Factors involved in decreasing the therapeutic effect of sitagliptin: a subanalysis of the JAMP study

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Abstract

Objective As a subanalysis of the Januvia Multicenter Prospective Trial in Type 2 Diabetes (JAMP study), we examined factors that decreased blood glucose control effect of sitagliptin after 3 months and patients requiring an addition or increase of diabetes treatment.

Methods We selected patients in whom glycated hemoglobin (HbA1c) levels decreased by month 3 after initiation of sitagliptin treatment and conducted two analyses: (1) in patients who did not change drugs until month 12, we compared changes in HbA1c levels between concomitant drugs and examined factors that decreased blood glucose control effect of sitagliptin; (2) compared changes in HbA1c levels and backgrounds between patients who did and did not require an addition to or increased dose of the antidiabetic agent.

Results Four hundred and ninety-eight patients were chosen. In 369 patients without drug change until month 12, changes in HbA1c levels during months 3–12 were not significantly different among concomitant drugs; factors causing rebound HbA1c were smoking and weight gain. Patient characteristics were compared between those who did and did not require an additional drug or a dose increase ($n = 114$) ($n = 384$). Drug changes were associated with longer disease duration, younger age, higher rate of smoking, and higher degree of insulin resistance but not with concomitantly administered drugs.

Conclusion Smoking and weight gain were factors that decreased the effect of sitagliptin on reducing blood glucose levels. Differences in concomitant drugs did not affect sitagliptin's effects on glycemic control. A dose increase or the addition of the antidiabetic drug was not associated with concomitant drugs.

Keywords DPP4-inhibitor · Type 2 diabetes mellitus · Sitagliptin · HbA1c rebound factor · Decreasing the therapeutic effect

Introduction

Sitagliptin controls blood glucose levels by increasing insulin secretion through inhibition of dipeptidyl peptidase (DPP)-4, an enzyme that degrades incretin, and by suppressing excess glucagon secretion. Hypoglycemia is unlikely to occur [1] because the action of the drug is dependent on blood glucose level; also, weight gain can be prevented [2].

Moreover, this effect lasts by administering sitagliptin once a day. Thus, sitagliptin is easy to use for both physicians and patients, and problems inherent to diabetes treatment, such as weight gain and dose frequency, can be solved by using sitagliptin. This drug is widely used in clinical settings.

Long-term studies of sitagliptin [3, 4] have described improvements after about 3–4 months of therapy, with the effect continuing thereafter. Fewer safety concerns were reported with sitagliptin therapy compared with placebo [3]. After long-term administration of sitagliptin, a reduction in the therapeutic effect was seen in a small number of patients. Kahn et al. reported that the effects of sulfonylurea, biguanide, and thiazolidinedione drugs on glycemic control are decreased when they are administered over the long term [5]. In the diabetes study, a certain number of patients had

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drugs added to their therapy or a dose increase to reduce glycemic levels. However, these patients are included in the full set or the intent-to-treat analysis. So, factors involved in reducing the efficacy of sitagliptin or patient background requiring a change in the administered drug must be analyzed separately.

Some factors that decrease long-term glycemic control by sitagliptin treatment have been reported [6–9]. A reduction in the effect 6 months after therapy initiation was caused by weight gain in some cases, which was generally a result of low adherence to diet/exercise therapy. However, those studies included discontinued antidiabetic drugs or drugs for which the dose was decreased at the start of sitagliptin treatment [6–8], and the influence of those other drugs could not be ruled out. Moreover, pretreatment drugs were not subdivided [9]. To analyze the factors that decrease the efficacy of sitagliptin, patients included in the analysis should be limited to those receiving sitagliptin in addition to other drugs that were neither discontinued nor reduced in dose at the start of the study. Additionally, it should involve patients undergoing monotherapy or multidrug therapy with different kinds of concomitant drugs, such as sulfonylureas, biguanides, and thiazolidinediones.

We conducted the JAMP study at multiple centers and obtained data for the 12-month period after additional administration of sitagliptin to the pre-existing therapy. As a subanalysis of the study, we examined factors that decreased sitagliptin's effect on controlling blood glucose after 3 months of treatment and of patients requiring addition/increased treatment.

Methods

Study design

This open-label, central registration, multicenter, prospective observational study was conducted at Tokyo Women's Medical University Hospital and 69 collaborating institutions in Japan. Patients were enrolled from 11 January 2011 to 30 June 2013 and followed up until 30 June 2014. This study was conducted with the approval of the ethics committee of Tokyo Women's Medical University (UMIN000019154).

Study subjects

The study subjects were male or female outpatients ≥ 20 years with type 2 diabetes mellitus (DM) with inadequately controlled blood glucose levels [glycated hemoglobin (HbA1c) level of $\geq 6.9\%$ or a fasting blood glucose level of ≥ 130 mg/dl during the observation period) after at least 1 month of receiving diet/exercise therapy and/or antidiabetic drug therapy orally. At the start of the study, in

2011, HbA1c values were expressed according to The Japan Diabetes Society levels, the standard system in Japan, but were changed to National Glycohemoglobin Standardization Program (NGSP) system values at the end of the study in accordance with the "Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus (Revision for International Harmonization)," issued by The Japan Diabetes Society [10]. Pursuant to the above change, the lower limit of inadequate blood glucose control was also changed. Therefore, patients with an HbA1c level of $\geq 6.9\%$ were enrolled at the start of the study.

Patients who met any of the following criteria were excluded from the study: (i) history of severe ketosis, diabetic coma, or precoma within the past 6 months; (ii) severe infection before or after surgical treatment, or serious external injury; (iii) pregnancy, possible pregnancy, or lactation; (iv) moderate renal impairment (serum creatinine level ≥ 1.5 mg/dl in men and ≥ 1.3 mg/dl in women); (v) on insulin therapy; (vi) on treatment with rapid-acting insulin secretagogues; (vii) history of allergy to any ingredients in the study drug; and (viii) a medical reason that made the patient unsuitable for participation in the study, as judged by the investigator.

Treatment

The pre-existing therapy for type 2 DM was not changed during the observation period or throughout the entire study period (for the first 3 months after add-on sitagliptin). Thereafter, sitagliptin (50 mg) was administered once daily as first-line treatment (single-drug therapy) or as additional treatment (combination therapy; Fig. 1). During the 3-month period after initiation (baseline), sitagliptin administration was continued without the addition of any other drugs or dose increases. At 3 months, sitagliptin dose was increased from 50 to 100 mg/day and other antidiabetic drugs were added, changed, or discontinued at the investigator's discretion. No restrictions were imposed on the use of drugs for treating concurrent diseases, but dose changes or the addition of new drugs were avoided whenever possible during the study period.

Assessments

Data from patients in whom HbA1c levels decreased by month 3 after were extracted. Patients whose HbA1c levels were measured until 12 months after the start of therapy were chosen. Because the study allowed for drug changes 3 months after treatment initiation, it was difficult to uniformly assess influencing factors in patients with or without drug change. To address this issue, we analyzed the factors influencing continuation or reduction of the effect according to the two steps below (Fig. 2):

Fig. 1 Study design. *Criteria on poor glycemic control: HbA1c $\geq 6.9\%$ or fasting blood glucose ≥ 130 mg/dl. #Study-specific test (arbitrary): GA, anhydroglucitol (1,5-AG), C-peptide, proinsulin/insulin ratio

Fig. 2 Analysis flow

1. Analysis of patients who did not require a drug change (comparison of changes in HbA1c levels in groups based on the concomitant drug used, and multiple regression analysis of factors that decreased the effect); and
2. Comparison of changes in HbA1c levels and medical history between patients who did and did not require an addition to or increased dose of the antidiabetic agent

(the latter included patients who had no drug change and those who had a drug discontinuation or dose reduction).

Statistical analysis

1. The changes in the HbA1c levels by concomitant drugs in the group without drug change were compared using analysis of variance (ANOVA). To analyze factors reducing the glycemic control effect of sitagliptin, single regression analysis was first performed with changes in HbA1c levels from 3 to 12 months after starting therapy used as objective variables, and parameters such as age or sex were used as explanatory variables. Multiple regression analysis was then performed on factors with $p < 0.25$ in the single-regression analysis.
2. Changes in HbA1c levels in patients with or without drug addition/dose increase were compared using the Student's t test. Patient characteristics were compared using the Student's t test (continuous data) or the chi-square test (nominal data).

The significance threshold was set at a two-sided p value < 0.05 . Multiplicity was considered. All statistical analyses

were performed using the JMP software program, version 12.1.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 651 patients in whom efficacy was assessed in the JAMP study, 498 were assessed in this subanalysis; these patients met requirements such as a decrease in HbA1c levels at month 3 of therapy and availability of HbA1c values until month 12 of therapy. Of these patients, 369 (74.1%) did not undergo any changes in their drug therapy, 15 (3.0%) had a dose discontinuation or reduction, and 114 (22.9%) had a drug added or a dose increase (Fig. 3).

In patients without drug change until month 12 of therapy, no significant differences in changes in HbA1c levels were found from months 3 to 12 of therapy, regardless of the kind of concomitant drug used (Table 1). Additionally, in the analysis of HbA1c rebound factor in cases without drug change until 12 months, smokers and patients who gained weight between months 3 and 12 were more likely to rebound HbA1c (Table 2). Factors affecting the change

Fig. 3 Patient flow

Table 1 Changes in glycated hemoglobin (HbA1c) levels by pretreatment drug

	<i>n</i>	0 months	3 months	12 months	0–3 months	3–12 months
Diet/exercise therapy alone	110	7.46 ± 0.76	6.67 ± 0.56	6.66 ± 0.62	− 0.79 ± 0.54	− 0.01 ± 0.56
Low dose of glimepiride	42	7.50 ± 0.52	6.67 ± 0.49	6.87 ± 0.77	− 0.83 ± 0.40	0.20 ± 0.51
Medium dose of glimepiride	22	8.05 ± 0.85	7.37 ± 0.79	7.59 ± 0.78	− 0.68 ± 0.45	0.21 ± 0.74
BG	51	7.74 ± 1.01	6.95 ± 0.92	6.99 ± 0.97	− 0.78 ± 0.46	0.04 ± 0.58
TZD	22	7.37 ± 0.46	6.52 ± 0.42	6.56 ± 0.51	− 0.85 ± 0.43	0.05 ± 0.34
α-GI	9	7.11 ± 0.43	6.47 ± 0.31	6.59 ± 0.42	− 0.64 ± 0.23	0.12 ± 0.24
Multidrug therapy	113	7.88 ± 0.98	6.97 ± 0.68	7.11 ± 0.91	− 0.91 ± 0.63	0.13 ± 0.6
<i>p</i> (ANOVA)		0.000	0.000	0.000	0.362	0.294

BG biguanide, TZD thiazolidine, α-GI α-Glucosidase inhibitor, ANOVA analysis of variance

Table 2 Factors decreasing glycated hemoglobin (HbA1c) in patients without drug change until month 12: analysis of factors causing changes in HbA1c levels (3–12 months)

Variables	Single regression analysis				Multiple regression analysis			
	Regression coefficients	Lower limit of 95% CI	Upper limit of 95% CI	<i>P</i> value	Partial regression coefficient	Lower limit of 95% CI	Upper limit of 95% CI	<i>P</i> value
Sex (male)	0.041	− 0.080	0.162	0.501				
Age	− 0.004	− 0.009	0.002	0.173	− 0.003	− 0.061	0.055	0.925
Smoking	0.226	0.079	0.373	0.003*	0.192	0.042	0.342	0.013*
Alcohol consumption	0.081	− 0.035	0.197	0.169	− 0.029	− 0.145	0.088	0.627
Duration of diabetes (year)	0.007	− 0.003	0.017	0.177	0.003	− 0.006	0.013	0.495
SBP (mmHg)	− 0.004	− 0.007	0.000	0.048*	− 0.004	− 0.008	0.000	0.060
BMI (kg/m ²)	0.006	− 0.008	0.021	0.366				
HbA1c (%)	0.001	− 0.067	0.069	0.982				
Weight variations (3–12 months) (kg)	0.085	0.057	0.113	< 0.001*	0.081	0.054	0.109	< 0.001*
Antihypertensive drug use	− 0.070	− 0.188	0.047	0.238	− 0.084	− 0.203	0.036	0.169
Diet/exercise therapy alone	− 0.136	− 0.263	− 0.009	0.036*	− 0.076	− 0.214	0.063	0.283
Low-dose glimepiride	0.131	− 0.053	0.315	0.161	0.148	− 0.036	0.331	0.114
Medium-dose glimepiride	0.138	− 0.109	0.385	0.272				
BG	− 0.054	− 0.223	0.115	0.532				
TZD	− 0.041	− 0.288	0.206	0.746				
α-GI	0.039	− 0.340	0.419	0.838				
Multidrug therapy	0.072	− 0.055	0.199	0.265				

BG biguanide, TZD thiazolidine, α-GI α-Glucosidase inhibitor, ANOVA analysis of variance, CI confidence interval

* *P* < 0.05 single or multiple regression analysis

in HbA1c from 0 to 3 months for reference are shown in supplemental Table S1.

Patient characteristics of those who did and did not have drugs added or dose increased are shown in Table 3. Although changes in HbA1c levels were associated with many parameters such as age or smoking between groups, no differences were associated with concomitantly administered drugs (Table 3). HbA1c levels at the start of the study were significantly higher and changes in HbA1c levels 3 months later significantly larger in the group with added drugs or a dose increase (Fig. 4).

Discussion

Many studies have reported that patients with higher baseline HbA1c levels are likely to show a larger decrease in HbA1c levels during therapy [11, 12]. Thus, the JAMP study first normalized changes in HbA1c levels to baseline values. Although the group received a medium dose of glimepiride, patients showed a smaller decrease in HbA1c levels at the start of the study [13]. No other factors significantly influenced these changes. In this study, analysis of

Table 3 Comparison of patient characteristics

	Drug addition/dose increase (<i>n</i> = 114)	No drug addition/dose increase (<i>n</i> = 384)	<i>P</i> value
Sex (male)	81 (71.1)	245 (63.8)	0.153
Smoking	36 (32.4)	69 (18.4)	0.002*
Alcohol consumption	56 (50.5)	170 (45.6)	0.366
Hypertension	66 (57.9)	238 (62)	0.432
Dyslipidemia	82 (71.9)	246 (64.1)	0.120
Hyperuricemia	9 (7.9)	39 (10.2)	0.472
Retinopathy	16 (14)	21 (5.5)	0.002*
Arteriosclerotic obliterans	19 (16.7)	25 (6.5)	0.001*
Atrial fibrillation	3 (2.6)	10 (2.6)	0.987
Renal disease	11 (9.6)	25 (6.5)	0.256
Antihypertensive drug use	57 (50)	205 (53.4)	0.525
Diet/exercise therapy	29 (25.4)	110 (28.6)	0.503
Low dose of glimepiride	11 (9.6)	45 (11.7)	0.539
Medium dose of glimepiride	9 (7.9)	23 (6)	0.466
BG	22 (19.3)	53 (13.8)	0.150
TZD	6 (5.3)	23 (6)	0.771
α -GI	3 (2.6)	9 (2.3)	0.860
Multidrug therapy	34 (29.8)	121 (31.5)	0.733
Age (year)	59.6 $\pm$ 10.8	65.6 $\pm$ 10.8	< 0.001*
Duration of diabetes (year)	10.1 $\pm$ 7.7	8.4 $\pm$ 6.2	0.017*
SBP (mmHg)	128.4 $\pm$ 14.6	131 $\pm$ 15.2	0.109
BMI (kg/m ²)	25.4 $\pm$ 3.5	25.1 $\pm$ 4.2	0.386
HOMA-R	8.49 $\pm$ 1.19	7.67 $\pm$ 0.87	< 0.001*
HOMA- β (%)	3.19 $\pm$ 1.99	2.7 $\pm$ 1.74	0.038*
Fasting C-peptide (ng/mL)	23.9 $\pm$ 15.3	35.8 $\pm$ 30.1	0.001*
UACR (mg/g Cre)	93.8 $\pm$ 369	51.8 $\pm$ 257.2	0.329
eGFR (mL/min/1073m ²)	82.8 $\pm$ 20.2	76.3 $\pm$ 17.3	0.001*
HbA1c (0 months) (%)	8.49 $\pm$ 1.19	7.67 $\pm$ 0.87	< 0.001*
HbA1c (3 months) (%)	7.44 $\pm$ 0.89	6.83 $\pm$ 0.69	< 0.001*
HbA1c (12 months) (%)	7.55 $\pm$ 0.99	6.92 $\pm$ 0.82	< 0.001*
Body weight (0 months) (kg)	69.5 $\pm$ 13.4	65.9 $\pm$ 14.3	0.018*
Body weight (3 months) (kg)	69.4 $\pm$ 13.4	66 $\pm$ 14.5	0.027*
Body weight (12 months) (kg)	69.1 $\pm$ 13.8	65.8 $\pm$ 14.2	0.031*
Body weight variation (3 months) (kg)	0.2 $\pm$ 1.9	- 0.1 $\pm$ 1.6	0.107
Body weight variation (3 months $\rightarrow$ 12 months) (kg)	- 0.3 $\pm$ 2.4	- 0.1 $\pm$ 2.1	0.606

BG biguanide, TZD thiazolidine, α -GI α -Glucosidase inhibitor, SPB systolic blood pressure, BMI body mass index, HOMA- β homeostasis model assessment–beta cell function, HOMA-R homeostasis model assessment–insulin resistance, UACR urine albumin-to-creatinine ratio, eGFR estimated glomerular filtration rate, HbA1c glycated hemoglobin

* p < 0.05 chi-square test or Student's t-test, Data presented as *n* (%) or mean $\pm$ SD

factors that decreased the therapeutic effect showed there was a more significant reduction in the effect of sitagliptin on lowering HbA1c levels in the group without drug changes when patients were smokers or had gained weight from between months 3 and 12 of therapy. These results suggest that the glycemic control effect of sitagliptin would decrease over time in smokers or who gained weight. The effect noted in smokers can be attributed to the inhibition

of endocrine pancreatic function due to smoking [14, 15]. In addition, the effect of sitagliptin is reduced in patients with high blood DPP-4 levels [16]; some reports indicate a correlation between blood DPP-4 levels and body mass index [17]. Weight gain was previously reported to weaken the glycemic control effect of sitagliptin [6, 8, 9], which was confirmed by the results of our study. Although sitagliptin is unlikely to cause increased appetite [18, 19], it is

Fig. 4 Changes in glycated hemoglobin (HbA1c) levels by drug addition/dose increase. * $P < 0.001$ vs month 0; repeated measures analysis of variance (ANOVA) with Bonferroni correction. † $P = 0.002$; Student's t test

important to not rely exclusively on its characteristics but rather to continue diet/exercise therapy to prevent weight gain. Kubota et al. reported that a high dose of glibenclamide administered concomitantly weakened the glycemic control effect of sitagliptin [9]. In our study, there was no significant difference by agent for reduction of effect, which may be one reason that sulfonylurea (SU) drugs were limited to glimepiride.

We then investigated the characteristics of patients who did and did not require addition/dose increase of antidiabetic agents to improve glycemic control. In multiple differences between groups, an inverse relationship was noted between blood DPP-4 levels and age in patients requiring increased or additional medication [17], and our study supported this finding. We also found that group to comprise younger patients. The significantly high estimated glomerular filtration rate in that group was largely a result of age differences rather than differences in renal function. The need for drug addition/dose increase in patients with long-term diabetes and insulin resistance might be explained by exhaustion of the pancreas.

Changes in HbA1c levels after 3 months were greater in the group requiring addition/dose increase after 3 months, indicating that the probable subsequent return of HbA1c levels to baseline or the need for addition/dose increase is difficult to anticipate based only on changes in HbA1c levels

after 3 months. An analysis by pretreatment drug showed no differences between groups, which also indicates the difficulty in detecting a future reduction in effect when drugs are administered concomitantly. However, smoking is considered a factor in HbA1c levels returning to baseline in the group not requiring drug change and a significantly higher rate in the group requiring addition/dose increase. Moreover, weight gain decreased blood glucose control among patients without drug change. Therefore, improving lifestyle is important to achieve a permanent effect. Our results showed that in the group that did not require addition/dose increase, HbA1c remained at almost the same level, ranging from 6.83% at 3 months to 6.92% at 12 months, and each value was <7% on average. This group included some patients whose values returned to baseline but who had favorable glycemic control in general; thus, glycemic control seemed to be generally maintained by sitagliptin alone. Of patients in whom lower HbA1c levels were noted at 3 months, 77.1% had a continuous effect when patients with a discontinuation/dose reduction were included. Some reports suggest that an increase in blood glucose levels in patients with type 2 diabetes mellitus, despite intervention with diet/exercise therapy or treatment, is caused by a decrease in the number of pancreatic beta cells [20, 21] or a decline in their function [22]. This data has not been reported for humans, but sitagliptin [23] and other DPP-4 inhibitors [24] seem to have

a protective or proliferative effect on pancreatic beta cells. These pharmacological mechanisms can explain the last-ing effect of sitagliptin, even with long-term administration. Given the safety and efficacy demonstrated by long-term studies, sitagliptin is considered a useful option for long-term diabetes treatment.

Limitations

This was an exploratory subanalysis performed under actual treatment conditions in clinics. Patients with no efficacy information at month 3 after starting therapy or with discontinuation/withdrawal before month 12 of therapy were excluded from the analysis. Thus, patient selection was likely biased. In addition, because there was a long interval between data collection (i.e., between months 3 and 12), it was impossible to assess action efficacy against HbA1c levels returning to baseline when the event occurred. Because glimepiride was the only SU drug used by patients in this study, results may not be applicable to other SU drugs.

Conclusion

Smoking and weight gain are factors that decreased the effect of sitagliptin on reducing blood glucose levels. Importantly, differences in concomitant drugs did not affect its effects on glycemic control. Patient characteristics that warrant an addition/dose increase of the antidiabetic drug included long disease duration, younger age, smoking, and high insulin resistance. On the other hand, if a patient shows an improvement in HbA1c levels after 3 months of therapy, glycemic control with sitagliptin can be continued without changing the drug. Additional administration of sitagliptin in patients with poorly controlled blood glucose levels indicates the possibility of long-term glycemic management. However, by considering factors that decrease the effect of sitagliptin, treatment for patients who have poorly controlled blood glucose levels may be more effective.

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Compliance with ethical standards

Conflict of interest Hiroshi Sakura received honoraria from Mitsubishi Tanabe Pharma Corporation and research grant from Ono Pharmaceutical Co., Ltd. Other authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The ethics committee at the Tokyo Women's Medical University approved the study (Approval Number: 2064) on 11 January 2011. Informed consent or substitute was obtained from all patients included in the study.

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