Use of Insulin Glargine in Japanese Patients with Type 1 Diabetes

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Abstract

Objective To evaluate the results of treatment with an insulin glargine-based regimen as compared with those of an NPH insulin-based regimen.

Methods We reviewed the charts of 83 Japanese patients with Type 1 diabetes treated with insulin glargine for 12 months.

Patients Median age, 56.9 years (range, 24.6-74.8 years), mean (±S.D.) body mass index, 21.2 (±2.2) kg/m².

Results The average HbA1c level of the cohort was 7.8 ± 1.2% at baseline and 7.7 ± 1.0% at the end of the 12-month treatment (P=0.34). The average insulin requirement per day in the cohort remained unchanged after the 12-month treatment (35.0 ± 11.6 units/day versus 35.2 ± 11.2 units/day (P=0.58). Of the 36 patients who were receiving twice or three times daily injections of NPH insulin, 30 could be switched to a single-daily injection of insulin glargine. The frequency of severe hypoglycemia with unconsciousness became lower after switching to the insulin glargine-based regimen than during treatment with the NPH-based regimen. The average ratio of the daily usage of insulin glargine to that of total insulin after 12 months was smaller than that reported from other countries (0.34 ± 0.09).

Conclusion These results obtained from a larger number of patients as compared to previous Japanese studies confirm earlier reports that insulin glargine provides equivalent glycemic control to human NPH insulin, with a lower incidence of severe hypoglycemia. Thus, treatment with insulin glargine provides some benefits to Japanese patients with Type 1 diabetes.

Key words: insulin glargine, Type 1 diabetes

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) demonstrates that tight glycemic control has long-term beneficial effects on the risks of microvascular complications and cardiovascular disease in patients with Type 1 diabetes (1, 2). Accordingly, multiple-injection insulin regimens combining intermediate-acting insulin, such as NPH insulin, with mealtime bolus insulin, such as regular insulin, have been used conventionally for the treatment of Type 1 diabetes.

These regimens have yielded improved glycemic control with a lower incidence of hypoglycemia.

Insulin glargine is a long-acting, basal insulin analog, which has a smoother time-concentration profile as compared to NPH insulin, with a duration of action of about 24 h (3). Clinical trials of insulin glargine for Type 1 diabetes in many countries including Japan have revealed that treatment with this insulin is associated with a reduced frequency of severe hypoglycemia while being at least as effective as NPH insulin therapy in maintaining glycemic control (4-7). The goals of the present retrospective study were to
examine 1) whether treatment with an insulin glargine-based regimen would be associated with a reduced frequency of nocturnal hypoglycemia and episodes of hypoglycemia with unconsciousness as compared with treatment with an NPH-based regimen, 2) whether a once-daily insulin glargine-based regimen would be sufficient in the clinical setting to improve long-term glycemic control in Japanese patients with Type 1 diabetes, and 3) whether there are any peculiarities in the usage of insulin in Japanese patients with Type 1 diabetes.

Method

We retrospectively examined the charts of 83 adult Japanese patients (62 males, 21 females) with Type 1 diabetes (including 31 patients with the slowly progressive form of Type 1 diabetes) who had visited the University of Tokyo or the International Medical Center of Japan located in Tokyo, Japan, and had been started on an insulin glargine-based regimen between December 2003 and November 2005.

The median age of the subjects was 56.9 years (range, 24.6-74.0) and the median age at onset of diabetes was 41.1 years (range, 20.2-65.5). The median duration of diabetes was 12.4 years (range, 1.2-40.8) and median duration of insulin therapy was 12.4 years (range 1.0-40.8). The (mean ± S.D.) body mass index of the subjects was 21.2 (±2.1) kg/m². Endogenous insulin secretion in the 83 patients was evaluated by measurement of the C-peptide levels by a chemiluminescence enzyme immunoassay in the fasting state (66 patients) and/or 2 hours postprandially (60 patients). The daily urinary C-peptide excretion was examined in 53 patients. The median serum C-peptide values in the patients were as follows: fasting state, 0.067 nmol/L (range <0.017-0.33 nmol/L); 2-hours postprandial state, 0.10 nmol/L (range ≤0.017-0.33 nmol/L); urinary C-peptide, 84 nmol/day (range ≤20-320 nmol/day).

Before the treatment was switched to the insulin glargine-based regimen, 75 patients were receiving NPH insulin (once-daily NPH injection, 39 patients; twice-daily injection, 32 patients; three-times-daily injection, 4 patients) plus preprandial bolus insulin (human regular insulin, 38 patients; insulin aspart, 9 patients; insulin lispro, 28 patients), 7 patients were receiving mixtures of human regular insulin and NPH insulin, and 1 patient was receiving a mixture of insulin aspart and NPH insulin. After the treatment was switched to an insulin glargine-based regimen, regular insulin used in 16 patients was switched to insulin lispro (4 cases) or insulin aspart (12 cases) (Table 1).

The data on the height, weight, HbA1c, and insulin dosages of the patients at baseline, after 6 months, and after 12 months’ treatment with insulin glargine were collected. The number of episodes of hypoglycemia with unconsciousness and nocturnal hypoglycemia was recorded. The starting dose of insulin glargine, types and doses of bolus insulin, and dosage adjustments were left to be determined at the discretion of the prescribing physician.

The values represent the mean ± SD. The insulin dosage and weight at the baseline and at 12 months after the treatment was switched to a glargine-based regimen were analyzed by a paired r test. Significance was set at a P-value of <0.05. The HbA1c before 6 months, at baseline, after 6-month treatment and after 12-month treatment with insulin glargine were analyzed by the one-factor repeated-measures analysis of variance (ANOVA). When the P value was <0.05, data were further analyzed by pair-wise comparisons with Tukey-Kramer’s honestly significant difference (HSD) test. The frequencies of occurrence of severe hypoglycemia with unconsciousness and the rates of nocturnal hypoglycemia were analyzed by Fisher’s exact test and Wilcoxon’s matched-pair signed-rank sum test, respectively. The correlations between the changes in the insulin requirements and changes in the HbA1c values, and the correlations between body mass index, HbA1c, or serum/urine C-peptide levels in the patients and the average ratio of the daily dose of insulin glargine to that of total insulin were analyzed by calculating Spearman’s coefficient of correlation. The average ratio of the daily dose of insulin glargine to that of the total insulin at the endpoint was analyzed by Steel-Dwass’ test. Glycemic control was categorized as excellent (HbA1c < 5.8%), good (5.8% ≤ HbA1c < 6.5%), fair (6.5% ≤ HbA1c < 8.0%), and poor (8.0% ≤ HbA1c) in accordance with the criteria of the Japan Diabetes Society (8).

Results

Insulin glargine was well tolerated by all of the patients, except for 5 episodes of failure of the injection system. The average body weight of the cohort remained unchanged at the end of the study period (56.5 ± 8.2 kg versus 56.8 ± 8.6 kg, P=0.14). Fewer patients reported severe hypoglycemia with loss of consciousness during treatment with the glargine-based regimen than during treatment with the NPH-based regimen; during treatment with the NPH-based regimen, 10 patients reported severe hypoglycemia with loss of consciousness, while during treatment with the glargine-based regimen, 8 of these patients no longer suffered from these episodes, either with (1 patient) or without (7 patients) change of the type of the mealtime insulin during the observation period. Two patients reported severe hypoglycemia with loss of consciousness during treatment with the glargine-based regimen (P =0.03). One of these patients suffered from severe hypoglycemia with loss of consciousness due to inadvertent use of human regular insulin in place of insulin glargine; as for the other patient, the type of insulin used at mealtime was changed from regular insulin to insulin aspart, and severe hypoglycemia developed with loss of consciousness due to anorexia from depression. The overall monthly rate of nocturnal hypoglycemia was reduced, but not significantly, following the switch to the glargine-based regimen (0.42 versus 0.26 episode/month; P>0.05). Five out of the 11 patients who suffered from nocturnal hypoglycemic episodes during the 12 months prior to the switch to the
insulin glargine-based regimen no longer suffered from these episodes after initiation of the insulin glargine-based regimen, with no change in the type of insulin used at mealtime. Four patients showed improvement of the HbA1c after introduction of the glargine-based regimen, but at the cost of the appearance anew of nocturnal hypoglycemia. These patients no longer suffered from hypoglycemia episodes after the dose and/or timing of the insulin injection was adjusted. Three patients suffered from hypoglycemia at dawn. This was prevented by reducing the bedtime dose of insulin glargine in two patients, and by dividing the once-daily bedtime injection of insulin glargine to twice-daily injections in the third patient. One patient suffered from hypoglycemia at midnight; this was prevented by reducing the dose of regular insulin at suppertime and by increasing the bedtime dose of insulin glargine.

The average HbA1c level in the entire cohort was not significantly changed following the switch to the glargine-based regimen (7.6 ± 1.1% before 6 months, 7.8 ± 1.2% at baseline, 7.5 ± 1.2% at the end of 6-months’ treatment, and

<table>
<thead>
<tr>
<th>Mealtime insulin at baseline →</th>
<th>6 months before insulin</th>
<th>At baseline</th>
<th>6 months after insulin</th>
<th>12 months after switch to glargine</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human regular insulin → human regular insulin (N=21)</td>
<td>7.2 ± 1.1%</td>
<td>7.5 ± 1.0%</td>
<td>7.1 ± 1.1%*</td>
<td>7.5 ± 1.0%</td>
<td>3.96</td>
<td>0.012</td>
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<tr>
<td>Human regular insulin → insulin lispro (N=4)</td>
<td>8.3 ± 0.6%</td>
<td>8.6 ± 1.3%</td>
<td>8.9 ± 1.8%</td>
<td>8.0 ± 0.6%</td>
<td>0.70</td>
<td>0.57</td>
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<tr>
<td>Human regular insulin → insulin aspart (N=13)</td>
<td>7.3 ± 1.1%</td>
<td>7.2 ± 0.8%</td>
<td>7.3 ± 1.1%</td>
<td>7.4 ± 1.1%</td>
<td>0.54</td>
<td>0.66</td>
</tr>
<tr>
<td>Insulin lispro → insulin lispro (N=28)</td>
<td>8.0 ± 1.2%</td>
<td>8.1 ± 1.4%</td>
<td>7.8 ± 1.3%</td>
<td>7.8 ± 1.0%</td>
<td>1.39</td>
<td>0.25</td>
</tr>
<tr>
<td>Insulin aspart → insulin aspart (N=9)</td>
<td>7.8 ± 1.0%</td>
<td>7.8 ± 0.6%</td>
<td>7.7 ± 0.5%</td>
<td>8.1 ± 1.2%</td>
<td>0.47</td>
<td>0.71</td>
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Mixtures of NPH insulin and
mealtime insulin → 7.8 ± 1.1% | 8.3 ± 1.0% | 7.7 ± 1.1% | 7.9 ± 1.1% | 1.51 | 0.24 |
mealtime insulin** (N=8)

Data are expressed as mean ± SD. Each row was analyzed according to one-factor repeated-measures analysis of variance (ANOVA).

*p < 0.05 at baseline with human regular insulin.

**Mixtures of NPH (neutral protamine Hagedorn) insulin and human regular insulin were changed to insulin glargine and human regular insulin (one patient), insulin aspart (2 patients), or insulin lispro (4 patients) and the mixture of NPH insulin and insulin aspart was changed to insulin glargine and insulin aspart (one patient).
7.7±1.0% at the end of the 12-month treatment; (F=1.12, P=0.34). The HbA1c values in the patients after the switch to glargine therapy were subsequently categorized according to the type of mealtime insulin used in the patients. No significant improvement or deterioration was observed at the end of 12 months after the switch to an insulin glargine-based regimen, irrespective of the type of mealtime insulin used (Table 1). While the glycemic control was improved at the end of the 12 months after the switch to an insulin glargine-based regimen in 18 patients, deterioration of the glycemic control was observed in 14 patients (Table 2). The glycemic control also deteriorated in three patients who still showed excellent glycemic control at the endpoint (the HbA1c values in the 3 patients were 5.6%, 5.6% and 5.7% at baseline and 6.3%, 6.3% and 6.0% at the endpoint, respectively). At the endpoint, one of these three patients was suffering from acute bronchitis and another from allergic dermatitis; for the third patient, who was suffering from hypoglycemia at night, the bedtime dose of insulin glargine was reduced.

At the end of 12 months after the switch to the insulin glargine-based regimen, 75 of the 83 patients required a once-daily injection of insulin glargine (before breakfast; 6 patients, before supper, 3 patients, at bedtime, 66 patients), and the remaining 8 required twice-daily injections of insulin glargine twice (before breakfast and before supper, 1 patient; before lunch and at bedtime, 2 patients; before breakfast and at bedtime, 5 patients) (Table 3). Of the 36 patients who were receiving twice- or thrice-daily injections of NPH, 30 could be switched to a single-daily injection of insulin glargine without deterioration of glycemic control of each patient at baseline and at 12 months after the switch to insulin glargine was categorized according to the criteria of the Japan Diabetes Society (8).

<table>
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<tr>
<th>Table 2. Glycemic Control Category after Treatment with Insulin Glargine in Comparison with that at Baseline</th>
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<td><strong>Category of</strong></td>
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<tr>
<td><strong>glycemic control</strong></td>
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<tr>
<td>at baseline</td>
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<tr>
<td>Excellent</td>
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<td>Good</td>
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<tr>
<td>Fair</td>
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<td>Poor</td>
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NPH: neutral protamine Hagedorn

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<th>Table 3. Injection Schedule of Basal Insulin in the Patients before (with NPH insulin) and 12 Months after the Treatment Switch to Insulin Glargine</th>
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<tr>
<td><strong>Daily injection schedule at baseline with NPH insulin</strong></td>
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<td></td>
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<tr>
<td><strong>NPH</strong></td>
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<tr>
<td>Once daily insulin glargine at the end of the 12-month's study period</td>
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<tr>
<td>Twice daily insulin glargine at the end of the 12-month's study period</td>
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the glycemic control (average HbA1c in the 30 patients was 7.8±0.9% at baseline versus 8.0±1.1% at the end of the 12-month study period; P>0.74) or increase in the frequency of nocturnal hypoglycemia (average frequency of nocturnal hypoglycemia in the 30 patients was 0.83 at baseline versus 0.21 at the end of the 12-months’ study period, P>0.1). In 3 patients who were receiving twice-daily injections of NPH insulin, an attempt to switch to once-daily injection of insulin glargine resulted in nocturnal hypoglycemia in one patient (as stated earlier) or hyperglycemia at breakfast in two cases. Hypoglycemia was no longer observed after the start of twice-daily injections of insulin glargine in these patients.

At the start of the insulin glargine-based regimen, 9 patients injected insulin glargine once daily before breakfast. After 12 months, while 4 of the 9 patients continued to receive the injection of insulin glargine before breakfast, the timing of injection of insulin glargine was changed in 5 patients (to before supper in 1 patient, to bedtime in 3 patients, and twice daily before breakfast and before supper in 1 patient because of the observation of hyperglycemia before breakfast).

The difference in insulin requirement between patients receiving an NPH insulin-based regimen and insulin glargine-based regimen was variable (increased maximally by 11 units/day and decreased maximally by 10 units/day). The changes in the insulin requirement were not correlated with the changes of the HbA1c value (P>0.05). The average insulin requirement per day in the cohort remained unchanged at 12 months after the start of the glargine-based regimen (35.0 ± 11.6 units/day (0.61 ± 0.17 units/kg/day) versus 35.3 ± 11.2 units/day (0.62 ± 0.16 units/kg/day); P=0.58). The average requirement of insulin glargine per day in the cohort also remained unchanged after the 12-month study period (12.5 ± 5.9 units/day versus 11.8 ± 4.8 units/day; P=0.55). At the end of 12 months after the treatment was switched to the glargine-based regimen, the average ratio of the daily dose of basal insulin to that of total insulin (basal / total insulin ratio) was 0.33 ± 0.09 (median; 0.32, range; 0.18-0.57). The average basal / total insulin ratio in the 75 patients receiving once-daily insulin glargine was 0.33 ± 0.09, and that in the 8 patients receiving twice-daily insulin glargine was 0.41 ± 0.06 (P<0.01). Of the 75 patients receiving once-daily insulin glargine, the average basal / total insulin ratio in the 20 patients receiving regular insulin at mealtime was 0.28 ± 0.05, that in the 32 patients receiving insulin lispro at mealtime was 0.36 ± 0.10 (P<0.05 versus the ratio in the patients receiving regular insulin at mealtime), and that in the 23 patients receiving insulin aspart at mealtime was 0.32 ± 0.08 (P=0.15 versus the ratio in the patients receiving regular insulin or insulin lispro at mealtime). The basal / total insulin ratio in the 75 patients receiving once-daily insulin glargine was not correlated with the HbA1c or serum/urine C-peptide levels (P>0.05). There was a weak correlation between the basal / total insulin ratio and the body mass index in the 75 patients (r=0.21, 0.01 < P < 0.05). A correlation between the basal / total insulin ratio and the body mass index was observed in the subgroup of 27 patients with poor glycemic control (8.0% ≤ HbA1c) (P=0.45, P<0.01) but not in the 48 patients with excellent (HbA1c < 5.8%), good (5.8% ≤ HbA1c < 6.5%), or fair (6.5% ≤ HbA1c < 8.0%) glycemic control (Fig. 1).

Discussion

In the present clinical chart review, we attempted to compare the efficacy of insulin glargine-based regimens with that of a variety of NPH-based regimens including not only once-daily NPH with a variety of mealtime insulins (human regular insulin, insulin aspart and insulin lispro). Previous reports on the efficacy of insulin glargine for Type 1 diabetics in Japan dealt with patients who were previously treated with once-daily NPH insulin and mealtime human regular insulin (6, 7) or insulin lispro / insulin aspart (9). It was shown in the present study, that insulin glargine based-regimens provided an equivalent glycemic control to human NPH insulin in Type 1 diabetics, irrespective of the type of mealtime insulin used (Table 1). Due to the small number of patients in the present study (4 patients were switched from regular insulin to insulin lispro, and 9 patients were switched from regular insulin to insulin aspart) and the study design (use of HbA1c as the main index to examine glycemic control), we could not evaluate the effect of the changeover from regular insulin to insulin lispro/aspart together with insulin glargine on the glycemic control. The number of episodes of severe hypoglycemia with unconsciousness in the patients was significantly lower after the switch to the insulin glargine-based regimen (with changeover from regular insulin to insulin aspart in one case) as compared to that noted while the patients were receiving an NPH-based regimen. These results confirm earlier reports that the use of insulin glargine might be associated with an improved quality of life with fewer episodes of life-threatening hypoglycemia also in Japanese adult patients with Type 1 diabetes.

In the present chart review, it was found that the treatment could be successfully switched from twice- or even thrice-daily injections of NPH insulin to once-daily injection of insulin glargine in 30 out of 36 patients (the switch failed in 3 patients). While in 5 out of 10 patients who started to receive a once-daily injection of insulin glargine before breakfast and in whom the same timing of the once-daily insulin administration could be continued until 12 months later, it became necessary to change the timing of the injection in the 5 remaining patients. While earlier reports had suggested that insulin glargine is a long-acting, basal insulin analog with a peakless time-concentration profile and duration of action longer than 24 h (3), recent reports have suggested that the mean duration of action of insulin glargine in Type 1 diabetics is shorter than that previously reported (10); evidence of a significant maximum in the glucose-lowering activity of this insulin analog, with waning the effect before the next injection has been shown (11). Thus, for
Figure. Correlation between the ratio of the daily dose of basal insulin to that of total insulin (basal / total insulin ratio) and the body mass index in 75 patients receiving once-daily insulin glargine with mealtime insulin injections. There was a weak correlation between the basal / total insulin ratio and the body mass index in the 75 patients receiving once daily insulin (\( \rho =0.21, 0.01<P<0.05 \)); the correlation was significant in the 27 patients showing poor glycemic control (8.0 % ≤ HbA1c, ◦) (\( \rho =0.45, P<0.01 \)), but not in the 48 patients showing excellent (HbA1c 5.8 %, ×), good (5.8 % ≤ HbA1c < 6.5 %, □), or fair (6.5 % ≤ HbA1c < 8.0 %, △) glycemic control.

some diabetic patients receiving insulin glargine, it is necessary to use twice-daily injections to obtain reasonable glycemic control (12).

The average ratio of the daily dose of insulin glargine to that of the total insulin noted at the end of the 12-months after the switch to a glargine-based regimen in this study (once-daily insulin + mealtime regular insulin: 0.29±0.05, once-daily insulin glargine + mealtime insulin lispro: 0.36±0.07) was consistent with previous reports for Japanese patients with Type 1 diabetes [once-daily insulin glargine + mealtime regular insulin, 0.31 (6, 7), once- or twice-daily insulin glargine + mealtime lispro or insulin aspart, 0.30 (9)], but smaller than that reported from other countries (once-daily insulin glargine + mealtime regular insulin, 0.43) (4). This finding implies that the basal insulin requirement in Japanese Type 1 diabetes patients may be smaller and the mealtime insulin requirements, larger. A recent report has suggested that patients with type 1 diabetes may also exhibit insulin resistance and that the degree of insulin resistance is correlated with the body mass index (13). The Japan Diabetes Society recommends that all diabetic patients, including those with Type 1 diabetes, maintain their body mass index at about 22 kg/m\(^2\) (8), as in our present cohort and in other reports from Japan (6, 7, 9). This value is lower than the value reported for Type 1 diabetes patients from other countries (4, 5, 13). Therefore, in the present review, we examined the correlation between the basal / total insulin ratio and the body mass index in Type 1 diabetes patients under treatment with insulin glargine. We found that the correlation between the basal / total insulin ratio and the body mass index was restricted to patients whose blood glucose level was difficult to control. Thus, there may also be factors other than the body mass index to explain the smaller basal / total insulin ratio observed in Japanese Type 1 diabetes patients. Japanese traditional meals which are low in fat and rather high in carbohydrate may be one such candidate factor. It has been shown that a low-carbohydrate diet lowers the postprandial blood glucose elevation and reduces the mealtime insulin requirements (14), while the fat content of the diet is correlated with the insulin resistance in patients with Type 1 diabetes (13).

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