Indian Expert Review on Use of Teneligliptin in patients with Diabetes and its Safety and Efficacy (INTENSE)

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Abstract

Introduction: Management of diabetes in India remains less than satisfactory despite a huge prevalence of type 2 diabetes (T2D). Associated obesity, inadequate lifestyle modifications and burden of treatment costs are certain major issues contributing to inadequate management of diabetes in India.

Aim: To evaluate the use of Teneligliptin in patients with diabetes and its safety, efficacy and cost effectiveness especially in Indian patients with T2D.

Methods: A detailed analysis of the best available scientific evidence (clinical trials, meta-analyses and real-world experience) was performed to create an evidence driven understanding of teneligliptin’s efficacy, safety and cost effectiveness. Fourteen leading endocrinologists contributed as experts and the modified Delphi process was followed. Evidences and clinical questions were discussed over a series of web and in a live meeting. Final draft was created based on the opinions endorsed by the experts.

Results: Teneligliptin is the most commonly used gliptin in India and exhibits pharmacokinetic and pharmacodynamic advantages as well as greater cost effectiveness compared to other gliptins. It has been recognized as an efficacious and well tolerated antidiabetic agent both as monotherapy and in combination based on multiple clinical trials, meta-analyses and real world studies. Teneligliptin as add on therapy to other antidiabetic drugs (OADs) or insulin has provided significant reductions in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels and is generally well tolerated with low risk of hypoglycemia both in short term and long term. Studies have also proven its efficacy in ameliorating glucose fluctuations, reducing post prandial insulin requirement, increasing active incretin levels and improving pancreatic β cells function. Efficacy and safety has also been proven in all age groups, all stages of renal disease and mild to moderate hepatic disease. QT prolongation is not seen even with maximum recommended dose of 40 mg/day.

Conclusion: Teneligliptin has firmly positioned itself as a very important drug in the armamentarium for managing T2D. It offers efficacy, safety and cost-effective therapeutic choice in Indian patients with T2D.

Challenges and Unmet Needs in Indian Diabetes Care

Diabetes is a global health emergency of this century. There has been a rapid rise of diabetes in India, affecting more than 77 million Indians, according to International Diabetes Federation (IDF) data from 2019.1 What is worrisome is that India has the highest number of people with Diabetes still undiagnosed, and by 2045 we are expected to cross 134.2 million (108.5–165.7).2 What is also worrying is that though a lot has been said about India and its epidemic proportion of Diabetes incidence, and despite various National guidelines and standards of care for diabetes which are now available, the management of patients with diabetes in practice remains less than satisfactory. This will continue to be a serious economic burden on our country more so because of sheer numbers and number of youths affected.3 While managing Indian patients with diabetes, it is imperative to recognize that due to associated obesity and inadequate lifestyle modifications, only metformin along with lifestyle management may not just be enough in initial management of patients, at least in some of them. While choosing Oral Anti-Hyperglycaemic Agents (AHA), apart from risk of hypoglycaemia, it is important to also look into impact on weight, renal safety and possible beta cell preservation. Gliptins usage has recently increased considerably in India after introduction of Teneligliptin in the year 2015. One of the most important factors while choosing any anti-diabetic agent, is cost of therapy, keeping in mind that majority of patients in India are not covered by insurance and also due to other co-morbidities and other therapies as well.

It is these issues which were a precursor for 14 leading Endocrinologists, Diabetologists

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across India, to develop this Expert Consensus Statement to address the use of Teneligliptin in patients with diabetes and its safety and efficacy, especially the advantage due to its cost effectiveness in diabetes care which is a lifelong economic burden on patients. A detailed analysis of the best available scientific data, trials, and meta-analysis and real-world experience was performed, so that an evidence driven understanding of teneligliptin’s efficacy, safety, impact on cost of therapy and compliance could be created. The process followed was modified Delphi, wherein evidences and clinical questions were discussed over a series of web followed by a live meeting; based on the opinion endorsed by the experts, the draft was created.

**DPP4 Inhibitors Place in Therapy**

Recent statement of Standards of Medical Care in Diabetes by the American Diabetes Association (ADA), American College of Endocrinology/ American Association of Clinical Endocrinologist, and Indian clinical practice recommendations, by RSSDI (Research Society for the Study of Diabetes in India) has recommended initial treatment with metformin as monotherapy after inadequate life style modification, followed by sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 inhibitor (SGLT2-i), glucagon-like peptide 1 (GLP-1) receptor agonist and insulin alone or in combination. It is still challenging to find an anti-hyperglycemic agent with long-term glucose control, minimal hypoglycemia, no weight gain and a relatively affordable price.³

In many randomized trials DPP4 inhibitors have found to be effective for glycemic control by declining the HbA1c, FPG, and PPG and improving the function of pancreatic β cells. In addition to targeting glycemic control, DPP4 inhibitors have low risk of hypoglycemia with neutral effect on body weight with a favorable safety profile. Also cardiovascular safety of DPP-4 inhibitors is established in large clinical trials.

In the past 17 years, 17 gliptins have been launched globally, and in India gliptins which are available are Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Teneligliptin and Evogliptin. The cost of therapy is one of the biggest drawbacks of this effective therapy, which becomes an economic burden to majority of Indian patients leading to their discontinuing the medications.

**Teneligliptin – Efficacy**

Teneligliptin has shown its efficacy and safety, in various trials. In a recently published 2018 meta-analysis (n=2119 T2D patients from 10 trials) by Xiao Xuan Li, et al; Teneligliptin improved blood glucose levels and β-cells function with low risk of hypoglycemia in patients with T2D. Teneligliptin produced absolute reductions in glycated hemoglobin A1c (HbA1c) levels [weighted mean difference (WMD) 0.82%, 95% confidence interval (CI) [−0.91 to −0.72], p < 0.00001] compared with placebo. Teneligliptin led to greater decrease of fasting plasma glucose (FPG) level (vs. placebo, WMD −18.32%, 95% CI [−21.05 to −15.60], p < 0.00001), significant decrease in the 2 h post-prandial plasma glucose (2h PPG) (WMD −46.94%, 95% CI [−51.58 to −42.30], p < 0.00001) and area under the glucose plasma concentration-time curve from 0 to 2 h (AUC0−2h) for PPG (WMD −71.50%, 95% CI [−78.09 to −64.91], p < 0.00001) compared with placebo. There was (0.96 risk ratio (RR), 95% CI [0.87, 1.06], p = 0.06). The risks of hypoglycemia were not significantly different between Teneligliptin and placebo (1.16 RR, 95% CI [0.59, 2.26], p = 0.66).⁴

Hong S, Park CY, et al. assessed 24-week efficacy and safety of Teneligliptin in Korean patients inadequately controlled with diet and exercise, in a multicenter randomized, double blind, placebo-controlled, parallel-group, phase III study. Incidence of hypoglycemia and adverse events were not significantly different between two groups.⁷

Kadowaki T, Marubayashi F et al. analyzed data from two Phase III clinical trials and concluded that long term use of Teneligliptin as monotherapy or combination therapy was evaluated to be well tolerated and effective as per the evidence generated from two trials.⁸

In a study by Tsuchimochi W, et al evaluated the effects of Teneligliptin on 24 hr. blood glucose control and gastrointestinal hormone responses to meal tolerance test and to investigate the glucose-lowering mechanisms of Teneligliptin. It was observed that Teneligliptin improved 24 hr. blood glucose levels by increasing active incretin levels and early phase insulin...
secretion, reducing the post prandial insulin requirement and reducing glucagon secretion and concluded even short-term Teneligliptin treatment may offer benefits for patients with T2D.9

Kurozumi A, Okada Y, et al, compared the effect of Teneligliptin and sitagliptin with respect to glucose fluctuation and effect on GLP-1 in T2D where daily dose of Teneligliptin improved AUC for plasma glucose at evening after meal tolerance test and it also significantly increases the GLP-1 activity after the meal test.10

Diabetes is manifested with various other health complications caused by blood glucose fluctuations. Teneligliptin shows potent and sustained effects on glycemic control without concern of hypoglycemia. It has a unique structure with J-shaped anchor-lock domain responsible for its action on 52 extensive subunit of DPP-4, which ultimately leads to its enhanced potency and selectivity. A long t1/2 of 24.8 hours with unique pharmacokinetic advantages allows its convenient once-daily administration. As it has dual mode of elimination via renal and hepatic route, it can be administered safely in renal impairment patients, along with no dose adjustment requirement in mild to moderate hepatic impairment. It also shows promising beta-cell preservation potential along with an added advantage of cost-effectiveness in comparison to other anti-glycemic agents. Potential differences in pharmacodynamic and pharmacokinetic characteristics between teneligliptin and other DPP-4 inhibitors, marks its underlying first-rate potency and sustained effect in diabetes management.10

### Table 1: Teneligliptin Effective as Monotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Placebo-subtracted LSM change from BL to study end</th>
<th>% of patients with target HbA1c ≤ 6.8% or &lt; 7.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. Kadowaki, 2013</td>
<td>TEN 20 mg</td>
<td>79</td>
<td>-0.9**</td>
<td>40.5% and 66.1%</td>
</tr>
<tr>
<td>M. Goda, 2013</td>
<td>TEN 20 mg</td>
<td>99</td>
<td>-0.79**</td>
<td>40.9%</td>
</tr>
</tbody>
</table>

BL baseline. FPG fasting plasma glucose. HbA1c glycated hemoglobin. LSM least-square mean. NR Not recorded. NA Not applicable. PL placebo. PPG postprandial plasma glucose. TEN teneligliptin. *p < 0.001 d Post-prandial glucose values after breakfast. **Studies also included Teneligliptin 10 mg arm but results are not tabulated here it is not recommended dose; b and c NGSP units (National Glycohemoglobin Standardization Program). In Japan, HbA1c (Japan Diabetes Society) values ≤ 6.5 and ≤ 7.0% are equivalent to HbA1c ≤ 6.8 and ≤ 7.3% in NGSP units.

**Eto T, et al;** once daily Teneligliptin (10 or 20 mg) administration showed significantly smaller 2-h PPG, 24-h mean glucose and FPG values than the placebo group. Once-daily teneligliptin improved blood glucose levels over 24h without hypoglycaemia.12

In a randomized, double-blind, placebo-controlled, parallel-group study by Kadowaki T, patients (n = 324) were randomized to receive teneligliptin 10, 20 or 40 mg, or placebo, once daily before breakfast for 12 weeks. Teneligliptin showed significantly greater reductions in HbA1c and FPG than the placebo group, across all the dose range studied and was well tolerated in Japanese T2D patients.13

Kutoh et al, explored the glycemic and non-glycemic efficacies of Teneligliptin in drug naïve T2D patients, and concluded that Teneligliptin was efficacious and safe as an initial therapy for newly diagnosed T2D, where glycemic efficacy was obtained by activating beta cell function as well as decreasing insulin resistance.14

Similarly, in an Indian study (multicentric, double-blind, placebo-controlled, Phase 3) by Suryawanshi et al, teneligliptin 20 mg daily in drug naive T2DM patients, resulted in a significant reduction in HbA1c (-0.55%, P = 0.0043) and 2h-PGG (-25.8 mg/dl, P = 0.0070) in comparison to placebo. Similarly, higher percentage of patients achieved the target HbA1c levels (<7%) in teneligliptin arm (43.4% vs. 27.3%, P = 0.026) in comparison to control arm, and “overall” the drug was well tolerated.16 (Table 1).

Teneligliptin as an add-on Therapy

Teneligliptin as an add-on to Metformin

Teneligliptin is efficacious and well tolerated as an add-on treatment with oral antidiabetic drugs (OADs) or insulin, in T2D patients on monotherapy with inadequate control. In an Indian study, Chatterjee AK reported that teneligliptin as an add-on therapy resulted in a significant reduction of HbA1c, FPG and PPG after 12-week treatment in patients inadequately controlled on monotherapy with OADs or insulin.16

In 2015, Kim MK conducted a 16-week, randomized, double-blind, placebo-controlled phase III trial, aimed to evaluate the efficacy and safety of Teneligliptin in combination with metformin in Korean T2D patients. It was concluded that Teneligliptin once daily add-on to metformin was effective and generally well tolerated.17

Similarly, Bryson A. Jennings PE et al investigated the efficacy and tolerability of Teneligliptin (5, 10, 20 or 40 mg) co-administered with metformin in T2D inadequately controlled with Metformin (> 1000 mg/day). 447 patients from 55 European centers were enrolled in this study, and were treated for 24 weeks. It was observed that teneligliptin (5 to 40 mg) add-on to metformin demonstrated a dose-related and statistically significant reduction in HbA1c (-0.30 to -0.63% placebo adjusted). At 40 mg -0.63% reduction in HbA1c was observed at week 24. Noticeably, the decrease in HbA1c levels in teneligliptin arm was greater at week 24 (-0.58 to -0.91%, p = 0.003 to <0.001; placebo -0.28%) than in Week 12. It was concluded that teneligliptin was well tolerated for 52 weeks, with a 2.3% incidence level of hypoglycemia.18

**Teneligliptin as an add-on with Sulfonylureas**

Kadowaki T and Kondo K (2014) conducted a study where 194 patients were randomized to either teneligliptin 20 mg or placebo once daily while continuing stable glimepiride therapy. It was concluded that Teneligliptin was effective and generally well tolerated in Japanese patients with T2D inadequately controlled with glimepiride monotherapy, and the improvements in glycemic control were maintained for up to 52 weeks.19

**Teneligliptin add-on with pioglitazone**

In 2013 Kadowaki T and Kondo K evaluated the efficacy and safety of Teneligliptin add-on with pioglitazone in Japanese T2D patients (n = 204), and they concluded that teneligliptin add-on therapy was effective and generally well tolerated in T2D...
Teneligliptin as add-on therapy to OADs or insulin provided significant reduction in HbA1c, FPG and PPG levels and generally is well tolerated with no episodes of hypoglycemia both in short term as well as in long term either as dual therapy or as triple therapy for T2D. Teneligliptin also reduces glycemic variability. It has been observed from data sources (ORG) that in Indian T2D patients teneligliptin is the most commonly used gliptin as an add-on therapy to other OHAs and insulin therapy.

Teneligliptin add-on with canagliflozin

Kadowaki T et al, evaluated the efficacy of teneligliptin add-on therapy (20 mg for 24 weeks) in T2D patients already on canagliflozin (100 mg) for ≥12 weeks (C + T group), in comparison to placebo (C + P group). The reduction in HbA1c levels at week 24 from baseline was greater in the C+T group (-0.94%; P < 0.001). No incidence of hypoglycemia was reported, and a comparable adverse event rate between both the groups was observed (55.8% and 49.4% in the C + T and C + P groups, respectively). FPG, body weight and the proinsulin/C-peptide ratio were significantly lower in the T+C group than in the T+P group. Teneligliptin added to ongoing canagliflozin monotherapy improved glycemic control and was well tolerated in patients with inadequately controlled T2D.

This same study was carried for 52 weeks for long term safety and efficacy of canagliflozin as add-on to Teneligliptin therapy in T2D. The mean changes in HbA1c, FPG and body weight were -0.99% (95% confidence interval [CI] -1.12 to -0.85), -38.6 mg/dL (95% CI -43.4 to -33.9) and -3.92% (95% CI -4.53 to -3.31), respectively suggesting the long-term co-administration of canagliflozin with Teneligliptin is well tolerated and effective in T2D who have inadequate glycemic control on Teneligliptin alone (Table 2).

Teneligliptin add-on with Insulin Therapy

Effect on Glucose variability when added to Insulin therapy

Tanaka S et al. added Teneligliptin in Japanese diabetes patients with insulin therapy to examine whether Teneligliptin ameliorated glucose fluctuation in hospitalized Japanese patients with T2D receiving insulin therapy with or without other antidiabetic drugs and using continuous glucose monitoring (CGM). It was concluded that addition of Teneligliptin to insulin therapy led to a significant improvement in diurnal glycemic control and significant reductions in glucose fluctuations in 24 hr. periods without increasing hypoglycemia.23

Yajima T, et al. also used Teneligliptin in addition to insulin therapy in T2D on hemodialysis and observed that the insulin dose reduced from 18U to 6 U (p<0.0001). The incidence of asymptomatic hypoglycemia on hemodialysis day detected by CGM was published in 2018 as an interim analysis of Post marketing Surveillance, A study by Ghosh S et al; was one of the largest retrospective analysis of 4305 Indian patients with Diabetes who were on Teneligliptin monotherapy or in combination therapy, they evaluated the efficacy of teneligliptin in real world by analysing the mean change in 3-month values of HbA1c, FPG, and PPG. A significant improvement in mean HbA1c, FPG, and PPG with teneligliptin therapy was reported. Mean 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 D-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. This is a very significant large group analysis of Indian patients with Diabetes which confirms Teneligliptin efficacy in real world clinical situations27 (Figures 2 and 3).

Teneligliptin in comparison to Sitagliptin added to dual therapy

Kim Y, et al. evaluated the efficacy of a triple drug combination where Teneligliptin was compared with sitagliptin in patients inadequately controlled with metformin and glimepiride. This was a phase 3, randomized, double-blind, non-inferiority study of adult Korean subjects with T2D (n=201), with HbA1c ranging from 7.0-11.0%, on stable doses of metformin plus glimepiride. It was observed that Teneligliptin was non-inferior to sitagliptin in the context of triple therapy for T2D26 (Figure 1).

Teneligliptin effect on β-cell Preservation

Eiji Kutoh et al. studied the effect of Teneligliptin 20 mg/day as an initial therapy in 31 newly diagnosed T2D patients mean age 58.29 ± 14.95 for 3 months. Significant reductions in HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%; p < 0.00001) and fasting blood glucose (from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL; p < 0.0002) levels were observed without any clinically significant adverse events. Homeostasis model assessment β-cell function (HOMA-β) significantly increased (from 24.04 ± 31.14 to 40.23 ± 40.98; p < 0.00001), Homeostasis model assessment-insulin resistance (HOMA-R) decreased (from 3.74 ± 4.28 to 2.90 ± 2.16; p-n.s.) after treatment with Teneligliptin.14

Rika Ito et al. studied changes in insulin secretion before and after Teneligliptin treatment for 12 weeks in 30 diabetic patients. β-cell function assessed by IGI 30min, AUC1 20min insulin, and the AUC1 20min SUIT index significantly increased (0.16 ± 0.05 vs. 0.28 ± 0.06, 2692 ± 333 μU·2h/ mL vs. 3537 ± 361 μU·2h/mL, and 4261 ± 442 vs. 8290 ± 1147, respectively; all p < 0.05). HOMA-β was unchanged.16

Teneligliptin: Real World Evidence in Indian Patients

TREAT-INDIA study by Ghosh S et al; was one of the largest retrospective analysis of 4305 Indian patients with Diabetes who were on Teneligliptin monotherapy or in combination therapy, they evaluated the efficacy of teneligliptin in real world by analysing the mean change in 3-month values of HbA1c, FPG, and PPG. A significant improvement in mean HbA1c, FPG, and PPG with teneligliptin therapy was reported. Mean 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 α-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. This is a very significant large group analysis of Indian patients with Diabetes which confirms Teneligliptin efficacy in real world clinical situations27 (Figures 2 and 3).
Table 2: Summary of Teneligliptin Trials

<table>
<thead>
<tr>
<th>Author name</th>
<th>Study design</th>
<th>Dose</th>
<th>Baseline values</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eto T, Inoue S et al. 2012 Nov 1</td>
<td>Randomized, double blinded, placebo controlled, parallel study (n=99)</td>
<td>Teneligliptin 10 mg (n=34), 20 mg (n=33)</td>
<td>HbA1c-8.3% FPG-162.1 mg/dL</td>
<td>DPP4 inhibition rate at 24 hrs (E24 h) was 66.9% ± 4.17%</td>
</tr>
<tr>
<td>T. Kadokawa and K. Kondo, 2013 Sep</td>
<td>Randomized double blinded, parallel group study (n=524)</td>
<td>Teneligliptin – 10 mg (n=84), 20 mg (n=79), 40 mg (n=81)</td>
<td>HbA1c-7.8% FPG-145.7 mg/dL</td>
<td>After 12 weeks, HbA1c was 7% and FPG was 129.5 mg/dL</td>
</tr>
<tr>
<td>Kadowaki T, Sasaki K et al. 2018 Apr 1</td>
<td>Open labelled, phase 3 clinical trials (n=702)</td>
<td>Teneligliptin-20 mg, 40 mg</td>
<td></td>
<td>HbA1c levels in teneligliptin 40 mg dose were 8.57 ± 0.77% at week 0, 7.93 ± 0.69% at week 28 and 7.85± 0.85% at week 52:</td>
</tr>
<tr>
<td>Kadowaki T, Haneda M et. Al. 2018 Jan 22</td>
<td>Interim analysis (n=10,532)</td>
<td>Teneligliptin-20 mg/day</td>
<td>HbA1c-7.57% FPG-147.6 mg/dL</td>
<td>Overall ADRs: 3.46% and most common ADRs were Hypoglycemia (0.32%) and constipation: 0.27%</td>
</tr>
<tr>
<td>Ito R, Fukui T et. Al. 2015 Sep 1</td>
<td>Open label clinical study (n=13)</td>
<td>Teneligliptin – 20 mg (n=8)</td>
<td>HbA1c-8.3% FPG-142.5 mg/dL</td>
<td>HbA1c significantly decreased from 8.3 ± 0.4% at baseline to 6.3 ± 0.2% after 12 weeks of teneligliptin treatment</td>
</tr>
<tr>
<td>Kutoh E, Hirate M et al 2014 Aug</td>
<td>Project of Monitoring the effects of oral hypoglycemic drugs in T2D patients (n=31)</td>
<td>Teneligliptin – 20 mg (n=31)</td>
<td>HbA1c – 10.34% FPG-211.3 mg/dL</td>
<td>Homeostasis model assessment (β-cell (HOMA-β)) significantly increased from 24.04 ± 31.14 to 40.23 ± 40.98</td>
</tr>
<tr>
<td>Kusunoki M, Sato D et al 2015 Oct</td>
<td>Study to investigate the effects of Teneligliptin on HOMA-R and insulin resistance (n=9)</td>
<td>Teneligliptin – 20 mg (n=9)</td>
<td>HbA1c-6.6% HOMA-R-2.5</td>
<td>After 14 week treatment with Teneligliptin, HbA1c value was decreased to 5.9% and HOMA-R was 1.6</td>
</tr>
<tr>
<td>Tanaka S, Suzuki k et al 2014 Dec 1</td>
<td>Prospective, non blinded, pilot study (n=26)</td>
<td>Teneligliptin – 20 mg, (n=26)</td>
<td>HbA1c – 10.8% Mean glucose levels – 148.8 mg/dL</td>
<td>Significantly decreased both fasting and postprandial glucose levels on Days 5 – 7, significant decrease in 24-hour mean glucose levels</td>
</tr>
<tr>
<td>Kurozumi A, Okada Y et al 2018 Mar 1</td>
<td>Randomized, cross over study (n=14)</td>
<td>Teneligliptin – 20 mg (n=7) Sitagliptin – 50 mg (n=7)</td>
<td>-</td>
<td>Teneligliptin once daily improved the plasma glucose and also resulted a significant increased in GLP-1 level at 30 minutes after the meal load</td>
</tr>
<tr>
<td>Kim Y, Kang ES et al 2018 Oct 26</td>
<td>Phase 3, randomized, double blind, non inferiority study (n=201)</td>
<td>Teneligliptin – 20 mg (n=103) Sitagliptin – 100 mg (n=98)</td>
<td>HbA1c – 8.11%</td>
<td>At 24 weeks, reduction from baseline in HbA1c : Teneligliptin: -1.03 ± 0.10% Sitagliptin: -1.02 ± 0.10%</td>
</tr>
<tr>
<td>Bryson A, Jennings PE et al. 2016 Jul 2</td>
<td>Multicenter, randomized single blind, placebo controlled study (n=447)</td>
<td>Teneligliptin – 5 mg, 10 mg, 20 mg, 40 mg</td>
<td>HbA1c – 7.89% FPG – 162.39 mg/dL</td>
<td>Greatest reduction in HbA1c was seen with Teneligliptin at 40 mg (-0.63) at week 24.</td>
</tr>
<tr>
<td>Kadowaki T, Inagaki N et al 2018</td>
<td>Multi center, randomized, double blind, placebo controlled, phase 3 clinical trials (n=154)</td>
<td>Teneligliptin – 20 mg (n=77) Canagliflozin – 100 mg (n=77)</td>
<td>HbA1c – 8.18% Men glucose levels – 173.9 mg/dL</td>
<td>Teneligliptin showed significant improvements in glycemic control, including HbA1c, FPG and PPC, compared with placebo</td>
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<tr>
<td>Kadowaki T, Kondo K, 2013 Nov 1</td>
<td>Double blinded, placebo controlled, parallel group study (n=204)</td>
<td>Teneligliptin – 20 mg (n=103)</td>
<td>HbA1c-8.1% FPG – 150.7 mg/dL</td>
<td>Significant reduction in HbA1c and FPG were observed with Teneligliptin treatment</td>
</tr>
<tr>
<td>Otsuki H, Kosaka T et al 2014 Feb 1</td>
<td>Bi center, prospective, non randomized study (n=43)</td>
<td>Teneligliptin – 20 mg (n=14)</td>
<td>HbA1c – 6.4%</td>
<td>Blood glucose level decreased 21-60 mg/dL at 28 weeks after Teneligliptin administration GA dropped 1.7-2.5% by 28 weeks and HbA1c fall 0.3-0.8% by 24 weeks</td>
</tr>
<tr>
<td>Tanaka K, Okada Y et al 2016 Dec 1</td>
<td>Randomized crossover study (n=13)</td>
<td>Teneligliptin – 20 mg, Linagliptin – 5 mg</td>
<td>HbA1c – 6.7% eGFR (ml/min/1.73 m2) – 28.2</td>
<td>Teneligliptin and Linagliptin significantly reduced the 24-h mean sensor glucose levels and AUC180 but did not increased the incidence of hypoglycemia</td>
</tr>
<tr>
<td>Hashikata T, Yamaoka-Tojo M et al 2016 Aug 1</td>
<td>Single center, pilot study (n=27)</td>
<td>Teneligliptin – 20 mg, 40 mg</td>
<td>HbA1c – 7.5% LVEF -63.7% E/e-13.4</td>
<td>Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes</td>
</tr>
<tr>
<td>Patel DK, Sharma RT et al. 2016 Dec 28</td>
<td>Randomized, double blinded, placebo controlled, parallel comparative study (n=240)</td>
<td>Teneligliptin – 40 mg (n=59), 160 mg (n=59) Moxifloxacin – 400 mg (n=62)</td>
<td>HbA1c – 7.5% FPG – 148.4 mg/dL</td>
<td>Teneligliptin was not associated with significant QT interval prolongation at 40 mg dose and QT prolongation was observed at 160 mg</td>
</tr>
<tr>
<td>Suryawanshi SY, Bhargava A et al 2016 Aug 1</td>
<td>Multicentric, double blinded, placebo controlled, phase 3 clinical trials (n=237)</td>
<td>Teneligliptin – 20 mg (n=58)</td>
<td>-</td>
<td>Treatment with once-daily Teneligliptin led to statistically significant and clinically meaningful reductions in HbA1c and FPG, and was well tolerated in Indian nationals with T2D</td>
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Glucose fluctuation using CGM: No significant difference

Teneligliptin significantly improved:
Plasma glucose (≥ 140 mg/dl) after supper (20:00-24:00)
GLP-1 level at 30 minutes after the meal load area under curve was better with Teneligliptin

No serious adverse effects, other than asymptomatic hypoglycemia.

Fig. 1: Teneligliptin in comparison to Sitagliptin

ORIGINAL RESEARCH

Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus Patients in India (TREAT - INDIA Study)
Sujay Ghosh,1 Shailesh Trivedi,7 Debmalya Sanyal,3 KD Modi,4 Sandeep Kharb5

Data of 4305 patients: To assess the efficacy of teneligliptin when prescribed as monotherapy as well as combination therapy.

4.32% Monotherapy
95.68% Add-on therapy
28.06% Teneligliptin + Metformin
27.97% Other Combinations
39.65% Teneligliptin + Metformin + SU

Expert comments:
Although TREAT-INDIA is the largest real-world data in India but longer follow-up is needed to evaluate the long-term benefits and risks of teneligliptin. Also, trials are needed to be conducted to assess the therapeutic effect of teneligliptin by comparing the effects with other DPP4 I. Another important issue here is to observe 24 h glucose fluctuations. Large fluctuations may increase the risk of complications, such as CV disease, so it is better to evaluate post-prandial glucose fluctuations over the entire 24 h dosing interval.

Fig. 2: Teneligliptin: Real World Evidence In Indian Patients- TREAT India Study

Teneligliptin Safety
Efficacy and safety of high dose (40mg) of Teneligliptin

Kadowaki T, et al. examined the treatment response when Teneligliptin dose was increased from 20 to 40 mg in post hoc pooled analysis of data from two 52 week open-label, phase III clinical trials where 204 patients received increased Teneligliptin dose from 20 to 40 mg/day at 28 week and then observed for another 24 weeks (28-52 weeks). In both studies, the dosage of teneligliptin was titrated to 40 mg once daily during weeks 28–40 for...
those patients who met the criteria for dose increase (HbA1c > 7.3% in Study 3000-A8; > 7.4% in Study 3000-A14) and for whom there were no safety concerns as judged by the investigator. Out of 204 patients, 108 (52.9%) showed a response to teneligliptin 40 mg (HbA1c change < -0.1% during weeks 28–52) and had mean ± SD HbA1c reduction of 0.50 ± 0.44%. Of patients showing re-elevation of HbA1c during treatment with teneligliptin 20 mg, 89/143 (62.2%) achieved HbA1c reduction after dose increase to 40 mg. It was concluded that increasing the dosage of Teneligliptin from 20 to 40 mg/day had a potential increase in estimated glomerular filtration rate (eGFR)30 However, this observational renal benefit was not corroborated by any dedicated phase 3 renal outcome data.

Halabi et al, evaluated the pharmacokinetics of teneligliptin in renally impaired (mild to end-stage) and healthy subjects. The results suggested that the C_max following single dose administration of teneligliptin (20 mg) was unaffected by mild, moderate and severe renal impairment. Post-dialysis ESRD patients displayed a higher C_max and AUC in comparison to healthy patients. An important conclusion of the study was the fact that the plasma protein binding (PPB) capacity in renally impaired subjects was <80%, which is in accordance with the FDA guidelines stating; drugs with low extent of PPB (<80%), alterations in protein binding is likely to be small in relative terms. It was concluded that single 20 mg dose of teneligliptin is well tolerated by healthy subjects and subjects with renal impairment or ESRD, so teneligliptin given predialysis, 90% CI for AUC_0-t was within the no effect boundaries and upper limit of 90% CI for C_max is also below 125% which indicates, teneligliptin can be given before dialysis without dose adjustment.31

Fig. 3: Results- Teneligliptin: Real World Evidence In Indian Patients- TREAT India Study

This confirmed the fact that dose adjustment of Teneligliptin in case of renally impaired patients is not required. This comes as an advantage for diabetic patients as the drug regimen can be followed by the patients in the same dose, even in the light of renal impairment.32

Teneligliptin effect in CKD

Otsuki H et al, conducted a prospective study to assess the utility of Teneligliptin for diabetic patients undergoing hemodialysis. It was concluded that Teneligliptin 20 mg is well tolerated, and significantly improves glycemic control in diabetic patients with ESRD. Teneligliptin 20 mg once daily was found to be more potent than voglibose 0.2 mg t.i.d. or vildagliptin 50 mg qd.33

Wada N et al, evaluated the efficacy and safety of teneligliptin in Type 2 DM on haemodialysis by CGM and concluded that this drug improves blood glucose AUC on both HD day (p=0.004) and NHD day (p=0.004) with significant reduction in glycated albumin (GA), HbA1c, FPG without severe hypoglycaemia.34

Fifteen patients with diabetes and CKD undergoing haemodialysis were treated with Teneligliptin 20 mg in Homma K et al, study. Teneligliptin significantly reduced plasma levels of RLP-C (Remnant-like particle cholesterol), FPG and HbA1c in
patients with CKD and undergoing hemodialysis.

Haneda M et al, published a data from Ruby surveillance regarding the safety and efficacy of Teneligliptin in impaired renal function patients. Where it was concluded that Teneligliptin was effective and well tolerated in patients with any stage of renal impairment from normal to end stage disease, including those on dialysis and improved glycemic control.

Kitada M, Ogura Y et al, observed the effect of switching to Teneligliptin from other DPP-4 inhibitors on glucose control and renoprotection in T2D patients with diabetic kidney disease. The plasma DPP-4 activity was significantly reduced after 24 weeks (0.57 ± 0.26 nmol/min/mL, P = 0.012, vs baseline), compared with baseline (1.49 ± 1.73 nmol/min/mL), with no significant change in Hba1c, FPG and UACR values. Switching to Teneligliptin from other DPP-4 inhibitors for 24 weeks reduced the DPP-4 activity which was associated with non-significant reduction of albuminuria (r value=-0.3038, p value= 0.1588 ns).

**Expert comments**

Teneligliptin in high doses (40mg/day) is well tolerated without any significant safety concerns, both at 24 and 52 weeks, and is an effective option for treatment of T2D. But the limitations of the study was that effect on QT prolongation has not been systematically studied at this dose.

Teneligliptin is well tolerated in impaired renal function patients and in patients undergoing hemodialysis with significant reduction in glycated albumin, HbA1c, FPG, RLP-C (Remnant Lipoprotein Cholesterol) levels without severe hypoglycemia. Teneligliptin is well tolerated in all stages of renal impairment and no dosage adjustment required.

**Teneligliptin – Hepatic Safety**

Teneligliptin is unlikely to cause conspicuous drug interactions or changes in its pharmacokinetics in patients with hepatic impairment, due to a balance in the elimination pathways. Halabi A et al, studied the pharmacokinetics of Teneligliptin in 3 groups of 8 subjects assigned according their degree of hepatic impairment (mild, moderate or matched healthy subjects). The lower mean total clearance in subjects with mild (9.79 L/h) or moderate (8.57 L/h) hepatic impairment resulted in longer mean half-lives (27.9 and 30.9 hours, respectively) than in healthy subjects (clearance: 13.11 L/h, half-life: 24.8 hours). It was concluded that Teneligliptin was well tolerated by subjects with mild to moderate hepatic impairment and was indicated that caution will be needed when administering Teneligliptin in patients with hepatic impairment. However, data on hepatic safety is small and based on a very small population. There is no clinical experience of Teneligliptin use in severe degree hepatic dysfunction patients.

**Teneligliptin and Cardiovascular Safety**

Cardiovascular events are commonly associated with T2D and the incidences are said to be frequent and often severe. Additionally, incidences of dyslipidaemia are also linked to T2D. The overall scenario as such highlights the gravity of the fact that even with glycaemic control, adverse effects of the disease tend to progress and aggravate. Hence, selecting the optimal therapy for individuals with T2D necessitates careful retrospection vis-à-vis cardiovascular safety and concurrent anti-diabetic therapy. In all published randomized controlled trial, no serious cardiac events have been attributable to teneligliptin. The important cardio-vascular and effects of Teneligliptin provide an alternative and safer mode of anti-diabetic care. However, no dedicated phase-3 cardiovascular outcome trial was done to establish the safety of this drug beyond doubt among diabetics with overt cardiovascular disease or heart failure. Therefore, more data for long-term effects on cardiovascular events are needed as rightly pointed out by Li X in a systematic review and meta-analysis of randomized controlled trials on teneligliptin.

**Teneligliptin: QT prolongation**

Reported evidences suggest that QT prolongations were not observed with teneligliptin 40 mg daily dose. However, mild and transient QTc prolongation was observed only at a supraclinical dose of 160 mg/day which is 8 times the daily dosage of teneligliptin. To confirm the effect of teneligliptin on QT prolongation a randomized, double-blind, placebo and moxifloxacin controlled, parallel-group comparative study was conducted in 240 healthy adult male and females to investigate the effect of multiple-dose administration of teneligliptin (40, 160 mg) on QTc intervals. Placebo, teneligliptin (40 mg and160 mg) were administered orally once daily for 4 days. In the moxifloxacin group (positive control group), placebo was administered orally once daily for 3 days and moxifloxacin 400 mg on day 4. QTc interval prolongation was observed only time points near tmax after administration of teneligliptin. No clinically significant QTc interval prolongation was observed at 40 mg. It was observed that teneligliptin was not associated with QT interval prolongation at clinically relevant dose (maximum recommended dose 40 mg) in healthy individuals. However, teneligliptin should be used with caution when co-administered with drugs known for QT prolongation like class 1A or class III antiarrhythmic drugs. There is scarcity of data regarding effect of teneligliptin on QT prolongation and the above findings on QT prolongation were not corroborated by other similar study.

A study was conducted by Erande et al., involving 66 uncontrolled T2D patients, with Hba1c >7.0 % and were gliptin naive at two dose of Teneligliptin (20 mg or 40 mg). The results showed significant reduction in FPG (p<0.002), PPG (p<0.001) and HBA1C (0.69%, p<0.001) with no effects on QT / QTc interval prolongation by Teneligliptin at both doses.

**Expert comments:**

Teneligliptin should be used with caution in patients with mild to moderate hepatic impairment. QT prolongation is seen only with higher doses (160mg/day) but not with maximum recommended dose of 40 mg/day, however caution should be exercised when Teneligliptin is co-administered with drugs known to cause QT prolongation such as class 1A or class III antiarrhythmic agents. There have been no reports of QT prolongation in India so far. Teneligliptin in Type-2 DM patients resulted in improvement of systolic and diastolic function at 3 months with increase in adiponectin levels making Teneligliptin a useful drug in cardiac and renal patients.

**Teneligliptin: non-glycaemic Benefits**

**Cardiovascular benefits:**

**Teneligliptin: Effect on LV function**

Hashikata T et al, evaluated whether Teneligliptin (3 months treatment) affects Left ventricular (LV) function in patients with T2D (n=29). There was a decrease in Hba1c levels (7.6 ± 1.0 % to 6.9 ± 0.7 %, p < 0.01) after the treatment, whereas the 5-anhydro-D-glucitol levels increased (9.6 ± 7.2 µg/mL to 13.5 ± 8.7 µg/mL, p < 0.01) significantly. The systolic and diastolic functions got significantly improved (LV ejection fraction, 62.0 ± 6.5 % to 64.5 ± 5.0 %, p = 0.01; peak early diastolic velocity/basal
septal diastolic velocity (E/e’) ratio, 13.3 ± 4.1 to 11.9 ± 3.3, p = 0.01. It was noticeable that teneligliptin could have beneficial effects on the cardiac pump but needs to be replicated in a study of longer duration with large population for further validation.41

Teneligliptin: Effect on Cardiovascular Markers

In a study, Okuda Y et al, assessed the effects of Teneligliptin on serum cardiovascular risk markers including soluble P-selectin (sP-selectin), platelet-derived microparticles (PDMPs), plasminogen activator inhibitor 1 (PAI-1), soluble E-selectin (sE-selectin), soluble vascular adhesion molecule 1 (sVCAM-1), and adiponectin in HD and non-HD patients with T2D. Teneligliptin therapy significantly reduced plasma levels of sP-selectin, PDMPs, and PAI-1 compared to baseline levels, while significantly increasing adiponectin levels. sE-selectin and sVCAM-1 levels were significantly decreased only at 6 months. The reduction in sP-selectin, PDMPs, and PAI-1 was more significant in hemodialysis patients than in non-hemodialysis patients. Interestingly however, the improvement in adiponectin levels was unchanged with hemodialysis. By modulating PDMPs or PAI-1, teneligliptin showed an anti-atherothrombotic effect that may be beneficial in the long run in the primary prevention of CVD in patients with T2D on hemodialysis.42

Teneligliptin Positive Effect on Oxidative Stress and Endothelial Function

Sagara M et al., compared the efficacy of Teneligliptin and Sitagliptin on oxidative stress and endothelial function in T2D patients with CKD. Reactive hyperaemia peripheral arterial tonometry was used to assess peripheral endothelial function. Endothelial dysfunction was defined as Reactive Hyperaemia Index (RHI) <0.670. T2D patients with CKD (n=45) receiving Sitagliptin for at least 12 months were randomized to receive either Teneligliptin (n=22) or continue therapy with Sitagliptin (n = 23) for 24 weeks.

This study showed Teneligliptin to be equivalent to Sitagliptin with regard to effects on HbA1c, eGFR and urinary albumin excretion. Only Teneligliptin, significantly improved reactive hyperaemia index values (1.49±0.32 to 1.55±0.29, p<0.01), reduced levels of 8-hydroxy-2’-deoxyguanosine, [oxidative stress marker (7.1±4.9 to 5.4±2.9 ng/m Cre, p<0.05)] and urinary liver type fatty acid binding protein (L-FABP) (p<0.05). Improvements in urinary L-FABP levels have been associated with beneficial outcomes for patients at high risk of renal disease and Atherosclerotic Cardiovascular Disease (ASCVD), in published literature.43

Teneligliptin: Effect on Lipids

As per study of Kusunoki M, et al, on the effectiveness of treatment with Teneligliptin (20 mg/day) given for 14 weeks in T2D patients (n=9) based on the HOMA-Ratio, an indicator of insulin resistance, and serum lipid profile, suggested that Teneligliptin not only improves blood glucose control, but also improves insulin resistance and serum lipid profile in T2D patients.44

Expert comments:

Teneligliptin has anti-atherothrombotic effect that may be beneficial in the primary prevention of cardio-vascular disease in patients with T2D on hemodialysis. Teneligliptin significantly improved reactive hyperaemia index values showing positive effect on oxidative stress and endothelial function, along with HOMA-R and serum lipid profile in T2D patient’s after 14 weeks of treatment. Teneligliptin also improved the histopathological appearance of NAFLD affected liver in mouse models with down regulation of hepatic lipogenesis related genes. Teneligliptin, a novel DPP-4 inhibitor may have anti-oxidant properties and protects endothelial cells exposed to high glucose levels, but not yet well established in randomized controlled trial.

Teneligliptin Effect in Non-Alcoholic Fatty Liver Disease (NAFLD)

A distinct hepatic condition, NAFLD is higher in prevalence amongst obese individuals and patients with T2D. Teneligliptin has been shown to improve the hepatic histopathology and decreased intrahepatic triglyceride levels in an NAFLD model mouse. This improvement was associated with AMPK activation and the subsequent down regulation of hepatic lipogenesis-related genes.45

Teneligliptin: Other Pleiotropic Effects

The vascular endothelium plays a crucial role in maintaining vascular integrity and function. Chronic exposure to high glucose generates oxidative stress leading to endothelial dysfunction. Considering the potential protective action of Teneligliptin in endothelial cells exposed to high glucose, Pujadas Get al, (2017), published a study showing Teneligliptin as novel dipeptidyl peptidase-4 inhibitor in terms of its antioxidant properties and has the potential of inducing a good metabolic memory. Human umbilical vein endothelial cells were cultured under normal (5 mmol/L) or high glucose (25 mmol/L) during 21 days or at high glucose during 14 days followed by 7 days (normal glucose), to reproduce the high-metabolic memory state, using different concentrations of Teneligliptin (0.1, 1.0 and 3.0 µmol/L) or Sitagliptin (0.5 µmol/L). RNA and protein expression were assessed for antioxidant response, proliferation, apoptosis and endoplasmic reticulum stress markers. Teneligliptin, was superior to Sitagliptin in counteracting reactive oxygen species production, inducing a robust antioxidant response and reducing endoplasmic reticulum stress. This study shows that.46

Conclusion

Challenges and gaps in diabetes care concerning Indian patients can be summarized as inadequate lifestyle management, early onset, cost of therapy, lack of uniform access to proper care and ever-growth problem of obesity, which at times is compounded by anti-diabetic agents. Teneligliptin a truly 3rd generation, gliptin has firmly positioned itself as a very important drug in the armamentarium of physicians managing diabetes, especially in Indian patients. Teneligliptin is the most commonly used DPP IV inhibitor option for diverse diabetic profiles in India. This can be attributed not only to its positive effect in controlling the Glycaemic parameter, but also to its efficacy and safety at very low cost in a developing country like India where diabetes is a major health care burden. Diabetes can be a very expensive disease; wherein incomplete control can lead to multiple complications adding to the cost of monthly therapy cost. Teneligliptin offers efficacy along with safety and cost-effective therapeutic choice especially in Indian T2D patients.

References

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7. Hong S, Park CY, Han KA, Chung CH, Kim HW, No M, Moon KY, Chung CH, Ahn