

Sitagliptin in Achieving Better Glycemic Control as added Drug Therapy in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 diabetes mellitus is progressive loss of glycemic control over a period of time. So the purpose of the present study was to evaluate the effectiveness and safety of the Sitagliptin as an 'add-on' to the ongoing drug therapy in patients with Type 2 Diabetes Mellitus (T2DM).

Material and Methods: It was a randomized, retrospective population based cohort study done in 259 patients for 36 weeks from July'12 – March'13. Patients were randomly divided into 2 groups. In 1st group, sitagliptin was added and no ongoing drug was withdrawn while in 2nd group sitagliptin was added and dose of ongoing therapy was reduced to half.

Results: The primary efficacy endpoint was reduction in glycated haemoglobin (HbA1C), fasting blood sugar, and 2 hour post prandial blood sugar evaluated after 4, 8, 12, 18 and 36 weeks. A better glycemic control was observed in 1st group than 2nd. Sitagliptin was well tolerated without side effects.

Conclusion: Addition of Sitagliptin 100mg once daily as 'add-on' drug therapy was well tolerated with significant glycemic control in T2DM after 36 weeks.

Keywords: T2DM (Type 2 Diabetes), Sitagliptin, Metformin, HbA1C(Glycosylated Hemoglobin A1C)

INTRODUCTION

Treatment with a single OHA (Oral Hypoglycemic Agent) is often not sufficient for glycemic control and combination of OHAs are required in T2DM. Hyperglycemia in T2DM is due to insulin resistance in muscle and other tissues, inadequate insulin secretion by pancreatic β cells and hepatic glucose production.

Sitagliptin is an oral selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. DPP-4 inhibitors increases active incretin hormone.¹ Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) account for the incretin action. In elevated glucose blood levels, GLP-1 and GIP increase insulin release and GLP-1 lowers glucagon secretion, thereby decreasing the post meal glucose blood level and reducing fasting glucose.² Both GLP-1 and GIP are inactivated by the enzyme DPP-4. Thus DPP-4 inhibitors increase active incretin levels and there by increasing incretin effects, leading to better glycemic control. This leads to new therapeutic approach for the management of type 2DM.³ Metformin is the most common first line antihyperglycemic agents in type 2 diabetes, which acts by decreasing hepatic glucose production and by decreasing insulin resistance.^{4,5} Since sitagliptin and metformin target potentially complementary pathways, the addition of sitagliptin to uncontrolled type 2 DM with metformin monotherapy may provide improved

glycemic control.

The purpose of the present study was to evaluate the effectiveness and safety of the Sitagliptin as an 'add-on' to the ongoing drug therapy in patients with Type 2 Diabetes Mellitus (T2DM).

MATERIAL AND METHODS

The present study was done in Rohilkhand Medical College, Bareilly with the approval of institutional ethical committee and consent of the patients involved in the study. It was a randomized, retrospective population based cohort study done in 259 patients for 36 weeks from July'12 – March'13. Men and women (aged 30 years and onwards) with type 2 diabetes and inadequate glycemic control (defined by an HbA1c [A1C] level ≥ 7 and $\leq 10\%$) while taking metformin monotherapy of at least 1,500 mg/day, or any combination of OHAs, either at entry into the study or after a metformin dose-stable run-in period, were eligible to be randomized.

Patients who were not currently taking an oral antihyperglycemic agent (OHA), or were taking any OHA in monotherapy, or were taking metformin in combination with another OHA were potentially eligible to participate in the study if their HbA1C level met the screening criteria. Patients were excluded if they had a history of type 1 diabetes, renal function impairment inconsistent with the use of metformin, or a fasting plasma glucose (FPG) (or a fasting finger stick glucose) at, or just before, randomization >14.4 mmol/l (260 mg/dl). Pregnant women and breast feeding women were also excluded from the study. Concurrent lipid-lowering and antihypertensive medications, thyroid medications, hormone replacement therapy, and birth control medications were allowed but were expected to remain at stable doses.

This was a prospective, randomized, parallel-group study. Patients who were already taking metformin at a dose of at least 1,500 mg/day whose A1C level was ≥ 7 and $\leq 10\%$

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directly entered and were eligible to be randomized. Patients were randomly divided into two groups. In the first group, the dose of the 'on-going' therapy was kept same. In the 2nd group, the dose of the 'on-going' therapy was reduced to half. Patients exceeding specific glycemic limits during the 24-week treatment period were excluded from the study. Rescue therapy with pioglitazone was initiated if FPG was >15.0 mmol/L (270 mg/dl) from baseline through week 6, >13.3 mmol/L (240 mg/dl) after week 6 through week 12, and >11.1 mmol/l (200 mg/dl) after week 12.

Patients were advised all the precautions to be taken in diet and were advised 150 minutes of exercise every week. After two weeks half run in period their fasting blood group glucose and HbA1C were measured. Sitagliptin 100mg was added and FBS and HbA1c were measured at the end of 4, 8, 12, 18, 24 and 36 weeks.

The primary efficacy end point was change from baseline at week 24 in A1C. Secondary efficacy end points included change from baseline at week 24 in fasting and post prandial glucose, insulin and C-peptide concentrations, measured immediately before and at 60 and 120 min after a standard meal, and a lipid panel (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride-to-HDL cholesterol ratio).

Monitoring for adverse effects, body weight, 12-lead electrocardiograms (ECGs), laboratory measurements comprising routine hematology, serum chemistry, and urinalysis were performed.

RESULTS

259 patients were screened and tested. Out of which 31 patients left the study in between and were excluded from the results. P value and statistical significance for HbA1C: The two-tailed P value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant. Table-1 shows age distribution for both the groups.

Treatment with sitagliptin 100 mg once-daily as add-on therapy with metformin therapy was well tolerated. There were no statistically significant differences in the incidence of hypoglycemia and gastrointestinal adverse effect between the groups. The incidence of other adverse effects including the cardiac side effects, infections and musculoskeletal problems were comparable between the two groups.

No meaningful difference between treatment groups were observed in mean changes from baseline or in the occurrence of elevations in alanine aminotransferase or aspartate aminotransferase (table-2). A small mean increase ($\leq 10\%$) was observed in white blood cell count related to an increase in absolute neutrophil count in the sitagliptin 100 mg group compared with placebo. These changes appeared to remain stable over the course of the treatment period. A small mean increase ($\sim 10 \mu\text{mol/l}$) from baseline in uric acid was observed in the sitagliptin group relative to the placebo group at week 24 (baseline uric acid levels: 330.7 $\mu\text{mol/l}$ for sitagliptin 100 mg once-daily vs. 335.5 $\mu\text{mol/l}$ for placebo); no laboratory adverse experiences of hyperuricemia or clinical adverse

Age (years)	Group 1	Group 2
30-39	16	18
40-49	36	38
50-59	27	28
60-69	19	16
70- onwards	8	12
Total	106	112

Table-1: Age distribution for both the groups

Age (years)	Group 1		Group 2	
	BSPP	HbA _{1C}	BSPP	HbA _{1C}
30-39	106	6.4	138	7.2
40-49	117	6.6	145	7.4
50-59	119	6.5	144	7.1
60-69	136	6.9	151	7.3
70-onwards	127	6.7	140	6.9

Table-2: Comparison of both the groups after 6 months

	Group 1	Group 2	Results
Mean	6.62	7.18	P < 0.001 extremely significant
SD	0.19	0.19	
N (number)	106	112	

Table-3: Comparison for HbA1C – p value and standard deviation.

	Group 1	Group 2	Results
Mean	121	143.6	P < 0.001 extremely significant
SD	11.24	5.02	
N (number)	106	112	

Table-4: Comparison for mean value and SD for BSPP

Age (years)	BSPP (mg%)	HbA1C
30-39	343	9.5
40-49	356	9.6
50-59	326	9.1
60-69	328	9.0
70 onwards	277	8.9

Table-5: Average BSPP and HbA1C in group 1

Age (years)	BSPP	HbA1C
30-39	362	10.2
40-49	372	9.8
50-59	333	9.8
60-69	313	9.6
70-onwards	268	9.0

Table-6: Comparison of BSPP and HbA1C in group 2

experiences of gout were reported (table-3). A small mean decrease ($\sim 4\%$) from baseline in alkaline phosphatase was also detected in the sitagliptin group compared with placebo at week 24. There was a slightly greater, albeit not statistically significant, incidence of hemoglobin values that met the predefined limit of change criteria for at least one decrease of $\geq 1.5 \text{ g/l}$ in the sitagliptin 100 mg group (5.7%) compared with the placebo group (3.5%). There was no

meaningful difference between the two treatment groups in mean change from baseline for hemoglobin. No meaningful differences were observed between treatment groups in the mean changes from baseline or in changes meeting predefined limits of change criteria for other laboratory assessments.

There were no clinically meaningful changes in ECGs or vital signs with sitagliptin treatment. Small (0.6–0.7 kg), but statistically significant ($P < 0.05$), mean decreases from baseline in body weight were observed in both treatment groups; however, the mean between-group difference was not significant ($P = 0.835$ for between-group comparison for change from baseline at Week 24). Table 5 and 6 shows average BSPP and HbA1C.

DISCUSSION

Sitagliptin 100 mg once-daily provided statistically significant reduction in HbA1C in group 1 as compared with group 2 when added to ongoing metformin therapy in type 2 diabetes mellitus. Secondary glycemic end points including fasting glucose and two hours postmeal glucose also showed clinically important and statistically significant improvements with sitagliptin 100 mg. The HbA1C-lowering responses to sitagliptin treatment were sustained during the 24 week treatment period, with a trend of continuing reductions in both end points throughout the treatment period. Nearly half of the patients receiving sitagliptin 100 mg once-daily achieved the current American Diabetes Association glycemic goal of A1C $<7\%$ compared with patients taking only metformin.

Sitagliptin 100 mg led to a statistically significant increase in the ability of pancreatic β -cells to secrete insulin under fasting conditions. Improvement in the fasting proinsulin-to-insulin ratio, consistent with improved β -cell function, was also observed with sitagliptin treatment. Preclinical studies have shown that GLP-1 can stimulate β -cell differentiation and proliferation, inhibit apoptosis of β -cells and stimulate β -cell neogenesis.^{1,2}

During this study, patients underwent a standard two hour meal tolerance test to assess the effect of treatment on postprandial glucose, insulin, and C-peptide and the ratio of insulin to glucose. Treatment with sitagliptin led to clinically important and statistically significant improvements in all of these end points.

Sitagliptin 100 mg was well tolerated in this study. No clinically meaningful differences in the overall adverse effects. The efficacy of sitagliptin has been demonstrated as both monotherapy and in combination with various oral antidiabetic drugs.⁶⁻⁹ The addition of sitagliptin to metformin did not increase in the incidence of gastrointestinal side effects. Sitagliptin was associated with a very low incidence of hypoglycemia and none of the hypoglycemia episodes exhibited marked severity. Treatment with sitagliptin led to a small, but statistically significant, mean decrease from baseline body weight and improvements in lipid profile. Sitagliptin was not associated with adverse biochemical, hematological and cardiac side effects.

CONCLUSION

In patients with type 2 diabetes who had inadequate glycemic control with metformin alone, the addition of sitagliptin 100 mg once daily was well tolerated with effective and sustained improvement in HbA1C, blood sugar, insulin secretion and β -cell function.

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