Original Research Article

Efficacy of vildagliptin and metformin combination in type II diabetes mellitus patients

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Abstract

Background: Several oral therapies are approved for use in combination with metformin; however, they are not always effective and are associated with side effects. Vildagliptin and metformin have independent glucose-lowering properties and demonstrated great glycemic control and tolerance in patients with T2DM. **Aim:** To evaluate the efficacy of vildagliptin-metformin combination treatment in type 2 diabetes mellitus patients. **Material and Methods:** A total of 35 patients with T2DM were given Vildagliptin(50mg)+ metformin(500mg) twice daily half an hour before meals was advised. Primary efficacy outcome was measured in terms of reduction in HbA1c levels from baseline to 12th week and reduction in FBS/PPBS levels from baseline to 6th and 12th week. **Results:** The mean fasting blood sugar levels at baseline (0 weeks) was174.03 ±19.19 mg/dl and the change in percentage at 12 weeks was -39.33%. The mean post prandial sugar levels at baseline (0 weeks) was 277.94 ±28.41 mg/dl and the change in percentage at 12 weeks was -43.88%. The mean HbA1c levels at baseline (0 weeks) was 8.99 ±0.37 and at 12 weeks it was 6.42±0.42 with change of -27.86%. **Conclusion:** Vildagliptin in combination with metformin also had good safety with low risk of hypoglycaemia and weight gain.
Key Word: Type 2 diabetes mellitus, Vildagliptin, metformin, vildagliptin-metformin combination, glycemic control

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INTRODUCTION

Diabetes is not an epidemic anymore but has turned into pandemic for the whole world.[1] The worldwide survey reported that diabetes is affecting nearly 10% of the population.[2] According to the World Health Organization (WHO) projections, the prevalence of diabetes is likely to increase by 35% by the year 2025.[3] India has a high prevalence of diabetes and the numbers are increasing at an alarming rate. In India alone, diabetes is expected to increase to 79.4 million by 2030.[4] Several oral therapies are approved for use in combination with metformin; however, they are not always effective and are associated with side effects.[5] Given these considerations, there remains a substantial unmet need for an agent that could improve β-cell function, improve glycaemic control, and have less adverse effects. Vildagliptin is a potent, oral and selective DPP-4 inhibitor for the treatment of patients with type 2 DM.[6] Vildagliptin and metformin have independent glucose-lowering properties and may increase GLP-1 levels by working through complementary mechanisms. When it comes to combination therapy, the agents demonstrated great glycemic control and tolerance in Asian patients with T2DM who had inadequate glycemic control with metformin or glimepiride.[7,8] This study was done to evaluate the efficacy of vildagliptin-metformin combination treatment in type 2 diabetes mellitus patients.

MATERIAL AND METHODS

This was a prospective randomized controlled open label comparative study for a period of 12 weeks. Patients attending the medicine out-patient department diagnosed with type 2 diabetes mellitus were included in the study for a period of 12 weeks.

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Sample size: The sample size was estimated in consultation with a biostatistician based on previous year's case load and the sample size was 35. Based on previous studies, in order to establish statistical significance for change in HbA1C and FBS/PPBS- it was required to study at least 35 patients. A total of 35 patients diagnosed with Type 2 diabetes mellitus attending outpatient clinic were recruited based on the inclusion and exclusion criteria mentioned below.

Inclusion criteria

- Patients diagnosed with type 2 diabetes mellitus.
- HbA1c levels between ≥ 7 and ≤10%.
- Age ≥ 40 years and ≤ 80 years.

Exclusion criteria:

- Type 1 diabetes mellitus.
- Patients with Known adverse reactions to Vildagliptin.
- Cardiovascular diseases: Severe uncontrolled hypertension defined as systolic blood Pressure ≥180 mmHg and ≥110 mmHg and any of the following within 6 months of enrolment visit: Cardiac surgery or revascularization, unstable angina, unstable congestive heart failure, [NYHA class 3 or 4], transient ischemic attack or significant cerebrovascular diseases and unstable/previously undiagnosed arrhythmias.
- Significant Gastrointestinal diseases like intestinal obstruction, malabsorption syndromes, irritable bowel syndrome, inflammatory bowel disease etc.
- Serum creatinine more than 1.2 mgs/dl.
- Those with raised Alanine Transaminase (ALT), Aspartate Transaminase (AST) ≥2 times normal.
- Pregnancy and lactation.
- Subject with any condition which, in the judgement of the clinician, may render the subject unable to complete the study or which may pose a significant risk to the subject.
- Concomitant medications with any other oral antidiabetic agents, chronic corticosteroids (oral or parenteral,>7 consecutive days of treatment) or any drugs which is known to alter the sugar levels are not permitted.

Investigations:

- FBS and PPBS at baseline, 6th week and 12th week.
- HbA1c, at baseline and at 12th week.

METHODOLOGY

35 patients diagnosed with type 2 DM, attending outpatient clinic were recruited after obtaining clearance from Ethical Review Board and taking written informed consent. A baseline demographic data (age, sex, weight, blood pressure, associated diseases, habits, and drug history) was collected at the time of recruitment. HbA1c, FBS and PPBS were done at the time of recruitment. Vildagliptin(50mg)+ metformin(500mg) twice daily half an hour before meals was advised. HbA1c, FBS, PPBS was repeated at the end of 3rd month. Also, patients with fasting sugars > 200 mg/dl and/or postprandial sugars > 300 mg/dl at the 6th week of study were also withdrawn from the study and treatment was given as per the American Diabetes Association [ADA] guidelines. Primary efficacy outcome was measured in terms of reduction in HbA1c levels from baseline to 12th week and reduction in FBS/PPBS levels from baseline to 6th and 12th week.

Statistical analysis: Quantitative data was summarized in terms of descriptive statistics like mean and standard deviation for patients who are treated for both the therapies. In order to test for statistical significance in mean values, appropriate T-test oblique non-parametric test was employed. Qualitative parameters between two groups were tested by employing Chi square test of significance, oblique non-parametric test to study before and after the treatment.

RESULTS

The number of subjects in age group 50-60 years were maximum i.e. 14 (20%) followed by 8 (11.43%) in 40-50 years, 7 (10%) in 70-80 years and 6 (8.57%) in 60-70 years age group with mean age of58.63 ±9.95 years. Among 35 subjects, 20 (28.57%%) were male and 32 (21.43%) were females. The mean weight of the included patients was 64.20±7.48 kgs and mean body mass index (BMI) was 24.09±3.98 kg/m^2. The mean fasting blood sugar levels at baseline (0 weeks) was 174.03 ±19.19 mg/dl and post prandial blood sugar level was 277.94 ±28.41 mg/dl. The mean glycated haemoglobin (HbA1c) levels at baseline (0 weeks) was 8.99±0.37.

Table 1: Effect of treatment on Blood Sugar levels

Time	Fasting BSL (Mean ±SD)	Post prandial BSL (Mean ±SD)	HbA1c levels (Mean ±SD)
0 week	174.03 ±19.19	277.94 ±28.41	8.99 ±0.37
6 week	109.54±12.53	158.82 ±15.64	--
12 week	104.57±11.52	154.45 ±13.91	6.42±0.42
Change from baseline to 12 week (%)	-39.33±8.54	-43.88±7.42	-27.86±5.96

The mean fasting blood sugar levels at baseline (0 weeks) was174.03 ±19.19 mg/dl. At 6 weeks it was 109.54±12.53 mg/dl and at 12 weeks it was 104.57±11.52 mg/dl. The change in percentage of fasting blood sugar at 12 weeks was -39.33%. The mean Post prandial sugar levels at baseline (0 weeks) was 277.94 ±28.41 mg/dl and at 6 weeks was 158.82 ±15.64mg/dl. At 12 weeks it was 154.45 ±13.91 mg/dl. The change in percentage of Post prandial blood sugar at 12 weeks was -43.88%. The mean HbA1c levels at baseline (0 weeks) was 8.99 ±0.37 and at 12 weeks it was 6.42±0.42 with change of -27.86%. The mean BMI at baseline (0 weeks) was 24.09 ±3.98 and at 12 weeks treatment was 23.56 ±3.80.

Table 2: Adverse effects

Adverse Effects	No. (%)
Edema	3
Headache	5
Elevated liver enzymes	3
Symptomatic hypoglycemia	2
Abdominal discomfort	2
Diarrhoea	8
Chest discomfort and dyspnea	3
Others	5

Diarrhoea was the commonest side effect observed in 8 patients followed by headache and others in 5 patients each.

DISCUSSION

The results in present study regarding plasma glucose and glycosylated hemoglobin (HbA1c) indicate that there was a successful improvement in plasma glucose levels and HbA1c after treatment courses of 6 and 12 weeks. The values were improved significantly after treatment with the drugs. However, this improvement was not enough to reach that of normal healthy individual values, in other words, there were partial improvements observed by these drugs. Accordingly, and based on the comparison of the treatment we conclude that combination of metformin + vildagliptin significantly reduced the values of FPG, PPG and HbA1c after 3 months. This might be due to the additive effect of these two drugs (metformin + vildagliptin). These results were in agreement with other studies[9,10] results that also indicate effectiveness of additive effect of metformin and vildagliptin. The incretin hormones play a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagons secretion, inhibiting gastric emptying and reducing appetite and food intake.[11,12] Both incretin hormones are rapidly degraded and removed from circulation by the enzyme dipeptidyl peptidase – 4 (DPP-4).[13,14] Therefore, there is considerable interest in enhancing incretin action for treatment of type 2 diabetes. The combination therapy with Vildagliptin and metformin lower glucose via enhancement of insulin secretion, suppression of glucagon secretion, and insulin sensitization by adipose tissue. The use of this combination in diabetes management will provide a greater degree of glycosylated hemoglobin - lowering than that seen with use of either drug as monotherapy.[15] Vildagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function[16] and preferably used in combination with Metformin in order to achieve the maximum reduction in HbA1c.[17,18] All recent clinical trials hint to the benefit of the early use of vildagliptin, alone or in combination, of any antidiabetic medication. In the present study Vildagliptin therapy appears to be safe and well tolerated by most, as outlined in the previous sections. When administered in combination with other agents vildagliptin therapy appears unlikely to cause hypoglycemia and is generally weight-neutral. Other adverse effects noted to occur in clinical trials of DPP-4 inhibition have included increased reports of nasopharyngitis, upper respiratory infection, and headache – these were not likely to be severe or result in discontinuation of the medication. The combination of Vildagliptin and metformin in type 2diabetes management has been shown in clinical trials to be effective in blood glucose lowering, with very low associated rates of hypoglycemia and no attenuation in the potential weight loss effects seen with metformin monotherapy.[15]

CONCLUSION

Vildagliptin in combination with metformin also had good safety with low risk of hypoglycaemia and weight gain.

REFERENCES

1. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94: 311–21.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(3):1047–53.
3. Mehta SR, Kashyap AS, Das CS. Diabetes mellitus in India: themodern scourge. Medical Journal Armed Forces India. 2009; 65: 50-54.
4. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R. Saxagliptin added to a submaximal dose of

sulphonylurea improvesglycaemic control compared with up titration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract. 2009; 63:1395–1406.
5. Gupta V, Kalra S. Choosing a gliptin. Indian J Endocrinol Metab. 2011;15(4):298–308.
6. Kahn SE, Porte D Jr. The pathophysiology of type II (non-insulin dependent) diabetes mellitus: Implications for treatment. In: Porte D Jr, Sherwin RS, eds. Ellenbergand Rifkin's Diabetes Mellitus, 5th ed. Stamford, CT: Appleton and Lange. 1997:487–512.
7. Ramachandran A, Das AK, *et al*. Current Status of Diabetes in India and Need for Novel Therapeutic Agents, supplement to JAPI 2010;58:7-9.
8. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahrén B, Byiers S, Shao Q, Dejager S. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus on metformin monotherapy. Diabetes ObesMetab. 2009;11(2):157–166.
9. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptinand gliclazide in combination with metformin in patients with Type 2diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med. 2010; 27: 318-26.
10. Combettes MM. GLP-1 and type 2 diabetes: physiology and new clinicaladvances. CurrOpinPharmacol 2006; 6: 598-605.
11. Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquidtest meal: effects of exogenous glucagon-like peptide-1 (GLP-1)- (7-36)amide in type 2 (noninsulin-dependent) diabetic patients. J ClinEndocrinol Metab 1996; 81: 327-332.
12. Toft-Nielsen MB, Madsbad S, Holst JJ. Continuous subcutaneousinfusion of glucagon-like peptide 1lowers plasma glucose and reducesappetite in type 2 diabetic patients. Diabetes Care. 1999; 22:1137-1143.
13. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon like peptide I are rapidly degraded from the NH2-terminus in type II diabeticpatients and in healthy subjects. Diabetes. 1995; 44: 1126-1131.
14. Harrigan RA, Nathan MS, Beattie P, Oral agents for the treatment of type2 diabetes mellitus: pharmacology, toxicity and treatment. Ann Emerg Med. 2001; 38:68-78.
15. Wajchenberg BL. Beta cell failure in diabetes and preservation by clinical treatment. Endocr Rev 2007; 28:187-218.
16. Chia CW, Egan JM. Incretin –based therapies in type 2 diabetes mellitus.J Clin Endocrinol Metab 2008; 93:3703-3716.
17. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardialinfarction and death from cardiovascular causes. N Engl J Med 2007; 356: 2457-2471.

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