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Sitagliptin in type 2 diabetes mellitus: Efficacy after five years of therapy

Giuseppe Derosa[a,b,c,*], Angela D'Angelo[a,c], Pamela Maffioli[a,d]

[a] Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
[b] Center for the Study of Endocrine-Metabolic Pathophysiology and Clinical Research, University of Pavia, Pavia, Italy
[c] Laboratory of Molecular Medicine, University of Pavia, Pavia, Italy
[d] PhD School in Experimental Medicine, University of Pavia, Pavia, Italy

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ABSTRACT

The aim of this study was to investigate whether the positive effects of sitagliptin were maintained even after five years of treatment.

Starting from 2008 to today, we treated 624 patients, not well controlled by current therapy, with the addition of sitagliptin 100 mg/die. Patients included 216 subjects treated with metformin, 206 treated with sulfonylureas, and 202 treated with pioglitazone. Sitagliptin was added to metformin, sulfonylureas and pioglitazone in monotherapy, respectively, and the data were compared with those of 620 patients treated with sulfonylureas + metformin, pioglitazone + metformin and pioglitazone + sulfonylureas matched for age, sex, diabetes duration.

We recorded that the addition of sitagliptin to current hypoglycemic therapy led to a reduction of HbA_{1c} similar to that obtained with sulfonylureas after two years. After five years of treatment, changes in HbA_{1c} suggest a better glycemic control over the long term with sitagliptin compared to other treatments, particularly when compared with sulfonylureas. The other parameters evaluated as fasting plasma glucose, post-prandial plasma glucose and insulin levels, confirm the trends observed for the value of HbA_{1c}. Regarding BMI, it increased with sulfonylureas and pioglitazone compared to sitagliptin.

Patients treated with sulfonylureas had a higher incidence of hypoglycemia compared to sitagliptin. In conclusion, sitagliptin seems to maintain its positive effects on glycemia and fasting plasma insulin on the long term.

1. Introduction

Type 2 diabetes mellitus is a chronic disease characterized by a state of insulin resistance in the phase of onset, followed by insufficient production of insulin by the β-cell in the later stages. Because of the progressive nature of the disease, patients with type 2 diabetes mellitus often require multiple therapies to achieve, but especially maintain, an adequate glycemic control [1]. Metformin is usually the first line therapy and it is effective in improving glycemic control, with a good tolerability. In patients who are intolerant to metformin or with contraindications to it, the use of sulfonylureas or pioglitazone is recommended by guidelines [2]. The use of sulfonylureas, however, is burdened with an increased risk of hypoglycemia, especially in elderly patients, with an increased risk of falls. On the other hand, in young patients a prolonged use of sulfonylureas can lead to an early exhaustion of the β-cell, with a therapeutic failure in the long term. Pioglitazone, instead, is surely effective in protecting the functionality of β-cell and in improving insulin sensitivity, but often, alone, is not sufficient to achieve an adequate glycemic control [3]. When monotherapy fails, combination therapy is indicated [2]. Several combinations are effective in reducing glycated hemoglobin (HbA_{1c}), however, the effects on long-term results are different for the various treatments [4,5]. For example, the combination of metformin and sulfonylureas or metformin and pioglitazone lead to a similar improvement in the value of HbA_{1c}, but with a different trend. Glycated hemoglobin value remains unchanged during the first weeks of treatment after the addition of pioglitazone and then falls into the following period. On the other hand, HbA_{1c} value decreased rapidly after the addition of sulfonylureas, but it

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin; FPG, fasting plasma glucose; PPG, post-prandial glucose.

* Corresponding author at: Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, P.le C. Golgi, 2, 27100 Pavia, Italy.
E-mail address: giuseppe.derosa@unipv.it (G. Derosa).

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goes up afterwards, probably due to a progressive depletion of the β-cell. To meet the need to maintain adequate glycemic control even in the long term, adding a dipeptidyl peptidase-4 (DPP-4) inhibitor could be a good alternative. In particular, sitagliptin was the first DPP-4 inhibitor [6] to be marketed. In previously published studies of 30 weeks, sitagliptin, in addition to metformin, significantly improved fasting plasma glucose (FPG) and post-prandial glucose (PPG) and improved parameters of β-cell sensitivity in patients not adequately controlled with metformin alone [7–9]. On the basis of these studies and the experience reported in the literature, we decided to investigate whether the positive effects of sitagliptin were maintained even after five years of treatment.

2. Material and methods

2.1. Study design

This observational study was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy.

The study protocol was approved by the local Ethical Committee and all eligible candidates had to provide signed informed consent before enrolling in the study.

2.2. Patients

We enrolled type 2 diabetic patients, aged >18 of either sex, according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria [10], with poor glycemic control with the current therapy, expressed as HbA_{1c} level ≥8.0%, and in overweight [body mass index (BMI) ≥25, and <30 kg/m^2].

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than three times the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anemia. Patients with serious cardiovascular disease (CVD) (eg, New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment also were excluded. Also patients with previous history of cancer or pathological fractures were excluded, such as patients with previous pancreatitis.

Suitable subjects, identified from review of case notes and/or computerized clinic registers were contacted personally or by telephone. All patients provided written informed consent.

2.3. Treatments

Starting from 2008 to today, we treated 624 patients, not well controlled by current therapy, with the addition of sitagliptin 100 mg/die. The patients included 216 subjects treated with metformin, 206 treated with sulfonylureas, and 202 treated with pioglitazone. Sitagliptin was added to metformin, sulfonylureas and pioglitazone in monotherapy, respectively, and the data were compared with those of 620 patients treated with sulfonylureas + metformin, pioglitazone + metformin and pioglitazone + sulfonylureas matched for age, sex, diabetes duration. During the study, the physicians in charge were allowed to change the dose of current anti-diabetic drugs, but they were not allowed to introduce any other anti-diabetic drugs. The dose of current anti-diabetic drugs could be adjusted at any time during the study to achieve glycemic goals, using standard local guidelines released by Italian Society of Diabetes [11], and as considered appropriate by the investigator for the individual subject. Adjustment to the anti-diabetic drug regimen was carefully implemented so as to avoid events of hypoglycemia. Subjects requiring the addition of other anti-diabetic treatment for safety reasons were discontinued from the study.

2.4. Diet and exercise

All subjects were following a controlled-energy diet (near 600 kcal daily deficit) based on American Heart Association (AHA) recommendations [12] that included 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Patients were not treated with vitamins or mineral preparations during the study.

Individuals were also encouraged to increase their physical activity by walking briskly for 20–30 min, 3–5 times per week, or by cycling. The recommended changes in physical activity throughout the study were not assessed.

2.5. Assessments

For all patients we evaluated: HbA_{1c}, FPG, PPG, fasting plasma insulin (FPI), and body mass index (BMI). We assessed these parameters at baseline, and every 6 months for 60 months since the addition of sitagliptin.

In order to evaluate the tolerability assessments, all adverse events were recorded, with particular focus on: hypoglycemia, developing of bladder cancer or femoral fracture, pancreatitis and pancreatic cancers, strongly debated over years [13–15].

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Glycated hemoglobin level was measured by a high performance liquid chromatography (HPLC) method (DIAMAT, Bio-Rad, USA; normal values 4.2–6.2%), with intra- and interassay coefficients of variation (CsV) of <2% [16].

Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV of <2% [17].

Plasma insulin was assayed with Phadiaseph insulin radio immuno assay (RIA) (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV 4.6 and 7.3%, respectively) [18].

2.6. Statistical analysis

We reported all continuous variables with a normal distribution as means and standard deviations. We used an analysis of variance to analyze continuous laboratory measurements and to perform comparisons among the study groups. For glycemic measures a mixed model for repeated measures was used to analyze the change from baseline.

Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 20.0 (SPSS Inc., Chicago, IL, USA) [19].

3. Results

3.1. Study sample

Patients characteristics are listed in Table 1. The trend of various parameters during the 60 months of follow-up is reported in Tables 2–4 and Figs. 1–3.