Efficacy of adding once- and thrice-daily voglibose in Japanese type 2 diabetic patients treated with alogliptin

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Abstract. We investigated the efficacy of once- and thrice-daily voglibose, an alpha-glucosidase inhibitor, as an add-on therapy to alogliptin, a dipeptidyl peptidase-4 inhibitor, on glycemic control in Japanese type 2 diabetic patients. In this 12-week, parallel-group, randomized, open-label, three-arm trial, 151 participants treated with alogliptin were randomly allocated to the following three arms; one was the group to initiate once-daily voglibose, another was to initiate thrice daily voglibose, and the other was the control group. The primary endpoint was the change of hemoglobin A1c levels at the end of the study, which was revealed to be significantly different among groups (p < 0.001). The once- and thrice-daily voglibose groups had a significantly greater reduction than the control group; the difference was -0.27% and -0.33% in the once- and thrice-daily voglibose group, respectively (both p < 0.001). No significant difference was observed between the two voglibose groups (p = 0.615). On the other hand, the increase of 1,5-anhydroglucitol levels were 3.3 and 5.5 μg/mL greater in the once- and thrice-daily voglibose groups than the control group (both p < 0.001). The thrice-daily voglibose group had a greater increase of 1,5-anhydroglucitol levels compared to the once-daily voglibose group (p = 0.005). In conclusion, once- and thrice-daily voglibose as an add-on to alogliptin significantly improved glycemic control in Japanese type 2 diabetic patients.

Key words: Alpha-glucosidase inhibitor, Dipeptidyl peptidase-4 (DPP-4) inhibitor, Once- and thrice-daily administration

NUMEROUS studies have reported the efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors on glycemic control in type 2 diabetes mellitus [1-15]. However, in the clinical setting, some patients receiving DPP-4 inhibitors fail to achieve strict glycemic control [16-19], and they often require an add-on therapy of another oral hypoglycemic agent. Although previous studies demonstrated the efficacy of the combined use of DPP-4 inhibitors with other oral hypoglycemic agents, most studies focused on the efficacy of DPP-4 inhibitors as an add-on to other agents [20-29]. To date, few data are available about the glucose-lowering effect of other agents as an add-on to DPP-4 inhibitors. It remains unknown to what extent hemoglobin A1c levels will be decreased after adding other agents to DPP-4 inhibitors.

Recently, a favorable effect of alpha-glucosidase inhibitors as an add-on to DPP-4 inhibitors has been suggested by some clinical studies [30-32]. In addition, it is also suggested that although the agents are usually administered thrice a day, only a once-daily administration might have some efficacy on glycemic control [33]. However, all of these studies were performed for only a several days. Their longer-term glucose-lowering effect, e.g., the change of hemoglobin A1c levels, remains unknown.

The current study therefore investigated the impact of 12-week administration of voglibose, an alpha-glucosidase inhibitor, as an add-on to alogliptin, a DPP-4 inhibitor, on glycemic control in Japanese type 2 diabetic patients.

Materials and Methods

Study design

This 12-week, parallel-group, randomized, open-label, three-arm trial assessed the efficacy and safety of
once- and thrice-daily voglibose as an add-on to alogliptin in Japanese type 2 diabetic patients. The current study was conducted at Shiraiwa Medical Clinic, Osaka, Japan, between March 2013 and September 2013. We performed the current study in accordance with the Declaration of Helsinki, and it was approved by the local ethics committee. Written informed consent was obtained from every participant in the current study. The trial was registered as UMIN000009516.

Study population and procedures

The study population comprised male and female Japanese adults (≥ 20 years old) with type 2 diabetes mellitus, who were treated with 25 mg per day of alogliptin. The exclusion criteria were: difficulty of regular visit, severe hepatic, and/or renal disease, and pregnant or breast feeding females.

Eligible participants were randomly allocated to the following three arms. One arm was to initiate 0.2-mg voglibose three times a day before meals (thrice-daily voglibose group), whereas another was to initiate 0.2-mg voglibose once a day, before the very meal at which alogliptin was administered (once-daily voglibose group). The other arm was the control group with no medication initiated. Alogliptin was continued, without change in dose, in all the three arms. All participants in the current study were asked to visit the clinic 4, 8, and 12 weeks after the allocation. Hemoglobin A1c, glycoalbumin, and 1,5-anhydroglucitol (1,5-AG) levels were measured at each visit. Data on side effects were collected to assess safety.

Study outcomes

The primary efficacy endpoint was the change of hemoglobin A1c levels at the end of the study, using the last observation carried forward (LOCF) data analysis. Secondary efficacy endpoints were the change of glycoalbumin and 1,5-AG levels at the end of the study, using the LOCF data analysis. Safety was evaluated with the prevalence of observed side effects. The change of body weight and serum transaminase levels, i.e., aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, were also assessed. In the current study we additionally evaluated the adherence to the administration of voglibose in the thrice- and once-daily voglibose groups. The adherence was judged when the extent to which patients took voglibose as prescribed was 90% or more. The data were based on their self-reports.

Statistical analysis

Data are given as means and standard deviations (SD) for continuous variables, or as numbers and percentages for discrete variables, if not otherwise mentioned. A p value less than 0.05 was considered to be significant. The difference among three groups was assessed by the one-way analysis of variance (ANOVA) for continuous variables, and the chi-square test for discrete variables. Post hoc intergroup comparison was performed using the Turkey’s honestly significant difference (HSD) test for continuous variables, and the Fisher’s exact test with the Bonferroni’s correction for dichotomous variables. The adherence to the administration of voglibose was evaluated by the generalized linear mixed model in which the time of medication (i.e., before breakfast, lunch, or dinner) as well as the intervention arms (i.e., the thrice- or once-daily voglibose group) were included as the fixed effects.

The sample size of at least 45 per group was enough to detect the difference of 0.2% in hemoglobin A1c levels, with SD of 0.25%, a two-sided significance level of 5%, and a power of 80%. The sample size was also enough to detect the difference of 0.8% in glycoalbumin levels with SD of 1.0%, and 3.0 μg/mL in 1,5-AG levels with SD of 4.0 μg/mL.

In the current study, we additionally investigated whether there were any clinical baseline parameters associated with the response to add-on of voglibose. The impact of clinical parameters on the response to voglibose was assessed by the interaction effect with the intervention arms on the primary efficacy endpoint (i.e., the change of hemoglobin A1c levels) in the linear regression model. We also performed the logistic regression analysis to investigate the association of clinical baseline parameters with the prevalence of observed side effects.

Results

A total of 156 patients were randomly allocated. After the allocation, one patient withdrew the participation, and another was lost to follow up before the first visit. Finally, the full analysis set comprised the remaining 154 patients (49 patients in the thrice-daily voglibose group, 50 patients in the once-daily voglibose group, and 55 patients in the control group). They were 64 ± 12 years old and 92 patients (60%) were male. The hemoglobin A1c levels were 6.8 ± 0.5% at the initiation of the study and 6.8 ± 0.5% one month
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before; the difference was 0.0 ± 0.1%, with no statistical significance ($p = 0.555$). There were no significant differences in baseline characteristics among the three arms (Table 1).

**Efficacy assessment**

Fig. 1 shows the change of hemoglobin A1c levels during the study period. At the end of the study, the change was significantly different among groups ($p < 0.001$ by the one-way ANOVA). The post-hoc Tukey's HSD test revealed that the once- and thrice-daily voglibose groups had a significantly greater reduction of hemoglobin A1c levels than the control group, with the difference of -0.27% (95% confidence interval (CI): -0.40% to -0.15%) in the once-daily voglibose group, and -0.33% (95% CI: -0.45% to -0.20%) in the thrice-daily voglibose group (both $p < 0.001$). The change of hemoglobin A1c levels in the thrice-daily voglibose group was not statistically different from that in the once-daily voglibose group; the difference was -0.05% (95% CI: -0.18% to 0.08%, $p = 0.615$).

The change of glycoalbumin and 1,5-AG levels is shown in Fig. 2. At the end of the study, the change of both measurements was significantly different among groups ($p < 0.001$ by the one-way ANOVA). As shown in Fig. 2A, the once- and thrice-daily voglibose group had a significantly greater reduction of glycoalbumin levels than the control group, with the difference of -1.0% (95% CI: -1.6% to -0.4%, $p = 0.001$) and -1.2% (95% CI: -1.8% to -0.7%, $p < 0.001$), respectively. There was no significant difference between the once- and thrice-daily voglibose group (95% CI: -0.3% to 0.3%, $p = 0.496$). On the other hand, as shown in Fig. 2B, the once- and thrice-daily voglibose group had a significantly greater increase of 1,5-AG levels than

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**Table 1 Baseline characteristics of the study population**

<table>
<thead>
<tr>
<th></th>
<th>Thrice-daily voglibose group ($n = 49$)</th>
<th>Once-daily voglibose group ($n = 50$)</th>
<th>Control group ($n = 55$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>29 (59%)</td>
<td>29 (58%)</td>
<td>34 (62%)</td>
<td>0.919</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 11</td>
<td>65 ± 12</td>
<td>65 ± 11</td>
<td>0.377</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 4.1</td>
<td>24.8 ± 3.6</td>
<td>24.2 ± 4.0</td>
<td>0.758</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.3 ± 17.2</td>
<td>63.8 ± 10.5</td>
<td>61.9 ± 15.0</td>
<td>0.783</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at the study initiation</td>
<td>6.7 ± 0.4</td>
<td>6.8 ± 0.6</td>
<td>6.7 ± 0.5</td>
<td>0.844</td>
</tr>
<tr>
<td>one month before</td>
<td>6.7 ± 0.5</td>
<td>6.8 ± 0.6</td>
<td>6.7 ± 0.4</td>
<td>0.738</td>
</tr>
<tr>
<td>change for the one month</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.2</td>
<td>0.0 ± 0.1</td>
<td>0.592</td>
</tr>
<tr>
<td>Glycoalbumin (%)</td>
<td>17.6 ± 2.8</td>
<td>17.9 ± 2.7</td>
<td>18.2 ± 2.6</td>
<td>0.502</td>
</tr>
<tr>
<td>1,5-anhydroglucitol (µg/mL)</td>
<td>13.9 ± 7.1</td>
<td>13.5 ± 8.3</td>
<td>12.5 ± 5.9</td>
<td>0.594</td>
</tr>
<tr>
<td>Sulfonylurea use</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
<td>4 (7%)</td>
<td>0.263</td>
</tr>
<tr>
<td>Metformin use</td>
<td>16 (33%)</td>
<td>17 (34%)</td>
<td>15 (27%)</td>
<td>0.731</td>
</tr>
<tr>
<td>Pioglitazone use</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
<td>0.515</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (24%)</td>
<td>21 (42%)</td>
<td>18 (33%)</td>
<td>0.180</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>24 (49%)</td>
<td>20 (40%)</td>
<td>25 (45%)</td>
<td>0.663</td>
</tr>
</tbody>
</table>

Data are mean ± SD or $n$ (percentage).

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![Fig. 1 Change of hemoglobin A1c levels during the study period](image)
the control group, with the difference of 3.3 μg/mL (95% CI: 1.7 to 4.9 μg/mL) and 5.5 μg/mL (95% CI: 3.9 to 7.1 μg/mL) (both \( p < 0.001 \)). Furthermore, the change of 1,5-AG levels in the thrice-daily group was significantly higher than that in the once-daily group, with the difference of 2.2 μg/mL (95% CI: 0.6 to 3.9 μg/mL, \( p = 0.005 \)).

**Safety and body weight change**

Table 2 summarizes side effects observed during the study period. Most of the side effects were gastrointestinal symptoms. Side effects were more likely observed in the voglibose groups, with statistical significance. Two patients in the once-daily voglibose group, but none in the other groups, voluntarily discontinued voglibose because of constipation (\( n = 1 \)) and vertigo (\( n = 1 \)), although the prevalence was not statistically different among groups (\( p = 0.122 \)).

The change of body weight and the fold-change of transaminase levels were not significantly different among groups (Table 3).

**Adherence to administration of voglibose**

Adherence to administration of voglibose was 96% (47/49) before breakfast, 73% (36/49) before lunch, and 94% (46/49) before dinner in the thrice-daily voglibose group, and 91% (39/43) before breakfast, 0% (0/1) before lunch, and 83% (5/6) before dinner in the once-daily voglibose group. Compared to the administration before breakfast, that before lunch, but not before dinner, was significantly associated with a lower adherence (\( p = 0.022 \) and 0.518, respectively). No signifi-
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cant association was observed between the intervention arm and the adherence ($p = 0.340$).

**Association of clinical parameters with the response to voglibose**

Table 4 shows the impact of clinical baseline parameters on the association of voglibose administration with the change of hemoglobin A1c levels. Thrice-daily voglibose administration brought a greater reduction of hemoglobin A1c levels in patients with higher glycoalbumin levels ($p$ for interaction = 0.012). A similar tendency was observed in those with higher hemoglobin A1c levels, although the impact was not statistically significant ($p$ for interaction = 0.065). No other baseline parameters had a significant interaction effect on the efficacy of thrice-daily voglibose (Table 4). On the other hand, once-daily voglibose administration brought a greater reduction of hemoglobin A1c levels in patients with higher glycoalbumin levels and with lower 1,5-anhydroglucitol levels ($p$ for interaction = 0.024 and 0.025, respectively). No baseline parameters were associated with the presence of any side effects (all $p > 0.05$) (data not shown).
Discussion

The current parallel-group, randomized, open-label, three-arm study demonstrated that the introduction of once- and thrice-daily 0.2 mg of voglibose brought a significant reduction of hemoglobin A1c levels in Japanese type 2 diabetic patients treated with 25 mg of alogliptin. No significant difference was observed in the change of hemoglobin A1c levels between the once- and thrice-daily voglibose group, whereas the thrice-daily voglibose group had a greater increase of 1,5-AG levels compared to the once-daily voglibose group. Most of the side effects observed in the voglibose groups were gastrointestinal symptoms.

DPP-4 inhibitors are now widely used in clinical practice. The monotherapy of the agents has a considerable glucose-lowering effect without hypoglycemia or weight gain, and have become one of the first-line medications in the management of type 2 diabetes [1-8]. However, some patients receiving DPP-4 inhibitors fail to achieve sufficient glycemic control. Although several studies assessed the efficacy of DPP-4 inhibitors as an add-on therapy to alpha-glucosidase inhibitors [28, 29, 34], few data are so far available about the efficacy of alpha-glucosidase inhibitors as an add-on to DPP-4 inhibitors. To the best of our knowledge, this is the first report investigating the 12-week efficacy of alpha-glucosidase inhibitors as an add-on to DPP-4 inhibitors. To the best of our knowledge, this is the first report investigating the 12-week efficacy of alpha-glucosidase inhibitors as an add-on to DPP-4 inhibitors.

In the current study, the once-daily voglibose group had a significantly greater reduction of hemoglobin A1c levels than the control group. In addition, interestingly, the reduction was almost similar and lacked a significant difference between the once- and thrice-daily voglibose groups (Fig. 1). The similar results were observed in glycoalbumin levels (Fig. 2A). Thrice-daily, i.e., frequent administration schedule is one major disadvantage of alpha-glucose inhibitors. It would be attractive in clinical practice that a less frequent administration could bring a similar effect in lowering hemoglobin A1c levels.

It remains unclear why once-daily voglibose demonstrated a considerable impact on the reduction of hemoglobin A1c levels similarly to thrice-daily voglibose. However, several possible explanations would be given. First, as some clinical studies on insulin therapy indicated, the correction of at least one glucose excursion might be actually effective in lowering hemoglobin A1c levels. Some clinical trials demonstrated that adding once-daily rapid-acting insulin to ongoing long-acting insulin did lower hemoglobin A1c levels in type 2 diabetic patients [35, 36]. In addition, it was demonstrated that once-daily rapid acting insulin as an add-on to long-acting insulin brought similar hemoglobin A1c levels compared to twice- and thrice-daily rapid-acting insulin [37]. These reports indicate that correcting even one glucose excursion would lead to a considerable reduction in hemoglobin A1c levels.

Second, the combined use of alogliptin might favorably modulate the glucose-lowering effect of voglibose, via enhancing its effect on incretin, especially glucagon-like peptide 1 (GLP-1) [30, 31, 43, 44]. Alpha-glucosidase inhibitors prolong and enhance the secretion of GLP-1 from the intestine [45-50], whereas DPP-4 inhibitors suppress the inactivation of the secreted incretin. The co-use of alogliptin might maximize the effect of once-daily voglibose on incretin. Indeed, one recent clinical study indicates that once-daily alpha-glucosidase inhibitors before breakfast would increase GLP-1 levels and possibly decrease postprandial glucose levels, not only after breakfast but also after lunch in type 2 diabetic patients treated with DPP-4 inhibitors [33], although their intervention period was only 2 days.

Third, a similar reduction in hemoglobin A1c levels between once- and thrice-daily voglibose might come from the limitation of hemoglobin A1c as a marker of glycemic control. Hemoglobin A1c levels in general represent the average of daily glycemic profiles, and postprandial glucose excursions are not always accurately reflected by hemoglobin A1c levels [51]. Indeed, 1,5-AG levels, more sensitive to glucose excursions [51], were higher in the thrice-daily voglibose group than in the once-daily voglibose group (Fig. 2B). This finding indicates that thrice-daily voglibose would more strictly correct postprandial glucose excursions compared to once-daily voglibose. The measurements of hemoglobin A1c might be unable to detect this difference.
In the current study, most of the side effects observed in the voglibose groups were gastrointestinal symptoms, e.g., flatulence, constipation, and abdominal distension, as was previously reported [52, 53]. The supplementary analysis showed that baseline parameters were not associated with side effects, indicating the difficulty to predict the presence of side effects by baseline parameters. The once-daily voglibose group had a relatively low frequency of gastrointestinal symptoms compared to the thrice-daily voglibose group, although two patients in the once-daily voglibose group, but none in the thrice-daily group, voluntarily discontinued voglibose because of the side effects. Future studies with a larger population size will be needed to reveal if the prevalence of side effects would be different between the once- and thrice-daily administration of voglibose.

In the current study, the adherence analysis suggested that as a whole, patients were less likely to be adherent to the administration of voglibose before lunch. For the avoidance of non-adherence, it might be better to prescribe voglibose before breakfast or dinner, but not before lunch, if it is to be administered once daily, although the current study sample size was too small to conclude that. Future prospective studies will be needed to validate this hypothesis.

The additional analysis showed that poorer glycemic control at baseline was associated with a greater reduction of hemoglobin A1c levels after voglibose administration (Table 4). These findings would be consistent with previous studies on hypoglycemic agents, which demonstrated a greater improvement of glycemic control in those with poorer glycemic control at baseline [54, 55]. No other baseline characteristic was associated with the effect of voglibose on glycemic control in the current study, indicating a similar efficacy of voglibose across background characteristics except baseline glycemic control.

There were some limitations in the current study. First, the study period was limited to 12 weeks and therefore a longer-term efficacy of once- and thrice-daily voglibose remains unknown. Second, daily blood glucose profiles were not assessed in the current study. Future studies examining the profiles will be needed to validate the glucose-lowering effect of once- and thrice-daily voglibose, which was evaluated using hemoglobin A1c, glycoalbumin, and 1,5-AG levels in the current study. Third, we did not assessed insulin or incretin levels. Detailed data on glucose metabolism were therefore unrevealed. Fourth, the patients’ satisfaction with the treatment was not surveyed. Previous studies revealed that the treatment satisfaction was positively associated with the glucose-lowering effect of the medications, whereas it was inversely associated with the presence of side effects [56-58]. The administration of voglibose was associated with both glucose-lowering effect and the presence of side effects. It remained to be investigated whether the treatment would satisfy the patients.

In conclusion, once- and thrice-daily voglibose as an add-on to alogliptin significantly lowered hemoglobin A1c levels in type 2 diabetic patients. There was no significant difference in the change of hemoglobin A1c levels between the once- and thrice-daily voglibose groups, although the change of 1,5-AG levels were significantly higher in the thrice-daily voglibose group than in the once-daily voglibose group.

Acknowledgements

Mitsuyoshi Takahara is a Research Fellow of the Japan Society for the Promotion of Science. There is no conflict of interest concerning this manuscript. The authors thank Akane Seo, Osaka Branch, Takeda Pharmaceutical Company Limited, Osaka, Japan, for her help in retrieving drug information and literature.

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