Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Effects of concomitant drugs on sitagliptin-mediated improvement in glycemic control in Japanese patients with type 2 diabetes

Takumi Hirata[a,*], *Kouichi Inukai*[b], *Jiro Morimoto*[c], *Shigehiro Katayama*[d], *Hitoshi Ishida*[b]

[a] *Foundation for Biomedical Research and Innovation, Kobe, Japan*
[b] *Third Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan*
[c] *Department of Internal Medicine, Saitama Social Insurance Hospital, Saitama, Japan*
[d] *Department of Endocrinology and Diabetes, School of Medicine, Saitama Medical University, Saitama, Japan*

ARTICLE INFO

Article history:
Received 16 December 2013
Accepted 18 January 2014
Available online 14 February 2014

Keywords:
Sitagliptin
Glycemic control
Concomitant drugs
Type 2 diabetes

ABSTRACT

Aims: We investigated to clarify factors associated with the efficacy of sitagliptin, a dipeptidyl peptidase (DPP)-IV inhibitor, for glycemic control including the confounding effect of concomitant drugs in patients with type 2 diabetes.
Methods: We included type 2 diabetes patients with HbA1c levels of ≥7% who were not under insulin treatment and were administered sitagliptin (50 mg/day for 6 months). Reduction or discontinuation of insulin sensitizers was not permitted during the study period. Outcomes included HbA1c level variations and attaining a target HbA1c level of <7%. Associated factors with each outcome were examined using multivariate analysis.
Results: Of the 313 patients enrolled in this study, 147 (47.0%) attained HbA1c levels of <7%. High baseline HbA1c levels were associated with HbA1c level variations but inversely associated with attaining the target HbA1c level of <7%. Concomitant use of an insulin sensitizer and a α-glucosidase inhibitor and maintenance of the baseline dose of concomitant drugs were significantly associated with each outcome.
Conclusions: Our results suggest that concomitant sitagliptin administration (50 mg/day) will improve glycemic control if treatment is initiated before HbA1c levels deteriorate. Other medication should be continued at initiation of sitagliptin administration.

1. Introduction

Sitagliptin is one of the major dipeptidyl peptidase (DPP)-IV inhibitors that has been commercially available in Japan since 2009, and it is currently a vital drug in diabetes treatment. Sitagliptin improves glycemic control because it inhibits glucagon secretion, augments glucagon-like peptide-1 (GLP-1) secretion, resulting in an increased insulin secretion [1–4]. Previous reports showed the hypoglycemia risk associated with sitagliptin was comparable with that with other antidiabetic agents, and sitagliptin treatment has been indicated to be safe

* *Corresponding author at*: Foundation for Biomedical Research and Innovation, 1-6-5 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan. Tel.: +81 78 302 5868; fax: +81 78 303 8482.
E-mail addresses: t-hirata@fbri.org, tkm2006diabetes@yahoo.co.jp (T. Hirata).
1751-9918/$ – see front matter
http://dx.doi.org/10.1016/j.pcd.2014.01.008

in a meta-analysis [5–8]. Several reports have revealed its efficacy for glycemic control and have listed the factors associated with its efficacy [9–11]. However, these studies have defined the outcome HbA1c level variations during the investigation, and no study has defined the outcome as attaining a target HbA1c level. Furthermore, none of these studies considered the confounding effect of concomitant drugs during DPP-IV inhibitor therapy, and few reports have provided a detailed analysis of concomitant drug use. Changes in the dose of insulin sensitizers, such as biguanides and thiazolidinediones, during the study period is known to alter insulin resistance levels, making it difficult to evaluate the individual effect of sitagliptin on glycemic control.

In this study, sitagliptin (50 mg/day for 6 months) was administered with fixed doses of insulin sensitizers to type 2 diabetes patients with inadequate glycemic control (HbA1c levels ≥7%), and the effects on glycemic control were examined. Factors associated with improved glycemic control, including the confounding effect of concomitant drugs, were also studied. Indicators of improved glycemic control were HbA1c level variations and the proportion of patients who attained the recommended target HbA1c level of <7% [12,13].

2. Methods

2.1. Participants, study design, and setting

We included type 2 diabetes patients with HbA1c levels ≥7% who visited Saitama Medical University and several other hospitals in Japan from January to March 2011. We excluded patients treated with insulin, incretin mimetics, and GLP-1 analogs, as well as those with severe liver dysfunction (alanine aminotransferase level ≥ 100 IU/L) and renal dysfunction (serum creatinine ≥ 2.0 mg/dL). All subjects provided informed written consent, and all participating hospitals followed the protocol approved by the Ethics Committee of Saitama Medical University.

Sitagliptin (50 mg/day) was administered to all participants during outpatient visits for a minimum of 24 weeks. Dose reduction or withdrawal from oral hypoglycemic agents (OHAs), such as the sulfonylureas (SUs), glinides, and α-glucosidase inhibitors (α-GIs), was permitted. In patients receiving high-dose SUs (glimepiride ≥ 3 mg/day), SU doses were decreased to recommended doses (glimepiride ≤ 2 mg/day) to allow for the appropriate use of incretin-related agents [14]. However, changes in the doses of biguanides or thiazolidinediones were not allowed after sitagliptin initiation. During the treatment period, all the doses of the co-administered OHAs remained constant.

2.2. Measurements

Clinical characteristics such as gender, age and height were obtained from medical records. Body weight was measured during outpatient visits conducted at 0 and 6 months of sitagliptin administration, and body mass index (BMI) was calculated at both time points. Plasma glucose, HbA1c, and immunoreactive insulin (IRI) levels were measured after overnight fasting. Plasma glucose was determined using the glucose oxidase method. HbA1c levels were measured using high-performance liquid chromatography and were expressed as national glycohemoglobin standardization program (NGSP) values. Serum IRI levels were determined using chemiluminescence enzyme immunoassay (CLEIA) methods. The homeostasis model assessment of insulin resistance (HOMA-IR) values was calculated using the following formula: HOMA-IR = IRI (μU/mL) × glucose (mg/dL)/405.

2.3. Statistical analysis

Continuous variables were presented as the mean ± standard deviation or the median and the interquartile range, whereas categorical variables were presented as numbers and percentages. The Wilcoxon signed-rank test was used to compare BMI, glucose, HbA1c, and HOMA-IR levels. The factors associated with HbA1c level variations during the 6 months were analyzed using univariate and multivariate linear regression analysis. The outcome variable in these analyses was the difference in the mean HbA1c level obtained at 0 and 6 months of sitagliptin administration (continuous). We also analyzed factors associated with attaining HbA1c levels of <7% at 6 months after sitagliptin initiation using univariate and multivariate logistic regression analyses. The outcome variable in this analysis was attaining the target HbA1c level of <7% at 6 months after sitagliptin initiation (categorical). The independent variables in both multivariate analyses were gender (categorical: male/female), age (continuous), baseline HbA1c level (continuous), baseline HOMA-IR value (continuous), concomitant administration of OHAs [insulin sensitizers (biguanides and thiazolidinediones), insulin secretagogues (SUs and glinides) and α-GIs] (categorical, yes/no for each drug) and reduction or withdrawal of OHA (insulin secretagogues and α-GIs; categorical, yes/no for each drug). Multivariate analyses were performed using a backward selection method. Variables with p values of ≥0.10 were removed from the model, p values of <0.05 was considered statistically significant. All analyses were used STATA SE 11 data analysis and statistical software (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Clinical characteristics of participants at baseline and endpoint

Clinical characteristics of participants at 0 and 6 months after sitagliptin initiation are shown in Table 1. The number of patients taking each concomitant drug before and after sitagliptin administration and the respective doses are shown in Table 2. There were 313 patients in this study, 62.0% were males and the mean age was 64.0 years. Two hundred and twelve patients (67.7%) were receiving SUs or biguanides (67.1%) before sitagliptin administration, and 134 patients (42.8%) were taking α-GIs. Thirteen of the 212 patients (6.1%) discontinued the SUs when sitagliptin administration began, whereas SU dose was decreased in 71 patients (33.5%). Forty-five patients (14.4%) were receiving high-dose SUs (glimepiride ≥ 3 mg/day) and SU dose was decreased to the recommended dose (equivalent to glimepiride ≤ 2 mg/day) in