GLYCEMIC EFFECT OF FIXED DOSE COMBINATION OF TENELIGLIPTIN AND METFORMIN IN TYPE-2 DIABETES MELLITUS PATIENTS

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ABSTRACT

**Background:** Teneligliptin is a potent, long acting and highly selective third generation dipeptidyl peptidase-4 (DPP-4) inhibitor recently introduced in India. The main objective of present study was to evaluate the effect of Teneligliptin and Metformin fixed dose combination on glycemic parameters in the treatment of type-2 diabetes mellitus in India. **Material and Methods:** In this prospective observational study total 70 patients were screened and among them 40 patients were eligible to be enrolled in our study. Teneligliptin (20 mg/day) Metformin (500 mg) fixed dose combination was prescribed in patients with type-2 diabetes and changes in the glycemic parameters were observed at every 4 weeks for 16 weeks treatment which were compared with the baseline. Analysis was done using t-test and a p-value of <0.05 was considered significant. **Results:** There was statistically significant improvement in mean HbA1c, FBG, and PPBG with teneligliptin and metformin fixed dose therapy. The change in HbA1c level from baseline was −0.79% (7.9 to 7.1%) at 16 weeks of treatment. Percentage of patients achieving target HbA1C (≤7) was 37.5% at 16 weeks. Reduction was also significant (P<0.001) in FBG - 32.4mg/dl (149.8-117.4mg/dl) and 2h PPBG 54.3mg/dl (234-179.7mg/dl) at 16 weeks of treatment. There were no cases of hypoglycemia or weight gain reported in the present study. **Conclusions:** Teneligliptin and Metformin fixed dose combination showed significant improvement in all glycemic parameters and well tolerated at the end of the study period in patients with type-2 diabetes.

KEYWORDS: Teneligliptin, Diabetes Mellitus, DPP-4 inhibitor, HbA1c.

INTRODUCTION

Type-2 diabetes mellitus is one of the most common chronic and complex metabolic diseases, with its prevalence increasing worldwide. The pathophysiology is characterized by defective insulin secretion and increased insulin resistance resulting in impaired glucose tolerance and inappropriately high fasting hepatic glucose production. Available treatments focus on reducing hyperglycemia and improving insulin sensitivity.\(^{[1-2]}\)

The primary goal of treatment is to target glycemic control by maintaining the HbA1c level at 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia.\(^{[3]}\) Currently available antidiabetic agents work by different mechanisms to lower blood glucose levels. Unfortunately, each of them has its tolerability and safety concerns that limit its use and dose titration.

Oral hypoglycemic drugs with various mechanisms, such as enhancing the pancreatic function to secrete insulin; reducing insulin resistance of the body tissues or increasing glucagon-like peptide-1, have been developed and are currently in use.\(^{[4]}\)

Metformin (an oral hypoglycemic drug) acts mainly by reducing insulin resistance of the body tissue. However, monotherapy with this drug showed an inadequate glycemic control over time, eventually requiring a number of antidiabetic medications in combination.

The combination therapy of Metformin with Teneligliptin (DPP-4 inhibitor) has been recently in clinical practice. Hence, it was thought worthwhile to conduct the study to assess the efficacy of Teneligliptin and Metformin fixed dose combination in Indian type-2 diabetes mellitus (T2DM) patients.

Teneligliptin is a novel third generation DPP-4 inhibitor and it is approved for type-2 diabetes mellitus patients.\(^{[5]}\) It has a unique chemical structure which is...
characterized by five consecutive rings (J-shaped), which might account for its unique potency and long half-life and binds to S1, S2, and S22 extensive subsite of DPP-4 enzyme.[6-7] It is recommended once-a-day administration. DPP-4 enzyme inhibition occurs maximum within 2 hours and >50% inhibition has been noted at 24 hours, with no drug–drug interaction. Excretion of Teneligliptin metabolites is by dual mode i.e. hepatic (~35%) and renal (~65%) routes. Drug dosage adjustment is not necessary even in patients with renal impairment due to its long half-life and it helps in stabilizing the glycemic fluctuations throughout the day.[6,8-10]

Teneligliptin was introduced in India in May 2015 and is available at almost one quarter to one fifth of the cost of other DPP-4 inhibitors. In a very short span of time (8–9 months) teneligliptin has become the most widely prescribed DPP-4 inhibitor in India.[11] Efficacy and safety of teneligliptin has been established in Japanese and Korean populations in several randomized controlled trials with limited sample size.[6] In India the only data available are in a small phase III clinical trial.[12]

MATERIAL AND METHODS
A prospective observational study was conducted by department of pharmacology in collaboration with the department of internal medicine at Lala Lajpat Rai Hospital (LLR Hospital), GSVM Medical College, Kanpur, U.P. Over a period of twelve months commencing from March 2016 to February 2017. Total 70 patients attending diabetes OPD were screened and among them 40 patients were eligible for our study. Patients were included after getting written informed consent. The study was approved by Institutional Ethical Committee. The glycemic effect was assessed by analyzing the mean change in values of glycated hemoglobin (HbA1c), FBG, and PPBG from baseline following Teneligliptin and Metformin fixed dose combination therapy.

Effect on glycemic parameters
Table 1: Change in glycemic parameters from baseline to 16wk.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>16wk</th>
<th>Mean difference</th>
<th>t-value</th>
<th>p-value</th>
<th>Significance at p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dl)</td>
<td>149.8±28.9</td>
<td>117.4±14.1</td>
<td>32.4±19.3</td>
<td>10.6</td>
<td>&lt; 0.001</td>
<td>Significant</td>
</tr>
<tr>
<td>2h-PPBG (mg/dl)</td>
<td>234±57.7</td>
<td>179.7±38.9</td>
<td>54.3±25.8</td>
<td>13.2</td>
<td>&lt; 0.001</td>
<td>Significant</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9±0.5</td>
<td>7.1±0.4</td>
<td>0.79±0.3</td>
<td>16.8</td>
<td>&lt; 0.001</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Note 1 All values expressed as mean±SD;
Note 2 Data analyzed with paired t-test

Table 2: Progressive changes in FBG and PPBG with Treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 day</th>
<th>4wk</th>
<th>8wk</th>
<th>12wk</th>
<th>16wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>149.8±28.9</td>
<td>136.9±27.3</td>
<td>130.6±21.3</td>
<td>123.9±16.5</td>
<td>117.4±14.1</td>
</tr>
<tr>
<td>PPBG</td>
<td>234±57.7</td>
<td>214.4±60.3</td>
<td>203.9±47.2</td>
<td>189.2±43.9</td>
<td>179.7±38.9</td>
</tr>
</tbody>
</table>

Inclusion criteria
- Men and women with type-2 diabetes (30–70 years of age)
- HbA1c ≥ 6.5%.

Exclusion criteria
- Patients with type-1 diabetes
- Pre-existing renal impairment (Serum Creatinine ≥ 1.4 mg/dl for males or ≥1.2 mg/dl in females)
- Pregnant and lactating females.

The enrolled 40 patients were put on Metformin (500) + Teneligliptin (20 mg) daily. After start of therapy patients were followed at 4, 8, 12 and 16 weeks. Fasting Blood Glucose (FBG) & Postprandial Blood Glucose (PPBG) were measured at baseline and at every follow-up and glycosylated hemoglobin (HbA1c) was measured at 0 and 16 weeks.

Statistical Analysis
The data were expressed as mean±standard deviation. The means and frequencies of variables were evaluated using Student’s t-test and the χ² test, respectively. All p values less than 0.05 were regarded as statistically significant.

RESULTS
The present study was conducted at Diabetes OPD, department of Internal Medicine and department of Pharmacology GSVM Medical College, Kanpur, U.P. The enrolled patients received the regimen (Teneligliptin + Metformin).

Patient’s characteristics and baseline data
In our study the mean age of patients was 58.3±12.9 years. Out of 40 patients 57.5% are males and 42.5% are females. Baseline values of HbA1c, FBG and PPBG were 7.9±0.5%, 149.8±28.9 and 234±57.7 respectively.

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Fig. 1: Progressive Changes in HbA1c with Treatment.

Fig. 2: Progressive Changes in FBG and PPBG with Treatment.

Fig. 3: Percentage drop in glycemic parameters.

The HbA1c level significantly decreased after 16 weeks of treatment compared to baseline (p < 0.05). The change in HbA1c level from baseline in the entire patient population was −0.79% (7.9 to 7.1) at 16 weeks of treatment. The change in HbA1c from baseline was the most important primary end point of our study. The percentage drop in the mean HbA1c was 10% at the end of treatment. Percentage of patients achieving target HbA1C (≤7) was 37.5% at 16 weeks.

Reduction was also significant (P<0.001) in FBG -32.4mg/dl (149.8-117.4mg/dl) and 2h PPBG 54.3mg/dl (234-179.7mg/dl) at 16 weeks of treatment. Percentage drop in the mean FBG and 2h PPBG was 21.6% and 23.2% respectively.

**DISCUSSION**

Our study demonstrated that Teneligliptin and Metformin fixed dose combination is clinically effective for achieving glycemic control in patients with type-2 diabetes mellitus. The total study period of 16 weeks showed a significant improvement in FBG and PPBG (p < 0.001). The improvement in HbA1c was also highly significant (p < 0.001) at the end of 16 weeks. DPP-4 inhibitor presents an alternative therapeutic strategy for patients with type-2 DM. Our study showed favorable, significant results for patients taking Teneligliptin and Metformin fixed dose combination, which were similar to those obtained in other studies, despite the differences in study conditions.

In our study, combination of Teneligliptin with Metformin in fixed dose caused −0.79% reduction in HbA1C. Similar results were reported by other studies. In study by Jayanthi C R et al,[13] showed 0.9%, Sharma et al,[14] showed 0.78%, Kim et al,[15] and Kadowaki et al,[16] study showed 0.87%, decrease in mean HbA1c in their study population at the end of study. In study by Ghosh et al.[17] showed percentage of patients achieving target HbA1C (≤7) was 37.75%.

In our study mean decrease in FBG was -32.4mg/dl (21.6%) which is statistically significant. Similarly studies conducted by Jayanthi C R et al, showed 40mg/dl (23.5%) and Abhijeet Jain et al.[18] study showed 40 mg/dl (26.8%) decrease in mean FBS.

In our study mean decrease in 2h PPBG was 54.3mg/dl (23.2%) which is statistically significant. Similarly studies conducted by Jayanthi C R et al, showed 57mg/dl (21.8%) and Abhijeet Jain et al, study showed 92 mg/dl (38.3%) decrease in mean 2-h PPBS.

In a study conducted by Lodhi et al,[19] it was observed that addition of teneligliptin to metformin cause more significant reduction in all glycemic parameters i.e. FBG (109.3±10.9 vs 118±12.7), PPBG (182.6±33.0 vs 203.1±38.4), HbA1c (7.44±0.35 vs 7.65±0.38) in comparison to metformin monotherapy.

Study conducted by Abhijeet Jain et al.[18] also showed more effective glycemic control with combination of metformin and teneligliptin in comparison to metformin alone i.e. FBG (109±18.4 vs 132±19.8), PPBG (148.4±24.4 vs 201.3±38.5) and HbA1c (6.1±0.5 vs 7.8±0.8).

There were no cases of hypoglycemia and weight gain reported in the present study. Teneligliptin is not so costly as compared to other gliptins. No significant drug interactions were present and usually well tolerated. No dose adjustment was needed in patients with renal or hepatic impairment.
Data were collected only for duration of 16 weeks, so there were limitations in commenting on durability of the treatment. Long-term studies to address the shortcomings of the present study are warranted.

CONCLUSION
Teneligliptin and Metformin fixed dose combination provided statistically significant and clinically meaningful reductions in the Glycosylated Hemoglobin level (HbA1c), Fasting and Post-Prandial Blood Glucose in Indian patients with type-2 diabetes mellitus. Teneligliptin and Metformin combination therapy was effective and well tolerated in patients with type-2 diabetes. Further larger studies with more number of patients are needed to evaluate the magnitude of antidiabetic effects of Teneligliptin and Metformin combination.

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REFERENCES