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The Efficacy of Vildagliptin in Korean Patients with Type 2 Diabetes

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It is well known that tight blood glucose control is necessary to prevent microvascular and macrovascular complications in type 2 diabetic patients. However, strict glycemic control is also associated with hypoglycemic events, and these have potentially harmful effects on the cardiovascular system and increased mortality [1]. Recent guidelines for managing hyperglycemia emphasize a 'patient-centered approach' with individualized treatment to optimize effects and minimize side effects of medications [2]. If HbA1c target is not achieved after lifestyle changes with metformin monotherapy, other options such as a dipeptidyl peptidase-4 (DPP-4) inhibitor can be considered.

Vildagliptin is a potent and selective DPP-4 inhibitor that blocks DPP-4 inactivation of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) and is approved in more than 70 countries worldwide [3]. Its mode of action has been described as a biphasic process that involves slow formation of a reversible covalent enzyme-inhibitor complex followed by slow blocker dissociation, resulting in the enzyme slowly equilibrating between active and inactive conformation [4]. Vildagliptin has high affinity for DPP-4 and decreases plasma activity of the enzyme by 70% to 90% in a sustained manner, thus increasing fasting and postprandial levels of intact GLP-1 and GIP [4]. Because of distinct features of vildagliptin, incretin levels were significantly elevated and remained so throughout the overnight postabsorptive period [5]. Sakamoto et al. [6] reported mean amplitude of glycemic excursions and mean 24-hour blood glucose were significantly lower in the vildagliptin treatment group than the sitagliptin group, and the differences in drug efficacy were attributed to the pharmacological characteristics of the two drugs. Vildagliptin's efficacy has been shown in various populations and used in both mono- and combination therapies. Because its action depends on plasma glucose concentration, vildagliptin has significantly lower hypoglycemia and neutral effects on body weight compared to other hypoglycemic agents [7]. Scherbaum et al. [8] reported vildagliptin 50 mg once daily with lifestyle modification significantly reduced hemoglobin A1c (HbA1c, -0.3%) compared to the placebo group in a 52-week study of drug-naïve type 2 diabetes mellitus (T2DM) patients (n=306) with a mean HbA1c of 6.7%. In addition, postprandial plasma glucose (PPG) as well as fasting plasma glucose (FPG) were significantly decreased by -0.9 and -0.4 mmol/L, respectively in the vildagliptin-treatment group. In a 52-week extension study (total study duration 104 weeks), vildagliptin showed continued improvement in glucose control and a placebo-adjusted change in HbA1c was reported -0.5% from core study baseline after 2 years. None of the subjects treated with vildagliptin experienced adverse effects such as hypoglycemia (0.0% vs. 3.2% placebo) over a 2-year period, and body weight decreased significantly by -1.1 kg (vs. -0.3 kg placebo). These results implied that vildagliptin mitigated the progressive loss of glycemic control observed in patients with mild hyperglycemia receiving placebo and lifestyle counseling without causing hypoglycemia or weight gain. This appears to be due to a corresponding attenuation of the deterioration of

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β-cell function as assessed by insulin secretion rate relative to glucose. In this study using an arginine-stimulated hyperglycemic clamp method, pancreatic β-cell function showed meaningful improvement with vildagliptin 100 mg once daily. A subsequent study of the same population, demonstrated that vildagliptin significantly increased the insulin secretory capacity of β-cells [9]. In drug-naïve patients with T2DM, vildagliptin monotherapy showed significant reduction from baseline in HbA1c of approximately -1.0%, without weight gain or serious adverse effects [7]. A clinically meaningful reduction in HbA1c sustained throughout 2-year treatment was seen in both vildagliptin and metformin (-1.0% vs. -1.5%, from baseline HbA1c 8.4% and 8.8%, respectively) [10]. Schweizer et al. [11] also reported similar results in patients with low baseline HbA1c (mean, 7.7%), vildagliptin monotherapy (100 mg once daily) was demonstrated reduction by -0.64% over 24 weeks and its glycemic efficacy was as effective as metformin (1.5 g daily, -0.75%, noninferiority established), with fewer gastrointestinal side effects. The clinical efficacy of vildagliptin was similar to other second-line agents with a lesser incidence of adverse effects such as hypoglycemia or weight gain. Vildaglitin monotherapy (50 mg b.i.d.) improved glycemic control and reduced HbA1c (-0.5%) were similar with gliclazid (320 mg/day, -0.6%) in drug-naïve patients with high baseline HbA1c (vildagliptin 8.5% vs. gliclazid 8.7%) over 2 years [12]. Although the noninferiority of glycemic efficacy was not proven statistically, vildagliptin had significant benefits in reducing hypoglycemia and weight gain. In a large randomized and active comparative study over 2 years, vildagliptin (50 mg b.i.d.)-metformin treatment had similar efficacy to glimepiride (6 g/day) add-on therapy with no weight gain and markedly reduced hypoglycemia risk [13]. They also reported that vildagliptin therapy, but not glimepiride, improved postprandial α-cell function, lasting for 2 years [14].

There have been a few studies on the efficacy of vildagliptin in Asian patients. In a 24-week monotherapy study in Chinese patients, vildagliptin (50 mg b.i.d) was not inferior to acarbose treatment (100 mg t.i.d) (-1.4% vs. -1.3% from a baseline of 8.6%), with better gastrointestinal tolerability [15]. A similar 12-week study included Japanese patients, who tend to have a high-carbohydrate diet, and the observed efficacy of vildagliptin was superior to that of voglibose (-0.95% vs. -0.38%, $P<0.001$) [16]. Jeon and Oh [17] reported that the efficacy of vildagliptin-metformin treatment was not statistically inferior to glimepiride-metformin treatment in Korean patients with T2DM. HbA1c reduction was -0.94±1.15% in the vildagliptin group and -1.00±1.32% in the glimepiride group from baseline to the 32-week endpoint. A similar reduction was observed for FPG as well as 2hr-PPG with lower risk of hypoglycemia and weight gain in the vildagliptin group [17]. In terms of drug action, it is presumed to be associated with residual capacity of pancreatic β-cells, but few studies have examined the predictive factors regarding responsiveness of vildagliptin treatment. Schweizer et al. [18] reported that vildagliptin add-on metformin therapy was effectual independently of disease duration, insulin resistance, duration of metformin use and body mass index (BMI), and that vildagliptin can be chosen irrespective of these factors. In a small study of Japanese patients, parameters reflecting the glucose-stimulated insulin secretion, such as the insulinogenic index and oral disposition index, but not insulin sensitivity, were found to be significantly different between responders and nonresponders [19]. Kim et al. [20] reported sitagliptin responders had lower BMI and were younger compared to nonresponders, but disease duration and homeostasis model assessment of β-cell function were not related with responsiveness.

On this issue, Chang et al.'s [21] results are consistent with previous studies. They reported that vildagliptin 50 mg twice daily significantly improved HbA1c from baseline, and this beneficial effect was identified regardless of mono-, add-on or switch-on therapy over 6 months. In addition, this study provides clinically relevant findings including significant decrements in FPG. Although group 5 (switch-over from glinide, $n=16$) had relatively few patients and did not show statistically significant improvement of FPG, obvious reductions in FPG levels were established in all another groups. The proven benefit of a DPP-4 inhibitor to PPG is well established, HbA1c was reduced by vildagliptin through control of FPG as well as PPG. In subgroup analysis according to HbA1c level, vildagliptin showed better glycemic profiles in HbA1c, FPG, and 2hr-PPG at higher glucose levels, especially group with A1c ≥8%, and small decrements in well-controlled group (A1c <7%). As well-known strength of DPP-4 inhibitor, these results imply vildagliptin had the advantage of glucose control with a lesser hypoglycemia. Although this study did not contain the analysis of safety, several pivotal studies and meta-analyses have proved that DPP-4 inhibitors including vildagliptin are safer than other insulin secretagogues [22]. Analyzing the clinical characteristics of 'responders' for vildagliptin treatment, the predictive factors were baseline HbA1c level and a history of

sulfonylurea. Chang et al.'s study [21] is the first study of predictive clinical parameters for the glycemic efficacy of vildagliptin in Korean diabetic patients, and these results may help clinical physicians to choose adequate candidates. However, this study had several limitations. Because heterogeneity of baseline characteristics among groups, it is difficult to compare glycemic efficacy directly. For example, baseline HbA1c and decrements of drug naïve patients were significantly higher (8.3%, -2.24%, respectively) than other groups. For single-center and small sized study, these results cannot be extrapolated to subjects in the general population. This study contained only patients with mild hyperglycemia using oral hypoglycemic agents, so more studies including various level of glycemic control are needed to clarifying the general characteristics of vildagliptin-responders.

We appreciate the devotion of other investigators who are conducting important studies on glycemic efficacy and predictive clinical parameters of vildagliptin in Korean subjects. We hope that expansions on these findings will yield even more useful results in the future.

CONFLICTS OF INTEREST

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

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