An Open Label, 2 Year Long Term Follow-Up Study to Assess the Efficacy, Safety and Tolerability of Teneligliptin in Indian Subjects with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes is a significant health burden and is emerging as a pandemic. Teneligliptin, oral DPP-4 inhibitor was introduced in India in May 2015 for the management of T2DM. This study was conducted to assess the efficacy of teneligliptin in Indian type 2 diabetes mellitus (T2DM) subjects. Methodology: This was an open-labeled, non-randomized, observational study to assess the Teneligliptin 20 mg (Tenepride) Efficacy, Safety and Tolerability in patients with Type 2 Diabetes. This observational study was from August 2015 to November 2017. Total duration of study was 3 months. Then the patients were followed up for 2 years. The Primary outcome was Change in the HbA1C (%) from baseline to end of study. The secondary outcome included changes in FPG and 2 hr PPG from baseline at 1 month, 3 months and every quarterly till 24 months. Results: A total of 47 subjects were screened and included between August 2015 to September 2017. Among them 32 (68.1%) were men and 15 (31.9%) were women. Mean age of the subjects during the recruitment was 58.9 ± 9.74 years. In our study, after 3 months of therapy with add on Teneligliptin, the fasting blood glucose reduced from 164.1 ± 41.10 to 113.64 ± 38.61 mg/dL (∆ 56.42 ± 39.85; P = 0.0001), The post prandial blood glucose reduced from 253.94 ± 68.42 to 176.88 ± 62.99 mg/dL (∆ 77.06 ± 65.7; P =0.0001). The mean change at 3 months (7.84% ± 1.59) from baseline (8.39% ± 1.78) were ∆ 0.55 ± 0.81. At 2 years follow up, the mean change in fasting blood glucose, post prandial blood glucose and HbA1c were ∆62.33 ± 23.69 mg/dL (164.1 ± 41.1 vs 101.77 ±22.19), ∆111.97± 22.22 mg/dL (253.94 ± 68.42 vs 141.97 ± 24.78) and ∆1.86% ± 0.44 (8.39 ± 1.26 vs 6.53 ± 0.41) respectively. Conclusion: The study demonstrated the efficacy and safety of add-on teneligliptin treatment in achieving glycemic control in patients poorly controlled with glimepiride and metformin.

Keywords: Teneligliptin, Type II diabetes mellitus, HbA1c, DPP-4 inhibitor

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1. INTRODUCTION

Diabetes is one of the leading causes of morbidity and mortality worldwide and a major burden in India [1,2]. Type 2 diabetes mellitus is a well-known risk factor for cardiovascular disease and chronic kidney disease [3]. The prevalence of diabetes continues to be higher in urban areas than in rural areas. However, the rural prevalence estimates are on the rise than identified in earlier studies. The main factors driving the diabetes epidemic in both urban and rural areas of India are obesity, age, and family history of diabetes [1]. The published evidence suggests that even 1% reduction in HbA1c reported significant reduction in the risk of long-term complications associated with T2DM. Various measures have been initiated to overcome this ever rising burden [4]. Since the last few years, the increased research in diabetes have led to the newer therapeutic options which include dipeptidyl peptidase-4 inhibitors (DPPi-4) [5]. Dipeptidyl peptidase 4 (DPP-4) inhibitor are the class of antihyperglycemic agents that are now recommended as second- or first-line agents in treatment of diabetes by guidelines like American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and American College of Endocrinology. DPP-4 inhibitors control fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels through selective inhibition of DPP-4, resulting in increased plasma concentrations of active glucagon-like peptide-1. DPP-4 inhibitors unlike sulfonylureas, meglitinides, or insulin are weight neutral and no risk of hypoglycemia [6].

Teneligliptin, oral DPP-4 inhibitor was introduced in India in May 2015 for the management of T2DM. Teneligliptin, which is classified as peptidomimetic, has a J-shaped structure having five consecutive rings. This unique structure, account for its potency, selectivity and half-life. Following its introduction in clinical practice, this study was conducted to assess the efficacy of teneligliptin in Indian type 2 diabetes mellitus (T2DM) subjects [7,8,9,10].

2. METHODS

This was an open-labeled, non-randomized, observational study to assess the Teneligliptin 20 mg (Tenepride) Efficacy, Safety and Tolerability in Indian subjects with Type 2 Diabetes.

The study was conducted after receiving approval from Independent Ethics Committee. This observational study was conducted at DiaHealth, Diabetes and Lifestyle Management Centre, Bangalore, India from August 2015 to November 2017 after taking ethics committee approval. Total duration of study was 3 months. Then each study subject was followed up for 2 years.

Subjects >18 years of age or older with known case of Type 2 Diabetes Mellitus, Subjects with glycated (or glycosylated) haemoglobin (HbA1c) > 7% despite dual therapy (Metformin 500 mg + Glimipiride 2 mg), Subjects uncontrolled on and life style modifications interventions were included. Informed consent was taken from all participating subjects. Subjects with history of Type 1 DM or a secondary form of diabetes, Pregnant or breastfeeding women, subjects with previous medical conditions, hypersensitivity to any of the components of the study drugs, participation in another trial with an investigational drug within 2 months prior to informed consent were excluded.

The Primary outcome was Change in the HbA1c (%) from baseline to end of study. The secondary outcome included changes in FPG and 2 hr PPG from baseline at 1 month, 3 months and every quarterly till 24 months; Change in body weight from baseline after end of the study; Global assessment for efficacy by the treating physician at the end of study. Tolerability and Safety assessment was based on the adverse effects as mentioned by the patient and evaluated by the investigator.

The subjects who met the inclusion and exclusion criteria were advised Teneligliptin 20 mg OD along with Metformin 500 mg + Glimipiride 2 mg.

Information collected included demograph data, antidiabetic medications, and glycemic status of the patient at the time of initiation and during the follow-up period of combination antidiabetic therapy. FBS, PPBS. HbA1c was done at the start of study and at every 12 weeks.

Statistics

Demographic characteristics and results of glycemic tests are summarized with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. t-Test is used and p≤0.05 at confidence interval of 95% is considered to be significant.

3. RESULTS

A total of 47 subjects were screened and included between August 2015 to September 2017. Among them 32 (68.1%) were men and 15 (31.9%) were...
women. Mean age of the subjects during the recruitment was 58.9 ± 9.74 years. Mean weight was 71.1 ± 9.78 kg, and mean BMI was 28.04 ± 3.78 kg/m². (Table 1).

The mean baseline fasting blood glucose was 164.1 ± 41.10 mg/dL and the mean baseline post prandial blood glucose was 253.94 ± 68.42 mg/dL. The mean HbA1c (%) was 8.28 ± 1.78 (table 1).

Change in FBG and PPBG
After 3 months, there was a significant reduction of glycemic parameters in the study subjects who had high levels of FPBG and PPG. Prior to treatment with Teneligliptin, the baseline values of FPBG and PPG were 164.1 ± 41.10 mg/dL and 253.94 ± 68.42 mg/dL respectively. There was a significant decrease both clinically and statistically after 3 months of Teneligliptin and Metformin therapy (table 2).

At the three months follow-up, the mean change in HbA1c at 3 months (7.84 ± 1.59) from baseline (8.39 ± 1.78) was Δ 0.55 ± 0.81; P<0.05 (fig. 1)

2-year Follow-up
41 subjects continued treatment in this 2-year open label extension during which they received teneligliptin 20 mg, metformin 500 mg and glimepiride 2mg once daily. 6 subjects were lost to follow-up. There was an incremental reduction in FPG and PPG was observed relative to corresponding baseline values (table 3, fig. 2). The results after 2 years follow-up was clinically and statistically significant (P =0.0001).

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**Table 1: Demographic data**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Values</th>
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</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>58.9±9.74 years</td>
</tr>
<tr>
<td>Men, N (%)</td>
<td>32 (68.1%)</td>
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<tr>
<td>Women, N (%)</td>
<td>15 (31.9%)</td>
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<tr>
<td>Mean weight</td>
<td>71.1 ± 9.78 kg</td>
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<tr>
<td>Mean BMI</td>
<td>28.04 ± 3.78</td>
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<tr>
<td>Baseline FBG (mg/dL); mean (SD)</td>
<td>164.1 ± 41.10</td>
</tr>
<tr>
<td>Baseline PPBG (mg/dL); mean (SD)</td>
<td>253.94 ± 68.42</td>
</tr>
<tr>
<td>Baseline HbA1c (%); (Mean ± SD)</td>
<td>8.28 ± 1.78</td>
</tr>
</tbody>
</table>

**Table 2: Change in the Glycemic parameters at 1 month and 3 months**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
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</thead>
<tbody>
<tr>
<td>FPBG mg/dL</td>
<td>164.1 ± 41.10</td>
<td>138.87 ± 36.73</td>
<td>(Δ 25.23 ± 38.91; P = 0.006)</td>
</tr>
<tr>
<td>PPBG mg/dL</td>
<td>253.94 ± 68.42</td>
<td>197.52 ± 42.38</td>
<td>(Δ 50.46 ± 59.9; P = 0.0001)</td>
</tr>
</tbody>
</table>

**Table 3: Changes in the Glycemic parameters among the study subjects during the 2-year study period**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>21 months</th>
<th>24 months</th>
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<tbody>
<tr>
<td>Fasting Blood Glucose Levels</td>
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<tr>
<td>Mean ±SD</td>
<td>164.1 ± 41.10</td>
<td>129.12 ± 30.51</td>
<td>121.69 ± 23.66</td>
<td>117.16 ± 26.93</td>
<td>111.37 ± 25.07</td>
<td>103.58 ± 20.76</td>
<td>105.41 ± 28.19</td>
<td>101.77 ± 22.19</td>
</tr>
<tr>
<td>Change</td>
<td>34.98 ± 36.55</td>
<td>42.41 ± 27.08</td>
<td>46.94 ± 20.29</td>
<td>52.73 ± 21.23</td>
<td>55.52 ± 27.91</td>
<td>58.69 ± 29.47</td>
<td>62.33 ± 23.69</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
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<tbody>
<tr>
<td>Post Prandial Blood Glucose Levels</td>
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<td></td>
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<tr>
<td>Mean ±SD</td>
<td>253.94 ± 68.42</td>
<td>184.22 ± 37.31</td>
<td>178.89 ± 41.81</td>
<td>174.55 ± 31.44</td>
<td>169.24 ± 37.87</td>
<td>163.62 ± 35.04</td>
<td>154.47 ± 33.67</td>
<td>141.97 ± 24.78</td>
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</tbody>
</table>
During the study period, only three patients reported hypoglycemia; however, the episode of hypoglycemia was mild in severity. There was no significant weight reduction in the study subjects at the end of 2 years follow-up. The mean change in the body weight was 3.1 ± 1.7 kg. Teneligliptin was well tolerated, and all the subjects were highly satisfied with the treatment.

4. DISCUSSION

Diabetes is one of the most challenging health burdens of this century. Around 415 million people worldwide, or 8.8% of adults, are estimated to have diabetes. About 75% live in low- and middle-income countries. It is estimated that by 2040, some 642 million people, or one adult in 10, will have diabetes [3].

Dipeptidyl peptidase 4 (DPP-4) inhibitor is a relatively new class of antihyperglycemic agents and recommended as second- or first-line agents in treatment of diabetes by various guidelines. Teneligliptin is a novel DPP-4 inhibitor, having a unique chemical structure which is characterized by five consecutive rings (J-shaped), which might account for its unique potency and half-life time. Teneligliptin was introduced in India in 2015. Clinical trials conducted have shown Teneligliptin to be safe and effective in T2DM patients when used either as monotherapy or in combination with other conventional OAD. There is paucity of long term published studies of Teneligliptin in Indian patients. In this study, Teneligliptin was evaluated for 2 years in subjects who had poor glycemic control to dual therapy of metformin and glimepiride [7,8,9,10].

Mean age of the subjects during the recruitment was 58.9 ± 9.74 years. The mean baseline fasting blood glucose was 164.1 ± 41.10 mg/dL and the mean baseline post prandial blood glucose was 253.94 ± 68.42 mg /dL. The mean HbA1c (%) was 8.39 ± 1.78 suggesting the study subjects had poor glycemic control. The several landmark studies including the UKPDS have proven that achieving gylcemic goal is important towards the prevention of complications resulting from uncontrolled diabetes [11].

A Cochrane review that included 11 trials with sitagliptin and 14 trials with vildagliptin reported reductions in HbA1c level of ∼0.7% and 0.6%, respectively, compared with placebo [12]. Another DPP-4 inhibitor, saxagliptin, was also shown to reduce HbA1c by 0.45–0.63% compared with the placebo.
group [13]. In a recent phase II study with 12 weeks of teneligliptin treatment (n = 324), significant LS mean reductions in HbA1c for 10-, 20- and 40-mg groups vs a placebo group were −0.9% (95% CI −1.0, −0.7), −0.9% (95% CI −1.1, −0.7), and −1.0% (95% CI −1.2, −0.9), respectively (all p < 0.001) [14].

Another recent study assessed the efficacy of teneligliptin when added to an ongoing metformin treatment at week 16, and the mean reductions in HbA1c and fasting plasma glucose level compared with placebo were −0.78% and −1.24 mmol/l, respectively.

In our study, after 3 months of therapy with add on Teneligliptin, the fasting blood glucose reduced from 164.1 ± 41.10 to 113.64 ± 38.61 (Δ 56.42 ± 39.85; P = 0.0001), The post prandial blood glucose reduced from 253.94 ± 68.42 to 176.88 ± 62.99 (Δ 77.06 ± 65.7; P=0.0001). The mean change at 3 months (7.84 ± 1.59) from baseline (8.39 ± 1.78) were Δ 0.55 ± 0.81. The results were similar to the studies published [14,15].

The results after 2 years follow-up was also clinically and statistically significant and this is the first study with 2 years follow-up of subjects. There was an incremental reduction in FPG and PPG was observed relative to corresponding baseline values. The mean change in fasting blood glucose, post prandial blood glucose and HbA1c were ∆62.33 ± 23.69 mg/dL (164.1 ± 41.1 vs 101.77 ±22.19), ∆111.97± 22.22 mg/dL (253.94 ± 68.42 vs 141.97 ± 24.78) and ∆1.86% ± 0.44 (8.39 ± 1.26 vs 6.53 ± 0.41) respectively at 2 years follow-up. The long-term efficacy of teneligliptin has been studied in two 52-week, open-label, multicenter, interventional Japanese studies and data presented as a pooled analysis. The changes in HbA1c (mean ± standard deviation [SD]) from baseline to week 52 were −0.63 ± 0.65% in the teneligliptin monotherapy group, and −0.81 ± 0.76% in the SU combination therapy group [16]. In our study, the reduction in glycemic parameters strongly correlated with baseline glycemic values, that is, higher the HbA1c at baseline; higher was the reduction at the end of 3 months. showed better results at 1-year with mean change in HbA1c of Δ1.13±0.92 %. The mean change in HbA1c at 2 years 1.86 ±0.44% was also significant both clinically and statistically. There was no significant weight reduction in the study subjects at the end of 2 years follow-up. The mean change in the body weight was 3.1 ± 1.7 kg, the results are similar to the published studies and the guidelines [17].

5. CONCLUSION

The present study has demonstrated that the teneligliptin treatment was effective in achieving glycemic control within 3 months in patients with inadequate control for dual therapy of glimepiride and metformin. The long-term follow-up of 2 years showed effective glycemic control. In conclusion, Teneligliptin is an effective addition to the therapeutic armamentarium of management of Diabetes in Indian population with good safety, efficacy and tolerability.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Manjula Shamanna and Krishna Kumar M are employees of Micro Labs Limited, India, the makers of Tenepride (Teneligliptin).

LIMITATIONS

The limitation of the study is that it had an open-label design and no control group. To overcome this limitation, we propose conducting a double-blind, randomized comparative study in future.