Efficacy and Safety of Vildagliptin as Add-on Therapy in Patients with Type 2 Diabetes Mellitus Poorly Controlled by Metformin Compared with Glimepiride

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is an incurable chronic disease needs long life treatment. So, the study of long-term safety and tolerability of oral hypoglycemic agents especially newer one is very important. The objective of this study was to compare safety and efficacy of vildagliptin with glimepiride in type 2 diabetic patients.

Patients & Methods: 40 patients with type 2 DM were randomized to receive vildagliptin 50 mg or glimepiride 2 mg once daily as add-on therapy for 16 weeks. A vildagliptin group (23 patients) was received 50 mg vildagliptin once daily as add-on therapy, and glimepiride group (17 patients) was received 2 mg once daily as add-on therapy. The end point was the number of patients achieving HbA1C (Glycated haemoglobin) <7%. Results: A total of 40 patients with type 2 DM uncontrolled with metformin monotherapy were randomized to receive vildagliptin or glimepiride as add-on therapy. There were 23 patients in vildagliptin group and 17 patients in glimepiride group. HbA1C was reduced in patients receiving vildagliptin as compared to patients receiving glimepiride but the difference was not statistically significant, P >0.05. Fasting blood sugar (FBS) was reduced in patients received vildagliptin as well as in patients received glimepiride, the reduction in FBS was not statistically significant (P > 0.05). Weight of patients in vildagliptin group were reduced while in glimepiride group there was increase in weight (- 5.2 kg. vs. + 4.3kg, p < 0.05).

Conclusion: Vildagliptin is effective as hypoglycemic agent, as glimepiride in controlling blood glucose level guided by reduction in fasting blood sugar and HbA1C. In addition to reduction in patient weight and is well tolerated.

Key words: Diabetes Mellitus type 2, vildagliptin, Glimepiride, HbA1C, FBS

Introduction

Diabetes mellitus (DM) is among the most common chronic diseases in the world. This high global burden of diabetes is continuously increasing with high incidence and prevalence of type 2 DM, due to increasing population age, obesity, and physical inactivity. The complications of diabetes are mainly due to developing microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease) (Alberti, and Zimmett, 1998). In addition to the consequences of abnormal metabolism of glucose (e.g., hyperlipidemia, glycosylation of proteins, etc.), there are a number of long-term complications associated with the disease. These include cardiovascular, peripheral vascular, ocular, neurologic and renal abnormalities, which are responsible for morbidity, disability and death in young adults (Alberti, and Zimmett, 1998; Lean, 2000).

The primary goal of treatment of DM is to control glucose blood level within normal range. This can be achieved by maintaining the HbA1C level at 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia.

Treatment with a single oral hypoglycemic agent is often inadequately in achieving glycemic control in patients with type 2 DM and many patients require combination of antidiabetic agents. 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 (Shaw and Chisholm, 2003; WHO, 1999; Signorovitch et al., 2011).

The US Food and Drug Administration approved vildagliptin as an oral hypoglycemic drug with highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor. It is potent drug taken once-daily; to improve glycemic control in adult patients with type 2 DM. Endogenous glucagon-like peptide-1 (GLP-1) is produced by L-cells, dispersed in intestinal mucosa. The GLP-1 is physiological substrate for DPP-4, which exists as a cell surface-enzyme present on numerous cell types including kidney, enterocytes, hepatocytes, and endothelial cells, and as a soluble form in the circulation. The importance of DPP-4 in incretin inactivation was established in animal

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studies (WHO, 1999; Kieffer et al., 1995). Inhibition of DPP-4 activity by vildagliptin enhances fasting and postprandial levels of the intact incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (WHO, 1999).

There is no significant data regarding the safety and efficacy of vildagliptin in diabetic patients, so this study was conducted to compare the safety and efficacy of vildagliptin to glimepiride in diabetic patients inadequately controlled with metformin alone.

Patients and Methods

Drugs
Vildagliptin 50mg (Galvus® 50 mg) produced by Novartis
Glimepride 2 mg (Amaryl®) produced by Sanofi Aventis, El Sawah El Amiriya Egypt.

Patients
Patients were diagnosed as type 2 DM. All were adult patients ageing 40 and above with HbA1C levels between 7% and 11.5% as well as serum Creatinine levels of less than 1.47 mg/dL were eligible in our study. Only patients who have not been treated with any type of DPP-4 inhibitor before the study were recruited.

40 Patients between 40-61 years of age with history of type 2 DM not adequately controlled with a stable dose of metformin (more than1500 mg/day) mono-therapy were randomized to two groups. A vildagliptin group (23 patients) received vildagliptin 50mg once daily as add-on therapy for 16 weeks, and a glimepiride group (17 patients) received glimepiride 2mg once daily as add-on therapy for 16 weeks.

Exclusion criteria:
Patients with history of hypersensitivity to the study drugs, type I DM, pregnancy, uncontrolled hypertension, unstable angina, myocardial infarction, impaired renal, and liver functions, all were excluded from our study.

All the patients were given the instructions to continue their dietary control and exercise program during the study. The following biological parameters were measured in all patients at week 0 and at week 16. The parameters were: HbA1C, FBS, weight (Kg), Alanine aminotransferase (ALT), serum urea and creatinine.

Study Design
A prospective, randomized, double arm, intervention study design was used. 23 patients were assigned to receive vildagliptin (50 mg daily) in addition to their previous medications (metformin) and 17 patients were assigned to receive glimepiride (2 mg daily) in addition to their previous medications (metformin). The collected data was conducted before and after 16 weeks of intervention. All patients were enrolled following signed written informed consents.

All data was analyzed using SPSS 20 for windows. Categorical variables like gender, age, and smoking were expressed as frequencies and percentages while continuous variables like, change in HbA1C, FBS, weight were expressed as Mean ± SD. Comparative analysis between the two groups were done using Chi-Square (x²) for categorical variables and paired ‘t’ test for continuous variables where appropriate. A P value of <0.05 was set as significant.

Results
A total of 40 patients having type 2 DM inadequately controlled with metformin mono-therapy were randomized to receive vildagliptin 50 mg or Glimepiride 2 mg as add-on therapy for 16 weeks. There were 23 patients in vildagliptin group and 17 patients in glimepiride group. Mean age of patients was 51.5± 8.2 years in vildagliptin group and 49.8±8.3 years in glimepiride group. There were 12 (52.17%) males and 11 (47.82%) females in vildagliptin group, while Glimepiride group consisted of 9 (52.94%) males and 8(47.07%) females.

Table 1: Demographic variables of the patients in vildagliptin and glimeperide groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vildagliptin group (n=23)</th>
<th>Glimepiride group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.90 ± 5.8</td>
<td>48.94 ± 4.5</td>
</tr>
<tr>
<td>Male</td>
<td>12 (52.17%)</td>
<td>9 (52.94%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (47.82%)</td>
<td>8 (47.07%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (74%)</td>
<td>13 (76%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (26%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.33±0.17</td>
<td>1.32±0.17</td>
</tr>
<tr>
<td>Female</td>
<td>0.9±0.12</td>
<td>0.88±0.10</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>18.14±2.42</td>
<td>18.19±2.83</td>
</tr>
</tbody>
</table>

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Hypertension was present in 17 (74%) patients in vildagliptin group and 13 (76%) patients in glimepiride group. There were 6 (26%) smokers in vildagliptin group and 4 (23.5%) smokers in glimepiride group.

HbA1c was reduced in patients receiving vildagliptin as compared to patients receiving glimepiride but the difference was not statistically significant, p=0.75, Figure 1.

In vildagliptin group FBS was reduced by 35.05% (from 176.3±8.3 to 114.5±10.15 mg/dl) while in glimepiride group FBS was reduced by 34.64% (from 177.5±8.56 to 116±7.54 mg/dl) at the end of study. The difference between the two groups was not statistically significant.

In vildagliptin group there was statistically significant reduction in the weight of the patients (-5.2 kg), whereas, the weight of patients in glimepiride group was statistically significant increase (+4.3kg), p < 0.05, Table 2.

### Table 2: Change from baseline in HbA1C, Fasting blood sugar (FBS) and body weight in vildagliptin group and glimepiride group after 16 weeks of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Vildagliptin Group n=23</th>
<th>Glimepiride Group n=17</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base line</td>
<td>week 16</td>
<td>Base line</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.21±0.43</td>
<td>6.56±0.41</td>
<td>8.18±0.46</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>176±3.08</td>
<td>114.5±10.15</td>
<td>177.5±8.56</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>86.2±8.16</td>
<td>81.8±8.35</td>
<td>84.4±7.41</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.33±0.17</td>
<td>1.3±0.11</td>
<td>1.32±0.17</td>
</tr>
<tr>
<td>Female</td>
<td>0.91±0.12</td>
<td>0.9±0.15</td>
<td>0.88±0.10</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>18.14±2.42</td>
<td>17.96±2.19</td>
<td>19±2.30</td>
</tr>
</tbody>
</table>

HbA1c = Glycated haemoglobin, FBS = Fasting blood sugar, BUN = Blood urea Nitrogen

Table 3 showed that, treatments in the two groups were well tolerated and the overall frequency and type of adverse events were similar. There were 4 cases of hypoglycemia in Glimepiride group as compared to 1 patient in vildagliptin group. There was only 1 patient from both the groups with ALT within 1-3 times the normal range of ALT, with no patients having ALT more than 3 times. No serious side effects were noticed in the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Vildagliptin Group (n=23)</th>
<th>Glimepiride Group (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>2 (8.6%)</td>
<td>4 (21.7%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>ALT (1-3 times)</td>
<td>1 (4.3%)</td>
<td>1 (5.8%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (13.02%)</td>
<td>2 (11.7%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (4.3%)</td>
<td>1 (5.8%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (4.3%)</td>
<td>4 (23.5%)</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Alanine aminotransferase = ALT
Discussion

Both microvascular and macrovascular complications are major risk factors for type 2 DM. The treatment goal is controlling blood glucose of the patient near to normal range to prevent or retard these complications and so, improve quality of patient life. When the HbA1C serum level near 6-7%, it will lead to decrease the incidence of microvascular and macrovascular complications (Lean, 2000; Shaw and Chisholm, 2003; Signorovitch et al., 2011).

The American Diabetes Association guidelines state that metformin, along with lifestyle changes, should be considered first-line therapy in patients with type 2 DM. If diabetes remains uncontrolled with first-line therapy, step 2 therapies including sulfonylureas, or thiazolidinediones (TZDs), may be employed (Nathan et al., 2006). The use of these traditional agents may be limited, however, because of several factors. Some medications, such as sulfonylureas, can lose their effectiveness over time (Nathan et al., 2006). While other agents like rosiglitazone, a TZD, increase the risk of cardiovascular disease (Wolski, 2007). Although metformin and TZDs treat insulin resistance, they do not address the progressive decline in beta-cell function observed in patients with type 2 DM.

So, new treatment options are required. GLP-1 (Glucagon-like peptide 1), which is an incretin hormone released when blood glucose levels are elevated, GLP-1 stimulates insulin secretion, decreases glucagon secretion, improves beta-cell function. GLP-1 production is reduced in patients with type 2 diabetes. GLP-1 is rapidly degraded by the DPP-4 (Dipeptidyl peptidase) (Nissen, and Wolski, 2007; Mbanza and Sobngwi, 2003). The use of agent which blocks this enzyme (DPP-4) prolongs the effect of GLP-1 hormone. So we can use the DPP inhibitor like vildagliptin to control blood glucose level in diabetic patients within normal range. As the blood glucose level approaches normal range, the amounts of insulin excreted and suppression of glucagon decreased. As a result no hypoglycemia is seen with the use of this agent, whereas, some other oral hypoglycemic agents may cause hypoglycemic effect (Nathan et al., 2006; Nissen and Wolski, 2007).

Hypoglycemia is a matter of great concern with anti-hyperglycemic agents. Our study demonstrated a statistically significant difference in hypoglycemia between the vildagliptin and glimepiride groups. Vildagliptin added to metformin showed a 1 (4.3%) hypoglycemia whereas metformin plus glimepiride group had 4 (23.52%) incidence of hypoglycemia. Signorovitch (Signorovitch et al., 2011) reported a 4.9% incidence of hypoglycemia in patients taking Vildagliptin and metformin and 32% incidence of hypoglycemia in patients taking glipizide and metformin.

In our study, higher reduction in percentage of HbA1C in vildagliptin group as compared to glimepiride group but the difference was not statistically significant. Similar results were reported by other studies. In study by Matthews et al., (2010). There were 52% of patients achieving target HbA1C of <7%. Similarly in a study by Zoungas et al. (2010), in patients using sitagliptin, 47% of them achieved target HbA1C. While Nauck et al., (2007) in his study reported 63% of patients achieving HbA1C using sitagliptin.

In our study, FBS was reduced in both groups but there is no statistically significant difference between the two groups. The result was similar to those reported by other studies. In study by Garber et al. (2008)14, vildagliptin caused reduction in FBS from baseline.

In this study there was a reduction in weight of patients in vildagliptin group while there was increase in weight of patients in glimepiride group. There is statistically significant difference in weight between the two groups at week 16 (the end of study). The study by Matthews et al. (2010), reported similar results. There was statistically significant weight loss in sitagliptin group as compared to glimepiride group. Similarly in study by Nauck et al. (2007) there was a significant weight reduction in vildagliptin group as compared to glimepiride group.

In this study, no major side effects were reported, which is similar to reported by other studies (Matthews et al., 2010; Zoungas et al., 2010; Nauck et al., 2007; Nauck et al., 2007; Green et al., 2015) Our study proved that the vildagliptin is as efficacious as glimepiride (oral hypoglycemic agent), as add-on therapy to metformin, in controlling blood glucose level and is tolerated without hypoglycemia, and serious side effects.

Conclusion

Vildagliptin, is a DDP-4 inhibitor, is effective as glimepiride in controlling fasting blood sugar (FBS), in decreasing percentage of HbA1C. Vildagliptin has lower risk of hypoglycemia relative to glimepiride. Vildagliptin showed a significant weight loss as compared to glimepiride. Generally vildagliptin is well tolerated.
References


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