Long-term Glycemic Control in Japanese Type 2 Diabetes Patients after Switching Treatment from Twice-daily Premixed Insulin to Once Daily Insulin Glargine

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Objective: To examine the clinical utility of once-daily insulin glargine, we studied the clinical course of patients who were switched to from twice-daily premixed insulin to once daily insulin glargine.
Methods: The study was conducted at Tokai University hospital in 20 patients with type 2 diabetes, whose treatment regimens were switched from twice-a-day premixed insulin formulation to once-a-day insulin glargine. Changes in various clinical indexes were studied during a 3-year period after the switch. We also compared the well-controlled group (hemoglobin A1c, HbA1c, levels maintained at less than 6.9%) and poorly-controlled group (HbA1c levels at 7.4% or higher).
Results: During the 3-year period, all patients showed significant decrease in HbA1c levels and tendency for reduced daily dose of insulin. Although both BMI and insulin dose tended to decrease in the well-controlled group, they increased in the poorly controlled group.
Conclusion: The findings suggest that in type 2 diabetes, once-a-day insulin glargine could be more useful than twice-a-day premixed insulin formulation. Poor adherence was observed in the poorly-controlled group, namely lack of thoroughness in self-monitoring of blood glucose and adherence to diet and exercise therapy, thus emphasizing the importance of diabetes education.

Key words: insulin glargine, type 2 diabetes, Japanese

INTRODUCTION

Compared to the multiple dose regimen (known as intensive insulin therapy, or basal-bolus therapy), the twice-daily injection method of premixed insulin product is more advantageous based on its ability to simultaneously compensate for both the basal and additional secretion, and also because it reduces the number of injections. The premixed insulin product is composed of a mixture of rapid-acting or ultra rapid-acting insulin and neutral protamine hagedorn (NPH) insulin. The twice-daily method of insulin administration is widely used in Japan and in 40% of type 2 diabetes patients worldwide [1]. However, in many cases, patients find it difficult to achieve strict glycemic control with premixed insulin formulations alone, and are also often anxious about the potential side effects of hypoglycemia.

Insulin glargine (referred to below as "glargine"), a sustained-release insulin, is characterized by no peaks, and its effect persists for nearly 24 hours. It is widely used to complement the basal secretion. Treatment with glargine could be potentially useful for patients who cannot achieve glycemic control with premixed insulin therapy.

In the present study, we analyzed the long-term changes in glycemic control, body weight, insulin usage, and the incidence of hypoglycemia in patients with type 2 diabetes who were initially treated with twice-a-day premixed insulin formulation but later switched to once-a-day glargine plus oral glucose-lowering agents (OGLA).

PATIENTS AND METHODS

Subjects and Study Protocol

This research project was conducted as an observational retrospective study. We included 20 patients with type 2 diabetes who received premixed insulin twice-daily at the Department of Nephrology and Metabolism Outpatient Clinic, Tokai University Hospital between February 2008 and January 2009. In all the patients, the treatment regimen was switched to once-a-day glargine + OGLA. Furthermore, the patients were followed up as outpatients at Tokai University hospital for 36 months after the switch in the treatment regimen. The frequency of insulin administration under the new regimen was once a day to reduce the dose to approximately 70% of the daily premixed insulin doses that were used until then. In addition, the dose of glargine was adjusted to obtain an early morning fasting blood glucose level of 100 mg/dl. The adjustment of insulin dose and change in

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the concurrently used OGLA were at the discretion of the attending physician.

The hemoglobin A1c (HbA1c) levels, daily dose of insulin, body mass index (BMI), and early morning fasting blood glucose levels, were recorded at the time of treatment regimen switch, and also at 12, 24, and 36 months after the change. In addition, based on the HbA1c levels at 36 months after the switch, those patients with HbA1c levels less than 6.9% were categorized as the well-controlled group (n = 10) and those with HbA1c levels of 7.4% or higher, as the poorly controlled group (n = 5). Differences in HbA1c levels, daily insulin dose, BMI, and early morning fasting blood glucose levels were compared between the two groups. Further, the status of administration of OGLA was studied prior to the change in treatment regimen and at 36 months after the change. Based on the values recorded by the patients during the self monitoring of blood glucose levels, which were presented to the attending physician during the hospital consultation, we selected those patients who mastered the technique of self monitoring of blood glucose and the mean values of early morning fasting blood glucose levels for a 2-week period prior to hospital consultation.

Statistical analyses and ethical considerations

Results were expressed as mean and range. Data were analyzed using repeated measure of ANOVA. A *P* value less than 0.05 denoted statistically significant differences. The study protocol was approved by the Institutional Review Board for Clinical Reserch of Tokai University and each patient signed a consent form. HbA1c (%) value is calculated using the formula HbA1c [%] = HbA1c [Japan Diabetes Society (JDS) (%)] + 0.4%, considering the rational expression of HbA1c [JDS] [%] measured by the previous Japanese standard substance and measurement methods and HbA1c (National Glycohemoglobin Standardization Program) [2].

RESULTS

Table 1 shows the background of all patients (n = 20). The premixed insulin formulations used before the treatment switch were as follows: 15 patients were treated with 30/70 formulations; 4 with 50/50 formulations; and 1 with another formulation. In addition, the OGLA used before the switch (including duplicates) were as follows: glinide in 10 patients; α-glucosidase inhibitors in 8; Metformin in 5; sulfonylurea (referred to as SU) in 3; thiazolidine derivative in 1; and no OGLA in 6.

HbA1c level at baseline (before the switch) was 7.6 ± 0.8%, but decreased significantly after the switch in treatment regimen and the decreased was maintained up to 36 months (6.9 ± 0.7%) (Figure a). The daily insulin dose at baseline was 19.2 ± 14.7 units/day, and then tended to decrease during the observation period, although the change was not statistically significant (Figure b). The BMI was 23.6 ± 3.0 at baseline and remained stable during the study period (Figure c). The fasting blood glucose was 159.0 ± 81.9 mg/dl at baseline and tended to decrease to 113.0 ± 35.4 at 12 months and to 121.5 ± 24.8 mg/dl at 24 months. At 36 months, fasting blood glucose level was still lower than the baseline (129.6 ± 23.6 mg/dl), though the difference in the level between the two time points was not significant. In addition, the standard deviation of fasting blood glucose also tended to decrease (Figure d). With regard to the types of OGLA used at 36 months (including duplicates): glinide in 8 patients; Metformin in 5; dipeptidyl peptidase-4 (DPP4) inhibitors in 5; α-glucosidase inhibitors in 4; SU in 2; and no OGLA in 5 patients. During the study period, none of the patients developed any serious hypoglycemic attack that required hospitalization.

Table 2 compares the clinical background of patients of the well-controlled group (n = 10) with those of the poorly controlled group (n = 5) at the time of treatment switch. There were no significant difference in the listed clinical parameters between the two groups. Fasting blood glucose was low in the poorly controlled group. All patients of the well-controlled group recorded their blood glucose levels by self-monitoring; however, 2 of the 5 patients of the poorly controlled group stopped recording the self-monitoring of blood glucose levels, resulting in lack of data.

Comparison of the two groups before the treatment switch and at 12, 24, and 36 months after the switch showed that in the well-controlled group, the HbA1c levels tended to decrease during the 36-month period. On the other hand, in the poorly controlled group, HbA1c levels that were unchanged at 12 months after the treatment switch and tended to increase subsequently. The daily dose of insulin tended to decrease in the well-controlled group during the 36-month period after the treatment switch. On the other hand, in the poorly controlled group, the daily dose of insulin tended to increase from 12 month after the treatment switch. However, no statistically significant intergroup differences were observed (Figure b). The BMI tended to decrease in the well-controlled group, whereas it tended to increase in the poorly controlled group, but no statistically significant intergroup differences were evident (Data not shown). Intergroup comparisons of fasting blood glucose levels could not be performed because the self-monitored blood glucose levels in the poorly controlled group were incomplete.

DISCUSSION

For type 2 diabetes patients who do not achieve good glycemic control despite adherence to treatment with OGLA, the consensus treatment recommended by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) is the addition of long-acting insulin to basal insulin [3]. In Japan, however, the twice-a-day administration of premixed insulin formulations has been frequently used because of their benefits such as the fewer number of injections by which treatment can be achieved. While insulin therapy using premixed insulin formulations is simple and easy to use, the formulations have a fixed ratio, and thus, it is often difficult to achieve strict management of postprandial blood glucose and early morning fasting blood glucose levels. In addition, there is a high risk of nocturnal hypoglycemia when optimizing early morning fasting blood glucose levels. Based on the identification of the

Table 1 Clinical and biochemical findings.

Age (year)	61.6 (38–89)
Duration of Diabetes (year)	13.6 (1.0–38.0)
BMI (kg/m^2)	23.5 (17.5–28.3)
Fasting Blood Glucose (mg/dl)	159.0 (60.0–388.0)
HbA1c (%)	7.6 (6.4–8.7)
Premixed insulin	
30/70	15 cases
50/50	4 cases
Others	1 case

Data are represented as median (range; min-max)

advantages of glargine, which is a peakless sustained-release insulin, treatments with once-a-day administration of sustained-release insulin + OGLA has become a promising therapeutic method for patients who cannot achieve good glycemic control by treatment with premixed insulin formulations. Hammer *et al.* [4] reported significant improvement of glycemic control after switching type-2 diabetes patients with poor glycemic control from treatment with premixed insulin formulations twice a day to once-a-day administration of glargine, and that this improvement was coupled with a significant decrease in body weight. However, the study was conducted for only a short period of 12 weeks. Interestingly, a few similar studies have been conducted in Japanese subjects with type 2 diabetes [5]. In our study, switching the treatment regimen from twice-a-day administration of premixed insulin formulations to once-a-day administration of glargine + OGLA resulted in significant reductions in HbA1c and fasting blood glucose levels for up to 3 years. One probable reason for the improvement of glycemic control is the use of glargine, which fully complements the basal insulin while reducing the risk of hypoglycemia. This could not be achieved in the past with the use of NPH insulin. The optimization of fasting blood glucose contributes largely to the overall glycemic control in patients with particularly high HbA1c levels [6]. In patients with HbA1c level exceeding 7.5% at the time of treatment regimen change similar to that in this study, first, medications need to be selected and the fasting blood glucose level should be optimized.

Another interesting and important finding of the present study was the marked decrease in the standard deviation of fasting blood glucose after the commencement of glargine treatment. When a premixed insulin preparation is used, attempts to optimize early morning fasting blood glucose levels could increase the chance of nocturnal hypoglycemia. Furthermore, the resulting Somogyi effect and supplementary meals consumed at night to prevent hypoglycemia increase the chance of early morning fasting blood glucose level becoming unstable, and occasionally, there are concerns that insulin injections before dinner are skipped. These concerns could probably be overcome by the stable resorbing effects of glargine, and particularly, the probable achievement of stable nocturnal glycemic control. Indeed, several study reported that glargine leads to a smooth time-action profile without pronounced peaks compared with NPH insulin by using glucose clump study [7, 8]. Furthermore, another closs-over designed clump study reported that glargine had a longer duration of action with lower variability across subjects [9]. Numerous clinical studies have investigated the effects of insulin therapy comprising premixed insulin formulation and insulin glargine in type 2 diabetes patients [10–14]; however, no conclusion has yet been made. Nevertheless, our study indicated that in patients similar to those in this study, in whom the twice-a-day administration of premixed insulin formulation was associated with poor glycemic control, changing the treatment regimen to "once-a-day administration of glargine plus OGLA" improved glycemic control. Recently, insulin degludec which is new sustained-release insulin is developed. The possibility that insulin degludec is more effective as concerned about risk reduction of hypoglycemia than glargine is reported [15], and a future study attracts attention.

Our results also showed no significant increase in body weight after the treatment change. Weight gain has been considered inevitable in type 2 diabetes patients who start insulin therapy [16]. In this regard, a study that compared insulin therapy using premixed insulin formulation with that using glargine showed that the former mode of therapy was associated with a significant increase in body weight [9]. On the other hand, one observational study of patients who switched treatment from premixed insulin formulation to glargine reported a significant decrease in body weight after the treatment change to glargine [4]. All the patients included in our study had learned the technique of self-monitoring of blood glucose, and this ability was probably the result of continuous education provided by the healthcare workers. Initiating insulin therapy after appropriate patient education is reported to result in significant suppression of weight gain [17]. Our study also demonstrated possible weight gain inhibition when patient education is provided before switching the treatment regimen to glargine.

The study of well-controlled and poorly controlled groups showed that at 12 months after switching the treatment regimen, glycemic control improved in patients of the poorly controlled group though the amount of insulin required by these patients and their body weight tended to increase. This could reflect a drop in motivation among both the patients and healthcare workers with long-term medical treatment. In this regard, Menard *et al.* [18] reported that inter-

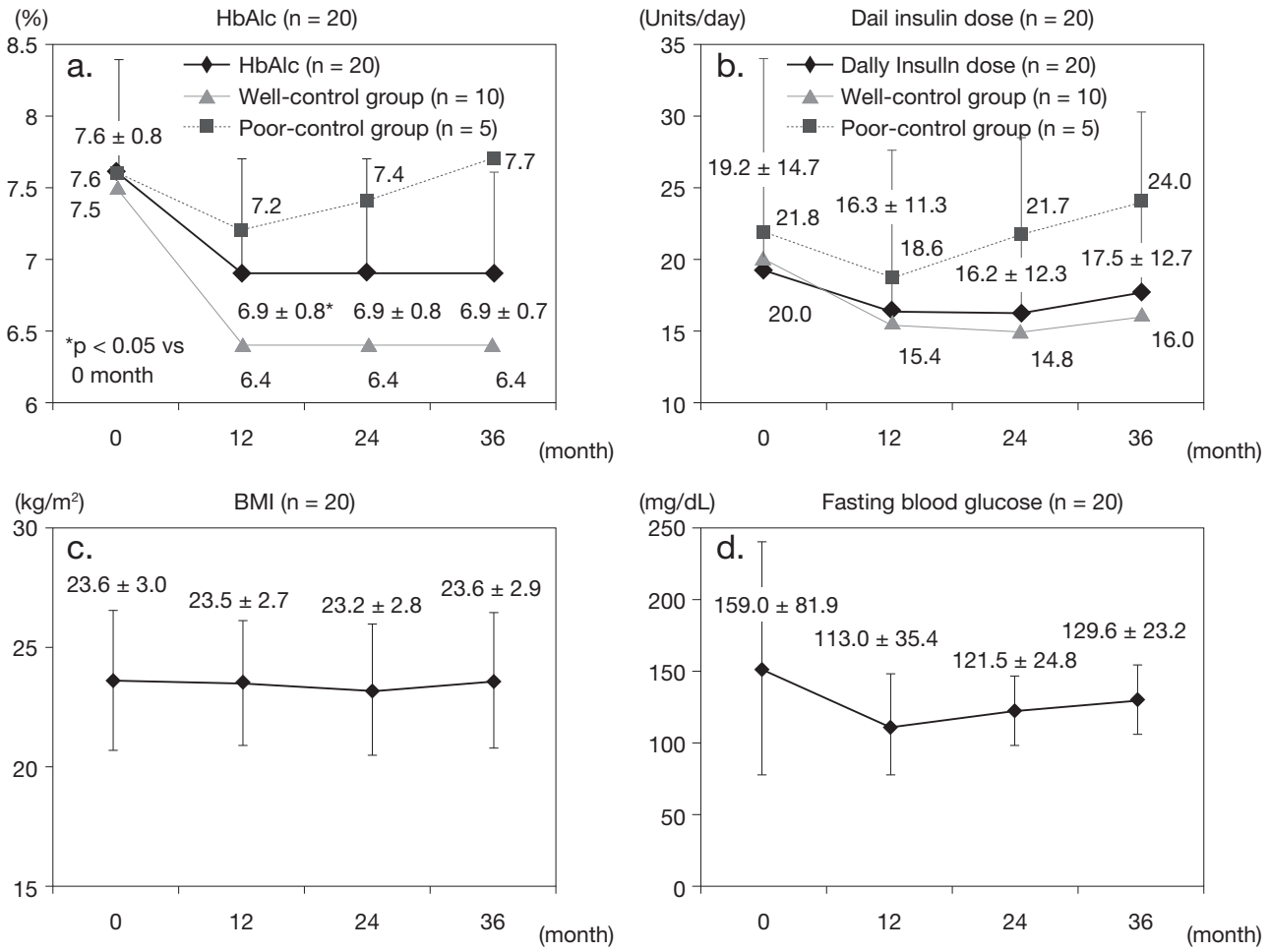

Figure Changes in clinical parameters over 36 months of patients (n = 20). Data are mean ± SD. *p < 0.05 versus 0 month.
Jointly noted about comparison of changes in HbA1c and daily insulin dose over 36 months between patients of the well control group (n = 10) and poor control group (n = 5).

Table 2 Clinical and biochemical findings on switch to insulin glargine in the well-control group and poor-control group.

	Well-control group (n = 10)	Poor-control group (n = 5)
Gender (male/female)	5/5	4/1
Age (year)	58.6 (38–53)	50.8 (41–74)
Duration of diabetes (year)	11.1 (2–25)	17.0 (2–31)
BMI (kg/m²)	24.5 (18.8–28.5)	22.2 (19.2–26.0)
Fasting blood glucose (mg/dl)	149.4 (68.0–388.0)	135.7 (104.0–141.0; n = 3)
Hemoglobin (g/dl)	13.4 (11.8–15.4)	13.8 (12.0–14.6)
Creatinine (mg/dl)	0.74 (0.5–0.9)	0.80 (0.5–1.1)
HbA1c (%) at 0 month	7.5 (6.4–8.7)	7.6 (6.8–8.0)
HbA1c (%) at 36 month	6.4 (5.3–6.5)	7.7 (7.0–8.2)

Data are represented as median (range; min-max)

ruption of intensive treatment of type 2 diabetes patients results in the disappearance of the therapeutic effect of such treatment in approximately 6 months. Thus, particularly in the treatment of diabetes, which requires good long-term systemic management, it is necessary to provide periodic patient education and to intervene promptly and initiate a new treatment regimen when the therapeutic effect is less than ideal.

There is a limitation in this study. This study is a retrospective study, and some bias may influence these results. A prospective study is necessary to investigate a precise therapeutic effect of insulin glargine.

In summary, in actual clinical practice, in type 2 diabetes patients who cannot achieve good glycemic control with treatment regimen of twice-a-day injection of premixed insulin formulation, changing the treatment regimen to "once-a-day administration of glargine plus OGLA" could help achieve significant improvement in early morning fasting blood glucose levels without causing severe hypoglycemia. Furthermore, this

method could maintain good glycemic control over a long period.

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