Research Article

Real-World Observational Study in Patients on Teneligliptin Therapy for the Management of Type 2 Diabetes Mellitus

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Abstract

Background: The rise in the burden of type 2 diabetes mellitus (T2DM) is causing global concern, especially in low-income countries. In addition, the American Diabetes Association recommends the use of DPP-4 inhibitors in combination with metformin. However, no studies using teneligliptin with or without metformin have been conducted in Iraqi patients with T2DM. **Objective:** To investigate the effects of teneligliptin in glycaemic control in patients with type 2 diabetes mellitus (T2DM) in Iraq. **Methods:** This was an open-label, multicentric, prospective, observational, post-marketing surveillance, single-arm study to observe the effect of teneligliptin monotherapy (Tiban®) and fixed-dose combination (FDC) with metformin (Tiban® M) on glycaemic control in real-world settings in Iraq. Patients aged ≥18 years diagnosed with T2DM with glycosylated haemoglobin (HbA1c) ≥6.5%, were included in the study. **Results:** A statistically significant reduction (p<0.0001) was observed in HbA1c, FBG and PPG at the end of 3 months. Change from baseline in PPG was statistically significant (p=0.029) among all age groups, with the greatest change in middle-aged patients. There was no statistically significant change from the baseline values for HbA1c and FBG among different age group patients. In addition, there was no statistically significant difference from baseline HbA1c, FBG and PPG amongst patients in different BMI (Body mass index) groups. Nineteen adverse events were noted in 15 patients during the study. Seventeen events were mild, and two were moderate. No serious adverse events were reported in the patients included in this study. **Conclusion:** Teneligliptin is effective, safe, and well-tolerated in managing T2DM in Iraqi patients≥18 years.

Keywords: Diabetes, Fasting blood glucose, Glycosylated haemoglobin, Hyperglycaemia, Metformin, Teneligliptin

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C o n t e n t s

1. Introduction

The rise in the burden of type 2 diabetes mellitus (T2DM) is causing globalconcern, especially in low-income countries. About 10.5% (536.6million) of the global population were affected with diabetes in the year 2021[1]. The diabetes prevalence worldwide is projected to reach 11.3% (643million) by 2030 and 12.2% (783million) by 2045. The prevalence of impaired glucose tolerance globally is estimated to reach 11.4% (730million) by 2045[1, 2]. The International Diabetes Federation estimated that the number of individuals with T2DM will double by 2030 in Middle East and North Africa (MENA) region. There are a total of 21 countries in MENA and Iraq is one of them. Out of 537 million diabetes patients in the world, 73 million are from MENA region, which is estimated to rise to 135.7 million by 2045 [3, 4].

T2DM is among the top ten primary causes of mortality, responsible for over one million deaths per year [1]. This condition is also associated with increased mortality due to cardiovascular disease, stroke, infections, chronic kidney disease, cancer, and chronic liver disease [5]. Dipeptidyl peptidase-4 (DPP-4) inhibitors belong to a class of medications that reduces blood glucose levels with low hypoglycaemia risk by enhancing insulin secretion and suppressing glucagon secretion. DPP-4 inhibitors act by increasing levels of endogenous intact glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Depending on the interaction with the DPP-4 binding subsites, DPP-4 inhibitors are classified into three subtypes, i.e., class 1, 2 and 3 [6].

The American Diabetes Association recommends the use of DPP-4 inhibitors in combination with metformin as the second line of treatment if target HbA1cis not achieved after metformin therapy for approximately three months. However, the second line of treatment choice depends upon various patient, disease and drug characteristics [7].Teneligliptin, a selective, potent, and long-lasting class 3 DPP-4 inhibitor with a half-life of approximately 24 h and unique pharmacokinetic properties, is a class 3 DPP-4 inhibitor. It is metabolized by cytochrome P450 (CYP) 3A4 and flavin-containing monooxygenase 3 (FMO3).

Teneligliptin gets excreted from the kidney in an unchanged form and has a very low potential for interaction with concomitantly administered drugs. Dose adjustment is not required in individuals with hepatic or renal impairment as teneligliptin has multiple elimination pathways. Also, teneligliptin can be used in elderly patients with diabetes [6, 7]. Diet and exercise, along with teneligliptin, are recommended to manage T2DM properly. It is safe, well tolerated, and efficacious in diabetes, as monotherapy and in combination with several other antidiabetic agents, such as metformin, glimepiride, pioglitazone, and insulin, in 12 weeks and 52 weeks studies. In the published literature, teneligliptin demonstrated glycosylated haemoglobin (HbA1c) reduction of 0.8%-0.9% within 12 weeks of treatment [8].

A study in 60 patients and compared the efficacy of teneligliptin and metformin combination to glimepiride and metformin combination. Change in FBG (Fasting blood glucose), PPG (Postprandial glucose), HbA1c and lipid profile was higher when teneligliptin was combined with metformin as compared to glimepiride and metformin therapy[9]. A systematic review and meta-analysis of 10 randomised trials including 2119 patients, indicated that teneligliptin produces a statistically significant reduction in FBG, PPG and HbA1c (p<0.00001 for each) as compared to placebo. However, there was no significant difference in the rate of adverse events. Therefore, teneligliptin can be used to improve the glucose levels in the blood with low hypoglycaemia risk in T2DM [10]. In addition to the above-mentioned studies, numerous previously published studies of teneligliptin as a monotherapy or in combination with metformin conducted elsewhere showed that both the treatments resulted in improved glucose control and are tolerable [11-14]. However, no studies using teneligliptin with or without metformin have been conducted in Iraqi patients with T2DM. Thus, we conducted an observational

study in real-world settings to evaluate the efficacy and safety in adult patients with T2DM who are on teneligliptin monotherapy or in combination therapy with metformin.

2. Methodology

Study design: This was an open-label, multicentric, prospective, observational, post-marketing surveillance, single-arm study to observe the effect of teneligliptin monotherapy (Tiban®) and fixed-dose combination (FDC) with metformin (Tiban M®) on glycaemic control in real-world settings in Iraq. The study design is demonstrated in Figure 1 below
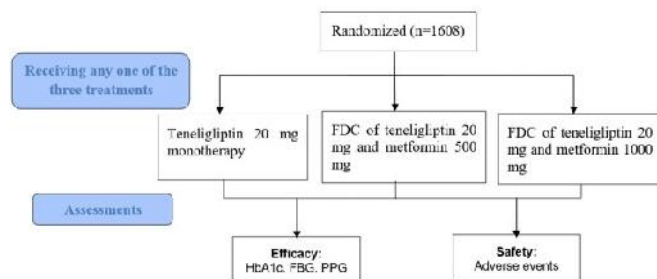

Figure 1: Study Design

FDC: Fixed dose combination; FBG: Fasting blood glucose; HbA1c: Glycosylated haemoglobin; N: Number of patients; PPG: Postprandial glucose

Patients: A total of 1608 patients per group were chosen for this study. The study was conducted in compliance with the Declaration of Helsinki and in compliance with local guidelines.

Inclusion criteria:
Patients aged 18 years and older diagnosed with T2DM with HbA1c ≥6.5% were included in the study. Patients taking teneligliptin 20 mg monotherapy, FDC of teneligliptin 20 mg and metformin 500 mg or FDC of teneligliptin 20 mg and metformin 1000 mg once daily before meals for the management of their diabetes were included in the study.

Exclusion criteria:
Patients with type 1 diabetes, severe diabetic complications (e.g., ketoacidosis), severe liver dysfunction, and hypersensitivity to the study medications were excluded. In addition, patients who were pregnant, lactating, or considered inappropriate based on the investigator's discretion were also excluded from the study.

Study endpoints: Primary efficacy endpoints of this study were change from baseline in HbA1c, fasting blood glucose

(FBG), and postprandial glucose (PPG) at the end of three months. Secondary safety endpoints were tolerance to the study drugs, including hypoglycaemia episodes during the study period.

Statistical analysis
Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Software, version 23 for MS Windows. The two groups were compared using Student's t-test for independent samples. Comparison within the treatment group was conducted using repeated measure ANOVA followed by paired t-test as a post hoc two-group comparison. A p-value less than 0.05 was considered statistically significant.

3. Results and Discussion

Demographic Characteristics
A total of 1608 adult male (n=918) and female (n=690) patients aged 20 to 98 years were included in the study. The baseline demographics of patients are demonstrated in Table 1.

Table 1: Baseline Demographics of the Study Participants

Baseline Demographics	Mean (N=1608)	Standard Deviation
Age (years)	53.447	11.3803
Weight (kg)	83.042	14.7817
Height (cm)	165.502	11.8605
Body mass index (kg/m^2)	29.87843	6.384982

N: Number of patients

Efficacy Results
The mean HbA1c (%) ± standard deviation (SD), FBG (mg/dL) ± SD and PPG (mg/dL) ± SD of patients at baseline was 8.935 ± 1.9130, 185.857 ± 60.4486 and 235.531 ±86.2229, respectively. Using a paired t-test, a statistically significant reduction (p<0.0001) was observed in HbA1c, FBG and PPG at the end of 3 months (Table 2,Figure 2). At three months, there was a total of 1061 (66%) and 547 (34%) patients with HbA1c more than and less than 6.5%, respectively. Change from baseline in PPG was statistically significant (p=0.029) among all age groups, with the greatest change in middle-aged patients and lowest in elderly patients. There was no statistically significant difference in change from baseline in HbA1c and FBG among different age group patients in the study. The change in glycaemic parameters from baseline for different age groups was assessed using an ANOVA test (Table 3).

Table 2: Mean Glycaemic Parameters at Baseline and Three Months

Glycaemic parameters	Mean (N=1608)	SD	SEM	t-value	p-value
HbA1c (%) at Baseline	8.935	1.9130	0.0477	72.6459	<0.0001
HbA1c (%) at 3 months	7.151	1.4649	0.0365		
FBG (mg/dL) at Baseline	185.857	60.4486	1.5075	54.11676	<0.0001

Glycaemic parameters	Mean (N=1608)	SD	SEM	t-value	p-value
FBG (mg/dL) at 3 months	132.348	41.6849	1.0395		
PPG (mg/dL) at Baseline	235.531	86.2229	2.1502	55.61745	<0.0001
PPG (mg/dL) at 3 months	154.251	54.5342	1.3600		

FBG: Fasting blood glucose; HbA1c: Glycosylated haemoglobin; N: Number of patients; PPG: Postprandial glucose; SD: Standard deviation; SEM: Standard error of Mean.

A significantly greater change from baseline to 3 months in PPG was observed in women compared to men. The change in glycaemic parameters from baseline for different sex (male and female) was assessed using a two-sample t-test (Table 4).

Table 3: Change from Baseline in Glycaemic Parameters Based on age Group

Change From Baseline in Glycaemic Parameters		N	Mean	SD	SEM	F-value	p-value
HbA1c (%)	**Young adults**	494	1.7241	0.92515	0.04162	2.193	0.112
	Middle-aged	806	1.8344	1.02266	0.03602		
	Elderly	308	1.7468	0.97149	0.05536		
FBG (mg/dL)	**Young adults**	494	52.7692	39.25073	1.76597	1.283	0.277
	Middle-aged	806	54.9553	42.28561	1.48945		
	Elderly group	308	50.9123	32.45717	1.84942		
PPG (mg/dL)	**Young adults**	494	78.2692	55.62915	2.50287	3.560	0.029
	Middle-aged	806	85.0943	62.14302	2.18889		
	Elderly	308	76.1299	52.93259	3.01611		

FBG: Fasting blood glucose; HbA1c: Glycosylated haemoglobin; N: Number of patients; PPG: Postprandial glucose; SD: Standard deviation; SEM: Standard error of Mean.

Table 4: Change from Baseline in Glycaemic parameters in Male and Female Patients Included in the Study

Change From Baseline in Glycaemic parameters	Sex	N	Mean	SD	SEM	t-value	p-value
HbA1c (%)	Male	918	1.7899	0.98009	0.03235	0.289	0.772
	Female	690	1.7755	0.99119	0.03773		
FBG (mg/dL)	Male	918	54.0218	39.17527	1.29298	0.598	0.55
	Female	690	52.8275	40.29082	1.53385		
PPG (mg/dL)	Male	918	73.4597	60.04008	1.98162	-6.245	<0.0001
	Female	690	91.6855	54.97635	2.09291		

FBG: Fasting blood glucose; HbA1c: Glycosylated haemoglobin; N: Number of patients; PPG: Postprandial glucose; SD: Standard deviation; SEM: Standard error of Mean: Standard error.

There was no statistically significant difference in change from baseline in HbA1c, FBG and PPG amongst patients in different BMI groups in the study; the change in glycaemic parameters from baseline was assessed using the ANOVA test (Table 5).

Table 5: Change from Baseline in Glycaemic parameters in Patients from Different BMI Groups Included in the Study

Change From Baseline in Glycaemic parameters		N	Mean	SD	SEM
HbA1c (%)	Severely underweight	1	0.6000	-	-
	Underweight	1	1.9000	-	-
	Normal weight	281	1.7982	1.01849	0.06076
	Overweight	626	1.7896	0.99514	0.03977
	Obesity class I	431	1.7487	0.92753	0.04468

	Obesity class II	163	1.8681	1.07328	0.08407
	Obesity class III	105	1.7324	0.92221	0.09000
PPG (mg/dL)	Severely underweight	1	10.0000	-	-
	Underweight	1	82.0000	-	-
	Normal weight	281	84.7011	58.44518	3.48655
	Overweight	626	80.5224	57.58961	2.30174
	Obesity class I	431	77.9791	55.70489	2.68321
	Obesity class II	163	81.4233	65.89937	5.16164
	Obesity class III	105	90.6476	64.23664	6.26885
FBG (mg/dL)	Severely underweight	1	21.0000	-	-
	Underweight	1	19.0000	-	-
	Normal weight	281	54.6868	36.84022	2.19770
	Overweight	626	55.0735	39.10909	1.56311
	Obesity class I	431	51.0835	38.88591	1.87307
	Obesity class II	163	52.8160	41.51844	3.25198
	Obesity class III	105	52.7048	49.42864	4.82374

BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Glycosylated haemoglobin; N: Number of patients; PPG: Postprandial glucose; SD: Standard deviation; SEM: Standard error of Mean; Note: SD and SE are not applicable when the group has only one patient.

BMI (kg/m^2) values for different groups: Severely underweight< 16.5; Underweight: 16.5-18.5; Normal weight: 18.5-24.9; Overweight: 25.0-29.9; Obesity class I: 30.0-34.9; Obesity class II: 35.0-39.9; Obesity class III: >40.0.[13]

Safety results

Nineteen adverse events were noted in 15 patients during the study. The adverse events experienced during the study included dyspepsia (seven events in six patients); gastrointestinal upset (four events in four patients); hypoglycaemia(two events in two patients); flatulence, pharyngitis, headache, epigastric pain, uncontrolled blood sugar and hunger (one event in one patient each).One event of dyspepsia and one event of epigastric pain were moderate. All the other events were mild. There were no serious adverse events observed in this study.

Discussion

A statistically significant reduction (p<0.0001) was observed in HbA1c, FBG, and PPG at the end of 3 months. Change from baseline in PPG was statistically significant (p=0.029) among all age groups, with the greatest change in middle-aged patients. A significantly greater change from baseline to 3 months in PPG was observed in women compared to men. There was no statistically significant change from baseline in HbA1c, FBG and PPG amongst patients in different BMI groups in the study. Nineteen adverse events were noted in 15 patients during the study. Seventeen events were mild, and two were moderate. There were no serious adverse events observed in this study.

Several clinical studies have evaluated the safety and efficacy of teneligliptin as a monotherapy or in combination with metformin. Hans N, 2019, conducted a study on 60 patients with T2DM uncontrolled with monotherapy. These patients were administered a daily dose of either teneligliptin 10 mg and metformin 1000 mg or glimepiride 1 mg and metformin 1000 mg for 12 weeks. The metformin dose was up-titrated to a maximum of 2000 mg/day based on glycaemic control. HbA1c and lipid profile were assessed at baseline and end of 12 weeks. There was a highly statistically significant difference in FBG (p<0.001), PPG (p<0.001), HbA1c (p<0.05) and total cholesterol (p<0.001), serum low-density lipoprotein cholesterol (p<0.001) and serum triglycerides (p<0.001) in the teneligliptin and metformin arm as compared to glimepiride and metformin arm. The difference in HDL between both arms was not statistically significant (p>0.05). This study concluded teneligliptin is more efficacious than glimepiride in managing T2DM[9].

A systematic review and meta-analysis analyzed ten clinical studies with a minimum of 4 weeks of teneligliptin therapy versus placebo in 2119 patients with T2DM. Teneligliptin therapy led to an absolute reduction in HbA1c compared to placebo (weighted mean difference 0.82%, p<0.00001). Teneligliptin therapy led to a higher reduction in FBG as compared to placebo (-18.32% versus -15.60%, p<0.00001); the reduction in PPG was also significant (p<0.00001) in the teneligliptin group as compared to the placebo group. Teneligliptin-treated patients achieved homeostasis model assessment of β cell function with 9.31 (p<0.00001). However, there was no significant difference in the rate of occurrence of adverse events, including the incidence of hypoglycaemia [10].

A retrospective observational study conducted in a diabetes clinic in India in patients with T2DM treated with

tenelgliptin 40 mg as an add-on to exercise, dietary modifications and maximal tolerable metformin dose for three months demonstrated a significant reduction in HbA1c (p≤0.001), PPG (p≤0.001) and FBG (p≤0.001). There was no significant reduction in body mass index from baseline to the end of 3 months. Treatment with tenelgliptin 40 mg and maximal tolerable metformin dose led to a borderline change in albumin to creatinine ratio and a statistically insignificant change in mean corrected QT interval [11].

A pooled analysis to evaluate the efficacy and safety of tenelgliptin 40 mg in patients with T2DM was conducted by Kadowaki T et al.,. In both the studies included in this pooled analysis, the dose was up-titrated from tenelgliptin 20 mg to 40 mg after 28 weeks of treatment. Of the total patients (n=204), 52.9% patients demonstrated response (HbA1c reduction of 0.5%) to tenelgliptin 40 mg during 28 to 52 weeks. There was no change in the incidence of adverse events after up-titration. Tenelgliptin 40 mg was safe and effective in the management of T2DM [12].

Bryson A et al., conducted a study in 447 patients underwent randomized double-blind treatment with 5, 10, 20, or 40 mg of tenelgliptin or a placebo once daily for 24 weeks after completing a 14-day screening and 14-day run-in phase. Tenelgliptin 20 mg once daily was administered to 364 patients throughout a 28-week open-label extension of the current course of therapy. Patients with T2DM who received tenelgliptin and metformin together saw significant drops in their HbA1c levels without seeing an increase in hypoglycemia risk (Bryson et al., 2016). In our current study also significant reduction (p<0.0001) was observed in HbA1c, FBG and PPG at the end of 3 months [13].

Chatterjee AK, 2018, retrospectively assessed the database, including patients with T2DM who were treated with tenelgliptin 20 mg/day as an add-on to an oral antidiabetic (OAD) agent or insulin. A significant change in glycaemic parameters, i.e., HbA1c (P<0.001), FBG (P<0.001) and PPG (P<0.001), was noted; a significant reduction was observed in patients with tenelgliptin as add-on therapy. After 12 week of treatment, 12.5% patients achieved HbA1c of <7% (P=0.004).In patients inadequately uncontrolled with either OADs or insulin monotherapy, tenelgliptin add-on led to a significant reduction in glycaemic parameters post-treatment for 12 weeks[14].

The published literature is in-line with the results of our observational study indicating the effectiveness and safety of tenelgliptin monotherapy as well as an add-on to metformin. Therefore, Tiban® and Tiban M® can be useful for managing T2DM in Iraqi patients.
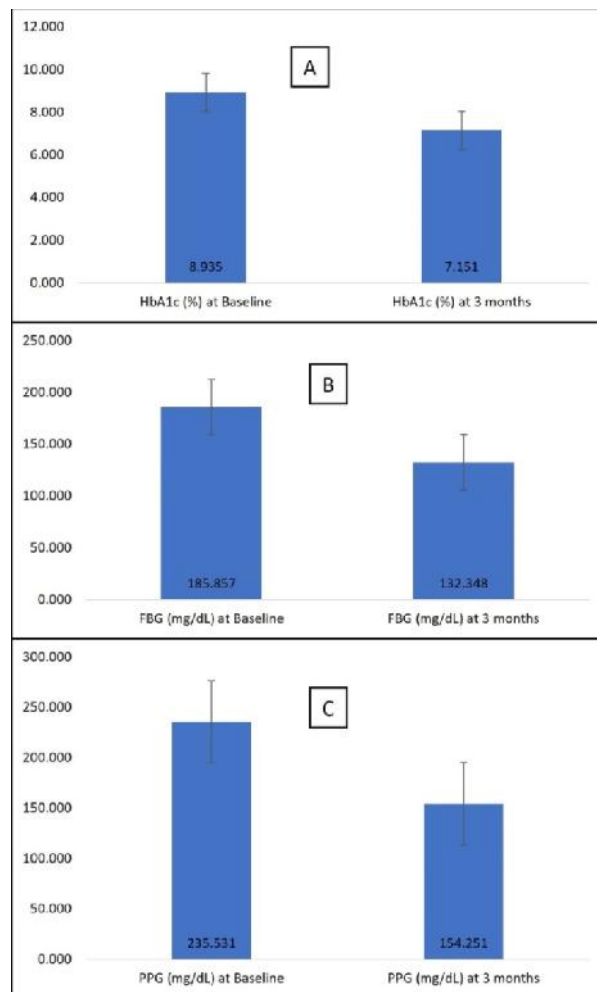

Figure 2: Mean Glycaemic Parameters (A: HbA1c; B: FBG; C: PPG) at Baseline and Three Months

4. Conclusion

Tenelgliptin, as monotherapy as well as in combination with metformin, demonstrated to be effective, safe, and well-tolerated in the management of T2DM in adult Iraqi patients of all age groups. Therefore, the results in Iraqi patients are similar to non-Iraqi patients indiacting that regional and ethnic differences have no impact in the effectiveness and safety of tenelgliptin and metformin in T2DM patients.

Conflicts of interest
Two authors in the manuscript Dr Shalini Kumar and Nitin Shelar belong to the same organization, Ajanta Pharma Limited, India.

Author contribution
All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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