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The effect of sitagliptin therapy in suboptimally controlled metformin-treated type 2 diabetes patients: A Middle Eastern experience

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Abstract
Because of the high cost of sitagliptin and its unknown long term effects, a retrospective study to evaluate its effectiveness was undertaken at our Abu Dhabi Medical Center after one year of treatment. Glycemic control and changes in body weight were analyzed in 53 UAE national patients (26 men, 27 women) with type 2 diabetes mellitus managed with a combination of sitagliptin and metformin. Sitagliptin 100mg once daily was added after inadequate glycemic control (HbA1c > 7%) on Metformin alone or with a Thiazolidinedione for > 3 months. Mean patient age 52 years; mean diabetes duration 8 years; mean HbA1c 8.2% at treatment start. Mean HbA1c difference between before and post treatment was 0.56% (95% CI 0.24% - 0.87%). This did not change with multivariable analysis of weight, body mass index and duration of diabetes. Weight reduction was not statistically significant. Side effects were minimal. The addition of sitagliptin in our patients who failed to achieve glycemic control with insulin sensitizers resulted in a minimal drop in HbA1c with neutral effect on weight reduction, similar to that reported in recent literature. Therefore to justify its high cost, sitagliptin should be used to its maximum potential.

Key words: *Sitagliptin, incretins, diabetes type 2, metformin, glycemic control, United Arab Emirates*

Introduction

There is currently a plethora of pharmaceutical drugs for the management of type 2 diabetes. The UKPDS study has clearly shown that most oral therapies for diabetes would fail with time, due probably to the progressive decline in beta cell function.[1]

Similarly most of the commonly used medications such as sulfonylureas, thiazolidinediones (TZDs), and insulin are associated with significant weight gain. Sulfonylureas seem to cause this weight gain mainly by producing hypoglycemia secondary to the sustained release of insulin and TZDs through significant fluid retention.

There is a promise that new therapies such as incretins would be effective in reducing HbA1c by maintaining beta cell function and without causing weight gain. This may be particularly advantageous in obese and overweight subgroups of diabetic patients. Two groups are included in this class of new drugs; incretin mimetics (Glucagon-like peptide (GLP-1) analogues such as Exenatide) and incretin enhancers (Dipeptidyl-peptidase four (DPP4) inhibitors, such as Sitagliptin and Vildaglipin).[2]

The first DPP4 inhibitor, Sitagliptin became available in the UAE shortly after approval by the US Food and Drug Administration in October 2006. It was approved for use as monotherapy or in combination with Metformin or a TZD.

Because of the high cost of Sitagliptin and its unknown long term effects and the possible misuse in clinical practice, our group elected to gather their own local experience with the use of Sitagliptin over a one year treatment period in patients who failed to achieve glycemic control (HbA1c < 7%) with insulin sensitizers (Metformin and TZDs). Approval was obtained from the institutional Review Board of the hospital prior of data collection.

Subjects and Methods

Glycemic control (HbA1c) and changes in body weight were analyzed in 53 UAE national patients with type 2 diabetes mellitus (26 men, 27 women) on a combination of Sitagliptin and Metformin. Sitagliptin 100mg once daily was added after inadequate glycemic control (HbA1c > 7%) on a maximum tolerable dose of Metformin (2 g) alone or with a TZD (Rosiglitasone or Pioglitazone) for more than 3 months. The mean age of patients was 52 years (range 21-73) and mean duration of diabetes was 8 years (range 2-21 years). The mean HbA1c at the start of treatment was 8.2% (SD 1.6).

Patients with a medication combination other than Metformin and TZD were excluded.

Exclusion criteria were also type 1 or secondary forms of diabetes, complications of acute metabolic diabetes in the

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past 6 months, congestive heart failure requiring pharmacologic treatment, myocardial infarction, unstable angina, coronary artery bypass surgery in the past 6 months, liver disease, or renal disease or dysfunction.

Statistical analysis

Average values (Mean ± SD) for HbA1c, body weight and BMI, were analyzed both for the period before the start of treatment and after treatment for all patients (n=53). Multivariate Analysis was done on the group of patients who had at least one non-missing value for HbA1c and body weight in both periods (n=44 patients).

The crude effect of treatment was calculated by a linear regression with repeated measurements (SAS PROC MIXED) taking into account the correlation between measurements within patients. In the same model, adjustments were made first for body weight, then for BMI and in the last model for BMI, gender, age, and duration of diabetes.

All analyses were carried out with SPSS 16.0 and SAS 8.01. A p-value of ≤ 0.05 was considered significant.

Results

Mean values of HbA1c, body weight and BMI (before and after treatment), are shown in Table 1, both for the whole sample of patients (n=53) and for those patients with at least one non-missing value before and one non-missing value after treatment (n=44). From the repeated measurements analysis, it was shown that the mean difference in HbA1c between before and after treatment was 0.56% (95% confidence interval 0.24%-0.87%) (Table2). This value doesn't change by adding body weight, BMI, and duration of diabetes to the model.

The trend in the drop in HbA1c was statistically significant ($p \leq 0.05$). The drop in weight and body mass index showed a similar trend to that of HbA1c but was not statistically significant.

Discussion

Type 2 Diabetes is characterized by progressive deterioration in beta cell function with 50% and 60% of the normal beta cell mass lost at the time of diagnosis and at necropsy respectively.[3] The decline in beta cell mass is attributable to accelerated apoptosis and is precipitated by glucotoxicity, lipotoxicity, proinflammatory cytokines, leptin and islet cell amyloid.[4]

The use of drugs such as the thiazolidinediones (TZDs) and incretin mimetics or enhancers has demonstrated antiapoptotic effect with clinical evidence of beneficial effect on human beta cell function.[4]

Incretin hormones are released from the gastrointestinal tract in response to nutrient ingestion to enhance glucose dependant insulin secretion from the pancreas, aid the overall maintenance of glucose homeostasis through slowing of gastric emptying, inhibit glucagon secretion and increase satiety. Of the two major incretins, glucagon-like peptide (GLP-1) and glucose- dependant insulinotropic polypeptide (GIP), only GLP-1 or its mimetics or enhancers have an effect on beta cell function.[5]

Several GLP 1 analogues known as "incretin mimetics" have been developed (e.g. Exenatide and Liraglutide) and are available as injectable forms. Oral "incretin enhancers" (e.g. Sitagliptin and Vildaglipin) exert their effect through the inhibition of an active enzyme dipeptidyl peptidase four (DPP-IV), thus preventing the rapid conversion of GLP1 into its inactive forms.[6] Like GLP-1, DPP4 inhibitors increase glucose insulin mediated secretion and suppress glucagon secretion.

Controversy is still ongoing regarding the cardiovascular safety of TZDs,[7] which has made the single or combined use of this new class of drugs, "incretin mimetics or enhancers", quite appealing. Conversely, The American Association of Clinical Endocrinologists and the European diabetes association have recently endorsed the use of GlP-1 and or DDP4 inhibitors as a second line treatment in the management of diabetes.[8]

The underlying pathophysiological concept is based on the beneficial additive effect of enhanced postprandial GLP-1 achieved with incretins plus the effect of the modifiers of insulin resistance e.g. Metformin or TZDs.[6, 9, 10-15]

Recent clinical trials on the use of DDP-4 inhibitors have shown that their use as single or additive agents is reflected by a drop in mean HbA1c of 0.5% to 1%, depending on the starting HbA1c or the type of therapeutic profile.

In a 24 week study, Chia showed that Sitagliptin reduces HbA1c by 0.6%-0.8% as monotherapy, 1.8% as initial combination therapy with Metformin and 0.7% as add-on-therapy to Metformin.[6]

Similarly, patients with HbA1c $\geq$ 9.0% had greater reductions in placebo subtracted HbA1c (-1.52%) than did those with baseline HbA1c 8.0-9.0% (-0.8%) or HbA1c < 8% (-0.5%).[16]

In addition, no difference in HbA1c measurements was observed between the Metformin-Sitagliptin arm and the Metformin-Rosiglitasone group in Scott's 18 weeks study (0.06%, confidence interval -0.14 to 0.25).[13]

It is of relevance to note that the effect of Sitagliptin on weight, contrary to that seen with insulin and TZDs, is neutral. This effect is observed whether Sitagliptin is used alone or in combination with Metformin or TZDs.[17]

Sitagliptin was used in our study as an adjunct to failed therapy with the insulin sensitizers (Metformin and TZDs) and our results are consistent with those reported above. Of note, the unique features of our study are its one year duration and the population consisting of Middle Eastern diabetics. Most reported studies so far, have evaluated the use of Sitagliptin in a western population and not exceeding 24 weeks duration of treatment.

Table 1: Average Values (±SD) before and after treatment

	For 44 patients with non-missing values* at least once before and once after treatment started		For all 53 patients	
	Average (SD) before treatment started	Average (SD) after treatment started	Average (SD) before treatment started	Average (SD) after treatment started
HbA1c (%)	8.3 (1.5)	7.7 (1.2)	8.2 (1.6)	7.8 (1.4)
Body Weight (kg)	88.0 (18.8)	87.1 (19.3) n.s	88.3 (18.6)	87.0 (18.6) n.s
BMI (m^2/kg)	33.8 (7.7)	33.5 (8.1) n.s	33.6 (7.3)	33.1 (7.5) n.s

*HbA1c/BodyWeight/ DM Duration; n.s: statistically non significant

Table 2: Results of Repeated Measurements analysis: HbA1c difference between before and after treatment for 44 patients with non-missing HbA1c/BodyWeight/Duration of diabetes at least once before and once after treatment started.

	HbA1c (before –after)	95% Confidence Interval	HbA1c (before-after	95% Confidence Interval
Crude	0.56	0.24 – 0.87	0.35	0.09 – 0.61†
Adjusted *	0.57	0.26 – 0.88		
Adjusted **	0.57	0.26 – 0.88		
Adjusted ***	0.56	0.25 – 0.88		

*for Body Weight; † $p \leq 0.001$; ** For BMI; *** For BMI, gender, age, and duration of diabetes

However, a serious limitation of our study is its observational, retrospective rather than prospective nature. Despite this limitation, it shows clearly that Sitagliptin use is associated with an expected, albeit small drop in HbA1c with no serious adverse events. Only 2 patients had to subsequently stop their medication, one patient because of a diffuse skin rash and the other one experienced difficulties in breathing.

To justify its high cost, Sitagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function[4] and preferably used in combination with Metformin in order to achieve the maximum reduction in HbA1c.[6,7]

All recent clinical trials hint to the benefit of the early use, alone or in combination, of any antidiabetic medication. More specifically, GLp-1 or DDP4 inhibitors, have their maximum effect observed when the diabetic process is in its early manifestations.[7] It is also important to note that the DPP4 inhibitors are highly specific with minimal or no effect on DPP-8 or 9. However, inadvertent inhibition of these enzymes has been shown to cause multiorgan toxicities in animals.[4] In addition, it is also relevant to note that the DPP4 system (or CD26) has an immunomodulatory role on T cell activation. Whether long term inhibition of DPP4 enzyme perturbs biological activities of T lymphocytes remains unknown and awaits further long term studies.

Hence, the use by family physicians of DDP4 inhibitors is to be initiated early in the process of the disease, more preferentially in combination with insulin sensitizers while being aware of the current insufficient data on their long term use.

References

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. UKPDS 33 Lancet 1998; 352: 837-853.
2. Halimi S. DPP-4 inhibitors and GLP-1 analogues: for whom? Which place for incretins in the management of type 2 diabetic patients? Diabetes Metab 2008; 34 Suppl 2: S91-S95.
3. Lebovitz HE. Type 2 diabetes: how far have we come? British J Diab & Vasc Dis 2002;2(6):446-49
4. Wajchenberg BL. Beta cell failure in diabetes and preservation by clinical treatment. Endocr Rev 2007; 28:187-218.
5. Drucker DJ. Incretin-based therapies: a clinical need filled by unique metabolic effects. Diabetes Educ 2006; 32:65S-71S.
6. Chia CW, Egan JM. Incretin –based therapies in type 2 diabetes mellitus. J Clin Endocrinol Metab 2008; 93:3703-3716.
7. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356:2457-2471.
8. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsman Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; 15: 540-559.

9. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of Vildaglipin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with Metformin. Diabetes Care 2007; 30:890-895.
10. Gallwitz B. Sitagliptin with Metformin: profile of a combination for the treatment of type 2 diabetes. Drugs Today 2007; 43:681-689.
11. Mikhail N. Combination therapy with DPP-4 inhibitors and pioglitazone in type 2 diabetes: theoretical consideration and therapeutic potential. Vasc Health Risk Manag 2008; 4: 1221–1227
12. Mikhail N. Incretin mimetics and dipeptidyl peptidase 4 inhibitors in clinical trials for the treatment of type 2 diabetes. Expert Opin Investig Drugs 2008; 17:845-853.
13. Scott R, Loeys T, Davies MJ, Engel SS: Sitagliptin Study Group 801. Efficacy and safety of sitagliptin when added to ongoing Metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2008; 10:959-969.
14. Pham DQ, Nogid A, Plakogiannis R. Sitagliptin: a novel agent for the management of type 2 diabetes mellitus. Am J Health Syst Pharm 2008; 65:521-531
15. Miller S, St. Onge EL. Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Ann Pharmacother 2006; 40:1336-1343.
16. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006;29:2632-2637
17. VanDeKoppel S, Choe HM, Sweet BV. Managed care perspective on three new agents for type 2 diabetes. J Manag Care Pharm 2008; 14:363-380.