Combination Therapy of Alpha-Glucosidase Inhibitor and a Sulfonylurea Compound Prolongs the Duration of Good Glycemic Control

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The aim of this study was to investigate whether combination therapy of alpha-glucosidase inhibitor and a sulfonylurea (SU) drug can prolong the duration of good glycemic control compared with SU alone in patients with type 2 diabetes. The open prospective study included 124 Japanese patients with type 2 diabetes and inadequate glycemic control (hemoglobin A_{1c} [HbA_{1c}] gt; 7.0%). Patients were given either voglibose plus a SU compound (glibenclamide or gliclazide, n = 61) or SU drug alone (n = 63). The first 6-month run-in period (targeted to $HbA_{1c} \leq 7.0\%$) was followed by treatment for 3 years. The endpoint was deterioration of glycemic control ($HbA_{1c} \geq 8.0\%$). Fifty patients on combination therapy and 48 patients on SU alone completed the trial. During the follow-up, 21 patients on combination therapy and 30 patients on SU alone showed deterioration of glycemic control and reached the endpoint ($P = .04$). The combination therapy significantly prolonged the duration of good glycemic control ($HbA_{1c} < 8.0\%$) compared with SU alone by Kaplan-Meier estimated survival analysis using a log-rank test ($P = .02$). Thus, combination therapy with voglibose and a SU agent prolongs the duration of good glycemic control compared with SU alone in patients with type 2 diabetes.

SULFONYLUREA (SU) compounds are commonly used for the treatment of patients with type 2 diabetes, and their clinical usefulness has been confirmed in several clinical studies such as the United Kingdom Prospective Diabetes Study (UKPDS).[1,2] However, it is well known that secondary failure could occur after treatment with SU compounds.[3] Indeed, it is reported that the use of SU alone could not maintain longstanding euglycemia in patients with type 2 diabetes.[2-4] The mechanism of this secondary failure of SU is not well established, although some studies suggested that it is caused by overwork of pancreatic β cells with subsequent β-cell dysfunction.[5,6]

Inhibitors of alpha-glucosidase activity delay the absorption of carbohydrates from the small intestine,[7] which in turn results in a reduction of postprandial glucose without hypersecretion of intrinsic insulin.[8,9] We previously reported that the use of voglibose (Takeda, Osaka, Japan), an alpha-glucosidase inhibitor, could reduce diurnal insulin secretion through improvement of postprandial hyperglycemia in patients with type 2 diabetes.[10] These results suggest that alpha-glucosidase inhibitor may suppress overwork of pancreatic β cells in patients with type 2 diabetes.

We postulated that combination therapy of voglibose and a SU agent may protect pancreatic β cells, and thus prevent the secondary failure of SU.[11] In the present study, we compared the duration of good glycemic control in patients with type 2 diabetes treated by voglibose and a SU agent with those by SU alone in a 3-year open prospective study.

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MATERIALS AND METHODS

A total of 124 Japanese patients (74 men and 50 women) with type 2 diabetes gave informed consent to participate in this open prospective study. The study protocol was approved by the ethics committee of Sasebo Chuo Hospital. Type 2 diabetes was diagnosed according to World Health Organization (WHO) criteria.[12] At recruitment into the study, patients were on either diet therapy or SU drug alone and had inadequate hemoglobin A_{1c} (HbA_{1c}) levels (>7.0%). After baseline examination (medical questionnaire, physical examination, and blood sampling), patients were assigned at random into 1 of 2 groups; treatment with SU alone or combination treatment of SU and voglibose (Fig 1). Patients of the latter group (n = 61) were treated with voglibose at a dose of 0.2 mg before each meal and with a SU drug. The other 63 patients received SU drug alone and served as control subjects. Glibenclamide (1.25 to 7.5 mg/d) or gliclazide (20 to 80 mg/d) was used as the SU compound. The dosage of SU drug in use was modified to achieve HbA_{1c} levels ≤7.0% within a 6-month run-in period in both combination therapy group and SU group. This 6-month run-in period was to exclude patients with primary failure to SU therapy and noncompliance to voglibose. When HbA_{1c} levels decreased to ≤7.0%, patients were allowed to enter the follow-up study and the dosage of SU drug was fixed thereafter. Fifty-three patients (32 men and 21 women) on combination therapy and 51 patients (29 men and 22 women) on SU alone were entered into a 3-year (156-week) follow-up study. All patients were instructed to follow diet therapy (25 to 30 kcal/ideal body weight) and moderate exercise therapy by dieticians and physicians, which were continued throughout the study period in both groups. Postprandial blood glucose and HbA_{1c} were measured every 4 weeks during the 3-year follow-up period. The dosage of SU agent was reduced if hypoglycemic attacks occurred frequently. Although plasma glucose or HbA_{1c} occasionally increased in few patients, no increase in the dosage of SU drug was allowed. The endpoint of the follow-up study was the time at which HbA_{1c} deteriorated to levels above 8.0%. When patients reached the endpoint, they were released from the study and promptly treated by a more appropriate method, such as insulin therapy.

HbA_{1c} level was measured by high-performance liquid chromatography (HPLC) method (Tosoh, Tokyo, Japan) with a reference range of 4.3 to 5.8%. Plasma glucose concentration was measured by the glucose oxidase method (Kyoto Daiichi Kagaku, Kyoto, Japan). Total cholesterol and triglyceride levels were measured by the enzymatic method (Kokusai Shiyaku, Kobe, Japan). High-density lipoprotein

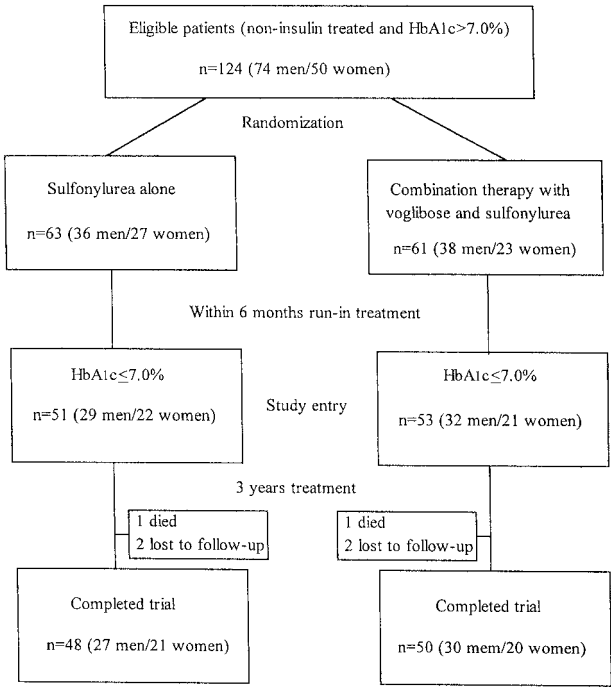

Fig 1. Trial profile.

(HDL) cholesterol was determined after isolation by precipitation method (Kyowa, Tokyo, Japan).

Statistical Analysis

Comparison between groups was conducted by Student's paired *t* test or contingency table analysis. The Kaplan-Meier analysis was used to estimate the survival curve using log-rank test to determine the difference in duration of good glycemic control ($HbA_{1c} < 8.0\%$) in the 2 treatment protocols. Data are presented as the mean ± SEM. Differences were considered statistically significant at $P < .05$. Statistical analysis was performed using the Statview 5.0 (SAS, Cary, NC) software package.

RESULTS

As shown in Fig 1, 51 patients of the SU alone group and 53 patients of the combination therapy group were recruited in the 3-year follow-up study. In the SU alone group, 1 patient died with acute myocardial infarction and 2 patients were lost to follow-up. In the combination therapy group, 1 patient died with stroke and two patients were lost to follow-up. Therefore, 48 patients of the SU alone group and 50 patients of the combination therapy group completed the trial. Table 1 shows the baseline clinical characteristics of those patients who completed the trial. Sex, age, duration of diabetes, and body mass index were comparable between the two groups. State of diabetic complication, family history of diabetes and hypertension, and treatment modality of diabetes before recruitment in the trial were also comparable between the groups. Furthermore, HbA_{1c}, postprandial glucose, and serum lipid levels were similar in the 2 groups.

During the follow-up period, 30 patients of the SU alone group and 21 patients of the combination therapy group failed to maintain good glycemic control and reached endpoint ($HbA_{1c} \geq 8.0\%$) ($P = .04$). Kaplan-Meier estimated survival analysis, using the log-rank test, compared the number of patients with good glycemic control ($HbA_{1c} < 8.0\%$) on SU alone and combination therapy (Fig 2). This analysis showed that the duration of good glycemic control was statistically significantly different between the 2 groups ($P = .02$). Combination therapy of voglibose and a SU compound significantly prolonged the duration of good glycemic control compared with SU alone in patients with type 2 diabetes.

Table 2 shows the changes in body weight, HbA_{1c}, and postprandial glucose levels throughout the study. Both in the SU alone and combination therapy groups, patients with good

Table 1. Baseline Clinical Characteristics of the Patients Who Completed the Trial

	SU Alone	SU + Voglibose
No. (males/females)	48 (27/21)	50 (30/20)
Age (yr)	59.7 ± 1.3	60.4 ± 1.4
Duration of diabetes mellitus (yr)	5.5 ± 0.8	7.6 ± 0.9
Body mass index (kg/m^2)	23.6 ± 0.4	22.9 ± 0.4
Prevalence of hypertension, no. (%)	26 (54.2)	20 (40.0)
Retinopathy, no. (%)	8 (16.7)	14 (28.0)
Nephropathy, no. (%)	7 (14.6)	4 (8.0)
Coronary artery disease, no. (%)	3 (6.3)	5 (10.0)
Stroke, no. (%)	4 (8.3)	2 (4.0)
Family history of diabetes mellitus, no. (%)	22 (45.8)	23 (46.0)
Family history of hypertension, no. (%)	16 (33.3)	17 (34.0)
Treatment modality at study recruitment (diet/SU drug)	32/16	29/21
HbA_{1c} (%)	9.5 ± 0.4	9.3 ± 0.3
Postprandial glucose (mmol/L)	12.9 ± 0.7	13.7 ± 0.6
Total cholesterol (mmol/L)	4.9 ± 0.1	4.9 ± 0.1
Triglyceride (mmol/L)	1.5 ± 0.1	1.3 ± 0.1
HDL cholesterol (mmol/L)	1.4 ± 0.1	1.3 ± 0.1

NOTE. Data are mean ± SEM, or number of patients (%).

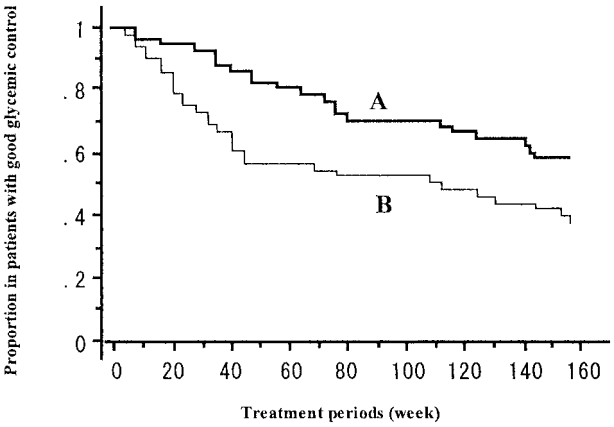

Fig 2. Proportion of patients with good glycemic control (HBA_{1c} < 8.0%) is plotted against weeks of treatment, using the Kaplan-Meier estimated survival analysis. (A) Combination therapy with voglibose and a SU drug. (B) SU alone.

Table 3. Comparison of Baseline Clinical Characteristics of Patients Who Maintained Good Glycemic Control and Those Who Reached Endpoint ($HbA_{1c} \geq 8.0\%$)

	Patients With Good Glycemic Control	Patients Who Reached Endpoint ($HbA_{1c} \geq 8.0\%$)
No. (males/females)	47 (32/15)	51 (25/26)
Age (yr)	63.2 ± 1.2*	57.2 ± 1.4
Duration of diabetes mellitus (yr)	6.8 ± 0.9	6.4 ± 0.8
Body mass index (kg/m^2)	23.0 ± 0.4	23.4 ± 0.5
HbA_{1c} (%)	9.6 ± 0.4	9.3 ± 0.3
Total cholesterol (mmol/L)	4.9 ± 0.1	4.9 ± 0.1
Triglyceride (mmol/L)	1.4 ± 0.1	1.4 ± 0.1
HDL cholesterol (mmol/L)	1.4 ± 0.1	1.4 ± 0.1
Treatment modality at recruitment (diet/SU)	29/18	32/19
SU and voglibose (yes/no)	29/18*	21/30

NOTE. Data are mean ± SEM or number of patients.
*$P < 0.05$ *v* patients who reached endpoint.

glycemic control maintained a steady body weight for 3 years. In contrast, a significant increase in body weight was noted in patients who reached endpoint (failure). Thus, increase in HbA_{1c} and postprandial glucose was associated with body weight gain. the magnitude of reduction in postprandial glucose from baseline to entry was greatest in combination therapy with good control (13.6 to 8.8 mmol/L, -4.8 mmol/L, $P < .01$), and smallest in SU alone with failure (13.1 to 9.3 mmol/L, -3.8 mmol/L, $P < .01$).

In the present study, the dosage of glibenclamide or gliclazide was fixed and was not allowed to increase. The final dosage of gliclazide in SU alone group significantly decreased, but the final dosage of gliclazide in combination therapy and of glibenclamide in both groups did not change significantly. The percentage of good control in gliclazide-treated patients was 45% (27/60) and in glibenclamide-treated patients was 45.5% (20/44) ($P = .96$). Thus, both SU compounds were almost equal effect. Restricted to combination therapy, the percentage of good control in gliclazide was 62.5% (15/24) and in glibenclamide was 48.3% (14/29) ($P = .30$). These results suggest that both gliclazide and glibenclamide are equally suitable for combination with alpha-glucosidase inhibitor.

To investigate the difference in glycemic control over the 3-year study period between the SU alone and combination therapy groups, we compared the baseline clinical characteristics of patients who maintained good glycemic control ($HbA_{1c} < 8.0\%$) and those who reached failure ($HbA_{1c} \geq 8.0\%$) (Table 3). Patients who maintained good glycemic control were significantly older; however, the duration of diabetes

Table 2. Changes in Body Weight, HbA_{1c}, and Postprandial Glucose Levels

		Baseline	Entry	Final (3 years)
Body weight (kg)				
SU alone	Good	58.0 ± 2.1	59.1 ± 2.0	59.0 ± 1.9
	Failure	61.8 ± 1.7	59.6 ± 1.7	60.8 ± 0.8*
SU and AGI	Good	59.8 ± 1.6	59.5 ± 1.6	60.0 ± 1.8
	Failure	58.7 ± 1.9	59.0 ± 2.3	61.8 ± 1.8*
HbA_{1c} (%)				
SU alone	Good	9.6 ± 0.9	6.4 ± 0.1	6.4 ± 0.1
	Failure	9.6 ± 0.3	6.7 ± 0.1	7.7 ± 0.1*
SU and AGI	Good	9.6 ± 0.4	6.6 ± 0.1	6.4 ± 0.1
	Failure	9.2 ± 0.3	6.7 ± 0.1	7.8 ± 0.3*
Postprandial glucose (mmol/L)				
SU alone	Good	12.3 ± 1.2	8.4 ± 0.6	8.4 ± 0.4
	Failure	13.1 ± 0.6	9.3 ± 0.6	12.7 ± 0.6*
SU and AGI	Good	13.6 ± 0.9	8.8 ± 0.6	9.1 ± 0.5
	Failure	12.9 ± 0.7	8.3 ± 0.6	12.2 ± 0.8*

NOTE. Data are mean ± SEM.
*$P < .05$ at final observation *v* entry.
Abbreviations: AGI, alpha-glucosidase inhibitor. Good, patients in whom good glycemic control was persistently observed; Failure, patients who reached endpoint.

was comparable in the 2 groups. Thus, in our patients, older-onset diabetes was easy to control with drug therapy. Sex, body mass index, HbA_{1c}, and lipid levels were comparable between the 2 groups. The treatment modality before recruitment into the trial did not affect the results. The percentage of patients who maintained a good glycemic control during the study period and received combination therapy was significantly higher than those treated with glibenclamide or gliclazide alone (61.7 *v* 38.3%, $P = .04$).

DISCUSSION

The major finding of the present study was that combination therapy of voglibose and glibenclamide or gliclazide resulted in a significant prolongation of the duration of good glycemic control compared with treatment with glibenclamide or gliclazide alone. About 58% patients on combination therapy and 38% of those on SU alone maintained a good glycemic control over a period of 3 years. Our results also demonstrated that treatment failure was associated with increase in the body weight. Birkeland et al[4] reported that 61% of patients who were treated with glibenclamide alone showed secondary failure during a 3.5-year follow-up period. Thus, maintenance of good glycemic control over many years is often difficult by treatment with a SU agent alone.

The exact mechanism of secondary failure of treatment with a SU agent is not clear. Several studies suggested the importance of the exhaustion of pancreatic β cells.[5,6] It is possible that such exhaustion is related to overwork of β cells and glucose toxicity.[5,6,13,14] Usually, treatment with a SU compound cannot correct the postprandial hyperglycemia, and the latter may lead to overwork of the pancreas and glucose toxicity.[10] Hence, the use of alpha-glucosidase inhibitor with SU agents may correct the postprandial hyperglycemia and protect the pancreatic β cells. However, in the present study, postprandial glucose levels were comparable between SU alone and combination therapy groups. In our previous study,[10] postprandial glucose levels after breakfast were comparable between voglibose group and control group. In contrast, postprandial glucose levels after lunch and dinner were tended to be lower in voglibose group compared with control group. Therefore, the proof of the decrease in postprandial glucose can be evidenced by the measurement of daily plasma glucose profiles.[10] Unfortunately, we did not evaluate the daily plasma glucose profile in the present 3 years open prospective study. However, some groups, including ours, reported the short-term advantage of combination therapy with alpha-glucosidase inhibitor and SU, and all studies demonstrated the reduction of postprandial glucose levels using this treatment protocol.[10,15-18] Furthermore, our group and Coniff et al[10,15,16] reported that the use of alpha-glucosidase inhibitor could reduce the requirement of intrinsic insulin secretion through reduction of postprandial glucose. These results suggest that the prolongation of the duration of good glycemic control by the combination therapy may be, at least partly, explained by reduction of postprandial glucose and protection of β cells from overwork and glucose toxicity.

In the present study, the dosage of SU drugs was fixed when HbA_{1c} levels decreased to $\leq 7.0\%$ (the time when good glycemic control was achieved) and was not allowed to increase (Table 3). Thus, this study did not investigate the "true" secondary failure of SU drug. In fact, the aim of this study was to compare the duration of good glycemic control achieved by a drug dosage that could achieve the targeted good glycemic control ($HbA_{1c} \leq 7.0\%$). However, we believe that the addition of alpha-glucosidase inhibitor to a SU agent may prolong the duration until secondary failure. In the UKPDS, significant effects of the combination therapy of acarbose and a SU drug were observed over 3 years.[19]

In the present study, older-onset diabetes was associated with a good glycemic control. The reason of this phenomenon is difficult to explain. Our group and Taniguchi et al[20-22] reported that insulin deficiency rather than insulin resistance was relatively dominant in the development of type 2 diabetes in Japan. Therefore, patients with older-onset diabetes may have preserved insulin secretion capacity than those with early-onset diabetes. Unfortunately, in the present study, we did not evaluate the insulin secretion capacity.

The most important limitation of our study is the open prospective study design. Some bias in carrying out the study is possible. To clarify the advantage of the combination therapy of alpha-glucosidase inhibitor and a SU agent, a randomized, placebo-controlled trial is needed.

In conclusion, we demonstrated in the present study that combination therapy with voglibose and a SU agent prolonged the duration of good glycemic control compared with SU alone in Japanese patients with type 2 diabetes. It is possible that overwork of pancreatic β cells might be inhibited by such treatment through amelioration of postprandial hyperglycemia.

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