

Efficacy and safety of teneligliptin

Awadhesh Kumar Singh

Department of Endocrinology, GD Hospital and Diabetes Institute, Kolkata, West Bengal, India

Incretin-based therapies (IBT) including dipeptidyl peptidase-4 inhibitors (DPP-4Is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been the cornerstone of therapy for type 2 diabetes mellitus (T2DM) since the evolution of incretin science. DPP-4Is are particularly popular in the treatment of T2DM as they are oral drugs, less costlier than GLP-RAs, with modest to moderate glucose lowering similar to sulfonylureas (SU) depending on the baseline glycemic load. DPP-4Is carries novel mechanism of action and also have additional potential to protect from hypoglycemia, through unique glucagon dynamics.^[1] Indeed, consensus statements from the American College of Endocrinology/American Association of Clinical Endocrinologist and the Latin American Diabetes Association consider DPP-4I ahead of SU, mainly driven by their lower risk of hypoglycemia as well as weight neutrality.^[2,3]

Moreover, Asians (mainly East Asians) have also been found to respond comparatively better to IBT, compared to Caucasian. However, incretin response in South Asians (including Indians) appears to be different from East Asians and thus currently there is no clear consensus whether Indians also exhibit exaggerated response to IBT, like East Asians.^[4] Consequently, at least 11 different compounds of DPP-4Is have been made available worldwide, of which mostly available in Japan.^[5] In India, 4 DPP-4Is are already available and marketed that includes sitagliptin, vildagliptin, saxagliptin, and linagliptin. Recently, two newer molecule teneligliptin and gemigliptin have been added to this segment. Importantly, teneligliptin has been already approved and marketed product in Japan since 2012 and in Korea since 2014. However, teneligliptin is neither approved in the USA or in Europe although it was registered in the US Food and Drug Administration (FDA) for Phase 1 clinical development in 2007 and Phase 2 clinical developments in European Medicines Agency in 2009, without any further progress.^[6]

Corresponding Author: Dr. Awadhesh Kumar Singh,
Department of Endocrinology, GD Hospital and Diabetes Institute,
Kolkata, West Bengal, India.
E-mail: drawadheshkumarsingh@gmail.com

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.^[7]

Here, we aimed to systematically review the efficacy and tolerability of teneligliptin and put a perspective from the available evidence.

REVIEW METHOD

A PubMed search was made using MeSH word “teneligliptin,” “cardiovascular (CV) outcome,” and “DPP-4Is” and all the clinical trials published till date in English language were retrieved. Dossier of teneligliptin approval from Japan FDA was also retrieved, and subsequently, all the data chronologically analyzed.

Pharmacological properties of teneligliptin

Teneligliptin appears to possess a different chemical structure when compared to other DPP-4Is and consists of five consecutive cyclic rings. An X-ray co-crystallography study of teneligliptin found that the key interaction between the phenyl ring on the pyrazole and binding to “anchor lock domain” of S2 extensive subsite, boosts its potency, duration of action *in vivo*, and enhances selectivity.^[8] However, whether this interaction translates into any higher percentage of DPP-4I remains a matter of conjecture. Nonetheless, the mean $t_{1/2}$ of teneligliptin is ~ 20 h for 10 and 20 mg dosage in humans.^[9] With regards to pharmacodynamics, about 34.4% of teneligliptin is excreted unchanged via the kidney and the remaining 65.6% teneligliptin is metabolized and eliminated via renal and

hepatic excretion.^[10] Any degree of renal impairment does not affect the maximum plasma teneligliptin concentration after a single oral dose of 20 mg. This pharmacodynamic profile suggests that teneligliptin can be administered in patients with any degree of renal impairment without dose adjustments. However, the mean ratios for maximal plasma concentration in subjects with mild and moderate hepatic impairment were 25% and 38% higher than in healthy subjects, respectively, and those for the area under the curve ($AUC_{0-\infty}$) were 46% and 59% higher than in healthy subjects, respectively. This indicates that caution may be needed when administering teneligliptin to subjects with hepatic impairment.^[11]

Teneligliptin is metabolized by CYP3A4 and flavin-containing monooxygenases (FMO1 and FMO3) and it is a weak inhibitor of CYP2D6, CYP3A4, and FMO *in vitro*, but it has neither any inhibitory effect nor inducing effect.^[10] There were no clinically relevant drug–drug interactions when teneligliptin was coadministered with ketoconazole (a potent CYP3A4 and P-glycoprotein inhibitor), metformin, or canagliflozin in healthy volunteers.^[12-14]

Although teneligliptin has higher potency, it has moderate selectivity to DPP-4 receptors. The IC₅₀ values of teneligliptin against other DPP-enzymes including DPP-8 and DPP-9 are ~160–850 times greater than that for DPP-4, whereas IC₅₀ for fibroblast protein activation is >10,000 times greater than that for DPP-4.^[9,15]

The most important pharmacodynamic parameter for any DPP-4Is that translates to clinical efficacy is the extent of percentile DPP-4 inhibition. While percentage of DPP-4 inhibition was 81.3 and 89.7% within 2 h after teneligliptin 10 and 20 mg, respectively, percentage inhibition of plasma DPP-4 activity at 24 h after administration was 53.1 and 61.8% in the teneligliptin 10 and 20 mg group, respectively, in a 4-week study conducted by Eto *et al.*^[9] Another study by Nabeno *et al.* demonstrated that the percentage inhibition of plasma DPP-4 activity 24 h after administration of 20 and 40 mg dose of teneligliptin was varying somewhere between 53.9–66.9% and 59.8%, respectively.^[15] Besides, only 80 mg doses of teneligliptin exhibited >80% (72–85%) plasma DPP-4 inhibition at 24h after administration.^[15] Table 1 summarizes the extent of DPP-4 inhibition at various time point with different dosage of teneligliptin. Interestingly, both 10 and 20 mg teneligliptin demonstrated higher concentrations of plasma active GLP-1, compared to placebo even at 24 h after administration. Moreover, the differences in AUC_{0-2h} for plasma active GLP-1 concentration between both

teneligliptin treated groups and placebo were statistically significant ($P < 0.001$).^[9]

Efficacy of teneligliptin

In a very small ($n = 99$), 4 weeks, Japanese, Phase 2 clinical trial, the teneligliptin 10 mg has been shown to reduce 2 h PPG after each meal (breakfast, lunch, and dinner) by -50.7 , -34.8 , and -37.5 mg/dl, respectively, against placebo in a drug naive T2DM patients (all, $P < 0.001$). Similarly, teneligliptin 20 mg also reduced 2 h PPG after each meal by -38.1 , -28.6 , and -36.1 mg/dl, respectively, against placebo at breakfast, lunch, and dinner (all P significant).^[9] Kutoh *et al.* in a 3-month study of 31 drug naive Japanese T2DM patients, evaluated teneligliptin daily 20 mg as a monotherapy. This study found a significant reduction in HbA1c (from 10.34 ± 2.06 to $8.38 \pm 2.23\%$, $P < 0.00001$) and fasting blood glucose (from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL, $P < 0.0002$) from the baseline. In addition, homeostasis model assessment-B (HOMA-B) levels significantly increased, whereas high HOMA-R levels significantly decreased. However, a significant increase ($P < 0.05$) in uric acid was also observed in this study.^[16]

Teneligliptin has also been studied for 12 weeks or longer placebo-controlled trials as monotherapy (in another Japanese Phase 2 and one Korean Phase 3 study), as a combination therapy to glimepiride, pioglitazone in Japanese T2DM patients (in Phase 3 trials) and as an add-on to metformin in Korean T2DM patients (in Phase 3 trial).^[17-21] Two out of the three Phase 3 trials also had an open-label, 40 weeks extension phase after initial 12 weeks of blinding period. In both their extension studies, all patients were given teneligliptin 20 mg daily and up-titrated to teneligliptin 40 mg daily at or after 24 weeks, if HbA1c were $>7.3\%$.^[19,20] Table 2 summarizes the results from all these studies including the Indian data.

The efficacy and safety when teneligliptin dose is increased to 40 mg in patients with insufficient response to 20 mg are also available from one of the integrated analyses of the Japanese long-term treatment study as a review file by Japan Pharmaceuticals and Medical Devices Agency (PMDA).^[22] This integrated analysis reported the pooled data of three studies including two published studies^[19,20] and one unpublished study. In this analysis, the teneligliptin dose was to be increased to 40 mg, if HbA1c target met the criteria for dose increase as per the protocol. Interestingly, results from the pooled data found that the dose was required to be increased to 40 mg in 45.9% (290 of 632 patients) of patients. Of 275 patients (275 of 290 patients) whose

Table 1: The percentage of dipeptidyl peptidase-4 inhibition with various dosages of teneligliptin (adapted from Japan Pharmaceuticals and Medical Devices Agency dossier)

Dosage	Percentage DPP-4 inhibition					
	Single dose study: Phase- 1	Multiple dose study: Phase-1		Clinical pharmacology study: After 4 weeks	Single dose non-Japanese study (nonelder/elder)	
		After 1 day	After 7 days		Male	Female
20 mg E _{max}	86	83.5	90.1	89.7	81.4/83.5	83.2/83.9
20 mg E _{24h}	53.9	53.7	66.9	61.8	49.9/57.2	51.4/56.4
40 mg E _{max}	90.7	-	-	-	-	-
40 mg E _{24h}	59.8	-	-	-	-	-
80 mg E _{max}	94.8	94.9	96.6	-	93.3/93.7	94.8/94.3
80 mg E _{24h}	73.2	77.8	85.0	-	72.0/74.3	70.6/75.6
160 mg E _{max}	95.8	-	-	-	-	-
160 mg E _{24h}	83.6	-	-	-	-	-

Table 2: Efficacy of teneligliptin 20 mg daily in type 2 diabetes in phase 2 or 3, randomized, double-blind, placebo-controlled multicenter trials

Study characteristics				Various glycemic efficacy parameters (Δ is placebo-subtracted)						Percentage of patients achieved HbA1c	
Study name (year)	Duration (weeks) (country)	Study arms (mg)	n	HbA1c (%)		FPG (mg/dl)		PPG (mg/dl)		<7.3%	<6.8%
				BL	Δ	BL	Δ	BL	Δ		
Monotherapy											
Kadowaki <i>et al.</i> (2013)	12 (Japan)	TEN 20	79	7.8	-0.9**	143	-16.9**	231.9	-56.8**	53.5**	37.9**
		TEN 40	81	7.7	-1.0**	141.9	-20.0**	224.2	-58.6**	67.0**	48.7**
		PBO	80	8.0	-	150	-	242	-	12.7	2.6
Hong <i>et al.</i> (2016)	24 (Korea)	TEN 20	99	7.6	-0.9***	155	-21.7***	NR	NR	69.4***	34.7***
		PBO	43	7.8	-	162	-	NR	NR	20.9	4.7
Suryawanshi <i>et al.</i> (2016)	16 (India)	TEN 20	145	7.7	-0.5*	144	-8.8	NR	-25.8*	43.4**	NR
		PBO	77	7.7	-	145	-	NR	-	27.3	NR
Add-on therapy [§]											
Kadowaki <i>et al.</i> (2014)	12 (Japan)	TEN 20 + GLIM	96	8.4	-1.0**	165.1	-27.1**	258.6	-49.1**	31.6	8.3
		PBO + GLIM	98	8.4	-	163.4	-	256.1	-	2.1	0
Kadowaki <i>et al.</i> (2013)	12 (Japan)	TEN 20 + PIO	103	8.1	-0.7**	150.7	-16.4**	230.9	-51.3**	NR	NR
		PBO + PIO	101	7.9	-	145.7	-	221.5	-	NR	NR
Kim <i>et al.</i> (2015)	16 (Korea)	TEN 20 + MET	136	7.8	-0.8***	151	-22.5***	NR	NR	64.7***	NR
		PBO + MET	68	7.7	-	151	-	NR	NR	13.2 [#]	NR

* $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$ versus placebo, [§]Patients received stable dosages of the specified concomitant active drug (glimepiride 1–4 mg/day, metformin 1000 mg/day, pioglitazone 15 or 30 mg/day), *Patients achieving a target HbA1c of <7.0%, [#]Patients achieving a target HbA1c of <6.5%. n: Number of patients in study, Δ: Difference in parameter at the end of the study from baseline, FPG: Fasting plasma glucose, PPG: Postprandial glucose, BL: Baseline, TEN: Teneigliptin, GLIM: Glimepiride, MET: Metformin, PIO: Pioglitazone, PBO: Placebo, NR: Not reported/retrievable, HbA1c: Glycated hemoglobin

HbA1c data were available at 12 weeks after the dose increase, 30.9% (85 of 275 patients) showed a $\geq 0.3\%$ decrease in HbA1c when switched to teneligliptin 40 mg. Overall, HbA1c level decreased to <7.0% at 12 weeks after the dose increase, in 15.6% of patients. Regarding safety after the dose escalation, a marginal increase in incidence of adverse events (AEs) were noted in teneligliptin 40 mg (73.8% versus 63.4% in teneligliptin 20 mg).^[22]

The long-term efficacy of teneligliptin has also been studied in two 52-week, open-label, multicenter, interventional Japanese studies and data presented as a pooled analysis.^[23] The changes in HbA1c (mean \pm standard deviation [SD]) from baseline to week 52 were $-0.63 \pm 0.65\%$ in the teneligliptin monotherapy group, $-0.76 \pm 0.70\%$ in the glinide combination therapy group, $-0.78 \pm 0.75\%$ in the biguanide combination therapy group, $-0.89 \pm 0.64\%$ in the alpha-glucosidase inhibitor

combination therapy group, and $-0.81 \pm 0.76\%$ in the SU combination therapy group. Nevertheless, reductions in HbA1c were dependent on the baseline values, with reductions of $-0.26 \pm 0.30\%$ for HbA1c <7.0% at baseline, $-0.57 \pm 0.47\%$ for HbA1c 7.0–8.0% at baseline, and $-1.02 \pm 0.87\%$ for HbA1c >8.0% at baseline.

In a very small ($n = 43$), short-term (28 weeks), observational, Japanese study, Otsuki *et al.* evaluated the efficacy and safety of teneligliptin ($n = 14$) to controls ($n = 29$) on existing antidiabetic therapy, in adults with T2DM, who had end-stage renal disease. The study found no significant difference ($P = 0.057$) between the teneligliptin and control group for changes in HbA1c levels at 24 weeks although significant drop in HbA1c was noticed in 7 patients on teneligliptin who switched from other antidiabetic therapy. Currently, no randomized controlled trial in

renal-compromised patients has been published with teleniglipitin.^[24]

Two studies that have studied the teleniglipitin effect on glucose variation also merit special mention although they are too short in duration and too small in a number of patient included and therefore may not be very conclusive. In one Japanese study in T2DM patients receiving insulin therapy ($n = 26$), with or without other antidiabetes drugs, teleniglipitin was found to improve indices of glucose fluctuations (the SD of 24 h glucose levels and mean amplitude of glycemic excursions [MAGE]) using continuous glucose monitoring without inducing hypoglycemia.^[25] In another very small ($n = 10$) report from Japanese T2DM patients, 3 days of teleniglipitin on ongoing insulin therapy found to improve 24 h glucose levels, SD of 24 h glucose levels, and MAGE.^[26] Collectively, these results suggest improvement in glucose fluctuations with teleniglipitin.

Safety and tolerability of teleniglipitin

Teleniglipitin as a monotherapy or add-on therapy to other agents such as glimepiride, metformin, and pioglitazone, was generally well tolerated in patients with T2DM participating in clinical trials.

In monotherapy study, adverse drug reactions (ADRs) and AEs occurred in $\geq 5\%$ of patients in any group were nasopharyngitis, positive urine ketone body, urine glucose, and urinary protein.^[17] The incidence of ADRs was not significantly different among the four groups although the adverse rate tended to be higher in the teleniglipitin 40 mg group. All ADRs were categorized as mild in intensity by the investigator.

In Phase 3 add-on to glimepiride study, the incidence rates of serious AEs were similar in both groups at week 12.^[19] In Phase 3 add-on to pioglitazone, specific AEs occurred in $>5\%$ and included nasopharyngitis and peripheral edema.^[20] Hypoglycemia was reported in two patients (1.9%) in the teleniglipitin group at week 12. In the pooled 52 weeks safety analysis, treatment-related hypoglycemia occurred with an overall incidence of 3.4% in teleniglipitin recipients, with all episodes of mild intensity. The incidence of hypoglycemia was numerically higher in the teleniglipitin plus SU (10.1%) and teleniglipitin plus glinide (5.0%) groups than in the teleniglipitin monotherapy (2.5%), teleniglipitin plus biguanide (1.1%), or teleniglipitin plus α -glucosidase inhibitor (1.3%) groups.^[23] Thyroid cancer was observed in one patient in the teleniglipitin monotherapy group.

Cardiac safety of teleniglipitin

Overall, in all published randomized controlled trial, no serious cardiac events have been attributable to teleniglipitin.

Interestingly, a thorough QT/QTc evaluation study of teleniglipitin 40 and 160 mg actively compared to moxifloxacin found a significant increase in latter dose. Teleniglipitin 40 mg/day which is currently the maximal recommended dose prolonged the placebo-corrected QTcF (QTc corrected for heart rate) by 4.9 ms after 3 h. The 160 mg/day of teleniglipitin significantly increased the QTcF by 11.2 ms after 1.5 h of the drug was administered, almost similar to 12.1 ms of QTcF prolongation as observed 2 h after moxifloxacin. The Japanese PMDA also concluded "In the Phase III studies of teleniglipitin, patients being treated for arrhythmia, patients with a history of ventricular tachycardia, and patients with abnormality in resting standard 12-lead electrocardiography (ECG) at the start and end of the run-in period were excluded. Therefore, the risks of QTc interval prolongation and arrhythmia in these patients have not been investigated. Furthermore, since the timing for ECG measurement was not specified in the Phase III studies, the possibility cannot be excluded that the effect of teleniglipitin on QTc interval prolongation was not thoroughly investigated. In addition, taking into account that there are diabetic patients who have concurrent diseases such as arrhythmia and ischemia, and that teleniglipitin may be administered to such patients for a long period of time, it is deemed necessary to raise caution in administering teleniglipitin to these patients and to collect information on proarrhythmic risk via postmarketing surveillance."^[22] Table 3 summarizes the QTc prolongation with various dosages of teleniglipitin.

This may also suggest that a great caution may be required in patients who are prone to QT prolongation such as those with episodes of bradycardia, ischemic heart diseases, heart failure, and hypokalemia. In addition, the coadministration of teleniglipitin with drugs known to cause QT prolongation

Table 3: QTc prolongation with various dosage teleniglipitin (adapted from Japan Pharmaceuticals and Medical Devices Agency dossier)

Treatment group	Subjects analyzed (n=240)	ddQTcF		
		Time of measurement (h) (postdose)	Maximum ddQTcF (90%CI)	
Teleniglipitin	40 mg group	All (n=59)	24	4.9 (1.9-8.0)
		Males (n=27)	0.5	5.1 (0.9-9.4)
		Females (n=32)	0	5.6 (1.2-9.9)
	160 mg group	All (n=58)	1.5	11.2 (8.1-14.3)
		Males (n=30)	1.5	11.5 (7.4-15.5)
		Females (n=28)	1.5	10.5 (6.1-14.9)
Moxifloxacin group	All (n=61)	1	12.1 (9.1-15.2)	
	Males (n=28)	1	11.7 (7.5-15.8)	
	Females (n=33)	4	12.0 (7.7-16.3)	

CI: Confidence interval

such as Class IA or Class III antiarrhythmic drugs must be performed with great caution.^[22]

Extraglycemic effect of teneeligliptin

Experimental studies conducted with teneeligliptin found notable improvement in metabolic features in rat and mice.^[27,28] Teneeligliptin 20 mg also appeared to improve vascular endothelial function at 2 weeks in a study of 11 elderly T2DM patients.^[29] Hashikata *et al.* in a 3-month study of 29 Japanese T2DM patients evaluated the effect of teneeligliptin 20/40 mg daily on left ventricular (LV) function using echocardiography at baseline and at the end of the study. A significant improvement in both LV systolic and diastolic function was observed at the end of 3 months. LV ejection fraction improved from $62.0 \pm 6.5\%$ to $64.5 \pm 5.0\%$, $P = 0.01$ and peak early diastolic velocity/basal septal diastolic velocity (E/e') ratio improved from 13.3 ± 4.1 to 11.9 ± 3.3 , $P = 0.01$. In addition, a significant improvement in endothelial function was also observed, as measured by reactive hyperemia peripheral arterial tonometry (RHPAT) index (RHPAT index improved from 1.58 ± 0.47 to 2.01 ± 0.72 , $P < 0.01$).^[30]

Collectively, available data may suggest that teneeligliptin is an important addition to the class of DPP-4I in the treatment of T2DM and is better than placebo.

SUMMARY

DPP-4Is are well established and a convenient once/twice daily oral regimen in the treatment of T2M, with a very low intrinsic potential of hypoglycemia and also bodyweight neutral. However, as a class, when there are already four molecules available in India with ample of scientific evidence available, a critical look is highly desirable.

With regard to pharmacological properties, teneeligliptin is moderately selective to DPP-4 against DPP-8 and DPP-9 receptors, *in vitro* studies. Available evidence although indirect one (no head-to-head study available) suggests that teneeligliptin selectivity to DPP-4 is lower than sitagliptin and linagliptin and perhaps better than saxagliptin and vildagliptin.^[5] Although the preclinical studies suggested several adverse effects including skin reaction, lymphopenia, and increased in mortality related to DPP-8 and or DPP-9 inhibition, importance of such finding has been questioned in human studies.^[31,32] Nevertheless, lymphopenia with saxagliptin (prescribing information) and higher potential of skin reaction observed with vildagliptin may theoretically suggest in favor of selective DPP-4 inhibition.^[33]

The magnitude of DPP-4 inhibition following teneeligliptin 20 mg daily appears to be at the best, modest, not

exceeding >70% at 24 h. This outcome is perhaps, somewhat lower as seen in head-to-head study of sitagliptin, vildagliptin, and saxagliptin.^[34] Whether that translates into any lower glycemic efficacy with teneeligliptin compared to other DPP-4Is is yet to be seen, as no head-to-head trial is being currently done or undergoing.

Teneeligliptin 20 or 40 mg once daily studied for 12–16 weeks, in placebo-controlled trials, as a monotherapy or in combination with metformin, glimepiride, or pioglitazone, was found to improve glycemic control. Moreover, teneeligliptin 40 mg daily was found to lower HbA1c to <7% in additional ~15%. Interestingly, HbA1c lowering efficacy of teneeligliptin 20 mg daily in Indian studies appeared less appealing compared to Japanese and Korean trials despite similar baseline HbA1c across the trial. Moreover, there was no significant reduction in FPG with teneeligliptin 20 mg daily compared to placebo, despite equivalent baseline FPG in Japanese and Korean studies.

Furthermore, no head-to-head trials currently exist against any active comparators although it is highly desirable. In contrast, trials exist with other four available DPP-4Is conducted against active comparator. In addition, safety of teneeligliptin in patients with high CV risk or with existing CV disease and or chronic kidney disease is not yet known. Studies in such high-risk group to determine their safety and efficacy are highly desirable.

With regard to general safety, teneeligliptin has been well tolerated in short-term studies, as well as in two 52 weeks extension studies, in combination therapy to glimepiride and pioglitazone. Lower hypoglycemia observed similar to placebo is similar in line with other DPP-4Is. However, long-term safety is still unknown. Significant increase in uric acid in one of the study needs further clarity.

While no obvious cardiac issues have been reported in these short-term trials, it should be noted that these studies were neither targeted nor powered to assess potential CV safety. And, thus a dedicated cardiovascular outcome trial (CVOT) is highly desirable. This appears really necessary and important given the difference in outcome with individual DPP-4Is. A significantly increased hospitalization due to heart failure (HHF) observed with saxagliptin in SAVOR-TIMI trials and in different subgroups of patients, as seen in subsequent *post hoc* analysis have already created a serious concern. Similar trend of HHF observed in EXAMINE and in some subgroups in *post hoc* analysis also with alogliptin have led to some controversy.^[35-39] This finding was seen in sharp contrast to sitagliptin CVOT trial (TECOS) which

found no cardiac risk signal including HHF. Consequently, both saxagliptin and alogliptin have been recently given additional prescribing information of labeling of heart failure.^[40] It should be noted, however, that this decision of FDA is based on an independent re-analysis from the US FDA conducted in April 2015 which found a definite increase in HHF with saxagliptin and almost similar signals observed with alogliptin.^[41]

Although no dedicated CVOT is currently being conducted for teneagliptin, one TOPLEVEL (Teneagliptin on the Progressive Left Ventricular Diastolic Dysfunction With Type 2 Diabetes Mellitus) study is currently examining the effect of teneagliptin on diastolic echocardiographic parameters (E/e' ratio) as a primary outcome. TOPLEVEL is a 2-year (mean) study and expected to recruit ~936 T2DM patients of age 20 to 85 years with the ejection fraction of >40%, with expected completion in June 2019.^[42] This study appears to be similar in line to vildagliptin in VIVID trial and may give some solace to practicing clinician.

From cardiac safety point of view, prolongation of QTc is a unique issue with teneagliptin not observed with any other available DPP-4Is. Current threshold set by US FDA for cardiac safety of any drugs in Phase 1 trial is a drug should not prolong QTc by 5 ms or the upper bound 90% confidential interval (CI) of QTc studies should not cross the threshold of 10 ms.^[43] While teneagliptin 160 mg (although not recommended for clinical use) is clearly associated with a prolonged QTc, even teneagliptin 40 mg also appears to approach that critical threshold of 5 ms or upper bound 90% CI of 10 ms. This threshold perhaps becomes even more important when teneagliptin will be prescribed with several other drugs which tend to prolong QTc including antibiotics (azithromycin), antihistaminics (astemizole, terfenadine), diuretics (thiazide), selective serotonin uptake inhibitors, haloperidol, and obviously antiarrhythmic drugs (amiodarone and sotalol). Moreover, hypoglycemia being one of the strong QTc prolongators, combination with other hypoglycemic drug may need strict pharmacovigilance.

Overall, the present study will be a valuable addition to the accumulating data on teneagliptin. Particularly, the Indian evidence has been lacking and is therefore welcome. However, several questions remain, on the efficacy and “in particular” safety of teneagliptin as discussed earlier. A robust pharmacovigilance program to watch out for safety signals is important as are mechanized and clinical studies on CVOT, especially a dedicated CVOT given the QT prolongation.

Till then, health-care providers must keep in mind, the limitation of the data with teneagliptin and discuss the same with their patients.

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