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Effectiveness of Sitagliptin in Asian Indian Patients with Type 2 Diabetes—An Indian Tertiary Diabetes Care Center Experience

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Abstract

Background: This study reports on the effectiveness of sitagliptin in Asian Indian type 2 diabetes patients seen at a tertiary diabetes care center who had inadequate glycemic control with oral hypoglycemic agents either alone or in combination, compared to a group of patients who received insulin glargine.

Patients and Methods: Patients with type 2 diabetes mellitus ($n = 2{,}817$) whose glycemia was not controlled adequately (glycated hemoglobin >6.5%) with oral hypoglycemic agents (either alone or in combination) received oral sitagliptin 100 mg once daily in addition to existing therapy for a period of 24 weeks. Patients who received insulin glargine as add-on therapy ($n = 2{,}743$) served as the reference group. Data analysis included glycated hemoglobin, fasting plasma glucose, lipid profile, body weight, and the occurrence of hypoglycemia.

Results: Significant reductions in glycated hemoglobin and fasting plasma glucose values were noted after 24 weeks of additional sitagliptin therapy that were comparable to those with insulin glargine. While sitagliptin addition resulted in a small weight loss (0.3 kg), insulin glargine addition resulted in a weight gain (0.7 kg). The overall incidence of adverse experiences was low and generally mild in both groups.

Conclusions: In a large group of Asian Indian type 2 diabetes patients seen at a tertiary diabetes center in whom glycemia was not controlled adequately by oral hypoglycemic agents (either alone or in combination), addition of sitagliptin helped to achieve glycemic control to a similar extent as insulin glargine but with a marginal weight advantage.

Introduction

At present, an estimated 285 million people have diabetes worldwide.[1] The prevalence of type 2 diabetes (T2D) is reaching epidemic proportions in India, which is home to over 50 million people with diabetes.[2,3] There are sufficient data to suggest that effective management of diabetes can decrease the risk for both the microvascular as well as macrovascular complications of diabetes.[4,5] Although basic and clinical research has provided effective treatments, the quality of care for people with diabetes remains suboptimal.[6] There is a well-documented gap between "best practices" established in randomized trials to improve outcomes and the care delivered in almost all primary care settings for diabetes and other chronic illnesses.[7]

During the last decade, new glucose-lowering drugs acting on novel pathways have been developed and launched. These drugs include the glucagon-like peptide agonists such as exenatide and liraglutide, dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin and vildagliptin,[8] and insulin analogs like glargine and levemir.[9] The safety and efficacy of sitagliptin are well established under controlled clinical conditions either as monotherapy[10–14] or when added to metformin,[15,16] pioglitazone,[17] or glimepride.[18] However, the results are difficult to translate into clinical practice because many randomized controlled clinical trials exclude clinically relevant patient subgroups (as defined by age, sex, race, ethnicity, and co-morbid conditions).[19] Moreover, there are few data on commonly used comparator interventions. Hence there is need for collecting data from diabetes centers across the globe, especially from developing countries such as India.

The issue of whether sitagliptin as monotherapy or as adjuvant to existing therapy is effective in controlling glycemia is of paramount importance because it is the first gliptin to be approved in the world and in India. To our knowledge, there is no large study that has addressed the efficacy of sitagliptin

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in an office care setup in India. This led us to look at the effectiveness and safety of sitagliptin at a tertiary diabetes care center in southern India. Insulin glargine was used as the comparator drug because addition of insulin is a common practice in the face of beta-cell failure after using oral hypoglycemic agents (OHAs).[20]

Patients and Methods

Study design

This study was a retrospective study of case records undertaken at Dr. Mohan's Diabetes Specialities Centre, a tertiary-care diabetes center in Chennai (formerly Madras) city in southern India, between July 2008 (the time when sitagliptin became commercially obtainable in India) and March 2010. The study patients were type 2 diabetes patients presenting to six (three urban, two semi-urban, and one rural) branches of the institution. Studies were performed at no extra cost to the participants, and patients were not compensated.

Patients

All patients treated at our center are informed at the time of registration itself that their medical records may be analyzed for scientific purposes, without revealing their identity, and over 95% of the patients sign the consent form. Accordingly, the electronic records of patients who signed the consent form and who were prescribed sitagliptin or insulin glargine for control of T2D as part of the routine care by the diabetologists of our center were reviewed. These were patients with beta-cell failure after use of OHA (loss of efficacy over time as reflected by glycemic control) either alone or in combination. Patients who were prescribed sitagliptin formed the study group, whereas those who were prescribed insulin glargine served as the reference group. The inclusion criteria were as broad as possible in order to maximize generalization and to reflect the "real-world" conditions. The data were extracted using a standardized data extraction form. The study was approved by the Institutional Ethics Committee of the Madras Diabetes Research Foundation.

Medications

Patients who were prescribed sitagliptin used a single dose (100 mg) of the medication (Januvia®, MSD Pharmaceuticals Private Ltd., Gurgaon, Haryana, India), after breakfast. Patients in the comparator group self-injected insulin glargine (Lantus®, Sanofi-Aventis, Mumbai, India) once daily, and the dose was titrated against fasting plasma glucose (FPG). While the doses of other OHAs remained the same during the study period, doses of statins or blood pressure-lowering drugs were adjusted based on the patient's need.

Assessments

Anthropometric measures such as height (cm) and weight (kg) were measured using standard methods.[21] Body mass index was calculated using the standard formula: weight (in kg) divided by height (in meters squared). The blood pressure was recorded in the right upper limb with the patient in the sitting position using a mercury sphygmomanometer. A fasting blood sample was taken after ensuring a minimum of 8 h of overnight fasting for the estimation of FPG as well as for other biochemical measurements. All biochemical assays were done in our laboratory, which is accredited by the College of American Pathologists as well as by the National Accreditation Board for Testing and Calibration Laboratories, India. Glycated hemoglobin (A1C) was estimated by high-performance liquid chromatography using a Variant™ machine (Bio-Rad, Hercules, CA). Low-density lipoprotein cholesterol was calculated using the formula of Friedewald et al.[22]

Outcome measures

The visit when sitagliptin or insulin glargine were initiated was considered as baseline, and the final outcome was 24 weeks later. The primary effectiveness variable was the change in A1C level from baseline. Effectiveness was assessed as "good" if the A1C level was $<7\%$, "fair" if between 7.1% and 8.5%, and "poor" if $>8.5\%$. The secondary effectiveness variables were the change from baseline in FPG, body weight, blood pressure, serum creatinine level, and lipid profile. Responder analysis was performed to determine the number of patients achieving the American Diabetes Association target of A1C $<7.0\%$.[23] In addition, the number of patients whose A1C level decreased by at least 0.5% was assessed, and those patients whose A1C did not decrease by 0.5% were designated as treatment failures.

Safety

Safety data were collected by noting the adverse experiences recorded in the case report forms. The intensity as well as the relationship to study drug, if any, was also recorded. Subjects were asked specifically about hypoglycemia during each visit, which was noted if any episodes had occurred. Symptomatic hypoglycemia was defined as a blood glucose measurement of <3.4 mmol/L (≤ 60 mg/dL) and/or symptoms such as excessive hunger, sweating, shaking, palpitation, or confusion. Severe hypoglycemia was defined as a hypoglycemic episode in which the patient required assistance from another person or had a blood glucose measurement of <2.8 mmol/L (≤ 50 mg/dL).The patients were specifically asked about symptoms of acute pancreatitis such as abdominal pain, nausea, and vomiting during each visit to the hospital. We also monitored the levels of serum amylase and lipase wherever relevant.

Statistical analysis

Data are presented as mean $\pm$ SD values. Standard descriptive analysis, independent-samples t test, and nonparametric tests were used where appropriate. The primary effectiveness analysis was performed with data from patients who had an initial A1C value and at least one post-baseline A1C measurement.

Results

The electronic records of 5,560 patients were reviewed, and their baseline demographic characteristics are shown in Table 1. Those who had received sitagliptin were older and had a longer duration of diabetes but had lower body mass index and waist circumference compared to those who received glargine.

Outcomes reflecting diabetes control

The effectiveness of sitagliptin and insulin glargine addition on glycemic control and degree of diabetes control is

Table 1. Baseline Characteristics of the Study Group

Characteristic	*Sitagliptin group*	*Insulin glargine group*	P *value*
Number	2,817	2,743	
Age (years)	55.9 ± 8.1	54.2 ± 9.2	<0.001
Women	1,087 (39)	961 (35)	<0.05
Body weight (kg)	75.4 ± 11.7	78.2 ± 8.3	<0.001
Body mass index (kg/m^2)	27.7 ± 4.2	28.3 ± 2.8	<0.001
Waist circumference (cm)	95.6 ± 10.2	98.8 ± 11.6	<0.001
Duration of diabetes (years)	16.9 ± 7.4	13.2 ± 6.7	<0.001
Previous therapy			
Sulfonylurea alone	397 (14.1)	366 (13.3)	NS
Metformin alone	438 (15.5)	397 (14.5)	NS
Pioglitazone alone	452 (16.0)	381 (13.9)	<0.05
Sulfonylurea plus metformin	421 (14.9)	572 (20.8)	<0.05
Sulfonylurea plus pioglitazone	569 (20.2)	443 (16.2)	<0.05
Metformin plus pioglitazone	540 (19.2)	584 (21.3)	NS

Data are mean (SD) values except for sex and previous therapy [number (%)].
NS, not significant.

reported in Table 2. There was a significant lowering of A1C levels after addition of either sitagliptin or insulin glargine. There was a modest but statistically significant ($P < 0.001$) decline in A1C values during the first 12 weeks of treatment, which remained generally stable with a slight trend toward further reduction over the subsequent follow-up period. Although the A1C reduction in the sitagliptin plus pioglitazone and sitagliptin plus sulfonylurea plus metformin subgroups were marginally greater, the differences were not significantly different. Addition of sitagliptin or insulin glargine led to a highly significant ($P < 0.001$) reduction from baseline at week 24 in FPG levels.

There was no significant difference in the number of patients who reached the American Diabetes Association target A1C of <7% after addition of sitagliptin and glargine (25.4% vs. 22%, respectively), nor was there a significant difference between the groups with respect to the number of patients having a reduction in A1C of at least 0.5% (Table 2). Furthermore, in 156 patients (6.5%), there was a rise in A1C value (range, 0.2–1.5%) after addition of sitagliptin compared to 132 patients (6.0%) after addition of insulin glargine (range, 0.1–1.4%).

Changes in body weight

After 24 weeks of therapy with additional sitagliptin, only small differences in body weight were observed (0.3 kg), which did not reach the level of statistical significance, and no clinically meaningful differences were observed between treatment subgroups (Table 2). Addition of insulin glargine led to a small weight gain of 0.7 kg, resulting in a significant net treatment difference of 1 kg between the sitagliptin-treated and glargine-treated groups.

Effectiveness on secondary efficacy profiles

Systolic and diastolic blood pressures remained unchanged, and there were no significant changes with reference to lipid profile (Table 2).

Safety and tolerability

A total of 62 episodes of minor hypoglycemia were reported by 59 patients, mainly in the subgroup of sitagliptin plus sulfonylurea during the study period, compared to 78 episodes by 48 patients in the insulin glargine group. Twelve patients complained of cough, rhinorrhea, and fatigue in the sitagliptin group. Diarrhea and nausea were reported by 42 patients after sitagliptin therapy. None of the patients receiving sitagliptin presented with either symptoms or signs of acute pancreatitis. There were no cases of carcinoma in those receiving insulin glargine.

Discussion

Knowledge about diversity in drug responses across populations/ethnicities would help clinicians to prescribe those classes of medicines with the highest therapeutic benefit with minimal dose. Asian Indians show several peculiarities in the clinical profile of diabetes[24] and also in response to pharmacological interventions. Indian trials have shown that metformin had a lesser effect in arresting the progression of impaired glucose tolerance to frank T2D in Asian Indians[25] compared to the western population.[26] A slightly lower level of effectiveness of rosiglitazone was noted in Asian Indians in the DREAM Trial[27] compared to the other populations, although the differences were not significant statistically. Also, pioglitazone was shown to be ineffective in enhancing the effectiveness of lifestyle modifications in preventing the conversion of impaired glucose tolerance to diabetes in Asian Indians.[28] Conversely, the DPP-4 inhibitor sitagliptin was found to have a better effect on A1C in Asian Indians and Koreans[14] compared to Caucasians.[15–18] Hence this study becomes important as it looks at a large series of Asian Indian patients with beta-cell failure after using OHAs.

DPP-4 inhibitors such as sitagliptin have been shown to improve glycemic parameters when added to existing therapy in patients whose glycemia was not controlled by metformin, sulfonylurea, or thiazolidinedione.[29] The addition of sitagliptin (100 mg) produced a placebo-corrected A1C reduction of 0.5–0.8%, FPG reduction of 10–25 mg/dL, and 2-h postprandial plasma glucose decrease of 35–50 mg/dL.[16,17,30] The present study provides data on the add-on efficacy and safety results for once-daily sitagliptin at a dose of 100 mg in a routine patient care setting and demonstrates a clinically meaningful and statistically significant reduction in A1C over

Table 2. Effectiveness of Therapy on Glycemia and Degree of Diabetes Control

	Sitagliptin group at week			*Insulin glargine group at week*		
Characteristic	*0* (n = *2,817*)	*12* (n = *2,618*)	*24* (n = *2,431*)	*0* (n = *2743*)	*12* (n = *2,584*)	*24* (n = *2,189*)
A1C (%)	9.2 ± 1.6	8.3 ± 1.3***	8.0 ± 1.2***	9.1 ± 1.4	8.6 ± 1.5***	8.1 ± 1.7***
Fasting plasma glucose (mg/dL)	177 ± 60	158 ± 64***	146 ± 46***	185 ± 65	161 ± 78***	161 ± 87***
Degree of diabetes control						
Good (A1C ≤7.0%)	0		613 (25.2%)*	0		493 (22.5%)*
Fair (A1C 7.1–8.5%)	969		941(38.7%)*	1,060		782 (35.7%)*
Poor (A1C >8.5%)	1,848		877 (36.1%)*	1,683		914 (41.8%)*
A1C reduction by 0.5%			1,625 (66.8%)			1,512 (69.1%)
Body weight (kg)	75.4 ± 11.6		75.1 ± 11.3	75.0 ± 10.6		75.7 ± 10.9**
Blood pressure (mm Hg)						
Systolic	130 ± 11		129 ± 18	131 ± 14		130 ± 16
Diastolic	82 ± 10		81 ± 9	81 ± 12		80 ± 9
Serum creatinine (mg/dL)	0.9 ± 0.1		0.9 ± 0.1	0.9 ± 0.2		0.9 ± 0.1
Cholesterol (mg/dL)						
Total	185 ± 35		185 ± 50	197 ± 15		193 ± 39
HDL	39 ± 4.0		39 ± 15	39 ± 8		39 ± 12
LDL	89 ± 23		89 ± 31	93 ± 4		89 ± 8
Serum triglycerides (mg/dL)[a]	195 ± 14		185 ± 10	195 ± 11		195 ± 12

[a]Geometric mean.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared to week 0 value.
A1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

a 24-week period in Asian Indian patients with T2D. Thus addition of sitagliptin may represent a new potential goal-oriented treatment approach for Asian Indians who require more intensive therapy for control of their diabetes. Our result (A1C reduction of 0.9% at 120 days) is in agreement with the result of a Belgian observational study (A1C reduction of 1.1% at 110 days) that evaluated the efficacy of once-daily additional oral sitagliptin at a dose of 100 mg to existing therapy in patients with uncontrolled T2D in real life conditions.[31] In the present study, FPG in the glargine group was higher compared to the sitagliptin group: 161 versus 146 mg/dL. This could be due to either our physicians not being aggressive enough in increasing the dose of insulin glargine or because the patients were less compliant with their insulin injections.

Addition of sitagliptin had been shown to provide substantial and sustained glycemic improvement (i.e., decrease from baseline A1C level of 1.4%) over a 2-year period in patients with T2D in an extension study of sitagliptin and the proportion of patients with an A1C <7% was 60%.[32,33] In the present study, sitagliptin was shown to provide similar glycemic control by 24 weeks, but only 25% reached the American Diabetes Association target by 24 weeks. It remains to be seen whether the glycemic control persists and the percentage of patients reaching the American Diabetes Association target rises, given the progressive beta-cell dysfunction and failure associated with T2D.[34]

The weight effect observed in this study is of interest. Unlike antidiabetes medications such as sulfonylureas or insulin that are associated with weight gain (particularly central weight gain), which is thought to be atherogenic[35] and limiting the overall efficacy,[36] sitagliptin is known to be weight neutral. The finding in the present study of weight reduction, albeit a small amount, would be a distinct advantage for the usage of sitagliptin compared to insulin in patients who do not respond to OHA.

In the present study, the number of episodes of hypoglycemia was low after sitagliptin or glargine addition. Because tight glycemic control is known to increase the risk for hypoglycemia,[37] a major barrier to sustained glycemic control, it is reassuring to note the lack of any episode of severe hypoglycemia in both groups. The low incidence of hypoglycemia observed in the present study would make sitagliptin or insulin glargine a useful option for those people who are prone for hypoglycemia. Furthermore, the absence of acute pancreatitis or cancer in this large series is also reassuring, as to our knowledge no case of pancreatitis following sitagliptin or cancer following insulin glargine has been reported from India to date.

The cost for a month's supply of sitagliptin in India is significantly more (28.5 US$) compared to insulin glargine (17.9 US$). This works out to approximately 23.7 US$ for each unit of lowering A1C resulting in an incremental cost ratio of 1.33. This limits the large-scale use of sitagliptin in India, as at present many patients cannot afford this therapy in the absence of insurance or Social Security. However, long-term studies are necessary because overall cost effectiveness requires sophisticated economic modeling that factors in not only direct medication expense, but also the expense of hypoglycemic episodes (emergency department/follow-up clinic costs), complications (microvascular, macrovascular, etc.), loss of work time, etc. Moreover, costs of insulin are approximate as the doses can vary in individual patients.

Although addition of sitagliptin helped to achieve glycemic control in a fair percentage of patients in this study, numerous factors should be considered while interpreting our results. First, the duration of the study was short (24 weeks). Second, the mean duration of diabetes in this study was long—16 years—and the mean baseline A1C was also high. Although standard treatment types and doses were used, our results apply only to the specific therapy that we used. Finally, the study results are restricted to those who came for follow-up, and we are not aware of the results of those who did not come back for follow-up. As our center has a follow-up rate of 50–60%, this is potentially another source of bias.

In conclusion, the results of the present study, carried out in a tertiary diabetes care setting in South India, show that the addition of sitagliptin to existing oral regimens is useful for patients with T2D whose glycemia is not controlled adequately by other OHAs, either alone or in combination. Potential advantages include ease of administration, low risk of hypoglycemia, and no weight gain. Nevertheless, long-term studies looking at the cardiovascular and other complications of diabetes are warranted as no long-term data on this class of compounds are currently available.

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