Potential approaches using teneligliptin for the treatment of type 2 diabetes mellitus: Current status and future prospects

Abstract

Introduction: Based on pharmacological properties and results from clinical studies, teneligliptin has a great potential to be used as an alternate day therapy and also the daily dose can be reduced to 10 mg. Clinical data also suggest its excellent efficacy and safety among older subjects.

Areas covered: We have reviewed and discussed potential approaches using teneligliptin for the treatment of type 2 diabetes mellitus (T2DM) including; alternate-day therapy and reduction of dose from 20 mg to 10 mg per day. We have also discussed the potential of teneligliptin to address the needs of older patients with T2DM.

Expert opinion: It is an excellent option for use in older patients as studies in the geriatric population have shown encouraging results. Teneligliptin has a desirable pharmacokinetic profile that makes it a potential drug for use on an alternate day basis. Teneligliptin has shown anti-diabetic efficacy even at a dose of 10 mg. These approaches may improve the treatment satisfaction, patient compliance and can lower the cost; however, this is crucial to identify the subset of T2DM patients who can obtain maximum benefits. However, to verify these effects, large clinical investigations need to be planned and robust clinical evidence should be generated.

Key Words: DPP-4 Inhibitors, Efficacy, Safety, Teneligliptin, T2DM,

Article highlights

- Anti-diabetic efficacy of teneligliptin has been well documented as monotherapy as well as add-on therapy
- Teneligliptin has a great potential to be used as an alternate day basis therapy and also its daily dose can also be reduced from 20 mg to 10 mg.
- Clinical studies have revealed its excellent efficacy and safety among older patients.
- We have reviewed and discussed the potential approaches using teneligliptin including; alternate-day therapy and reduction of dose from 20 mg to 10 mg per day. We have also discussed the potential of teneligliptin to address the needs of older patients with T2DM.
- These approaches seem to be promising and can improve the treatment satisfaction, patient compliance and can lower the treatment costs.
- However, it is crucial to identify the subset of T2DM patients who can obtain maximum benefits.
- Large clinical investigations need to be planned and robust clinical evidence should be generated.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent public health problem leading to several serious health problems, including heart disease, vision loss, and kidney disease [1,

2]. Globally, approximately 8.8% of the population was living ~~lived~~ with diabetes mellitus (DM) in 2019, with an increase of 2.4% from 2010 (6.4%), and it is predicted that by 2040, there will be up to 642 million people living with DM around the world [2]. The global prevalence of T2DM is expected to reach 7079 per 100,000 individuals by 2030, reflecting a continuing increase in all regions of the world [3]. It is recommended to select the appropriate pharmacological treatment of DM by following a patient-centered approach. It involves considering the following factors: 1) efficacy and patient factors such as comorbidities like atherosclerotic cardiovascular disease (ASCVD) and indicators of ASCVD risk, chronic kidney disease (CKD), and heart failure (HF), 2) hypoglycemia risk, 3) effects on weight, 4) adverse effects, 5) cost, and 6) patient preferences [4]. As soon as T2DM is diagnosed, pharmacotherapy should begin, unless there are contraindications. For many patients, this will be metformin monotherapy (if not contraindicated) in combination with lifestyle modifications. The use of additional and/or alternative agents may be considered in patients with established or increased risk of cardiovascular or renal complications [4]. Many patients with DM tend to adhere poorly to their antihyperglycemic medications [5,6]. Adherence to medication aids in the successful treatment of DM patients and results in better intermediate outcomes, such as values of glycated hemoglobin (HbA1c), lower hospitalization rates, and lower healthcare costs [5]. Several factors contribute to nonadherence, including age, information, perception, ongoing disease, the complexity of dosing regimens, polypharmacy, psychological factors, safety, tolerability, and cost [6]. Several practical measures that clinicians can take to increase the adherence of patients with medications include the use of fixed-dose combinations, less frequent dosing regimens, and medications with better efficacy and fewer adverse effects [7]. Reducing the pill burden can lead to increased safety, cost savings, and improved patient compliance. A less frequent dosing, (alternate day therapy rather than a daily doing) with anti-diabetic agents that are desirable to use in such circumstances based on their pharmacodynamic and pharmacokinetic properties, may also be considered.

Gliptins or dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antidiabetic agents used for the management of T2DM in adults. These drugs inhibit DPP-4, an enzyme that breaks down incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1). This leads to increased glucose-dependent insulin secretion and decreased glucagon secretion after meals [8]. The standard treatment guidelines recommend the use of DPP-4 inhibitors in combination with metformin and oral antidiabetic agents if the target HbA1c level is not reached with the primary agents [9]. Sitagliptin, the first DPP-4 inhibitor, was approved for the treatment of T2DM in 2006 in conjunction with lifestyle changes and. Subsequently, many DPP-4 inhibitors have been developed and marketed, including alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, teneligliptin and vildagliptin [8-10].

Teneligliptin is a newly developed oral DPP-4 inhibitor, indicated for the management of T2DM in adults along with diet and exercise. It is generally well tolerated, with a safety profile similar to that of other DPP-4 inhibitors [10]. Patients with mild, moderate, or severe renal impairment or those with end-stage renal disease can be treated with teneligliptin

without adjusting the dose [10]. The purpose of this review is to explore the potential future approaches of using teneligliptin for the treatment of T2DM. In addition, we will discuss the potential benefits and concerns of using this approach. For searching relevant literature, we used terms such as "teneligliptin," "type 2 diabetes mellitus," “elderly,” "monotherapy," "add-on drug," "efficacy," and "safety" (by applying filters AND/OR where appropriate) and searched databases like PubMed/MEDLINE and CENTRAL.

2. Teneligliptin: Regulatory approvals in different regions.

In Japan (2012) and Korea (2016), teneligliptin was approved as a treatment for T2DM. Teneligliptin is approved for oral administration at a dosage of 20 mg once daily. In Japan, increasing the dose of teneligliptin to 40 mg/day is also being practiced (with close monitoring) [11]. Similarly, teneligliptin 20 mg was approved in India in 2015 as an adjunct to diet and exercise for the treatment of T2DM [12]. Although the European Medicines Agency (EMA) and the United States Food and Drug Administration (US-FDA) have not approved teneligliptin, it has been approved in Argentina for the treatment of T2DM [13, 14]. In addition to this, the Thailand Food and Drug Administration approved teneligliptin 20 mg in April 2020 for the treatment of T2DM [15]. Similarly, the drug regulatory authority of China, the National Medical Products Administration (NMPA), approved Tenelia (teneligliptin hydrobromide hydrate, 20 mg) as a therapeutic agent for T2DM in September 2019 [16].

2.1 Current status of teneligliptin for the management of T2DM

Teneligliptin is indicated for adults with T2DM who have failed to respond to diet and exercise treatment, as well as to treatment with biguanides, sulfonylureas, and thiazolidinediones [14]. It was evaluated as monotherapy and used in combination with α-glucosidase inhibitors, glinides, biguanides, or sulfonylureas in a post-hoc pooled analysis that included data from 702 Japanese patients from two Phase III clinical studies. Teneligliptin monotherapy and combination therapy groups experienced similar rates of adverse events, except for those treated with sulfonylurea. In the sulfonylurea combination therapy group, hypoglycemia was more common than in other groups. After 52 weeks, there was a significant decrease in HbA1c with teneligliptin monotherapy (-0.63 ± 0.65%, $p<0.001$) or combination of teneligliptin with other anti-diabetic agents ($p < 0.001$), and this effect was maintained for 52 weeks. At the end of 52 weeks, all groups had a slight increase or no change in body weight [17].

In another study, 31 Japanese patients newly diagnosed with T2DM were treated with teneligliptin monotherapy to determine the effect on their glycemic and non-glycemic parameters. There was a significant reduction in fasting blood glucose (FGB, from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dl, $p < 0.0002$) and HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%, $p < 0.00001$) after 3 months of treatment, as well as a significant decrease in insulin resistance. However, this study had limitations in terms of the number of subjects and the duration of the study [18]. A study where teneligliptin was administered to Korean patients with T2DM (uncontrolled with diet and exercise) in a randomized, double-blind, placebo-controlled phase III trial to evaluate its efficacy and safety, patients (n=142) were randomized into a 2:1 (teneligliptin 20 mg to placebo) group who had not been taking an oral antihyperglycemic agent for the previous eight weeks. As a monotherapy, teneligliptin was well tolerated and led to a

significant decrease in the HbA1c level ($p < 0.001$). There were no significant differences between the two groups in terms of incidences of adverse events [19].

The monotherapy of teneligliptin (20 or 40 mg once daily) or the combination of it with metformin, glimepiride, or pioglitazone had improved glycaemic control in clinical trials, including in patients undergoing haemodialysis (HD) [14].

In a large real-world study performed in Indian population (n=10,263), anti-diabetic effects of teneligliptin were found to be significant, whether given as monotherapy or as an add-on therapy [20]. Teneligliptin was studied in Chinese patients (age ≥18 years) with T2DM who were not adequately controlled with metformin alone, to determine its efficacy and safety as an adjunct therapy to metformin. In combination with metformin treatment, teneligliptin 20 mg once daily for 24 weeks significantly lowered HbA1c ($p < 0.0001$) and FPG levels ($p < 0.0005$) compared to placebo. Furthermore, the combination was well tolerated and safe [21].

In a randomized controlled trial 148 subjects with T2DM (whose glycemic control was not achieved with insulin therapy), were assigned to either placebo or teneligliptin 20 mg. Results indicated that teneligliptin is effective (significant HbA1c reduction as compared to placebo, $p < 0.001$) and safe option for such patients [22]. In one more Phase III randomized controlled study conducted at multiple centres, T2DM subjects (whose glycemic control was not achieved with diet and exercise) were assigned to either teneligliptin 20 mg or a placebo (n =127, in each group) for a duration of 24 weeks. Teneligliptin therapy was found to be significantly effective (significant HbA1c and FBG reduction; teneligliptin vs placebo, $p < 0.0001$ for both HbA1c and FBG), well-tolerated and safe [23].

In a prospective study, teneligliptin 20 mg or sitagliptin 100 mg was administered orally once daily for 12 weeks as an addition to the current metformin or sulfonylurea medication was given to 76 Indian patients (1:1). Both the gliptins showed similar he reductions in glycemic parameters ($p<0.0001$ for HbA1c and $p=0.0005$ for FBG) and both were found to be well tolerated well-tolerated (no difference in the number of adverse events). No changes were observed in QT/QTc intervals and other ECG parameters in both treatment arms. Interestingly, post-hoc comparison revealed that teneligliptin therapy led to greater proportion of patients achieving glycemic target (HbA1c <7%) as compared to sitagliptin (33.3% vs. 19.4% subjects achieving target HbA1c) [24].

In another multicentre, randomized, double-blind, placebo-controlled, parallel-group comparative study, Japanese patients treated with canagliflozin (100 mg) for 12 weeks, were randomly assigned to receive an add-on teneligliptin (20 mg; C + T group) or placebo (C + P group) for 24 weeks. Teneligliptin, when combined with canagliflozin, enhanced glycemic control ($P < 0.001$ for HbA1c reduction) while also being well tolerated [25].

An evidence-based systematic review and meta-analysis of randomized controlled trials assessing teneligliptin's efficacy and safety of teneligliptin in T2DM patients with inadequate glycemic control showed absolute reductions in glycated HbA1c levels in comparison to placebo (weighted mean difference = 0.82%, 95% CI -0.91 to -0.72, $p < 0.00001$). It was concluded that the teneligliptin not only improves the blood glucose levels and β-cells function

in patients with T2DM but also has a low tendency to cause hypoglycemia in those patients [26].

In a prospective, multi-centric, randomized controlled study, 100 subjects with T2DM who were not able to achieve the glycaemic control with a combination therapy of metformin, sulphonylurea, and sodium-glucose co-transporter-2 inhibitor, were randomly assigned teneligliptin and placebo-teneligliptin (1:1). At the end of 12 weeks, the teneligliptin group led to a significant decline in HbA1c (difference of -0.75% vs placebo group, 95% CI -0.99%, -0.51%, $p < 0.001$) and after 24-week treatment period, both groups showed significant reductions in HbA1c level (placebo-teneligliptin group, -0.8% ± 0.6%, $p < 0.001$, teneligliptin group, -0.9% ± 0.6%, $p < 0.001$]). No significant difference was observed in the incidence of adverse drug reactions and both treatment arms had favourable safety profiles [27].

Lee et al, in a 52-week, prospective, multi-centric, observational study, evaluated the efficacy and safety of switching to teneligliptin 20 mg daily from other DPP4 inhibitors in nearly 3000 patients with T2DM who were inadequately controlled with a stable dose of other agents of this class. Treatment with teneligliptin led to a significant decrease in HbA1c as compared to the baseline value at different follow ups (weeks 12, 24, and 52, overall HbA1c = 7.94% at baseline, reduced to 7.53% (− 0.39%, $p < 0.0001$) at week 12, reduced to 7.45% (− 0.44%, $p < 0.0001$) at week 24, and further reduced to 7.42% (− 0.52%, $p < 0.0001$) at week 52. Also, the proportion of the T2DM subjects achieving glycemic control increased throughout the study period. The authors did not observe any significant safety concerns [28].

3. Potential approaches using Teneligliptin in patients with T2DM

3.1 Safe and effective agent in geriatric patients with T2DM: - Teneligliptin, a DPP-4 inhibitor, received approval for the treatment of T2DM in Japan in 2012. However, older patients are generally not included in clinical trials involving drug testing and this could be a case with teneligliptin too. A post-marketing surveillance study was conducted in Japan to assess the safety and efficacy of teneligliptin in older patients (less than 65 years, between 65 and 75 years of age and 75 years or older). No significant difference was observed with respect to adverse drug reactions (ADRs) among subjects of different age groups (though incidence of serious ADRs was found to be more in older subjects). Decrease in HbA1c values were found to be significant in each sub-group and it was maintained till 3 years. In conclusion, teneligliptin therapy was found to be safe and effective in older patients with T2DM [29].

In a randomized controlled, multicentre study, 65 subjects aged 65 or above (with 50% of the participants above 70 years of age), who had not previously been treated with metformin or were being treated with stable metformin doses, were randomly assigned to either teneligliptin 20 mg (n=35) or placebo (n=30) for a duration of 12 weeks. Teneligliptin therapy led to a significant reduction in HbA1c (by 0.84% from baseline intergroup (vs placebo) least square mean difference of –0.76%, 95% CI, –1.08 to –0.44, $p<0.001$), duration above the target glycemic range, and without any safety concern like hypoglycemic episodes [30].

An observational retrospective study was conducted using a predesigned structured questionnaire to collect data from medical records ~~at~~in 18 hospitals across India. The study included patients (n=10,623) with T2DM who had been treated with teneligliptin for at least 12 weeks (either individually or in combination with other antidiabetic medications). In all three age categories tested, teneligliptin reduced HbA1c by 1% in patients under 60 years of age, by 1.15% in patients between 60 and 75 years of age, and by 0.88% in patients over 75 years of age ($p<0.001$). As monotherapy or as a component of a combination of other commonly prescribed antihyperglycemic medications, teneligliptin improved glycaemic parameters in Indian patients with T2DM [20,31].

In a retrospective study, teneligliptin 20 mg once daily was administered to T2DM patients (n=175) for 6 months to assess its effects. The study subjects were categorized in two groups: the elderly (70 years of age or older, n = 66) and the less-elderly (less than 70 years of age, n = 71). The authors analyzed the data separately for study participants receiving teneligliptin monotherapy, those requiring additional therapy, and those requiring switching from the other DPP-4 inhibitor. Subjects who received monotherapy (n = 56) or additional therapy (n = 29) had significantly lower HbA1c levels than those who received switching therapy (n = 52). The effect of teneligliptin was same for elderly patients with T2DM as for non-elderly patients (change in the HbA1c levels at 6 months, after the initiation of teneligliptin therapy, was not significantly different among two groups i.e. -0.6 ± 0.5 and -0.8 ± 1.1, respectively in patients receiving monotherapy, and -0.8 ± 0.8 and -0.8 ± 0.5, respectively in those receiving additional therapy, $p>0.05$) [32].

In a cross-sectional observational study conducted in Indian geriatric patients, teneligliptin was found to have treatment satisfaction ($p=0.63$ for comparison of Diabetes Treatment Satisfaction Questionnaire Scores), efficacy ($p=0.21$ for HbA1c comparison) and safety, similar to those of sitagliptin and vildagliptin [33].A retrospective study (n=164) was conducted to assess decreases in blood glucose levels in older (>65 years old) T2DM patients when switching from linagliptin to teneligliptin for more than 12 weeks. The switch from linagliptin to teneligliptin not only improved FBG, HbA1c and PPG, but also helped in preserving kidney function [34]. Summary of the studies, along with important findings, have been provided in table 1.

3.2 Reduction in Dosing frequency: Possible alternate day therapy:

Teneligliptin is a potent, selective, and long-lasting inhibitor of DPP-4 with a half-life of approximately 24 hours [11]. Within two hours after administration, the inhibition of plasma DPP-4 activity was found to be a maximum of 81.3% and 89.7% for 10 and 20 mg of teneligliptin, respectively. Even 24 hours after administration, the active concentration of GLP-1 in the plasma remains considerably lower with teneligliptin 10 mg and 20 mg [35]. Teneligliptin has a substantially greater affinity (around 5-fold as compared to other agents like sitagliptin) for S1, S2, and S2 extensive subsites of DPP-

4 enzyme; different reasons may contribute to this; teneligliptin contains a relatively rigid "J" structure, formed by five rings, four of which are directly linked, and has little entropy loss when it binds to DPP-4. Also, the interaction of teneligliptin with sub-site S2 is due to the formation of hydrogen bond between its carbonyl group and Asn710's side chain. Lately, there is strong hydrophobic interaction of teneligliptin (mediated by an “anchor lock domain) with the S2 extensive sub-site of DPP-4 enzyme. In vivo, binding of the anchor lock domain may be correlated with long residence times of DPP-4 inhibitors and long in vivo duration of action [36]. Teneligliptin has been found to be metabolized by cytochrome 3A4 and flavin-containing monooxygenase 3 (FMO3). About one-third of the excretion of teneligliptin is governed through the renal route, and almost two-third is found to be metabolized and eliminated by the liver and kidneys.

Teneligliptin has multiple elimination pathways, making it appropriate for patients with hepatic/renal impairment; it does not require dose adjustment, and its drug-drug interactions are minimal [11,35]. Teneligliptin has a half-life of 24 hours. In view of this fact, a non-inferiority study was conducted to evaluate the effectiveness and safety of teneligliptin given on alternate day Japanese T2DM subjects. Fifty- one subjects were randomized to receive teneligliptin 20 mg daily for 12 weeks (Group A) or teneligliptin 20 mg on alternate days (Group B). After 12 weeks of therapy, HbA1c levels improved in both groups (p value equals to or less than 0.05 in both groups). The criterion for non-inferiority (of group B to group A) was fulfilled. Further, there were no significant differences between the two groups in terms of treatment satisfaction, adverse events, or adherence [37].

Summary of the studies, along with important findings, have been provided in table 1.

Therefore, by virtue of its useful pharmacological properties and positive hints from the preliminary clinical data, teneligliptin has got a great potential to be used as an alternate day therapy. However, further long-term studies will be required to fully explore this concept.

3.3. Possible reduction in dose (from 20 to 10 mg) and evidence from the literature:

Another promising approach is to reduce the dose of teneligliptin from 20 mg to 10 mg per day. Few clinical studies have explored this effect, and it needs further investigation.

In a double-blind, placebo-controlled study, 99 Japanese diabetes patients with type 2 diabetes mellitus inadequately controlled with diet and exercise were randomly assigned to take either teneligliptin 10 mg, 20 mg or placebo for a duration of four weeks. As compared to placebo, teneligliptin treated subjects (at 10 mg and 20 mg doses) showed a significant reduction in 2-hour postprandial glucose (PPG), mean glucose and FPG. ($p<0.01$ for all comparisons) In contrast, 2-hour PPG, mean glucose and FPG did not differ between the teneligliptin 10 mg and teneligliptin 20 mg groups

(p>0.05). Also, no safety concerns or serious adverse drug reactions were observed with teneligliptin therapy [38].

In another double-blind, placebo-controlled, parallel-group study, teneligliptin 10, 20, or 40 mg, or placebo, was administered once daily before breakfast for 12 weeks, to 324 Japanese patients with T2DM inadequately controlled with diet and exercise. As compared to placebo, once-daily teneligliptin therapy at different doses (10 mg, 20 mg, and 40 mg led to a significant reductions in HbA1c ($p < 0.001$for all), FPG ($p < 0.001$for all), and 2-hour PPG ($p < 0.001$for all parameters). However, no difference was observed between different doses of teneligliptin with respect to HbA1c (p>0.05) [39].

A double-blind, parallel-group study was conducted, recruiting patients from 55 centres in seven European countries to evaluate the efficacy and safety of teneligliptin and metformin together when administered to subjects with T2DM not adequately controlled by metformin monotherapy. The subjects received either placebo or teneligliptin in different doses (5 mg, 10 mg, 20 mg, or 40 mg) for a duration of 24 weeks over and above metformin therapy. At the end of the treatment, teneligliptin (at different doses) led to a significant reduction in HbA1c ($p =0.003$ for 5 mg dose and <0.001 for all other doses) in a dose dependent manner (with maximum reduction observed at a dose of 40 mg, $p<0.001$) [40]. Also, teneligliptin therapy was found to be well tolerated even at week 52.

Summary of the studies, along with important findings, have been provided in table 1.

Reduction in the dose to one half in carefully selected T2DM subjects (while retaining the reasonable efficacy), may reduce the adverse effects, cost, and help in improving the patient compliance.

3.4. Benefits beyond glycemic control:

Teneligliptin offers many beneficial effects, in addition to its anti-diabetic effect. Although these effects are not the indications for teneligliptin therapy, but these are additional effects which can be promising in the treatment of patients suffering from multiple health conditions in addition to T2DM.

In an open-label, prospective, multicentric trial, patients with T2DM and HbA1c >7.0 percent but no history of gliptin use, were enrolled. The purpose of this study was to assess the safety of teneligliptin in T2DM patients with respect to QTc prolongation. Teneligliptin therapy at recommended doses of 20-40 mg per day led to a significant improvement (from baseline) in glycemic parameters ($p<0.001$ for both HbA1c and FBG). Also, it was not associated with prolongation the QT/QTC interval. As secondary endpoints of the teneligliptin studies, lipid profiles were examined among 31 patients receiving teneligliptin monotherapy. A little or no effect was observed on lipid parameters such as total cholesterol (T-C), triglycerides (TG), non-high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and free fatty acids (FFA) [18].

Teneligliptin treatment in Indian patients with T2DM 20 mg or 40 mg of teneligliptin every day as monotherapy or add-on therapy did not result in prolonged QTc intervals and was impressively effective in maintaining glycaemic control [24,41].

Teneligliptin has been shown to be safe and effective; however, the supporting data, regarding its use in patients with moderate or severe renal impairment, is limited. Data generated in a surveillance programme (11,677 patients were examined and the authors collected 11,425 patient case report forms to perform the interim analysis. The results of the interim analysis indicated that the ADR profiles of patients with different stages of renal impairment were similar even after receiving a long-term therapy with teneligliptin. Moreover, teneligliptin therapy was associated with a clinically meaningful improvement in glycemic parameters in T2DM patients having renal dysfunction [42].

In an observational study (single arm), switching to teneligliptin therapy (from other DPP-4 inhibitors) for a period of 24 weeks led to a reduced plasma activity of DPP-4 ($p = 0.012$, vs baseline) along with a decrease in albuminuria in patients with DM and diabetic kidney disease, irrespective of blood glucose levels [43].

Another study reported that patients undergoing haemodialysis (HD) who have DM and CKD, teneligliptin treatment decreased their FBG ($p=0.0015$) and HbA1c ($p=0.0011$) and lipid parameters (decreased as compared to control but this was not significant). In this study, diabetes and CKD patients undergoing HD were categorized into two groups; 15 patients were treated with teneligliptin 20 mg/day for 12 weeks, and 10 patients were allocated to the control group [44]. Patients with T2DM receiving HD may benefit from using teneligliptin to improve glycemic control.

An open label and single arm trial was performed by including 10 diabetic patients undergoing HD (with glycated albumin levels of 18.3%). In these patients, treatment with teneligliptin was given on days with and without HD sessions (HD and non-haemodialysis days). Study authors observed an improved blood glucose AUC on both HD and non-haemodialysis days ($p=0.004$ for each) [45]. In a study, teneligliptin (20mg/day) was given to nine Japanese patients with T2DM for 14 weeks to examine the impact it had on the homeostasis model assessment ratio (HOMA-R), an indicator of insulin resistance, and serum lipid profile. Treatment resulted in a significant decrease in blood glucose levels ($p=0.008$) and HbA1c ($p=0.038$) as well as an improvement in HOMA-R ($p=0.039$). Treatment with teneligliptin also led to an increase in HDL levels ($p=0.032$) and a trend towards decrease in TG levels. In this study, teneligliptin not only improved blood glucose control, but also insulin resistance and serum lipid profiles [46].

Add-on teneligliptim therapy in 26 Japanese subjects with T2DM receiving insulin therapy (with or without other anti-diabetics), showed a significant diurnal glucose control a reduction in glucose fluctuations over 24-hour periods without increasing the incidence of hypoglycemia [47]. A preclinical study revealed that teneligliptin (10mg/kg/day/per oral) reduced hypertension and cardiac remodeling in spontaneously hypertensive rats (SHR) by normalizing angiotensin-II (AngII) levels. AngII promoted hypertrophy, by improving the expression and activity of cardiac

Sodium-proton pump exchanger type 1 (NHE-1). A higher level of cardiac NHE-1 expression was seen in SHR, and this was restored after teneligliptin treatment [48].

Studies in murine models have indicated that DPP-4 inhibitors (sitagliptin, vildagliptin, alogliptin, and teneligliptin) attenuated the formation of abdominal aortic aneurysm (AAA) by causing a decreased differentiation of monocytes, by decreasing the reactive oxygen species (ROS) release and inhibiting metalloproteinases (MMP-2 and MMP-9) [49].

Teneligliptin seems to possess a multidimensional role in providing beneficial effects, in addition to its anti-diabetic effect. This can be further investigated by conducting specific and adequately powered studies.

3.5 Cost considerations

There is a lot of burden with respect to cost of managing T2DM among Low- and middle-income countries (LMICs) and this should be a priority for the global health community to provide universal healthcare access. The cost of T2DMs care may be extremely high for patients living in LMICs since most of them lack health insurance and paying for diabetes treatment out of pocket may pose a significant burden on them [50]. DM is not just a chronic disease affecting LMICs, but also in developed countries like the United States. DM account for one out of every four dollars spent on health care in the US and total economic cost increased by 60% from 2007 to 2017 [51].

It has been found in a systematic review of the global evidence on the costs of T2DM that direct costs are generally higher than indirect costs. [52].

The results of a systematic review of studies that investigated the costs (direct and indirect) of treating T2DM in LIMCs found that the average annual cost per person for treating the disease ranged between USD29.91 and USD237.38. Hospitalization costs were the largest contributor to direct costs, followed by drug costs [53]. According to the study by Kwon et al., metformin plus DPP-4 inhibitors were more cost-effective than metformin plus sulfonylureas as a long-term second-line treatment for T2DM, from the perspective of US health care payers. It may provide clinicians and third parties with important information on the cost-effectiveness of second-line therapy for people with T2DM after metformin monotherapy has failed [54]. In a study by Tandon et al., it was found that cost-effectiveness (per unit decreases in HbA1c and FPG) was higher in the metformin plus glimepiride group as compared with the metformin plus teneligliptin. However, the cost-effectiveness for per unit decreases in PPG was not significantly different among both groups [55]. Agrawal et al. reported that teneligliptin was able to provide an effective second-line treatment for T2DM at a lower average price than other DPP-4 inhibitors [56]. In a developing country like India with a high prevalence of T2DM, the rationale for this can be attributed not to the control of the glycaemic parameter, but also to its efficacy and safety, at a low cost [57].

In addition to its promising efficacy and safety profile, teneligliptin is an affordable agent (cost-effective) and is one of the most commonly prescribed gliptins in India [20,39]. Although many brands are available, but the cost of teneligliptin is significantly

lesser as compared to other commonly used gliptins in India (sitagliptin, vildagliptin, linagliptin etc.) [58].

4. Pros of using new approaches:

T2DM is a significant health problem in both, high-income countries as well as in low-income countries [59]. The important pharmacokinetic and pharmacodynamic properties make the teneligliptin a potential anti-diabetic of choice in the older population [11]. In clinical studies, teneligliptin administered as monotherapy or in combination with antihyperglycemic agents has demonstrated effectiveness and safety in people with T2DM, including older people and patients with renal impairment [20, 29-34]. Clinical studies have shown that teneligliptin at different doses (10 mg, 20 mg, and 40 mg) shows clinically relevant reductions in HbA1c, and blood sugar levels [38,39]. A dose-related and statistically significant reduction in HbA1c has been observed when teneligliptin was co-administered with metformin [39]. Teneligliptin (in doses of 10 mg and 20 mg) led to improvement in blood glucose levels over 24 h without hypoglycemia or serious adverse events. Therefore, the reduction in doses could help reduce adverse events without affecting glycemic control.

Possible alternate day teneligliptin treatment could be hypothesized due to its ability to selectively inhibit DPP-4 and its long half-life (approximately 24 hours). In addition to reducing the economic burden, this approach may be helpful in improving adherence and patient satisfaction. Kamiko et al. reported similar efficacy, patient satisfaction levels, and safety for teneligliptin (20 mg) when administered every other day instead of daily administration. Hypoglycemia was experienced by both groups, but it was not severe enough to require them to discontinue the drug [37].

There was no significant difference in overall adverse effects between teneligliptin and placebo in a systematic review and meta-analysis of randomized controlled trials. Furthermore, the risk of hypoglycemia was not significantly different between teneligliptin and placebo [26]. In a meta-analysis of randomized controlled trials, it was found that DPP-4 inhibitors led to a lower cancer risk when compared to placebo/none, but no significant differences were identified with other comparator treatments [60]. Results of a network meta-analysis performed of DPP-4 inhibitors have shown that DPP-4 inhibitors less commonly associated with gastrointestinal adverse events as compared to other commonly used anti-diabetic agents (glucagon-like peptides, metformin, and α-glucosidase inhibitors) [61]. In a randomized phase 3 trial, commonly associated adverse events with teneligliptin 20 mg and placebo were; upper respiratory tract infection, hyperuricemia, and hyperlipidemia [21]. Teneligliptin administered on alternate days can reduce the concentration of the drug in the body, which may reduce the likelihood of adverse effects. The proposed approaches could be promising for improving the management of T2DM among low-income or low- to middle-income countries. Therefore, this may improve the treatment satisfaction, quality of life for patients as well as help to accomplish better treatment outcomes.

Besides improving glycemic parameters, teneligliptin does not prolong the QT/QTC interval [18,41] which shows that it is free from arrhythmogenic potential. In patients with T2DM and

renal impairment, teneligliptin has been found to be associated with improved glycemic control [42]. Furthermore, switching from another DPP-4 inhibitor to teneligliptin for 24 weeks decreased the plasma activity of DPP-4, which decreased albuminuria in patients with diabetes mellitus or diabetic kidney disease [43]. There is an evidence that patients with T2DM receiving HD may benefit from the use of teneligliptin to improve glycemic control [44,45]. A study of teneligliptin (20 mg/day) showed an increase in HDL-cholesterol levels, along with a tendency toward reducing triglyceride levels. The results indicate that teneligliptin can improve both the insulin resistance and lipid profile of Japanese T2DM patients as well as improve blood glucose control [46]. An animal study showed that teneligliptin reduced hypertension and cardiac remodeling in spontaneously hypertensive rats [48].

From the above discussion, it is evident that by adopting these new strategies of teneligliptin dosing and dosing frequency, we can offers multiple clinical benefits to T2DM subjects.

5. **Potential concerns with these new approaches**

Though the use of teneligliptin, in older patients or reduction in dose of teneligliptin or proposing alternate day therapy, seems to be promising, but concrete evidence is needed. We can only confirm these claims by generating data from larger studies and clinical evidence based on focused randomized controlled trials. One of the main concerns regarding these new approaches is the risk of loss of efficacy (glycemic control). Older patients are vulnerable to adverse effects and comorbidities might contribute to the failure of treatment. Some individuals may forget to take alternate day therapy and they might be comfortable with daily administration. It becomes important to provide supervision or reminders after starting such therapy. Alternate day dosing may affect compliance if the patient forgets when they took their last dose [24]. One of the emerging safety concerns reported with the use of vildagliptin and teneligliptin and few other DPP-4 inhibitors is the bullous pemphigoid. It is more commonly seen in older subjects, however the pathogenic mechanism of gliptin associated bullous pemphigoid is unknown [62,63,64]. Other less well explored aspect of teneligliptin use includes the cardiac safety data. Although, no serious cardiac issues have been identified but it needs more data to fully explore this association. QT/QTc evaluations have been performed for teneligliptin but it was not found to cause QT prolongation even at 40 mg daily (20 mg/day is the most commonly used dose in usual clinical practice [35]. However, at supra-clinical doses, a mild and transient QTc transient prolongation was observed, hence it requires a caution while using teneligliptin for a long period or when it is to be co-administered with other drugs causing QT prolongation [35,65]. Erande et al also observed that teneligliptin, in doses of 20-40 mg/day, does not lead to QT prolongation [66] On the other hand, teneligliptin treatment has been found to enhance the left ventricular function and to decrease endothelial dysfunction which points towards its beneficial cardiovascular effects [67]. A preclinical study found that teneligliptin can lead to reduction in blood pressure and cardiac remodeling in spontaneously hypertensive rats (SHR) [48]. However, additional data is needed to fully explore its cardiac safety data. At the same time, in this review, we have proposed the use of teneligliptin in lower doses or as alternate therapy (low exposure as compared to the conventional dose), which seems to be safer

as till now there are no reports on cardiotoxicity observed with currently recommended dose of teneligliptin.

6. Conclusions

Teneligliptin has a long half-life and therapeutic benefits beyond glycemic effects, making it an attractive choice for the treatment of older patients with T2DM. Its use may reduce the incidence of adverse effects, improve adherence and quality of life, and reduce cost. In addition, the economic burden could also be reduced by reducing the drug dose or adopting the alternate-day regimen in patients with T2DM.

7. Expert opinion

The anti-diabetic efficacy of teneligliptin has been well documented in several studies, both as monotherapy and in combination therapy, and it has been found to be well-tolerated. Teneligliptin is suitable for patients with hepatic/renal impairment; it does not require dose adjustments, and drug-drug interactions are limited. This characteristic makes it an excellent choice for use in older patients. Few studies on the geriatric population have shown encouraging results, albeit a larger study on a diverse population is warranted. Teneligliptin may help in glycemic management, cost reduction, and safety. It has a half-life of 24 hours which can be helpful in patients with T2DM in terms of adding teneligliptin to ongoing monotherapy or combination medication on an alternate day basis without losing efficacy. However, this approach may not be desirable in T2DM patients with severely uncontrolled hyperglycemia and who have developed /or are at higher risk of developing T2DM related complications. Therefore, this is very important to identify the subset of T2DM patients who can obtain maximum benefit from this approach. Teneligliptin can be used as a second-line medication in a subpopulation of patients who are unlikely to experience major swings in glycemic control or complications. Furthermore, with reduced drug exposure, there are fewer drug-related adverse effects, and this can be specifically helpful in improving the patient compliance. Teneligliptin therapy at different doses (10 mg, 20 mg, and 40 mg resulted had shown significant decreases in HbA1c and other glycemic parameters [38,39]. This hints towards another approach by lowering the dose of teneligliptin, however, with caution. Therefore, we can consider a lower dose of 10 mg per day. This will not only decrease the pill burden but it could also be cost-effective. Alternate day therapy with teneligliptin 20 mg, has also been found to be effective and safer, and it also led to adequate treatment satisfaction and adherence to therapy [37]. The use of some anti-diabetic agents on alternate day-based therapy has been considered with other agents which have more or less similar pharmacokinetic properties like teneligliptin [68, 69].

In a study conducted by Chowdhury et al, 2021 (by an expert panel of leading endocrinologists), the scientific evidence was synthesized by analysing the data from various published clinical trials, meta-analyses and real-world studies to evaluate the cost-effectiveness of teneligliptin in Indian patients with T2DM. The findings of this analysis indicated that teneligliptin is most commonly used gliptin in India and it has desirable pharmacokinetic and pharmacodynamic properties and it is the most cost-effective DPP4 inhibitor available in India.

They also suggested that teneligliptin is well tolerated (both in monotherapy as well as in combination) [57]. This study also validates the ideas behind our review.

Patients with T2DM, who require almost lifetime treatment, will benefit from these strategies because these may help in lowering their treatment costs and pill burden. This is particularly important for T2DM in developing countries like India where there is high prevalence of TDM and identifying even small subset of patients who can obtain benefit from these strategies, would cater a large number of individuals. Considering the efficacy, safety and cost-effectiveness of teneligliptin, the Ministry of Health and Family Welfare (MoHFW) of India has decided to include teneligliptin 20 mg in the National List of Essential Medicine (NLEM), 2022 which is a very promising decision and it also confirms the need for teneligliptin to treat a large T2DM population [70,71,72]. An important reason behind the increasing use of teneligliptin (or other DPP-4 inhibitors) is the safety concerns of pioglitazone (which has shown a great efficacy) that discourages the clinical use of pioglitazone [73]. In such a scenario, a cost-effective and a relatively safer agent like teneligliptin can gain more popularity.

Teneligliptin could be a very promising agent for older patients with T2DM, and a new approach (change in dosing strategy) could be used in older patients with a relatively stable glycemic profile. Older patients are more susceptible to side effects, and comorbidities may contribute to treatment failure due to lack of adherence. Loss of glycaemic control is one of the most serious problems and higher doses can lead to hypoglycaemia, which could be dangerous.

Since T2DM is a major public health problem throughout the world, these new strategies may be promising in serving millions of patients with T2DM. However, before reaching any conclusion, we need thorough clinical research to verify these claims. Although many small-scale studies and secondary data are available, larger investigations need to be planned and robust clinical evidence should be generated. However, pilot studies could also be initiated at the institution level, which can be the basis for conducting larger randomized trials.

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Table 1. Summary of the important clinical studies of teneligliptin involving older subjects and modification in dose and dosing frequency

Study and Reference	Study Methods/Approach	Results with respect to efficacy and/or safety of teneligliptin
Kadowaki et al, [29]	In this 3-year follow-up post-marketing surveillance study, (on T2DM subjects registered between May 2013 and February 2015 in Japan), data were collected on demography, treatment of T2DM, ADRs, and laboratory parameters. Data was analyzed for subjects age sub-groups (< 65, ≥ 65 to < 75, or ≥ 75 years old). incidence of ADRs was assessed to evaluate the safety and efficacy was evaluated with respect to glycemic control (assessed by HbA1c), till 3 years.	HbA1c decreased significantly at 6 months in all three sub-groups (patients aged < 65, ≥ 65 to < 75, and ≥ 75) and reductions were sustained till 3 years The baseline-adjusted least square differences were − 0.66 ± 0.02%, − 0.72 ± 0.02%, and− 0.77 ± 0.03%, respectively (p < 0.001). ADRs were found to be similar in each age sub-group and were observed among 3.35% patients aged < 65 years, 4.42% patients aged ≥ 65 to < 75 years, and 3.99% patients aged ≥ 75 years. A higher tendency for serious ADR were observed o in older subjects as compared those with < 65 years.
Bae et al, [30]	In a randomized controlled multicentre study conducted at 8 different centres in Korea, 65 subjects aged 65 or above (with 50% of the participants above 70 years of age), who had not previously been treated with metformin or were being treated with stable doses of metformin, were randomly assigned to either teneligliptin	Teneligliptin therapy led to a significant reduction in HbA1c (by 0.84% from baseline intergroup (vs placebo) least square mean difference of –0.76%, 95% CI, –1.08 to –0.44, p<0.001), duration above the target glycemic range, and glycemic variability in geriatric T2DM subjects. During the study period, 15 and 10 AEs were reported (in 14.3% subjects in teneligliptin group 23.3% in placebo

	20 mg (n=35) or placebo (n=30) for a duration of 12 weeks. the study endpoints were change in HbA1c, continuous glucose monitoring derived time in range, and glycemic variability.	group, p=0.349), Most of the AEs were of mild severity and mild hypoglycemia was observed only in one subject in each group. Tenelgliptin therapy was found to safe and well tolerated
Ghosh et al, [31]	In this real-world study, the information was collected from the prescribing physicians with respect to efficacy of teneligliptin (as monotherapy as well as in combination therapy) in subjects with T2DM. The efficacy was evaluated by mean change in 3-month values of HbA1c, FBG, and PPG.	Data regarding 4305 patients was found to be suitable for analysis. Teneligliptin therapy led to a significant reduction mean HbA1c, FPG, and PPG (means changes for the above parameters were −1.37%±1.15%, 51.29±35.41 mg/dl, and 80.89±54.27 mg/dl, respectively). Subgroup analysis revealed that teneligliptin added to metformin plus sulfonylurea therapy led to a significant decrease in HbA1c, FBG, and PPG ($p < 0.0001$). Also, a significantly higher percentage of patients achieved HbA1c value of less than 7%, indicating achievement of glycemic control.
Abe et al, [32]	In this retrospective study, teneligliptin 20 mg per day was administered to subjects with T2DM (n=175) for 6 months. The study subjects were divided in two groups: the elderly (≥70 years, n = 66) and the less-elderly (<70 years, n = 71). The authors analyzed the data separately for study participants receiving teneligliptin monotherapy, those requiring additional therapy, and those requiring switching from the other DPP-4 inhibitor	Older T2DM subjects receiving monotherapy or additional therapy had significantly lower HbA1c levels than those who received switching therapy (n= 2). The effect of teneligliptin was found to be similar for elderly patients with T2DM as that for non-elderly patients and change in HbA1c levels (at 6 months, after the initiation of teneligliptin) was not found to be significantly different among two groups i.e. −0.6 ± 0.5 and −0.8 ± 1.1, respectively in patients receiving monotherapy, and −0.8 ± 0.8 and −0.8 ± 0.5, respectively in those receiving additional therapy, $p>0.05$).
Han et al, [34]	In this retrospective study (n=164), the authors evaluated the changes in glycemic parameters in older (>65 years) T2DM patients when switching from linagliptin to teneligliptin for more than 12 weeks of duration. The primary outcome was the change in the glycemic parameters after switching from linagliptin to teneligliptin	The switch from linagliptin to teneligliptin significantly improved the levels of FBG (from 148.1 ± 47.1 to 139.6 ± 43.4 mg/dl, $p<0.05$), HbA1c (from 7.9 ± 1.3 to 7.5 ± 1.2%, $p<0.05$) and postprandial blood glucose (from 224.8 ± 77.4 to 205.8 ± 70.8 mg/dl, $p < 0.05$). Also, renal function was preserved after switching the older T2DM from linagliptin to teneligliptin
Kamiko et al, [37]	In a randomized, non-inferiority study, the effectiveness and safety of teneligliptin in once daily vs alternate day therapy, was evaluated. Fifty- one subjects were randomly assigned to receive teneligliptin 20 mg once daily for 12 weeks (Group A) or teneligliptin 20 mg on alternate days (Group B).	After 12 weeks of teneligliptin treatment, HbA1c levels improved in both groups (from 7.5% ±0.4% to 6.6% ± 0.4% in group A and from 7.6% ±0.6% to 6.7% ± 0.5% in group in group B, p value equals to or less than 0.05 in both groups). The HbA1c difference among the two groups was found to be 0% with a 95% CI ranging from - 0.3% to 0.1%. The criterion for non-inferiority (of group B to group A) was fulfilled. Also, no significant differences were observed between group A and B with respect to treatment satisfaction, AEs, and adherence to treatment
Eto et al, [38]	In this double-blind, placebo-controlled study, 99 Japanese diabetes patients with T2DM who were inadequately controlled with diet and exercise, were randomized to receive either teneligliptin 10 mg, teneligliptin 20 mg or placebo for a duration of four weeks.	Compared to placebo, teneligliptin 10 mg and 20 mg treated groups led to a significantly reduced 2-h PPG, 24-h mean glucose and FBG. The differences were; teneligliptin 10 mg vs placebo, changes in 2-h PPG (after each meal i.e., breakfast, lunch and dinner) were −50.7 ± 7.8, −34.8 ± 9.2 and −37.5 ± 7.5 mg/dl, respectively, ($p < 0.001$ for all). For teneligliptin 20 mg vs placebo, the differences were −38.1 ± 7.8 ($p < 0.001$), −28.6 ± 9.2($p < 0.01$), and −36.1 ± 7.5 mg/dl ($p < 0.001$), respectively. Both teneligliptin doses, i.e., 10 mg and 20 mg led to an increased concentration of glucagon-like peptide-1 as compared with

		placebo. The results of this study support the possibility of using teneligliptin at a lower dose.
Kadowaki et al, [39]	In this double-blind, placebo-controlled, parallel-group study, teneligliptin 10, 20, or 40 mg, or placebo, was administered once daily for a duration of 12 weeks (n= 324 T2DM subjects) inadequately controlled with diet and exercise. The primary endpoint of this study was change in levels of HbA1c from baseline to 12 weeks of therapy.	Once-daily teneligliptin therapy at different doses (10 mg, 20 mg, and 40 mg led to a clinically significant reductions in HbA1c (difference in HbA1c levels were -0.9 LS mean; 95% CI= -1.0, -0.7, -0.9 LS mean, 95% CI= -1.1, -0.7 and -1.0 LS mean; 95% CI= -1.2, -0.9 %, respectively ($p < 0.001$). Also, there were significant reductions in FPG ($p < 0.001$), and 2-h PPG ($p < 0.001$) as compared to placebo. No significant difference was observed between different doses of teneligliptin with respect to HbA1c ($p>0.05$). No difference was observed with respect to incidence of AEs and ADRs. Similarly, incidence of hypoglycaemic events was not found to be significantly different at different doses of teneligliptin.
Bryson et al, [40]	In this double-blind, parallel-group study, the authors evaluated the efficacy and tolerability of teneligliptin in subjects with T2DM who were not adequately controlled by metformin monotherapy at a dose of ≥ 1000 mg/day. The subjects received either placebo or teneligliptin in different doses (5 mg, 10 mg, 20 mg, or 40 mg) for a duration of 24 weeks over and above metformin therapy.	At the end of the treatment, teneligliptin (at different doses) led to a significant reduction in HbA1c (from -0.30 to -0.63%, $p =0.003$ for 5 mg dose and <0.001 for all other doses) in a dose dependent manner (with maximum reduction observed at a dose of 40 mg i.e., -0.63 %, $p<0.001$). Also, a dose-dependent trend was observed in increase in proportion of T2DM subjects achieving glycemic control (HbA1c < 7.0%). Teneligliptin therapy at different doses, was found to be well tolerated even at 52 weeks and the and the overall incidence of hypoglycemia was found to be 2.3%.

ADR= Adverse drug reactions, AE=Adverse event, FBG= Fasting blood glucose, HbA1c= glycosylated hemoglobin, LS= Least square, 95% CI= 95 percent confidence interval, T2DM= type 2 diabetes mellitus, 2-h PPG= 2- hour postprandial glucose