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Predictive Clinical Parameters and Glycemic Efficacy of Vildagliptin Treatment in Korean Subjects with Type 2 Diabetes

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Background: The aims of this study are to investigate the glycemic efficacy and predictive parameters of vildagliptin therapy in Korean subjects with type 2 diabetes.
Methods: In this retrospective study, we retrieved data for subjects who were on twice-daily 50 mg vildagliptin for at least 6 months, and classified the subjects into five treatment groups. In three of the groups, we added vildagliptin to their existing medication regimen; in the other two groups, we replaced one of their existing medications with vildagliptin. We then analyzed the changes in glucose parameters and clinical characteristics.
Results: Ultimately, 327 subjects were analyzed in this study. Vildagliptin significantly improved hemoglobin A1c (HbA1c) levels over 6 months. The changes in HbA1c levels (ΔHbA1c) at month 6 were -2.24% (P=0.000), -0.77% (P=0.000), -0.80% (P=0.001), -0.61% (P=0.000), and -0.34% (P=0.025) for groups 1, 2, 3, 4, and 5, respectively, with significance. We also found significant decrements in fasting plasma glucose levels in groups 1, 2, 3, and 4 (P<0.05). Of the variables, initial HbA1c levels (P=0.032) and history of sulfonylurea use (P=0.026) were independently associated with responsiveness to vildagliptin treatment.
Conclusion: Vildagliptin was effective when it was used in subjects with poor glycemic control. It controlled fasting plasma glucose levels as well as sulfonylurea treatment in Korean type 2 diabetic subjects.

Keywords: Diabetes mellitus; Dipeptidyl peptidase 4; Dipeptidyl peptidase 4 inhibitor; Vildagliptin

INTRODUCTION

Recent studies have explored the incidence of complications in diabetic populations and emphasized the need for strict glucose control to reduce the incidence of these complications [1,2]. However, tight glycemic control is associated with hypoglycemic events and is an especially big burden in patients with type 2 diabetes mellitus (T2DM) who are at risk for cardiovascular disease [2]. Although many patients with T2DM require treatment with a combination of oral hypoglycemic agents to achieve the goal of glycemic control, clinicians must consider choosing a hypoglycemic agent in individual patients carefully, and should be aware of the complex pathophysiological defects associated with diabetes.

Vildagliptin is an orally administered dipeptidyl peptidase-4 (DPP-4) inhibitor that increases active glucagon-like peptide-1 (GLP-1) by inactivating the DPP-4 enzyme. Vildagliptin improves glycemic control in type 2 diabetic subjects by increasing both α- and β-cell sensitivity to glucose [3-6] and decreases the risk of weight gain and hypoglycemia. Because the vilda-

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gliptin/DPP-4 interaction has slow kinetics, vildagliptin continues to raise intact incretin levels beyond detectable plasma drug levels [7]. A regimen of 50 mg twice daily increases intact GLP-1 fasting plasma levels by more than 2-fold [4]. The elevation of intact GLP-1 plasma levels in patients on vildagliptin treatment can have several favorable metabolic effects. There are many randomized controlled clinical trials that showed the efficacy of vildagliptin [8-10] and compared it to other oral antidiabetic drugs. Vildagliptin is effective when used as an add-on to metformin [11-13], thiazolidinediones [14,15], sulfonylureas [16], and insulin [17,18]. However, only a few studies have shown the efficacy of vildagliptin in Asian type 2 diabetic subjects [19-21]. Here, we address not only the efficacy of vildagliptin, but also the factors affecting the effectiveness of vildagliptin in real practice with type 2 diabetic subjects in Korea.

METHODS

Subjects

In this retrospective study, we recruited subjects with T2DM who were initially prescribed vildagliptin in Seoul St. Mary's Hospital between August 2009 and February 2011. Subjects aged 18 to 85 years were included. Subjects either had a history of using 1 or 2 oral hypoglycemic agents, including metformin, with a stable dosage for more than 3 months, or had never used any antidiabetic medications. Subjects who had taken vildagliptin for less than 6 months, or combined with insulin during the observational period, were excluded from the analysis. We also excluded subjects who had received drugs that may affect blood glucose status during the study period, such as systemic glucocorticoids, or who had a serious medical illness, such as liver cirrhosis, end-stage renal disease, or any kind of cancer.

Assessments

Based on previous medication use, the subjects were divided into the following five treatment groups: group 1, drug naïve subjects treated with a combination of metformin and vildagliptin; group 2, vildagliptin added to existing metformin treatment; group 3, vildagliptin added to existing metformin and sulfonylurea treatment; group 4, sulfonylurea replaced with vildagliptin in existing metformin and sulfonylurea treated group; and group 5, glinide replaced with vildagliptin in existing metformin and glinide treated group (Fig. 1). We have thus called groups 1, 2, and 3 "add-on" vildagliptin groups (since vildagliptin was added to their treatment), and groups 4 and 5 "switch-over" vildagliptin groups (since these subjects were switched to vildagliptin from sulfonylurea or glinide treat-

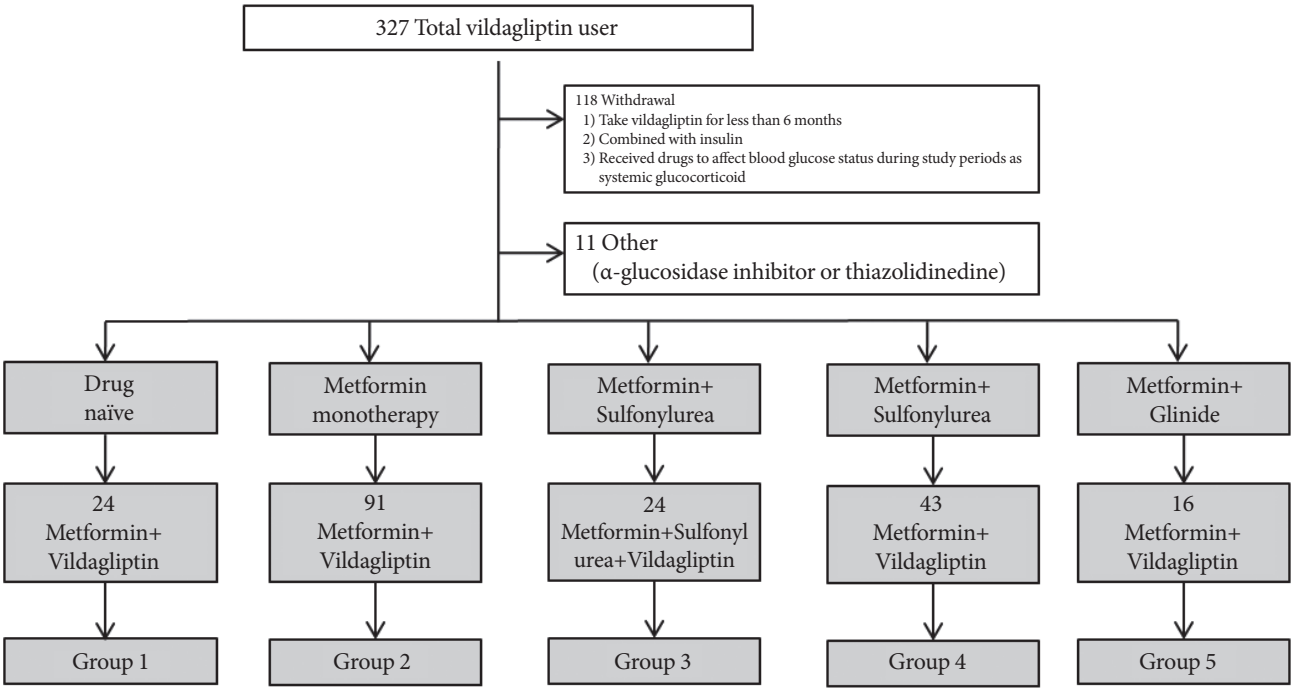

Fig. 1. Subject profiles.

ment). The following parameters were recorded and analyzed: anthropometric parameters at baseline for each group; changes in prescription dosage of metformin and other oral hypoglycemic agents at baseline and after 6 months; and changes in glucose parameters (fasting plasma glucose [FPG], postprandial glucose [PPG], and hemoglobin A1c [HbA1c]) at baseline and after 6 months. To examine the characteristics that affect response to vildagliptin administration, we defined nonresponders as subjects who did not achieve an HbA1c reduction from baseline after 6 months of treatment. We calculated body mass index (BMI) as weight/height^2 (in kilograms per square meter). Total cholesterol, high density lipoprotein cholesterol, triglyceride, and low density lipoprotein cholesterol levels were measured by an enzymatic method using the 7150 Autoanalyzer (Hitachi Ltd., Tokyo, Japan), and insulin and C-peptide were determined by radioimmunoassay. Insulin resistance (IR) was assessed using the homeostasis model assessment (HOMA) formula [HOMA-IR (mg/dL×μU/mL)=fasting glucose (mg/

Table 1. Baseline characteristics of the subjects

Variable	Total (n=198)	Add-on groups			Switch-over groups		P value
		Group 1 (n=24)	Group 2 (n=91)	Group 3 (n=24)	Group 4 (n=43)	Group 5 (n=16)	
Age, yr	56.8±11.9	53.2±12.3	56.1±11.3	60.9±12.5	58.8±10.7	54.9±15.0	0.043
Male sex	106 (53.5)	11 (45.8)	49 (53.8)	19 (76)	22 (52.4)	5 (31.3)	0.064
Duration of diabetes, yr	4.0 (1.0-9.0)	0.0 (0.0-2.0)	5.0 (1.0-8.5)	10.0 (5.8-15.5)	5.0 (2.0-10.0)	4.0 (1.0-9.0)	0.000
Height, cm	163.8±8.4	164.3±8.6	163.5±8.1	167.6±6.6	162.1±9.2	162.5±9.9	0.147
Weight, kg	66.6±12.1	66.5±12.2	67.6±12.0	70.8±12.6	63.7±9.4	60.0±12.7	0.044
BMI, kg/m^2	24.8±3.1	24.5±3.1	25.2±3.3	25.4±3.1	24.2±2.4	23.0±2.4	0.038
FPG, mg/dL	141.0 (119.0-165.0)	153.0 (143.3-205.3)	136.0 (117.0-156.0)	149.0 (124.0-189.0)	139.0 (120.0-157.0)	121.5 (103.5-159.0)	0.005
HbA1c, %	7.3 (6.8-8.0)	8.3 (7.2-10.8)	7.1 (6.8-7.8)	7.7 (7.4-8.5)	7.0 (6.4-7.7)	7.1 (6.4-7.5)	0.000
Postprandial 2 hr glucose, mg/dL	222.6±73.8	249.1±67.7	222.5±88.5	216.4±51.5	224.8±58.4	175.6±38.9	0.051
Total cholesterol, mg/dL	174.5±41.4	186.1±40.8	177.3±41.2	162.9±37.0	174.1±49.1	162.9±30.2	0.301
Triglyceride, mg/dL	128.5 (98.3-193.3)	123.5 (92.5-164.0)	136.0 (98.8-195.0)	121.0 (103.0-216.0)	130.0 (105.0-225.0)	103.0 (42.0-158.0)	0.320
HDL-C, mg/dL	46.6±11.9	44.4±10.9	48.1±11.8	44.3±10.1	43.3±10.8	51.1±14.1	0.185
LDL-C, mg/dL	98.8±35.8	112.3±35.2	98.4±34.2	87.1±32.0	103.5±42.5	86.6±24.6	0.114
C-peptide (fasting), ng/mL	2.3±1.0	1.9±0.9	2.3±1.0	2.5±1.0	2.6±1.1	1.0±0.5	0.385
C-peptide (stimulating), ng/mL	5.2±2.7	5.9±2.9	4.8±2.6	5.0±1.8	5.9±3.3	1.7±0.7	0.533
Insulin (fasting), μU/mL	10.1±6.9	7.4±4.6	9.5±6.6	14.4±12.1	11.4±5.8	8.8±3.8	0.207
Insulin (stimulating), μU/mL	31.9 (15.9-44.2)	28.8 (15.9-55.3)	30.5 (16.2-47.6)	31.2 (13.1-62.8)	34.9 (24.1-42.9)	12.8 (9.3-26.4)	0.631
HOMA-IR, mg/dL ×μU/mL	4.3±3.4	2.9±1.9	4.6±3.8	6.7±5.3	4.1±2.1	4.9±4.1	0.323
HOMA-β, mg/dL×μU/mL	33.5 (16.0-53.9)	17.7 (13.1-55.5)	28.3 (9.8-43.2)	34.0 (17.4-79.1)	35.8 (30.4-80.4)	26.9 (14.9-42.0)	0.308
Metformin dose (baseline), mg/day	1,000 (850-1,500)	-	1,000 (1,000-1,700)	1,000 (850-1,250)	1,000 (687.5-1,000)	1,000 (887.5-1,700)	0.755

Values are presented as mean±standard deviation or number (%). Duration of diabetes, FPG, HbA1c, triglyceride, insulin (stimulating), HOMA-β, and metformin dose are presented as median (interquartile range).
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

dL)×fasting insulin (μU/mL)/405] and β-cell function was assessed using the HOMA-β formula [HOMA-β (%)=fasting insulin (μU/mL)×360/fasting glucose (mg/dL)-63].

Statistical analysis

All statistical analyses were performed with PASW statistics software version 18.0 (SPSS Inc., Chicago, IL, USA). We performed the Kolmogorov-Smirnov test to determine whether the data were normally distributed. Continuous variables with normal distribution were expressed as mean±standard deviation, or as medians (interquartile range [IQR]) if they were not normally distributed. Discrete variables were expressed as percentages. Wilcoxon signed rank tests were used to compare values before and after vildagliptin use. For more than three groups, analysis was performed using the Kruskall-Wallis test. Statistical comparisons between groups with responder and nonresponders were performed using the Mann-Whitney *U* test and chi-square test, which is nonparametric statistical method. Spearman's correlation coefficient (a nonparametric correlation analysis) was used to determine the relationships between glycemic efficacy and the continuous variables. Multivariate logistic regression analysis was used to estimate multiple correlations between predictive parameters of vildagliptin efficacy and clinical and laboratory variables. Data with a *P* value of less than 0.05 were considered significant.

RESULTS

Baseline clinical characteristics of subjects

We reviewed 327 subjects with diabetes who visited Seoul St. Mary's Hospital between August 2009 and February 2011. Fig. 1 shows subjects' profile. We did not evaluate a group of subjects who took an α-glucosidase inhibitor or a thiazolidinedione because of the small sample size (n=11) and excluded subjects with a short duration of administration of vildagliptin or those using insulin (n=118). Of the 198 type 2 diabetic subjects, 106 were men and 92 were women. Table 1 summarizes the baseline characteristics of the subjects by group. The mean age of the subjects was 56.8±11.9 years and the median duration was 4.0 (IQR, 1.0 to 9.0) years. Group 3 had an especially long duration (median duration, 10.0 years; IQR, 5.8 to 15.5 years). The mean BMI of all subjects was 24.8±3.1 kg/m^2. At baseline, the median HbA1c level was 7.3% (IQR, 6.8% to 8.0%), the median FPG level was 141.0 mg/dL (IQR, 119.0 to 165.0 mg/dL), and the mean postprandial 2-hour blood glucose (PP2) level was 222.6±73.8 mg/dL.

Effect of vildagliptin on plasma glucose and HbA1c levels

Fig. 2 displays mean changes from baseline to 6 months in HbA1c, FPG, and PPG levels. After 6 months, the mean change from baseline for HbA1c was -2.24% (P=0.000) for group 1, -0.77% (P=0.000) for group 2, -0.80% (P=0.001) for group 3, -0.61% (P=0.000) for group 4, and -0.34% (P=0.025) for group

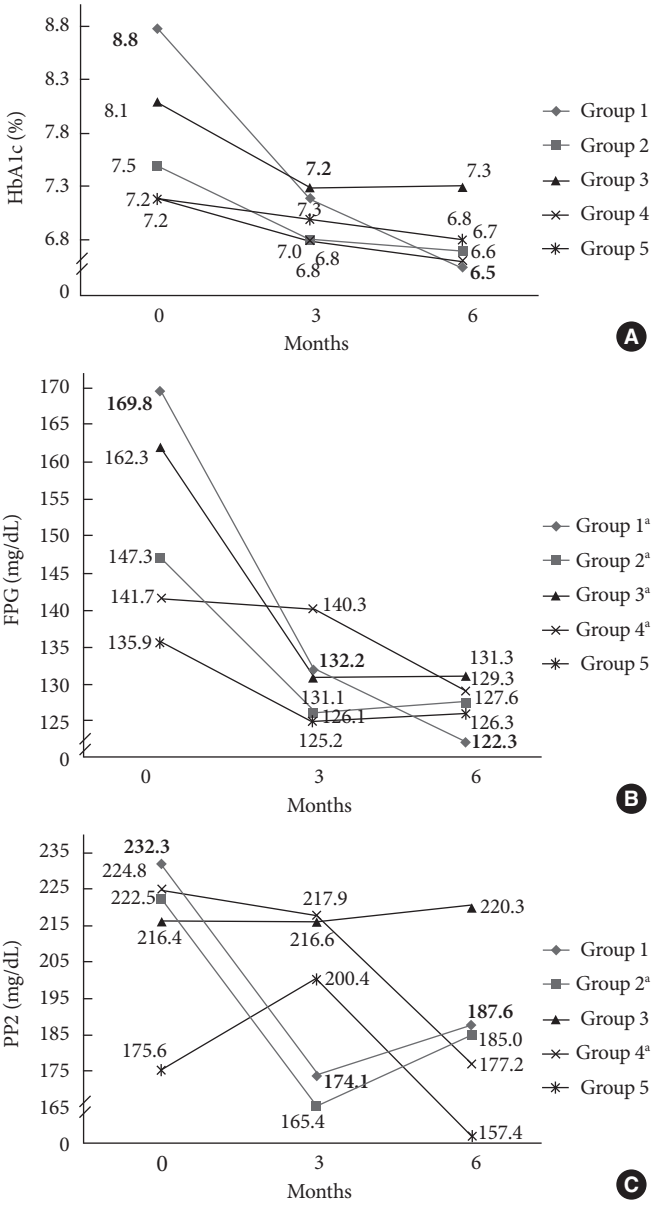

Fig. 2. Mean change from baseline in (A) hemoglobin A1c (HbA1c), (B) fasting plasma glucose (FPG), and (C) postprandial glucose 2 hours (PP2) values by group. (A) All at 6 month: P<0.05. (B, C) At 6 month: ^aP<0.05.

5. There were significant decrements in FPG levels in group 1, group 2, group 3, and group 4 (-48.4 mg/dL, $P=0.000$ in group 1; -18.9 mg/dL, $P=0.000$ in group 2; -33.1 mg/dL, $P=0.002$ in group 3; -11.6 mg/dL, $P=0.020$ in group 4). There were also decrements in FPG levels in group 5; however, they were not significant ($P=0.629$) because of the small number of subjects in this group. PP2 levels in groups 2 and 4 decreased significantly compared to those of groups 1, 3, and 5 (-49.9 mg/dL, $P=0.110$ in group 1; -31.5 mg/dL, $P=0.013$ in group 2; -14.2 mg/dL, $P=0.570$ in group 3; -44.7 mg/dL, $P=0.005$ in group 4; and -5.4 mg/dL, $P=0.611$ in group 5).

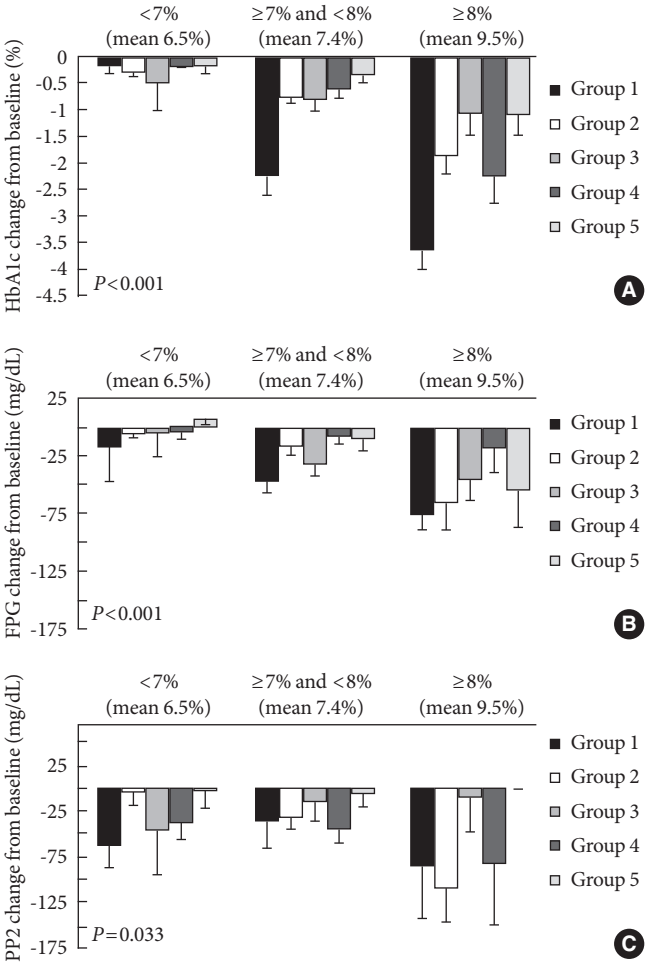

Fig. 3. Mean changes (SEM) from baseline in hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose 2 hours (PP2) values according to baseline HbA1c subgroup were significant. (A) Change in HbA1c level according to baseline HbA1c level. (B) Changes in FPG level according to baseline HbA1c level. (C) Changes in PP2 level according to baseline HbA1c level.

Predictive clinical characteristics of the vildagliptin response group

We performed a subgroup analysis to determine the characteristics influencing the response to drug administration according to baseline HbA1c level. Greater reductions in HbA1c levels from baseline were observed in a subgroup with initial HbA1c levels of more than 8% (mean HbA1c level, 9.5±1.3%) in all subjects ($P<0.001$). In addition, FPG increased from baseline according to increases in the initial HbA1c level in all groups ($P<0.001$) and PP2 increased from baseline according to increases in the initial HbA1c level ($P=0.007$) (Fig. 3). Cases where lower HbA1c levels were detected after 24 weeks of vildagliptin administration were classified as vildagliptin responders. Subjects who did not show any reduction in HbA1c level were classified as nonresponders. In this analysis, we excluded group 1 as their significant hyperglycemic status could disturb the results. Among the 154 subjects eligible for this analysis, 123 (79.9%) were classified as responders. Biochemical and clinical factors that affected response to vildagliptin were evaluated between the response group and the nonresponder group. As shown in Table 2, we carried out the Mann-Whitney *U* test and chi-square test for several factors (sex, age, diabetes mellitus duration, BMI, C-peptide, fasting insulin, FPG, HbA1c, HOMA-IR, and HOMA-β values, and sulfo-

Table 2. Characteristics of responders and nonresponders to vildagliptin ($n=154$)

Characteristic	Responder ($n=123$)	Nonresponder ($n=31$)	*P* value
Male sex	67 (54.47)	18 (58.06)	0.719
Age, yr	56.46±12.20	58.55±9.79	0.435
DM duration, yr	6.70±6.69	7.37±6.70	0.384
BMI, kg/m^2	25.07±3.20	24.43±2.74	0.314
C-peptide, ng/mL	2.38±1.08	2.37±0.63	0.656
Fasting insulin, μIU/mL	10.47±7.67	13.04±6.40	0.115
FPG, mg/dL	152.11±51.00	133±25.03	0.071
HbA1c, %	7.68±1.18	7.03±0.67	0.004
HOMA-β, mg/dL×μU/mL	42.71±35.83	57.75±39.14	0.284
HOMA-IR, mg/dL×μU/mL	5.41±4.05	3.77±1.88	0.509
SU user	42 (34.17)	16 (51.61)	0.076

Values are presented as number (%) or mean±standard deviation.
DM, diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; SU, sulfonylurea.

Table 3. Logistic regression analysis for predictive parameters of clinical efficacy of vildaglipitin as dependent variables and its component as independent variables

	OR	95% CI	*P* value
Age	0.967	0.893-1.046	0.404
Sex	0.891	0.208-3.810	0.876
DM duration	0.843	0.300-2.367	0.746
BMI	0.800	0.602-1.063	0.123
HbA1c	0.176	0.036-0.862	0.032
FPG	1.015	0.984-1.046	0.350
SU user	0.143	0.026-0.789	0.026

Adjusted for age, sex, DM duration.
OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; BMI, body mass index; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; SU, sulfonylurea.

nylurea use) to evaluate the characteristics of responders to vildagliptin treatment. We found that HbA1c levels differed significantly between the responders and nonresponders. We used logistic regression analysis to identify the independent factor affecting the glucose lowering effect of vildagliptin. HbA1c level at baseline and history of sulfonylurea use were factors that correlated with responsiveness to vildagliptin treatment upon logistic regression analysis (P=0.032 and P=0.026) (Table 3).

DISCUSSION

Only limited data are available on T2DM patients treated with vildagliptin in Asia [22], especially in actual clinical practice. In the present study, we analyzed data for 198 type 2 diabetes patients who were administered vildagliptin and evaluated the factors influencing their response to vildagliptin administration. The subjects were divided into groups based on treatment regimens and their data were retrospectively reviewed. Vildagliptin was shown to decrease mean HbA1c levels by 0.9% (P<0.001). A decrement in PPG levels was also observed, as expected; indeed, the decrements in FPG levels were significant and somewhat dominant. Overall reductions in FPG levels in all groups were noticeable. Although results on the efficacy of vildagliptin treatment were recently published [23,24], we did not expect more exceptional reductions in FPG levels than reductions in PPG levels at the start of vildagliptin administration. In a recent study, vildagliptin decreased FPG levels [24]; its effect was inferior to that of thiazolidinediones, metformin, and sulfonylureas, and this observation may be attributed to the specific activities of vildagliptin on postprandial sugars, such as acarbose and glinides. However, in this study, even though decrements in PPG levels were insignificant in the group that received a combination treatment with sulfonylureas and in the drug-naïve group, decrements in FPG and HbA1c levels were significant. The pharmacokinetics of vildagliptin differs from that of sitagliptin. Even though the time to reach peak serum concentration and the half-life of vildagliptin are short, the duration of DPP-4 inhibition is long lasting, owing to the powerful interaction of vildagliptin with DPP-4. Vildagliptin inhibits DPP-4 activity by more than 80% for 15.5 hours postdose, and increases active GLP-1 levels [25]. It has also been shown that less fluctuation in glucose concentrations occurs with vildagliptin treatment than with sitagliptin treatment, when using a continuous glucose-monitoring system [26]. This finding could also support the pharmacokinetic characteristics of vildagliptin. Vildagliptin improves β-cell function, augments plasma insulin levels and reduces plasma glucagon concentrations, and decreases overnight plasma glucose levels, which are correlated with a significant reduction in endogenous glucose production [27].

In terms of our retrospective study method, it has both strengths and limitations, and we would like to see it complemented by further study. The present retrospective observational design covered a wide range of subject populations and data on the use of vildagliptin in real clinical practice. Prospective randomized trials, however, have strengths in statistical significance and reliance on data [28]. The vildagliptin-treated subjects were not randomized, and the endocrinologists' preferences and ideas affected who was treated with vildagliptin and when, which reflects real clinical practice. We analyzed the predictive parameters of vildagliptin treatment, and found that the factors correlated with the efficacy of vildagliptin were baseline HbA1c and history of sulfonylurea use (Table 3). From the results of studies in animal models, it is generally accepted that DPP-4 inhibitors are more beneficial in subjects with shorter disease duration [29,30]. Vildagliptin is an efficacious add-on therapy to insulin in subjects with renal impairment and long-standing T2DM [17,31,32]. In a recent study, the impact of T2DM duration, insulin resistance, duration of metformin use, and BMI on the efficacy of vildagliptin with metformin treatment was evaluated. That study showed that vildagliptin with metformin treatment was effectual independent of these factors [33]. When considering an add-on therapy to

metformin or the initiation of combination therapy, vildagliptin can be chosen, regardless of diabetic duration, BMI, and insulin resistance.

This study has several limitations. First, because of the single university hospital and retrospective nature of the study, the impacts and powers of the results may be weakened. We did not assess the potential benefits or side effects, including weight change and hypoglycemic events, in detail in this retrospective study. Second, because of the inclusion criteria and classification, the number of eligible participants in each group was small. Third, because this was not a randomized and controlled study, some confounders may have influenced the results. We found that the doctors tended to increase the dose of metformin when they prescribed vildagliptin. In our analyses, the increase in metformin dose was approximately 100 mg/day (initial dose, 1,124.4±442.5 mg/day; dose 6 months later, 1,234.0±436.5 mg/day). In a previous study, there was no significant difference in the percentage of glycated hemoglobin, despite a 13% increase in metformin daily dose in type 2 diabetes subjects [34]. In another study in Japan, the efficacy of metformin monotherapy at 500 and 750 mg/day was compared, and no significant differences in HbA1c and FPG levels were found 6 months later [35]. Therefore, we postulate that the change in metformin dose in the current study was not a definite confounder. Also, the response level after vildagliptin treatment could be different for each underlying management condition. However, we confirmed that there were no significant correlations between response to vildagliptin and underlying management conditions (P=0.057). Finally, the preservation of pancreatic β-cell function with vildagliptin administration could not be confirmed clinically because fasting insulin levels were not usually measured after administration of vildagliptin. We can presume that vildagliptin could preserve β-cell function by reducing insulin resistance owing to reduced lipotoxicity [4,36].

In conclusion, vildagliptin was efficacious for glycemic control, especially for lowering FPG and HbA1c levels, in drug naïve diabetes subjects where it was combined with metformin treatment, where it was added to existing metformin or sulfonylurea treatment, and where it replaced sulfonylureas. The glucose-lowering effect of vildagliptin was independent of T2DM duration, BMI, and insulin resistance. However, well-designed, prospective, and long-term studies need to be performed to obtain relevant information on the use of vildagliptin in clinical practice.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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