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To Assess the Efficacy and Safety of Fixed-Dose Combination of Teneligliptin and Pioglitazone (Tiban P) in Iraqi Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To assess the efficacy and safety of combination of teneligliptin and pioglitazone on glycemic control in patients with type 2 diabetes mellitus (T2DM) in real-world settings in Iraq. **Methods:** This was a 3-month, prospective - post-marketing surveillance study to observe the efficacy and safety of dual-drug fixed-dose combination (FDC) of teneligliptin 20 mg and pioglitazone 15 mg (treatment 1 – Tiban P) and teneligliptin 20 mg and pioglitazone 30 mg (treatment 2 – Tiban P) in patients with T2DM in real-world settings in Iraq. Inclusion criteria for patients were –age ≥18 years, diagnosed with T2DM with glycated hemoglobin (HbA1c) ≥ 6.5%, agreed to provide informed consent, and had been prescribed FDC of teneligliptin 20 mg and pioglitazone 15 mg or teneligliptin 20 mg and pioglitazone 30 mg once daily for the management of T2DM. The study exclusion criteria were –patients with type 1 diabetes, severe diabetic complications, severe liver dysfunction, hypersensitivity to any ingredient of the study medications, and those who were pregnant, lactating, or considered ineligible based on the doctor's opinion. **Results:** A statistically significant reduction ($p<0.0001$) was observed in HbA1c, fasting blood glucose, and postprandial blood glucose in patients with diabetes being treated with FDC of pioglitazone + teneligliptin. Twelve adverse events (AEs) were noted in 12 patients during the study. No serious AEs or hypoglycemia events were reported in this study. **Conclusion:** Teneligliptin and pioglitazone combination is effective and safe in managing T2DM in adult Iraqi patients.

Keywords: Diabetes, Fasting blood glucose, Glycated hemoglobin, Pioglitazone, Teneligliptin

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C O N T E N T S

1. Introduction

Type 2 diabetes mellitus (T2DM) stands as the predominant form of diabetes worldwide, comprising over 90% of all cases. Its prevalence is markedly high and rising across the globe. This surge is propelled by factors such as population aging, economic advancement, and burgeoning urbanization, all of which foster a sedentary lifestyle and increased consumption of unhealthy foods associated with obesity.[1]

A comprehensive local investigation including over 5,400 individuals within the city of Basrah, Southern Iraq, revealed a 19.7% age-adjusted prevalence of diabetes among participants aged 19 to 94 years. The dearth of epidemiological studies and randomized controlled trials (RCTs) for diabetes in Iraq presents a challenge in gauging the prevalence of diabetes within the country and determining therapeutic approaches tailored to the Iraqi population.[2] According to the International Diabetes Federation (IDF) 2021 report, Iraq registered 2,011,400 adults aged 20 to 79 years living with diabetes, equating to a prevalence of 9.4%. Moreover, IDF data indicate that 946,400 adults in Iraq remain undiagnosed for diabetes.[1]

As per IDF 2021 report, by 2045, 94% of new diabetes cases will occur in low- and middle-income countries, which are expected to experience a substantial population growth. In 2021, the Middle East and North Africa (MENA) region displayed the highest prevalence of diabetes among individuals aged 20 to 79 years, standing at 18.1%. This figure is expected to rise, with the MENA region maintaining its position as the area with the highest comparative prevalence by 2045, reaching 20.4%.[1]

The management of T2DM involves adopting lifestyle changes alongside pharmacological interventions. Ideally, these interventions should meet the criteria of being effective, long-lasting, safe, and cost-efficient.[3] Dipeptidyl peptidase-4 inhibitors (DPP-4Is), commonly referred to as "gliptins," represent a relatively new class of drugs used widely in T2DM management. While all DPP-4Is share the same mechanism of action, individual gliptins may vary in their pharmacokinetic properties, pharmacodynamic effects and potency. Teneligliptin, classified as a class 3 DPP-4I, has a unique structure that enhances its potency and selectivity. Consequently, it exhibits an approximately five-fold higher activity compared to other gliptins, resulting in more extensive inhibition of DPP-4s.[3] About 34% of the teneligliptin dose is excreted unchanged through the kidneys and has minimal potential to interact with concomitant medications. Due to its multiple elimination pathways, dose adjustments are not necessary for individuals with renal and hepatic impairment. Furthermore, it is safe for use in elderly patients with T2DM.[4-6]

Li et al, 2018, conducted a systematic review and meta-analysis of 10 RCTs encompassing 2,119 patients. The baseline mean glycated haemoglobin (HbA1c) and baseline mean fasting blood glucose (FBG) in the studies included in this analysis were between 7% to 9% and 145 mg/dL to 165 mg/dL, respectively. The study revealed that teneligliptin induces a statistically significant reduction in FBG, postprandial blood glucose (PPBG), and HbA1c levels ($p<0.00001$ for each) in comparison to placebo. There was no notable distinction in the incidence of adverse events (AEs). Consequently, teneligliptin emerges as a useful treatment for improving blood glucose levels in patients with T2DM with a minimal risk of hypoglycemia.[6]

Thiazolidinediones, another unique class of antidiabetic medications, primarily serve as insulin sensitizers within peripheral and hepatic tissues by binding to and activating nuclear peroxisome proliferator-activated receptor γ expressed in those regions.[7] Pioglitazone, a thiazolidinedione, demonstrates swift absorption, achieving peak plasma concentrations within 2 to 4 hours. It is recommended as a second or third-line treatment option for T2DM.[8] In addition to its well-documented efficacy in reducing HbA1c levels, treatment with pioglitazone stands out for the rare occurrence of hypoglycemic events. Moreover, clinical evidence supports its role in reducing triglyceride levels, thereby mitigating cardiovascular risks in patients diagnosed with T2DM.[9]

As per the Iraqi Experts Consensus on the management of T2DM, the glycemic targets were HbA1c<7% (53 mmol/mol), FBG 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and 2-hour PPBG <180 mg/dL (9.9 mmol/L).[2] Data from a study published in 2022 revealed that in a prospective randomized, double-blind, comparative, parallel-group multicenter study, there was a significantly superior improvement ($p<0.0001$ for each) in HbA1c, FBG, and PPBG levels when patients with T2DM were treated with a fixed-dose combination (FDC) of teneligliptin and pioglitazone compared to monotherapy with

teneligliptin or pioglitazone. Additionally, the target HbA1c of <7% laid down by the Iraqi Experts Consensus was met by a higher proportion of patients in the FDC groups by week 24 as compared to patients in the monotherapy groups.[2,10]
Therefore, we conducted an observational study in real-world settings to assess the glycemic parameters of Iraqi adult patients with T2DM who prescribed FDC therapy with teneligliptin and pioglitazone were.

2.Materials and methods

Study design

This was a3-month, prospective, post-marketing surveillance study to observe the efficacy and safety of dual-drug FDC of teneligliptin 20 mg and pioglitazone 15 mg (treatment 1 –Tiban P) and teneligliptin 20 mg and pioglitazone 30 mg (treatment 2 –Tiban P) in patients with T2DM in real-world settings in Iraq. The study design is demonstrated in Figure 1.

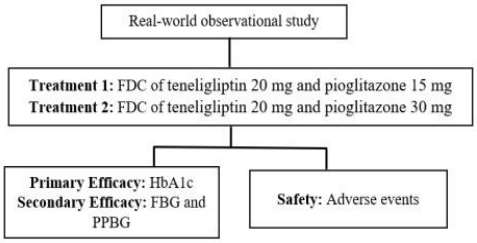

Figure 1:Study Design

FBG: fasting blood glucose; **FDC**: fixed-dose combination; **HbA1c**: glycated hemoglobin; **PPBG**: postprandial blood glucose

Study population

A total of 1,192 patients were included in this study.

Inclusion criteria

Patients aged 18 years and older, with T2DM with an HbA1c ≥6.5%, who agreed to provide informed consent, and were prescribed FDC of teneligliptin 20 mg and pioglitazone 15 mg or FDC of teneligliptin 20 mg and pioglitazone 30 mg once daily for T2DM management were included in the study.

Exclusion criteria

Patients with type 1 diabetes, severe diabetic complications (e.g., ketoacidosis), severe liver dysfunction, or hypersensitivity to any ingredient of the study medications were excluded. In addition, patients who were pregnant, lactating, planning a pregnancy or considered ineligible based on the doctor's opinion were also excluded from the study.

Study endpoints

The primary efficacy endpoint of this study was a change in HbA1c from baseline to end of 3 months. Secondary efficacy endpoints were changes in FBG and PPBG from baseline to end of 3 months. The safety endpoints were intolerance to study drugs, including hypoglycemia episodes and adverse drug reactions (ADRs) during the study period. Adverse drug reactions were defined as AEs for which the causal relationship with FDC of teneligliptin and pioglitazone was assessed as definite or probable or for which a causal relationship with the FDC drugs could not be excluded by the doctor.
Observational points were at baseline and end of 3 months.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Software, version 23 for MS Windows. Comparison from baseline to end of three months was conducted using paired t-test. A p-value less than 0.05 was considered statistically significant.

3. Results and discussion

Overall, data from 1,192 adult patients with T2DM [704 men (59.1%) and 488 women (40.9%)] were included in the analysis. The baseline demographics of the patients are seen in Table 1.

The results from fitting the data to these models are detailed in Table 4. The analysis indicated that the drug release behavior from the formulated buccal patches of atenolol best followed the Higuchi model, with a correlation coefficient of R^2=0.989.

Primary efficacy results

Overall, the mean difference in HbA1c from baseline to end of 3 months was 1.45%. Thus, teneligliptin and pioglitazone combination demonstrated a statistically significant improvement in HbA1c from baseline to end of 3 months (p<0.0001) (Table 2 and Figure 2).

In patients administered treatment 1, the mean difference in HbA1c from baseline to end of 3 months was 1.12% and in patients administered treatment 2, it was 1.75%. Both the treatments demonstrated statistically significant improvement in HbA1c from baseline to end of 3 months (p<0.0001, each) (Tables 3 and 4).

Secondary efficacy results

Overall, the mean difference in FBG and PPBG from baseline to end of 3 months was 79.22 mg/dL and 104.08 mg/dL, respectively. Teneligliptin and pioglitazone combination demonstrated a statistically significant improvement in both FBG and PPBG from baseline to end of 3 months (p<0.0001, each) (Table 2 and Figure 3).

Each treatment group (on lower as well as higher dose of pioglitazone) demonstrated statistically significant improvement in FBG and PPBG as well, from baseline to end of 3 months. Patients taking treatment 1 demonstrated a mean difference of 69.58 mg/dL and 97.23 mg/dL in FBG and PPBG, respectively (p<0.0001, each). Patients taking treatment 2 demonstrated a mean difference of 86.75 mg/dL and 109.40 mg/dL in FBG and PPBG, respectively (p<0.0001, each) (Tables 3 and 4).

In addition, at the end of 3 months, a statistically significant improvement in FBG levels of patients taking treatment 2 was noted as compared to treatment 1 (p=0.0000). However, there was no statistically significant difference in HbA1c and PPBG improvement in patients taking the two treatments.

Safety results

Twelve AEs were noted in 12 patients (five women and seven men) during the study. The AEs experienced during the study included hypotension (one event each in two

patients), gastrointestinal upset (one event each in four patients), headache (one event in one patient), and leg swelling, sinusitis, visual disturbances, insomnia, and skin rash (one event in one patient each). No serious AEs were observed. No hypoglycemia event was reported during the study.

Discussion

Irrespective of the dose of the FDC, a statistically significant reduction ($p<0.0001$) from baseline was observed in mean HbA1c, mean FBG and mean PPBG at the end of 3 months. When glycemic parameters of patients on treatments 1 and 2 were analyzed individually, both treatment groups demonstrated a statistically significant improvement in HbA1c, FBG and PPBG ($p<0.0001$, each) from baseline to end of three months. Patients taking treatment 2 showed a greater improvement in glycemic parameters, including HbA1c, FBG and PPBG than patients taking treatment 1, which could be attributed to the higher dose of pioglitazone in treatment 2. Twelve AEs were noted in 12 patients during the study. There were no serious AEs observed in this study.

Clinical studies have evaluated the efficacy and safety of teneligliptin and pioglitazone as monotherapies or in combination and have indicated the importance of the use of the drugs in managing various glycemic parameters, including HbA1c, FBG and PPBG.

Rao AG et al., in 2022, conducted a phase 3 randomized double blind comparative study to evaluate the safety and efficacy of FDCs of teneligliptin 20 mg + pioglitazone 15 mg tablets and teneligliptin 20 mg + pioglitazone 30 mg tablets versus their respective monotherapies, i.e., teneligliptin 20 mg and pioglitazone 30 mg, in patients with T2DM inadequately controlled with metformin therapy. The primary outcome –HbA1c demonstrated a notably greater change in the FDC groups compared to the monotherapy groups, both at weeks 12 and 24 ($p<0.0001$). Similarly, FBG and PPBG exhibited significantly greater changes in the FDC groups compared to monotherapies ($p<0.0001$). A higher mean change in HbA1c, FBG and PPBG was noted in the FDC group with a higher dose of pioglitazone, as compared to the FDC group with a lower dose of pioglitazone, which is in-line with our current observational study. Additionally, by week 24, a higher proportion of patients in the FDC groups achieved HbA1c levels <7% compared to those in the monotherapy groups. Hypoglycemic episodes occurred in 3.48% of cases on dual therapy, while only 1.74% were observed in patients on pioglitazone monotherapy, all of which were mild in severity and resolved by the end of the study. The study concluded that FDC of teneligliptin and pioglitazone has superior and significant control on glycemic parameters as compared to respective monotherapies.[10]

In a 2013 study, Kadowaki T and Kondo K investigated the efficacy and safety of combining teneligliptin with pioglitazone in Japanese patients with T2DM. Over a 12-week initial phase, 204 patients were randomly assigned to receive either teneligliptin 20 mg or placebo once daily alongside their stable pioglitazone therapy. This phase was followed by a 40-week open-label period where all patients received teneligliptin once daily.

Results revealed that patients in the teneligliptin group experienced significantly greater reductions in HbA1c levels compared to the placebo group at week 12 ($p<0.001$). The mean changes in HbA1c from baseline to week 12 were $-0.9 \pm 0.0\%$ in the teneligliptin group and $-0.2 \pm 0.0\%$ in the placebo group. Moreover, the reduction in FBG levels from baseline to week 12 was more pronounced in the teneligliptin group. These blood sugar-lowering effects of teneligliptin were sustained throughout the 40-week open-label period. Although AEs and ADRs were slightly more common in the teneligliptin group, the incidence of hypoglycemia was low.[11]

Wang B et al., 2018, conducted a meta-analysis, in which seven RCTs were analyzed to compare the efficacy and safety of DPP-4I and pioglitazone combination therapy with pioglitazone monotherapy in T2DM patients. When compared to using pioglitazone alone, the combined therapy of a DPP-4I and pioglitazone showed a notable increase in the reduction of HbA1c (mean difference -0.64%) and FBG levels (mean difference -0.94). Additionally, a greater proportion of patients in the combination therapy groups achieved an HbA1c level <7% at the end of the studies (odds ratio 2.52) compared to those in the pioglitazone monotherapy groups. However, this combination therapy did not lead to a further reduction in the risk of hypoglycemia, edema, or other AEs. Furthermore, it was observed that combined therapy of a DPP-4I and pioglitazone was linked to enhanced improvement in pancreatic β-cell function.[12] The published literature is in-line with the results of our observational study, indicating the effectiveness and safety of FDC of teneligliptin and pioglitazone. Therefore, Tiban P, an FDC of teneligliptin and pioglitazone can be considered useful for managing T2DM in Iraqi patients.

Strengths and limitations:

Patients undergoing monotherapy with teneligliptin or pioglitazone could also be included to obtain more details regarding the efficacy and necessity of dual-drug FDCs in patients with diabetes. In addition, not recording comorbidities might affect the results of glycemic control since other health conditions can impact diabetes management. However, the recording of comorbidities is patient-reported information in observational studies, and thus, it may have a recall bias.

4. Conclusion

The FDC of teneligliptin and pioglitazone has demonstrated efficacy, safety, and good tolerability in treating T2DM in adult Iraqi patients. These findings suggest that the outcomes observed in Iraqi patients are consistent with those reported in non-Iraqi populations, indicating that regional and ethnic variations do not significantly influence the efficacy and safety profile of teneligliptin and pioglitazone in managing T2DM.

Table 1: Baseline Demographics of the Study Population

Baseline Demographics	Mean ± SD (N=1,192)
Age (years)	54.53 ± 12.41
Weight (kg)	79.29 ± 12.53
Height (cm)	168.11 ± 8.61
BMI (kg/m^2)	28.12 ± 4.45

Demographics of the Study Population
BMI: body mass index; **N**: number of patients; **SD**: standard deviation

Table 2: Overall Mean Glycemic Parameters of Patients Taking FDC of Teneligliptin and Pioglitazone at Baseline and 3 Months

Glycemic Parameters	N	Mean	Mean difference	SD	SEM	t-value	p-value
HbA1c (%) at baseline	1192	9.14	1.45	1.60	0.05	30.0487	<0.0001
HbA1c (%) at end of 3 months	1192	7.69		0.10	0.01		
FBG (mg/dL) at baseline	924	229.91	79.22	80.69	2.69	37.5268	<0.0001
FBG (mg/dL) at end of 3 months	907	150.70		52.05	1.73		
PPBG (mg/dL) at baseline	797	291.25	104.08	100.80	3.65	37.2566	<0.0001
PPBG (mg/dL) at end of 3 months	771	187.18		56.61	2.04		

FBG: fasting blood glucose; **FDC:** fixed-dose combination; **HbA1c:** glycated hemoglobin; **N:** number of patients; **PPBG:** postprandial blood glucose; **SD:** standard deviation; **SEM:** standard error of mean; **Note:** Paired t-test was used to compare data between baseline and 3 months.

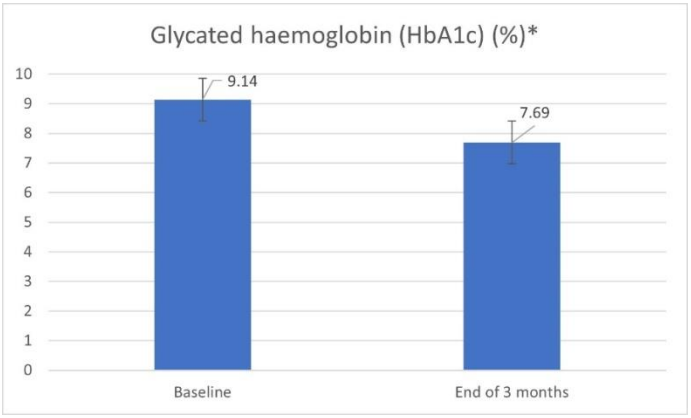

Figure 2: Overall Mean HbA1c at Baseline and End of 3 Months

*****p<0.0001 (from baseline to end of three months)

Table 3: Mean Glycemic Parameters of Group 1 (FDC of teneligliptin 20 mg and pioglitazone 15 mg) at Baseline and End of 3 Months

Glycemic parameters	Mean	SD	SEM	t-value	p-value
HbA1c (%) at baseline (n=548)	8.83	1.57	0.07	15.0363	<0.0001
HbA1c (%) at end of 3 months (n=548)	7.70	1.03	0.04		
FBG (mg/dL) at baseline (n=418)	210.2	69.33	3.45	24.9188	<0.0001

Glycemic parameters	Mean	SD	SEM	t-value	p-value
FBG (mg/dL) at end of 3 months (n=404)	140.69	38.94	1.94		
PPBG (mg/dL) at baseline (n=354)	281.37	102.01	5.56	23.0692	<0.0001
PPBG (mg/dL) at end of 3 months (n=337)	184.15	50.33	2.74		

FBG: fasting blood glucose; **FDC:** fixed-dose combination; **HbA1c:** glycated hemoglobin; **n:** number of patients; **PPBG:** postprandial blood glucose; **SD:** standard deviation; **SEM:** standard error of mean; **Note:** Paired t-test was used to compare baseline and 3-month data.

Table 4: Mean Glycemic Parameters of Group 2 (FDC of teneligliptin 20 mg and pioglitazone 30 mg) at Baseline and 3 Months

Glycemic parameters	Mean	SD	SEM	t-value	p-value
HbA1c (%) at baseline (n=619)	9.41	1.55	0.06	28.0406	<0.0001
HbA1c (%) at end of 3 months (n=619)	7.66	0.92	0.04		
FBG (mg/dL) at baseline (n=482)	246.49	86.45	3.95	27.4351	<0.0001
FBG (mg/dL) at end of 3 months (n=479)	159.75	59.56	2.72		
PPBG (mg/dL) at baseline (n=422)	298.14	100.27	4.93	28.2216	<0.0001
PPBG (mg/dL) at end of 3 months (n=413)	188.74	58.58	2.88		

FBG: fasting blood glucose; **FDC:** fixed-dose combination; **HbA1c:** glycated hemoglobin; **n:** number of patients; **PPBG:** postprandial blood glucose; **SD:** standard deviation; **SEM:** standard error of mean; **Note:** Paired t-test was used to compare data between baseline and 3 months.

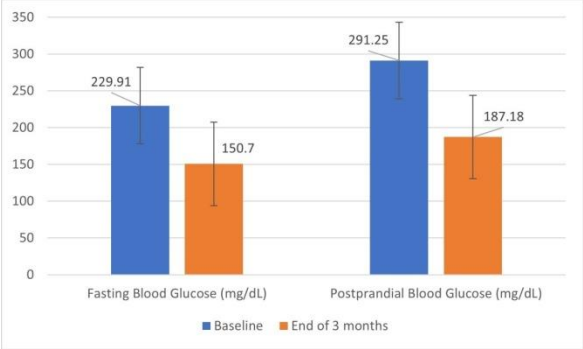

Figure 3: OverallMean Fasting and Postprandial Blood Glucose at Baseline and End of 3 Months

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