 95% confidence intervals; $p<0.05$ was considered statistically significant. AEs and SAEs were summarized using count and percentage by body system and preferred term. Patients who prematurely discontinued the study had their last non-missing post-baseline values carried forward. Statistical analyses were performed using Statistical and Analytical Software (version 9.4).

Results

A total of 79 patients were screened of which 76 were randomized to treatment with teneligliptin (n=38) or sitagliptin (n=38). Patient disposition is presented in Figure 1; four patients discontinued the study prematurely and were excluded from the ITT population-efficacy. Baseline demographics and clinical characteristics were comparable between the treatment arms (Table 1). The mean ± SD age of patients was 49.4 ± 9.49 years with marginal female predominance (51.3%). The mean ± SD weight, BMI, and HbA1c at baseline were 68.7 ± 14.4 kgs, 27.5 ± 4.61 kg/m^2, and 8.7 ± 0.7%, respectively. At baseline, mean ± SD dose of metformin was 1104 ± 257 mg per day and 83% (n=63) patients were receiving sulphonylureas. None of the patients reported any prevalent co-morbidity such as hypertension or dyslipidemia.

Efficacy outcomes

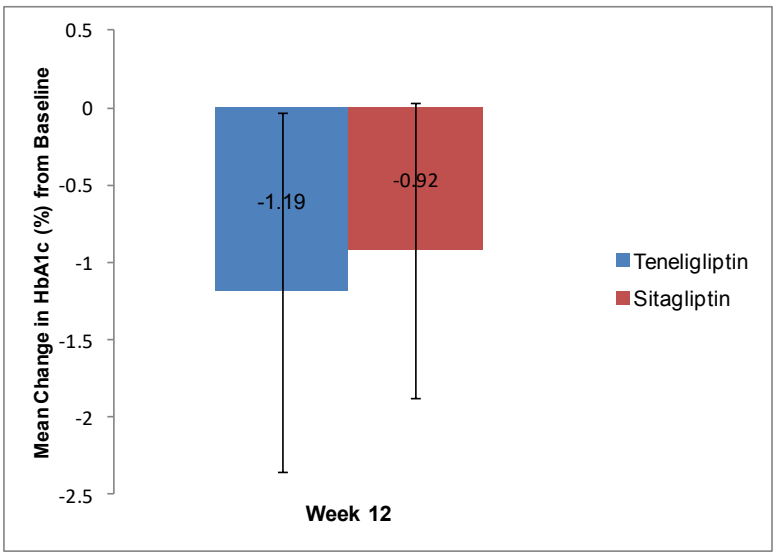
Glycemic control

Treatment with both teneligliptin and sitagliptin showed a statistically significant reduction in mean HbA1c from baseline at week 12 (−1.19 ± 1.16% and -0.92 ± 0.95% respectively, $p<0.0001$) (Figure 2). By week 12, teneligliptin reduced the mean HbA1c from 8.82 ± 0.78% to 7.63 ± 1.09% and sitagliptin reduced HbA1c from 8.66 ± 0.69% to 7.74 ± 0.83%. The mean reduction in HbA1c was comparable between the two gliptins with inter-group difference being -0.16% (95% confidence interval [CI]: -0.61, 0.28; p=0.4675) with post-hoc construed 95% CI for the difference between two arms as per USFDA guidance indicating non-inferiority of teneligliptin vs. sitagliptin.

Table 2 presents change from baseline in primary and secondary efficacy endpoints. In post-hoc comparison of percentage of patients achieving target HbA1c <7% (target as per the American Diabetes Association [ADA] guidelines) by 12 weeks of treatment, the results favored teneligliptin treatment arm over sitagliptin treatment arm (33.3% vs. 19.4% patients).

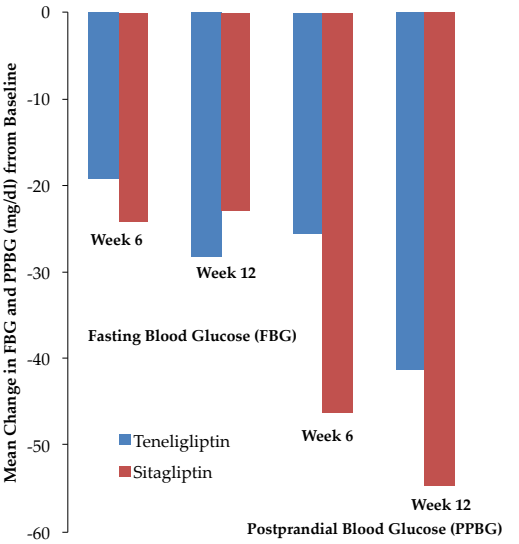
Teneligliptin demonstrated a statistically significant reduction in mean FBG from baseline at week 12 (-28.3 ± 63.0 mg/dL, p=0.01). However, the reduction at week 6 was statistically not significant (-19.4 ± 68.8 mg/dL, p=0.10). The mean reduction in FBG with sitagliptin was statistically significant at both week 6 (-24.2 ± 38.9 mg/dL, p=0.0007) and week 12 (-22.9 ± 47.4 mg/dL, p=0.0064) (Table 2). The reductions in FBG at 6 and 12 weeks were comparable (p>0.05) between both gliptins. The inter-group difference was 6.9 mg/dL (95% CI: -15.6, 29.6) at 6 weeks and -3.6 mg/dL (95% CI: -27.0, 19.8) at 12 weeks.

Both teneligliptin and sitagliptin showed statistically significant reduction in PPBG levels at week 12 (-41.3 ± 85.4 mg/dL, p=0.006 and -54.7 ± 85.6 mg/dL, p=0.0005); change at week 6 was statistically significant for sitagliptin (-46.2 ± 69.3 mg/dL, p=0.0003) and not for teneligliptin (-25.6 ± 113.1 mg/dL, p=0.18). The reductions in PPBG at 6 and 12 weeks were comparable (p>0.05). The inter-group difference was 19.3 mg/dL (95% CI: -13.2, 51.7) at 6 weeks and 12 mg/dL (95% CI: -15.0, 39.0) at 12 weeks.



p-value<0.0001

Fig. 2a: Mean (SD) change in HbA1c from baseline to week 12



Teneligliptin (FBG): Week 6 change, SD=68.8, p=0.1; Week 12 change, SD=62.99, p=0.01; Sitagliptin (FBG): Week 6 change, SD=38.9, p=0.0007; Week 12 change, SD=47.38, p=0.006; Teneligliptin (PPBG): Week 6 change, SD=113.06, p=0.18; Week 12 change, SD=85.37, p=0.006; Sitagliptin (PPBG): Week 6 change, SD=69.69, p=0.0003; Week 12 change, SD=85.6, p=0.0005

Fig. 2b: Mean (SD) change in fasting and postprandial blood glucose from baseline to weeks 6 and 12

Table 2: Primary and secondary efficacy endpoints at 6 and 12 weeks

Parameters, mean (SD)	Teneligliptin (N=36)			Sitagliptin (N=36)		
	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12
HbA1c (%)	8.82 (0.79)	-	7.63 (1.09)	8.66 (0.69)	-	7.74 (0.84)
Change from baseline[a]	-	-	-1.19 (1.16)	-	-	-0.92 (0.95)
FBG (mg/dL)	175.1 (46.4)	155.9 (57.7)	146.9 (54.4)	172.2 (39.0)	148.0 (40.3)	149.3 (50.1)
Change from baseline[b]	-	-19.2 (68.8)	-28.2 (63.0)	-	-24.2 (38.9)	-22.9 (47.4)
PPBG (mg/dL)	283.2 (82.6)	257.7 (79.1)	241.9 (53.0)	284.9 (73.1)	238.7 (59.5)	230.2 (64.2)
Change from baseline[c]	-	-25.6 (113.1)	-41.3 (85.4)	-	-46.2 (65.4)	-54.7 (85.6)
Lipid Profile						
HDL-C (mg/dL)	38.22 (7.35)	-	38.03 (6.75)	38.08 (6.10)	-	38.06 (6.41)
Change from baseline[d]	-	-	-0.19 (5.86)	-	-	-0.03 (4.30)
LDL-C (mg/dL)	110.97 (41.37)	-	98.72 (31.11)	106.69 (32.92)	-	91.72 (26.28)
Change from baseline[e]	-	-	-13.00 (37.93)	-	-	-14.97 (28.39)
TC (mg/dL)	180.42 (45.42)	-	164.78 (33.68)	176.56 (39.08)	-	157.47 (33.23)
Change from baseline[f]	-	-	-15.64 (47.85)	-	-	-19.08 (33.47)
TG (mg/dL)	169.19 (110.53)	-	141.33 (63.91)	158.83 (79.18)	-	138.28 (80.65)
Change from baseline[g]	-	-	-27.86 (91.65)	-	-	-20.56 (64.25)
VLDL (mg/dL)	29.56 (12.31)	-	28.25 (12.86)	31.78 (15.84)	-	27.69 (16.14)
Change from baseline[h]	-	-	-1.85 (9.66)	-	-	-4.08 (12.90)

FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; PPBG: post-prandial blood glucose; SD: standard deviation; TG: triglyceride; TC: total cholesterol; VLDL: very low density lipoprotein; a- Teneligliptin, p<0.0001; Sitagliptin, p<0.0001; b- Teneligliptin, p=0.1 (Week 6) and p=0.01 (Week 12); Sitagliptin, p=0.0007 (Week 6) and p=0.006 (Week 12); c- Teneligliptin, p=0.18 (Week 6) and p=0.006 (Week 12); Sitagliptin, p=0.0003 (Week 6) and p=0.0005 (Week 12); d- Teneligliptin, p=0.84; Sitagliptin, p=0.96; e- Teneligliptin, p=0.054; Sitagliptin, p=0.003; f- Teneligliptin, p=0.057; Sitagliptin, p=0.001;g- Teneligliptin, =0.07; Sitagliptin, p=0.06; h- Teneligliptin, p=0.27; Sitagliptin, p=0.06

Effect on Lipid Profile

Treatment with teneligliptin or sitagliptin for 12 weeks did not demonstrate a statistically significant change in any of the lipid parameters. Mean total cholesterol and low density lipoprotein cholesterol levels were numerically lower after 12 weeks of treatment with both DPP-4i; however, the changes were not statistically significant. Change in mean triglyceride was greater in teneligliptin arm than sitagliptin arm; however, difference was also not statistically significant (Table 2).

Safety and Tolerability

Of 76 enrolled patients, 9 patients experienced at least 1 AE. Of the total 11 AEs (8 in teneligliptin arm and 3 in sitagliptin arm), the most common AE was hypertension in teneligliptin arm (n=5, 13.2%). All the AEs were mild in severity, found to be 'not related' to either of the gliptins and recovered without sequelae. There was no difference in number of AEs reported between the two gliptins (p=0.48) (Table 3). No significant changes were reported in hepatic or renal parameters in both arms at week 6 and week 12. There were no reported hospitalizations or deaths during the study conduct.

At baseline, mean ± SD QTc interval and heart rate were 429.09 ± 24.05 ms (teneligliptin: 429.37 ± 18.12 ms and sitagliptin: 428.82 ± 29.04 ms) and 81.37 ± 11.93 beats per minute (teneligliptin: 82.97 ± 13.36 bpm and sitagliptin: 79.76 ± 10.24 bpm), respectively. ECG parameters (HR, PR interval and QT interval) did not change significantly during 12 weeks of treatment in both arms (Table 4). The QTc interval did

Table 3: Summary of safety events

Body system/ Preferred term	Teneligliptin n (%) (N=38)	Sitagliptin n (%) (N=38)
Number of patients with at least one AE*	6 (15.79)	3 (7.89)
Blood and lymphatic system disorders	0 (0.00)	1 (2.63)
Eosinophilia	0 (0.00)	1 (2.63)
Eye Disorders	1 (2.63)	1 (2.63)
Diabetic Retinopathy	1 (2.63)	1 (2.63)
Immune System Disorders	1 (2.63)	0 (0.00)
Seasonal Allergy	1 (2.63)	0 (0.00)
Metabolism And Nutrition Disorders	1 (2.63)	0 (0.00)
Hyperglycemia	1 (2.63)	0 (0.00)
Vascular Disorders	5 (13.2)	1 (2.63)
Hypertension	5 (13.2)	1 (2.63)

n = Number of subjects in respective categories; N = Total number of subjects in the respective treatment arm/safety population; percentages are calculated based on total number of subjects in the respective treatment arm/safety population; p-value compared the treatment groups using chi-square/fisher's exact test
*p-value: 0.4799

Table 4: Summary of ECG at Week 6 and 12

Parameters, mean (SD)	Baseline	Teneligliptin		Baseline	Sitagliptin	
		(N=38)	Week 12		(N=38)	Week 12
PR interval (ms)	148.82 (21.14)	147.17 (19.77)	147.66 (20.68)	148.92 (18.78)	148.86 (17.69)	150.64 (18.68)
Change from baseline[a]	-	-0.33 (8.69)	-0.63 (8.00)	-	-0.42 (8.73)	1.36 (8.38)
QT interval (ms)	367.42 (25.99)	370.89 (29.24)	372.83 (32.68)	373.47 (27.1)	376.86 (30.81)	372.42 (24.53)
Change from baseline[b]	-	3.50 (30.34)	5.14 (29.14)	-	-0.28 (24.21)	-4.72 (22.22)
QTc interval (ms)	429.37 (18.12)	438.22 (33.49)	433.23 (25.72)	428.82 (29.04)	436.50 (35.89)	433.14 (22.87)
Change from baseline[c]	-	10.00 (28.79)	4.91 (20.33)	-	5.11 (29.33)	1.75 (18.02)
Heart Rate (bpm)	82.97 (13.36)	83.94 (11.02)	81.74 (8.91)	79.76 (10.24)	81.31 (11.38)	82.03 (11.26)
Change from baseline[d]	-	1.39 (10.56)	-0.74 (11.87)	-	2.17 (11.55)	2.89 (11.23)

bpm: beats per minute; ms: millisecond; QTc: corrected QT interval; SD: Standard Deviation; p-value is calculated using independent t-test; a- Teneligliptin, p=0.8194 (week 6), p=0.6450 (week 12); Sitagliptin, p=0.7764 (week 6), p=0.3367 (week 12); b- Teneligliptin, p=0.4933 (week 6), p=0.3039 (week 12); Sitagliptin, p=0.9455(week 6), p=0.2108 (week 12); c- Teneligliptin, p=0.0445 (week 6), p=0.1619 (week 12); Sitagliptin, p=0.3030 (week 6), p=0.5638 (week 12); d- Teneligliptin, p=0.4354 (week 6), p=0.7136 (week 12); Sitagliptin, p=0.2680 (week 6), p=0.1318 (week 12)

not change significantly at week 12 in both teneligliptin and sitagliptin arms.

Discussion

To the best of our knowledge, this randomized, active-controlled study is the first to evaluate the efficacy and safety of teneligliptin in comparison with sitagliptin as an add-on therapy to metformin and/or sulfonylureas in Indian patients with T2DM. The findings of our study demonstrated that 3-month treatment with either teneligliptin or sitagliptin reduced HbA1c significantly by about 1%; where numerically higher reduction was observed with teneligliptin with post-hoc analysis indicating non-inferiority of teneligliptin vs. sitagliptin as well as numerically higher percentage of patients achieving target HbA1c levels (≤7%) in teneligliptin arm. Additionally, there was a significant decrease in the fasting and postprandial glucose levels at week 12 with both DPP-4i. There was no change in metformin and sulfonylurea dosage during the study period which enabled ideal comparison of the study treatments. At study entry, patients were overweight (BMI: 27.5 ± 4.61 kg/m^2) with uncontrolled glycemia (HbA1c: 8.7 ± 0.7%) consuming about 1 gm of metformin per day and >80% of patients were receiving a second OAD (sulphonylurea). This represents the common clinical situation in India when gliptins are often considered as an add-on therapy.

The mean ± SD HbA1c level achieved after 12 weeks of teneligliptin and sitagliptin treatment was 7.6 ± 1.1% and 7.7 ± 0.8%, respectively; this is close to the target HbA1c level (<7.0%) recommended by the ADA. The mean reduction in HbA1c at week 12 was statistically significant and comparable between the treatment arms. Similarly, mean reductions in FBG and PPBG at week 6 and 12 were comparable between teneligliptin and sitagliptin. Recently, Kim et al. has reported similar reduction in mean HbA1c from baseline at 24 weeks (teneligliptin, −1.03 ± 0.10% and sitagliptin, −1.02 ± 0.10%) in Korean patients.[27] The proportion of patients achieving HbA1c <7.0% at week 24 was 50.0% and 59.2% in the teneligliptin and sitagliptin arms, respectively. The change in FBG at week 12 reported in our study (teneligliptin, −28.3 ± 63.0 mg/dL and sitagliptin, −22.9 ± 47.4 mg/dL) were much greater than reported by Kim et al. (teneligliptin, −12 ± 3.4 mg/dL and sitagliptin, −14.4 ± 3.5 mg/dL). This greater decrease in FBG levels in our study population was most probably due to a higher baseline FBG (by about 20 mg/dL) in our study than the Korean study. The long-term 52-week pooled analysis of Japanese studies also demonstrated that the reductions in HbA1c were dependent on the baseline values: −1.0 ± 0.9% for HbA1c >8.0% at baseline.[18] An Indian study reported a significant −0.55% change in HbA1c with teneligliptin monotherapy (p=0.0043) compared to placebo at week 16 in drug- naive T2DM patients (n= 237).[28] The real world data from TREAT-INDIA study (n=4305) also demonstrated significant HbA1c reduction with teneligliptin monotherapy (-1.0 ± 0.5%) and when used as add-on to metformin (-1.1 ± 0.8%) or add-on to metformin plus sulfonylurea combination (-1.46 ± 1.33%).[29]

We did not observe significant changes in any of the lipid parameters with either teneligliptin or sitagliptin in line with the finding reported by Kim et al.[27] This shows that gliptins are perhaps neutral in terms of any effect on lipid profile.

Both teneligliptin and sitagliptin were well-tolerated with no difference in the number of AEs. QTc interval is an independent predictor of all-cause and CVD mortality in patients with T2DM.[30] Sitagliptin shortened QT interval in Japanese patients with no significant difference in QTc interval.[31] Teneligliptin (40 mg daily) does not cause QT prolongations, which is the maximal dose in usual clinical practice.[32] In the present study, the QT interval did not increase significantly from baseline to week 12 with either of the two gliptins. There was no statistical difference between the two arms for changes in ECG parameters.

None of the study patients reported any hypoglycemic event, while the incidence of hypoglycemia was 31.3% and 28.5% respectively in teneligliptin and sitagliptin arm in the Korean study.[27] In another Japanese study in drug-naive patients, two episodes (14.3%) of hypoglycemia (<64 mg/dL) with teneligliptin (n=7) and one episode (7.2%) with sitagliptin ((n=7)) were reported using continuous

glucose monitoring. However, none of these episodes were associated with any hypoglycemic symptoms.[33] Generally DPP-4i carry very low risk of hypoglycemia and the results of our study have confirmed the same. However, hypoglycemia has been reported in some other studies which call for vigilance and close monitoring while prescribing teneligliptin in patients who are prone to hypoglycemia.[34]

With increasing prevalence of T2DM in the Indian subcontinent, optimum pharmacotherapy is necessary to delay macro- and microvascular complications. Several of the OADs used as monotherapy, or in combinations are associated with AEs such as weight gain, hypoglycemia and gastrointestinal distress.[35] Incretin-based therapies such as DPP-4i and GLP-1 agonists have emerged as preferred drugs in the past few years because of their efficacy and acceptable safety profile. DDP-4 inhibitors are less costly than GLP-1 agonists and have lower risk for hypoglycemia through unique glucagon dynamics. Sitagliptin requires dose adjustments in patients with renal and hepatic impairment which can be overcome by teneligliptin, which due to dual mode of excretion, offers a notable advantage in T2DM patients with hepatic and renal impairment, including patients on dialysis, without the need for dose reduction.

This study had few limitations mainly due to its open-label study design, shorter treatment duration of 12 weeks and smaller sample size. Despite these limitations, the study provided much needed insights about the comparative efficacy and safety of teneligliptin with the prototype DPP-4i, sitagliptin. However, future studies with large sample size and longer duration should be planned to provide further evidence in terms of long-term efficacy, safety and tolerability.

Conclusion

To conclude, teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, fasting and postprandial glucose values significantly within 12 weeks of treatment. No significant change was observed in the lipid profile with either of the two DPP-4i. Both teneligliptin and sitagliptin were found to be safe and well-tolerated. Teneligliptin can thus be used as an affordable add-on gliptin for treating T2DM patients who fail to achieve optimum glycemic control with metformin and/or sulfonylureas.

Acknowledgement

Authors would like to thank Medical Team of Wockhardt Pharmaceuticals for manuscript writing support.

Conflict of Interest

Study was sponsored by Wockhardt Pharmaceuticals Ltd.

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