Clinical study of repaglinide efficacy and safety in type 2 diabetes mellitus patients with blood glucose levels inadequately controlled by sitagliptin

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases chiefly characterized by chronic hyperglycemia resulting from insufficient insulin action. Approximately ≥90% of diabetic patients have type 2 diabetes mellitus. The ideal glycemic control is to correct fasting and postprandial hyperglycemia without causing hyperglycemia and hypoglycemia throughout the day, consequently normalizing the levels of glycated hemoglobin (HbA1c), a commonly used index of blood glucose levels. While intensive glycemic control has been shown to prevent microangiopathy onset, a 1% decrease in HbA1c levels prevents the onset of microangiopathy by 37% according to the United Kingdom Prospective Diabetes Study, a leading study targeting patients with type 2 diabetes mellitus. Moreover, in Japan, an HbA1c level of <7.0% is recommended as a glycemic control target for preventing complications of diabetes mellitus. The following points should also be considered: according to the Kumamoto study, the onset and progression of microangiopathy can be prevented in a majority of patients with an HbA1c level of <6.9%; the upper HbA1c limit in people with normal glucose tolerance is 6.2%; and the glycemic control targets used in other countries should be considered. Furthermore, postprandial glycemic control is considered effective for preventing the progression of cardiovascular diseases in Japanese patients with early stage type 2 diabetes mellitus who have postprandial hyperglycemia as a result of delayed or decreased postprandial insulin secretion despite preserved basal insulin secretion.
Currently, drugs with various action mechanisms are prescribed for type 2 diabetes mellitus patients. Diabetes is a progressive disease and therefore, it is not always easy to maintain good glycemic control with a single class of hypoglycemic agents. Eventually, the majority of patients concomitantly receive ≥2 classes of hypoglycemic agents with different action mechanisms. Repaglinide is a short-acting insulin secretagogue with biliary excretion that, unlike sulfonylureas, rapidly stimulates postprandial insulin secretion shortly after a meal and corrects abnormal patterns of insulin secretion. Meanwhile, the dipeptidyl peptidase-4 (DPP-4) inhibitor exerts a hypoglycemic effect by selectively inhibiting DPP-4, which elevates active incretin levels, stimulates insulin secretion depending on blood glucose levels and suppresses glucagon secretion. Therefore, when sufficient glycemic control cannot be achieved with a DPP-4 inhibitor alone, the combination of DPP-4 inhibitor and repaglinide, which has a direct insulinotropic effect, can be expected to improve glycemic control and provide a new treatment option for diabetes mellitus in Japanese clinical practice.

To evaluate the efficacy and safety of a long-term repaglinide and a DPP-4 inhibitor combination therapy, we carried out an uncontrolled, long-term study in patients with type 2 diabetes mellitus whose blood glucose levels were not sufficiently controlled by oral administration of sitagliptin in addition to diet and exercise therapies.

METHODS
Enrolled Patients
The present study included outpatients aged ≥20 years with type 2 diabetes mellitus who had been receiving sitagliptin at a fixed dosage and administration pattern (oral administration of 50–100 mg once daily) in addition to certain diet and exercise therapies for ≥12 weeks before starting the study treatment, and whose blood glucose levels had been poorly controlled (6.9% ≤ HbA1c ≤ 9.4%). Patients who had been treated with insulin or sulfonylureas during the previous 24 weeks or oral-dose hypoglycemic agents except sitagliptin, glucagon-like peptide 1 receptor agonist and corticosteroid (oral preparation, suppository or injection) during the previous 12 weeks were excluded. Patients who met any of the following criteria were also excluded: those with diabetic retinopathy (diabetic proliferative and pre-proliferative retinopathy); serious diabetic neuropathy; hepatic dysfunction (aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels were at least 2.5-fold higher than the upper limit of the reference value); renal dysfunction (creatinine level ≥2.0 mg/dL); heart diseases (heart failure [New York Heart Association class III and IV], unstable angina and a history of myocardial infarction within the previous 12 months); severe hypertension; a heavy drinking habit; severe ketosis and those with diabetic coma or precoma; severe infection, pre- or postoperative patients and patients with serious trauma; malignant tumors; and pregnant women, possibly pregnant women, women who might become pregnant without using any adequate contraceptive method and lactating women.

The present study was examined and approved by the institutional review boards of each participating institution, and subsequently conducted in accordance with the Ministerial Ordinance on Good Clinical Practice and relevant Notifications. This study conforms to the provisions of the Declaration of Helsinki. Furthermore, the objectives and contents of this study were explained to each patient by using a leaflet and consent form authorized by the institutional review boards. Patients provided written consent of their own free will to participate in this study.

Study Design and Methods
The treatment duration was 52 weeks. Repaglinide was orally administered three times daily immediately before each meal (within 10 min). The dose of repaglinide was 0.75 mg/day until the patients visited the institution at 2 weeks after treatment. If no safety problem was noted at this visit, the dose was increased to and maintained at 1.5 mg/day. During the visit at ≥16 weeks after treatment, the dose was increased to 3 mg/day, if no safety problem was noted and patients receiving repaglinide at 1.5 mg/day had an HbA1c level of ≥7.4% during the two immediate consecutive visits. If adverse events (AEs) occurred or might occur, or if the HbA1c level decreased to <6.2%, the dose could be reduced to either 1.5 or 0.75 mg/day, or repaglinide could be temporarily discontinued.

The primary end-point was the HbA1c level. HbA1c levels were expressed as National Glycohemoglobin Standardization Program values that were converted from the Japan Diabetes Society values. Secondary end-points included fasting plasma glucose (FPG), glycoalbumin (GA), postprandial plasma glucose (PPG) and postprandial serum insulin levels, as well as the proportion of patients achieving the glycemic control targets set by the Japan Diabetes Society. Meal tolerance tests (the retort pouch food and rice whose energy unit was adjusted to approximately 400 kcal) were carried out before, and 24 and 52 weeks after the start of treatment. Sitagliptin (before the start of treatment) or repaglinide and sitagliptin (at 24 and 52 weeks after the start of treatment) were orally administered after blood sample collection and immediately before breakfast (within 10 min); blood samples were again collected 30 min, and 1, 2 and 3 h after starting breakfast.

An AE was defined as the occurrence of any unfavorable and unintended event during the study period. The occurrence of any AE that was causally related to repaglinide was regarded as an adverse drug reaction. Laboratory tests (hematology and biochemistry), and bodyweight and vital sign measurements (blood pressure and pulse rate [sitting position]) were carried out before the start of treatment (week 0), 2 weeks after the start of treatment and every 4 weeks from week 4 to week 52. Twelve-lead electrocardiography was carried out between the time of consent and enrollment, and at 24 and 52 weeks after starting repaglinide administration. As a means of self-monitoring the
blood glucose after the start of treatment, a self-monitoring blood glucose device was provided to each patient.

**Statistical Analysis**

**Efficacy Parameters**

Among the patients who received repaglinide, those with HbA1c levels measured at baseline (before the start of treatment) and at least once after treatment were included in the full analysis set (FAS), and the efficacy analysis set was defined as FAS. The change from baseline to the end of the study was calculated as mean differences and 95% confidence intervals (CI). Descriptive statistics were calculated at the end of study for measurement values and for changes from baseline. The proportion of patients achieving glycemic control targets was calculated based on the number and proportion of the patients at the end of the study.

**Safety Parameters**

The safety analysis set was defined as all patients who received repaglinide at least once during the study period. The number of patients with AEs, adverse drug reactions, serious AEs and hypoglycemia, and the incidence rates and number of these events, were calculated. When patients were suspected of having severe central neural dysfunction (i.e., impaired consciousness caused by hypoglycemia) and required intervention (i.e., intramuscular injection of glucagon and intravenous injection of glucose), they were defined as ‘major hypoglycemia’. ‘Minor hypoglycemia’ was defined as a condition in which a patient has symptoms, such as hyperhidrosis, tremor, palpitation, nausea, anxiety, hot feeling, hunger, headache and malaise, but did not require intervention by any other individual. Minor hypoglycemic patients also had blood glucose levels of ≤60 mg/dL as determined by a casual blood glucose test or self-monitoring blood glucose meter when the symptoms appeared.

**RESULTS**

The patient demographics are shown in Figure 1. Of 105 enrolled patients, 100 patients started the study treatment and 90 patients completed it. All 100 patients who had started treatment were included in the FAS and safety analysis set.

Patient characteristics are shown in Table 1. The 100 patients who started the study comprised of 68 men and 32 women with a mean age of 58.1 ± 11.8 years (mean ± standard deviation). There were 66 patients aged <65 years and 34 patients aged ≥65 years. The body mass index was 25.08 ± 3.87. The average of the drug compliance of repaglinide was 94.88%.

The summary of glycemic control changes is shown in Table 2. The HbA1c level decreased from 7.43 ± 0.57% at baseline to 6.93 ± 0.91% at the end of the study. The fluctuations in HbA1c levels are shown in Figure 2. The proportion of patients who achieved the target goal of an HbA1c level <7.0% was 58.0% (58/100) at the end of the study, compared with 23.0% (23/100) at baseline (Table 2 and Figure S1).

Fluctuations in PPG levels according to assessment points are shown in Figure 3. Compared with the baseline value (680 ± 103 mg*mH/dL), the PPG area under the concentration
Table 2 | Changes in glycemic control

|                        | Baseline       | End of study | Change from baseline (95% CI) |
|------------------------|----------------|--------------|------------------------------|
| HbA1c (%)              | 7.43 ± 0.57 (100) | 6.93 ± 0.91 (100) | –0.50 ± 0.82 (–0.66, –0.33)  |
| HbA1c according to BMI |                |              |                              |
| <25                    | 7.40 ± 0.62 (56) | 6.78 ± 0.83 (56) | –0.62 ± 0.75 (–0.82, –0.42)  |
| ≥25                    | 7.47 ± 0.51 (44) | 7.13 ± 0.98 (44) | –0.35 ± 0.90 (–0.62, –0.07)  |
| HbA1c according to age |                |              |                              |
| ≥65 years              | 7.51 ± 0.61 (66) | 6.99 ± 0.94 (66) | –0.51 ± 0.90 (–0.74, –0.29)  |
| <65 years              | 7.29 ± 0.46 (34) | 6.82 ± 0.85 (34) | –0.47 ± 0.65 (–0.69, –0.24)  |
| PPG AUC0–3h (mg/dL)    | 268 ± 103 (93)  | 212 ± 125 (93)  | –72 ± 117 (–96, –48)         |
| Postprandial serum insulin AUC0–3h (µU*h/mL) | 89.60 ± 58.83 (92) | 121.12 ± 74.78 (91) | 32.56 ± 36.33 (24.99, 40.13) |
| AUC0–3h (%)            | 155.1 ± 25.4 (99) | 141.1 ± 28.5 (99) | –140 ± 26.8 (–193, –86)      |
| Proportion of patients achieving the glycemic control targets |                |              |                              |
| <8.0%                  | 82 (82.0%)      | 85 (85.0%)    | –                            |
| <7.0%                  | 23 (23.0%)      | 58 (58.0%)    | –                            |
| <6.0%                  | 0              | 9 (9.0%)      | –                            |

AUC0–3h, area under the curve from 0 to 3 h; BMI, body mass index; CI, confidence interval; PPG, fasting plasma glucose; GA, glycoalbumin; HbA1c, glycated hemoglobin; PPG, postprandial plasma glucose. Baseline and end of study data are represented as mean ± standard deviation (n). The change from baseline data is represented as mean ± standard deviation (95% confidence interval [CI]). The proportion of patients achieving glycemic control targets are represented as n (%).

A total of 352 AEs occurred in 86 of the 100 patients (86.0%). A causal relationship with repaglinide was not ruled out in 104 AEs (adverse drug reactions) that occurred in 21 patients (21.0%; Table S1). Although none of the patients died, three patients each developed a serious AE: a meniscus lesion, appendicitis and complete atrioventricular block. AEs did not result in permanent treatment discontinuation or dose reduction in any patients, but two patients temporarily discontinued treatment. AEs that led to temporary treatment discontinuation were appendicitis (serious AE) and alcoholic liver disease. All serious AEs and the AE resulting in temporary treatment discontinuation subsided, disappeared or resolved, and their causal relationships with repaglinide were ruled out. A total of 14 episodes of hypoglycemia occurred in five of the 100 patients (5.0%); all of these episodes were determined to be adverse drug reactions. With the exception of abnormalities reported as AEs, laboratory test results and electrocardiograms did not show any clinically problematic fluctuations or clinically important abnormalities throughout the study period. The change in bodyweight from baseline to the end of study was 1.22 ± 2.17 kg, showing no marked fluctuations. Both blood pressure and pulse rates remained nearly constant. The incidence of major AEs (≥2%) and adverse drug reactions is shown in Tables 3 and S2, respectively. AEs with a high incidence rate included nasopharyngitis in 31.0% (31/100) and bronchitis in 8.0% (8/100) of the patients; constipation and dental caries were observed in 7.0% (7/100), and diarrhea, gastroenteritis, influenza and arthralgia were observed in 6.0% (6/100). The reason why the incidence rate of nasopharyngitis is high is that nasopharyngitis included the common cold. Adverse drug reactions with a high incidence included hypoglycemia and tremor, both of which were observed in 5.0% (5/100) of patients.

Although there was no incidence of ‘major hypoglycemia’, all episodes of hypoglycemia resolved or subsided after the patients ingested glucose or food at their own discretion. The incidence rates of hypoglycemia were low throughout the study and did not increase during any specific period (Table S3). Furthermore, no specific trend in the repaglinide dosage at hypoglycemia onset (0.75 and 1.5 mg/day in 3 patients each, including 1 patient who experienced hypoglycemia at both doses) was observed. Regarding the incidence rates of hypoglycemia according to the time between a meal and onset, 12 of the 14 hypoglycemia episodes occurred between 4 h and 7 h after a meal, and 11 episodes occurred after lunch (Table S4). No episodes were observed after dinner and during the night.
DISCUSSION

Although the American Diabetes Association/European Association for the Study of Diabetes consensus guidelines\(^7\) recommend starting treatment with metformin at the time of or soon after type 2 diabetes mellitus diagnosis, appropriate drug selection according to pathophysiological conditions is recommended in Japan because of differences in disease pathophysiology and patients’ lifestyles\(^1\). The DPP-4 inhibitors stimulate insulin secretion and suppress glucagon secretion by inhibiting the degradation of active incretin, which is secreted depending on blood glucose levels\(^9,10\). Monotherapy with this drug causes virtually no adverse drug reactions, including hypoglycemia, and therefore, DPP-4 inhibitors have been widely used as one of the first-line drugs in Japan\(^12,13\).

In Japanese type 2 diabetes mellitus patients with poorly controlled blood glucose levels, repaglinide monotherapy was superior to nateglinide, another short-acting insulin secretagogue, for reducing HbA1c levels\(^14\). Furthermore, we have already reported that in Japanese type 2 diabetes mellitus patients with poorly controlled blood glucose levels despite metformin treatment, adding repaglinide produced an excellent reduction in blood glucose levels\(^15\). In the present study, we evaluated the efficacy and safety of a long-term combination therapy with repaglinide and sitagliptin in type 2 diabetes mellitus patients with blood glucose levels that had been poorly controlled by sitagliptin monotherapy.

Regarding efficacy, FPG and GA levels decreased 2 weeks after starting treatment; HbA1c levels decreased after 4 weeks. These effects were maintained up to 52 weeks after starting treatment, which were confirmed by the long-term efficacy of repaglinide and sitagliptin combination therapy, and were the same as the results of the monotherapy\(^14\) and the combination therapy with metformin\(^15\). According to the body mass index level and age brackets (Table 2), the HbA1c level tended to improve in patients with a lower body mass index, but there was no significant difference (\(P = 0.101\)), and a similar HbA1c level improvement was observed in both age groups (<65 and \(\geq 65\) years). The PPG AUC\(_{0–3\ h}\), decreased at 24 and 52 weeks compared with before repaglinide administration, showing long-term improvement. However, postprandial serum insulin levels increased, which indicated that the insulinotropic effect was maintained for a long period. Although glucagon levels were not measured in the present study, repaglinide has been reported to exert no effects on glucagon secretion at the same concentration level at which it exerts the insulin-releasing action\(^16\). Therefore, it was assumed that adding repaglinide might further enhance the insufficient postprandial insulinotropic action of sitagliptin alone, leading to the suppression of postprandial hyperglycemia and decreased HbA1c levels. As a result, an HbA1c level of <7.0%, which was one of the glycemic control targets, was achieved in more than half (i.e., 58.0% \([58/100]\)) of the patients. In contrast, the insulin resistance and the fasted insulin level might affect the result that some patients could not achieve the treatment goal, although the clear tendency was not observed.

The ultimate goals of the treatment for type 2 diabetes mellitus are to prevent the onset and progression of microangiopathy and macroangiopathy, to maintain a quality of life similar to those without type 2 diabetes mellitus, and to lead to a life comparable with that of people without type 2 diabetes mellitus\(^17\). It has been suggested that the microangiopathy incidence and prevalence rates are higher in patients with higher FPG levels\(^5\), and that postprandial hyperglycemia is strongly associated with the risk of developing macroangiopathy\(^17,20\). Therefore, it is expected that the effects of repaglinide and sitagliptin combination therapy on
decreasing HbA1c levels and resolution of postprandial hyperglycemia could contribute not only to better glycemic control, but also to preventing the development and progression of microangiopathy and macroangiopathy in many patients. Regarding safety, all AEs for which a causal relationship with repaglinide could not be ruled out (adverse drug reactions) were mild. The major adverse drug reactions were hypoglycemia and tremor, which were observed in five patients (5%) each. Although hypoglycemia is a common adverse drug reaction to drugs with insulinotropic action, all episodes of hypoglycemia observed in the present study resolved or subsided after the patients ingested glucose or food at their own discretion. Furthermore, 12 of the 14 hypoglycemia episodes occurred between 4 h and 7 h after a meal; no episodes were observed after dinner. This suggests that hypoglycemia onset could be prevented by eating an appropriate amount of meals at appropriate intervals. These results regarding the incident rate and the onset of hypoglycemia were the almost same as those in the previous studies\textsuperscript{14,15}.

Combination repaglinide and sitagliptin therapy was confirmed to be tolerable, and provide long-term improvement in HbA1c levels and other blood glucose parameters, including PPG levels. This therapy should be considered as an effective treatment option for type 2 diabetes mellitus patients in clinical practice in Japan.

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Table 3 | Incidence of major adverse events (≥2%)

| System organ class | Preferred term | No. adverse events (%) |
|--------------------|----------------|------------------------|
| Cardiac disorders  | Palpitation     | 4 (4.0)                |
| Eye disorders      | Diabetic retinopathy | 4 (4.0)    |
|                    | Conjunctivitis allergic | 3 (3.0)   |
| Gastrointestinal disorders | Constipation | 7 (7.0) |
|                    | Dental caries   | 7 (7.0)                |
|                    | Diarrhea        | 6 (6.0)                |
|                    | Gastritis       | 4 (4.0)                |
|                    | Abdominal discomfort | 3 (3.0)   |
|                    | Abdominal distension | 2 (2.0)  |
|                    | Abdominal pain  | 2 (2.0)                |
|                    | Gastroesophageal reflux disease | 2 (2.0) |
|                    | Nausea          | 2 (2.0)                |
|                    | Vomiting        | 2 (2.0)                |
|                    | Hypesthesia oral| 2 (2.0)                |
| General disorders and administration site | Hunger | 3 (3.0) |
|                    | Asthenia        | 2 (2.0)                |
| Infections and infestations | Nasopharyngitis | 31 (31.0) |
|                    | Bronchitis      | 8 (8.0)                |
|                    | Gastroenteritis | 6 (6.0)                |
|                    | Influenza       | 6 (6.0)                |
|                    | Periodontitis   | 3 (3.0)                |
|                    | Enteritis infectious | 3 (3.0) |
|                    | Acute tonsillitis| 2 (2.0)       |
|                    | Cellulitis      | 2 (2.0)                |
|                    | Cystitis        | 2 (2.0)                |
|                    | Gingivitis      | 2 (2.0)                |
|                    | Pharyngitis     | 2 (2.0)                |
| Injury, poisoning and procedural complications | Contusion | 3 (3.0) |
|                    | Ligament sprain | 2 (2.0)                |
|                    | Wrist fracture  | 2 (2.0)                |
| Investigations | Blood creatine phosphokinase increased | 4 (4.0) |
|                    | Alanine aminotransferase increased | 2 (2.0) |
| Metabolism and nutrition disorders | Hypoglycemia | 5 (5.0) |
|                    | Hyperlipemia    | 3 (3.0)                |
|                    | Decreased appetite | 2 (2.0)   |
| Musculoskeletal and connective tissue disorders | Arthralgia | 6 (6.0) |
|                    | Back pain       | 4 (4.0)                |
|                    | Myalgia         | 2 (2.0)                |
|                    | Pain in extremity| 2 (2.0)                |
| Nervous system disorders | Dizziness | 5 (5.0) |
|                    | Tremor          | 5 (5.0)                |
|                    | Headache        | 4 (4.0)                |
|                    | Head discomfort  | 2 (2.0)                |

Table 3 (Continued)

| System organ class | Preferred term | No. adverse events (%) |
|--------------------|----------------|------------------------|
| Psychiatric disorders | Insomnia | 5 (5.0) |
| Respiratory, thoracic and mediastinal disorders | Rhinitis allergic | 4 (4.0) |
|                    | Oropharyngeal pain | 4 (4.0) |
|                    | Upper respiratory tract inflammation | 3 (3.0) |
| Skin and subcutaneous tissue disorders | Hyperhidrosis | 4 (4.0) |
|                    | Eczema          | 3 (3.0)                |
|                    | Pruritus        | 3 (3.0)                |
|                    | Cold sweat      | 2 (2.0)                |
| Vascular disorders | Hypertension   | 4 (4.0)                |

Data are represented as n (%). Safety analysis set (n = 100).

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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:

Figure S1 | Achievement rate of treatment goal of glycated hemoglobin.
Figure S2 | Change in postprandial serum insulin levels.
Table S1 | Incidence of adverse events.
Table S2 | Incidence rates of all adverse drug reactions.
Table S3 | Incidence rates of hypoglycemia according to the time of the initial episode.
Table S4 | Incidence rates of hypoglycemia according to the elapsed time after a meal