Dipeptidyl Peptidase-4 Inhibitor Switching as an Alternative Add-on Therapy to Current Strategies Recommended by Guidelines: Analysis of a Retrospective Cohort of Type 2 Diabetic Patients

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Abstract

**Objective:** This retrospective cohort study aimed to investigate the significance of dipeptidyl peptidase-4 (DPP-4) inhibitor switch therapy, which is currently not recommended by major diabetes guidelines.

**Methods:** The subjects were 238 outpatients with type 2 diabetes who had been prescribed sitagliptin 50 mg daily, which was subsequently changed in one of three ways. Patients whose sitagliptin was switched to vildagliptin 50 mg twice daily were defined as the switched group. Patients whose sitagliptin was increased to 100 mg once daily were defined as the increased group. Patients who received an additional alfa-glucosidase inhibitor (α-GI) three times daily prior to meals and sitagliptin 50 mg once daily were defined as the added group. The primary endpoint was the glycated hemoglobin (HbA1c) value at 6 months after the medication change. Patients whose oral hypoglycemic agents were changed within 6 months after switching to vildagliptin, increasing sitagliptin, or adding α-GI were excluded from the full analysis set and the remaining patients were included in the per protocol analysis.

**Results:** The per protocol analysis revealed that the HbA1c level decreased significantly in the switched group (n=71) and the added group (n=18) but did not change significantly in the increased group (n=69). Analysis of the full set showed that the HbA1c level decreased significantly in all three groups (switched [n=92], increased [n=88], and added [n=25]).

**Conclusion:** Switching DPP-4 inhibitors can adequately reduce HbA1c compared with increasing original DPP-4 inhibitor dose or adding an α-GI. When the original DPP-4 inhibitor did not significantly improve glycemic control, making a DPP-4 inhibitor switch, which is not recommended by major diabetes guidelines, can be an alternative strategy.

Keywords: Dipeptidyl peptidase-4; Oral hypoglycemic agent; Medication adherence; Sitagliptin; Vildagliptin; Safety; Medical cost

Introduction

Diabetes mellitus is a chronic and progressive disease that poses a growing public health problem worldwide. Patients who have diabetes long term require many classes of oral hypoglycemic agents (OHAs), often at relatively high doses, because glycemic control decreases with age [1].

Diabetes guidelines issued by American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend metformin as the first-line medication for type 2 diabetes mellitus [2]. However, it is usually difficult for diabetic patients to achieve glycemic control goals using metformin only. In such cases, ADA and EASD guidelines recommend add-on therapy, which is the addition of another class of hypoglycemic agents to metformin [2].

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been used widely because of their high efficacy, low risk of hypoglycemia, and neutral effect on body weight [3,4]. In fact, DPP-4 inhibitors have generally been accepted as the second- or third-line therapies in patients receiving first-line metformin therapy [2]. However, a step-up strategy from regimens including DPP-4 inhibitors has not yet been established. In the clinical setting, glycemic control sometimes improves after the switch to a different DPP-4 inhibitor. Many doctors exchange DPP-4 inhibitors rather than add other classes of OHAs, which are expected to exert additive glycated hemoglobin (HbA1c)-lowering effects through mechanisms that differ from those of DPP-4 inhibitors. The reason for this is not clear. There are no theoretical bases for the efficacy of this practice, and the current guidelines do not provide clinical advice relating to DPP-4 inhibitor switching.

Alfa-glucosidase inhibitor (α-GI), the use of which is not currently recommended by the ADA/EASD guidelines, is a readily available OHA whose usefulness is not limited by patient age or renal function in contrast to other OHAs available in Japan. Although its gastrointestinal adverse effects are common, this class of medicine is relatively safe and effective for improving postprandial hyperglycemia [5]. Additionally, this class of OHA is shown to reduce the risk of cardiovascular diseases [6].

Considering these circumstances, we focused on diabetic patients taking sitagliptin 50 mg daily, the standard dose of this drug in Japan, who displayed inadequate glycemic control. The objectives of this study were to evaluate the effectiveness and safety of DPP-4 inhibitor switch therapy.
switch therapy, which is currently not recommended by diabetes guidelines, and validate the feasibility of this regimen. We compared three regimens: 1) switching sitagliptin to vildagliptin; 2) increasing sitagliptin dose; and 3) adding α-GI to sitagliptin. Specifically, we examined changes in HbA1c, body weight, liver function, and kidney function.

**Patients and Methods**

**Study design**

This retrospective cohort study analyzed data from the medical records of 238 outpatients with type 2 diabetes mellitus who attended the Department of Internal Medicine, Keio University Hospital, between November 2011 and October 2014. The primary endpoint was the HbA1c value at 6 months after the medication change. The secondary endpoints were changes in body weight, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and estimated glomerular filtration rate (eGFR) from baseline to 6 months after the medication change.

Inclusion criteria were: 1) patients prescribed sitagliptin 50 mg daily (in the morning) for at least 2 months without any changes to their OHAs; and 2) medication was subsequently changed in one of the following three ways. Patients whose sitagliptin was switched to vildagliptin 100 mg daily (50 mg in the morning and 50 mg in the evening) were defined as the switched group. Patients whose sitagliptin dose was increased group. Patients who received an additional α-GI (three times just before meals) with sitagliptin 50 mg daily were defined as the added group regardless of α-GI type (acarbose, voglibose, or miglitol) or dose. The patients were excluded from the analysis if they exhibited poor drug compliance (assessed from medical record information), their HbA1c value was <6.5%, their eGFR was <30 mL/min/1.73 m², AST or ALT were >3 times upper limit, they received cancer medication, they were referred to another hospital, or they were lost to follow-up. A flow chart of the patient enrollment process is shown in Figure 1.

The protocol was approved by the Ethics Committee of Keio University School of Medicine and conducted in accordance with the Declaration of Helsinki.

**Data collection**

Basic demographic data were collected for all patients from their medical records, including sex, age, height, weight, duration of diabetes, baseline HbA1c, eGFR, AST, ALT, and systolic and diastolic blood pressure. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m²).

All measurements were performed by the Department of Laboratory Medicine of Keio University School of Medicine using routine automated laboratory methods as previously described [7]. The HbA1c level was expressed in accordance with the National Glycohemoglobin Standardization Program guidelines as recommended by the Japanese Diabetes Society [8]. Estimated glomerular filtration rate (eGFR) was

![Flow chart of the patient selection process.](image)
mg daily did not improve HbA1c levels. On the other hand, increasing 50 mg sitagliptin to 100 mg daily and adding α-GI to sitagliptin 50 mg daily significantly lowered control with sitagliptin 50 mg daily (once in the morning) alone. The patients with type 2 diabetes who did not achieve adequate glycemic control with sitagliptin 50 mg daily (once in the morning), or combination of sitagliptin 50 mg and α-GI did not change significantly in all three groups.

Safety parameters by group

The time courses of clinical parameters are presented in Table 3. Body weight significantly decreased in the increased group (P<0.05). None of the other clinical parameters changed significantly.

Discussion

The present study compared the effects among vildagliptin 100 mg daily (50 mg in the morning and 50 mg in the evening), sitagliptin 100 mg daily (once in the morning), or combination of sitagliptin 50 mg and α-GI (three times just before meals) on glycemic control in patients with type 2 diabetes who did not achieve adequate glycemic control with sitagliptin 50 mg daily (once in the morning) alone. The per protocol analysis showed that switching to vildagliptin 100 mg daily and adding α-GI to sitagliptin 50 mg daily significantly lowered HbA1c levels. On the other hand, increasing 50 mg sitagliptin to 100 mg daily did not improve HbA1c levels. The full set analysis showed that all three regimens decreased HbA1c levels. The per protocol analysis results are consistent with those of several previous reports. It was reported that sitagliptin 50 mg daily and 100 mg daily showed similar improvements in HbA1c [10]. On the other hand, a possible superiority of vildagliptin over other DPP-4 inhibitors regarding a hypoglycemic effect [11,12] was also reported. The IC_{50} for vildagliptin and sitagliptin, the concentration required to achieve 50% inhibition of DPP-4 activity, is reportedly 5 nmol/L [13] and 26.3 nmol/L [14], respectively, which suggests that vildagliptin might be a potent DPP-4 inhibitor. Accordingly, a previous study showed that elevated levels of intact incretins hormones are maintained for a longer period following the administration of vildagliptin than that following the administration of sitagliptin [15]. Nonetheless, the evidence of superiority of one medicine over another can be only derived from head-to-head prospective trials.

The addition of α-GI to a DPP-4 inhibitor is an effective diabetes treatment strategy that leads to a 0.3–0.5% HbA1c improvement [16–18]. α-Glucosidase inhibitors decrease glucagon-like peptide-1 secretion from L cells in the lower duodenum, while DPP-4 inhibitor inhibits glucagon-like peptide-1 degradation, potentiating its hypoglycemic activity, meaning that this combination therapy is quite effective.

The results of this study do not mean that a changeover from sitagliptin to vildagliptin is effective for all patients with type 2 diabetes; rather, only those patients who do not respond adequately to sitagliptin might benefit from this transition. The pharmacokinetics/pharmacodynamics of sitagliptin and vildagliptin differ among patients. If the patients respond well to sitagliptin, it is difficult to obtain an increased effect by switching to vildagliptin because the DPP-4 inhibition rate already peaked with sitagliptin use in such patients.

The prices of the drugs appeared in this paper at present in Japan (since April 2016) are as follows. Sitagliptin 50 mg tablet, 136.50 yen; vildagliptin 100 mg tablet, 205.40 yen; vildagliptin 50 mg tablet, 80.10 yen; acarbose 50 mg tablet, 160.20 yen; miglitol 5 mg tablet, 52.40 yen; and voglibose 0.2 mg tablet, 35.00 yen. Therefore, vildagliptin 100 mg (2 of 50 mg tablet, 80.10×2=160.20 yen) is cheaper than sitagliptin 100 mg (205.40 yen) or sitagliptin 50 mg plus α-GI three times daily (acarbose 136.50+20.20×3=197.10 yen, miglitol 136.50+52.40×3=293.7 yen, voglibose 136.50+35.00×3=241.50 yen). Accordingly, the switched group featured the most favorable medical cost.

Patients in the switched group took vildagliptin twice daily. Patients in the added group took a α-Gl three times daily in addition to sitagliptin

### Table 1: Patients' baseline characteristics by study group values are expressed as mean ± standard deviation (SD).

<table>
<thead>
<tr>
<th></th>
<th>Switched</th>
<th>Increased</th>
<th>Added</th>
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<tbody>
<tr>
<td>N</td>
<td>92</td>
<td>88</td>
<td>25</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (60.9)</td>
<td>59 (67.0)</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (39.1)</td>
<td>29 (33.0)</td>
<td>11 (44.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.5 ± 10.5</td>
<td>67.0 ± 11.0</td>
<td>71.8 ± 6.6</td>
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<tr>
<td>Diabetes duration (years)</td>
<td>17.5 ± 9.2</td>
<td>16.5 ± 8.9</td>
<td>16.9 ± 9.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 4.7</td>
<td>25.6 ± 4.1</td>
<td>24.3 ± 4.2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133 ± 15</td>
<td>134 ± 18</td>
<td>132 ± 16</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 ± 12</td>
<td>76 ± 11</td>
<td>74 ± 9</td>
</tr>
</tbody>
</table>

### Table 2: Mean HbA1c level by study group values are expressed as mean ± standard deviation (SD).

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>6 months</th>
<th>P value</th>
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<tr>
<td>PPS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Switched</td>
<td>8.15 ± 0.83</td>
<td>7.86 ± 0.86</td>
<td>&lt; 0.001</td>
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<td>Increased</td>
<td>8.13 ± 0.80</td>
<td>7.95 ± 1.04</td>
<td>0.119</td>
</tr>
<tr>
<td>Added</td>
<td>8.26 ± 0.88</td>
<td>7.96 ± 0.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switched</td>
<td>8.22 ± 0.68</td>
<td>7.88 ± 0.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Increased</td>
<td>8.16 ± 0.81</td>
<td>7.88 ± 0.97</td>
<td>0.014</td>
</tr>
<tr>
<td>Added</td>
<td>8.18 ± 0.92</td>
<td>7.53 ± 0.90</td>
<td>&lt; 0.001</td>
</tr>
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</table>
once daily. Therefore, the patients in the switched group had a simpler regimen, which means a lower medication frequency and fewer tablets, than those in the added group. Treatment adherence generally deteriorates as frequency and number of daily doses increases [19,20]; thus, simplifying dosing regimens improves medication adherence [21]. Furthermore, patients taking α-GI sometimes complain of gastrointestinal symptoms such as constipation or diarrhea. Although mild in most cases, such side effects can deteriorate patient quality of life. A switch from a DPP-4 inhibitor to vildagliptin might be more favorable than the addition of α-GI in such cases.

Many older patients were included in this study. The number of old and fragile diabetic patients is increasing worldwide. Such patients often suffer from vital organ insufficiencies and tend to be vulnerable to the adverse events of diabetic medications. For such patients, monotherapy with a DPP-4 inhibitor is relatively safe and valuable compared to combination therapy since fewer potential adverse events are involved.

Among the secondary endpoints of this study, the only significant change was a decrease in body weight in the increased group. Although statistically significant, this change was minimal and appeared not to be clinically relevant. AST, ALT, and eGFR did not change significantly. None of the regimens worsened liver or kidney function. We observed no drug-related adverse events that led to drug discontinuation.

There are several limitations to the present study. First, because of its retrospective design and limited number of patients, the existence of confounding factors and biases cannot be ruled out. Second, even though patients who switched from sitagliptin to vildagliptin showed a significantly decreased HbA1c level, we cannot draw any conclusions about the superiority/inferiority about these DPP-4 inhibitors as mentioned above. Finally, the participants of this study were patients who attend a university hospital, who are special in some regard. Therefore, the study’s results may not be applicable to the general population or to diabetic patients who are treated in primary care settings.

In conclusion, switching DPP-4 inhibitors adequately lowers HbA1c levels compared with increasing the dose of the original DPP-4 inhibitor or adding another OHA class. By switching DPP-4 inhibitors, advantages including decreased medical cost, increased patient adherence, and increased safety can be anticipated. When the first-line DPP-4 inhibitor does not adequately improve glycemic control, a DPP-4 inhibitor switch, which is not currently recommended by major diabetes guidelines, can be an alternative strategy.

References

Table 3: Changes in clinical parameters by study group. Values are expressed as mean ± SD. Switched: Switched group; Increased: Increased group; Added; Added group; before: Baseline value; after: Value at the end of the study period; BW: Body Weight; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.
