Evaluation of insulin regimens as an effective option for glycemic control in patients with type 2 diabetes: A propensity score-matched cohort study across Japan (JDDM31)

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ABSTRACT

Aims/Introduction: We evaluated the long-term efficacy of insulin regimens in patients with type 2 diabetes mellitus and poor glycemic control despite oral antidiabetic drugs (OAD).

Materials and Methods: We carried out a propensity score-matched cohort study using the CoDiC® database of the Japan Diabetes Data Management Study Group across 54 institutions in Japan from 2005 to 2010. A total of 10,854 patients on OAD in 2005 were studied, and 1,253 patients (11.5%) were treated with insulin until 2010. The changes in insulin regimens and glycated hemoglobin (HbA1c) levels were analyzed over this study period.

Results: Propensity score matching showed no differences in the baseline patient characteristics. A total of 96 patients transferred to insulin, and HbA1c gradually and significantly decreased in the patients on a twice-daily premixed preparation of rapid-acting human-insulin analogs (twice-daily MIX) and basal–bolus therapy with rapid-acting human-insulin analogs (RA) plus long-acting insulin analog (LA; \( P < 0.001 \)). A total of 418 patients had insulin added to OAD treatment, and HbA1c decreased in the patients with a twice-daily MIX (\( P < 0.001 \)), but HbA1c did not differ from the baseline values in the patients on basal LA (\( P = 0.497 \)). The mean decline in HbA1c at the end of the study was therefore larger in the patients receiving twice-daily MIX than in the patients receiving basal LA (\( P < 0.05 \)).

Conclusion: The present study could suggest the potential loss of opportunity for many patients treated using basal LA to have received alternative insulin regimens and to achieve better glycemic control.

INTRODUCTION

Type 2 diabetes mellitus is a progressive disease in which poor glycemic control is exacerbated over time and pancreatic \( \beta \)-cell function declines. Most patients require oral antidiabetic drugs (OAD) in addition to lifestyle intervention (LSI), although it remains difficult for them to achieve normoglycemic levels. The majority of patients eventually need the addition of insulin therapy despite treatment by multiple OAD. In a consensus algorithm for the medical management of type 2 diabetes regarding the second medication added to metformin, insulin can be initiated with a basal (intermediate- or long-acting) insulin. Once-daily basal insulin, long-acting insulin analog (basal LA) plus OAD, has been regarded as an effective option for glycemic control in type 2 diabetes. However, a randomized, control trial (RCT) showed that the addition of
biphasic or prandial insulin reduced glycated hemoglobin (HbA1c) levels more than the basal insulin administration.

A recent review of RCTs showed heterogeneous results, and indicated that a single RCT could not provide a gold standard result that applies to all clinical situations, and that evidence both from RCTs and from well-designed observational studies can and should be used to find the optimal treatment regimen. However, the results obtained from the cohort studies for diabetes treatments might have been affected by biases and confounding baseline factors that might have influenced treatment selection. One approach to reduce or eliminate the effect of treatment selection bias and confounding effects is the use of propensity score matching, which allows the design and analysis of an observational study so that it mimics some of the characteristics of a RCT.

To more robustly evaluate the effectiveness of choice of insulin regimens on glycemic control, we analyzed results from a matched case–control study, using the propensity score-matching method to minimize or eliminate selection biases and confounding effects related to treatment selection and patient data collected from multiple institutions across Japan to establish the CoDiC database. CoDiC is a diabetes data collection and management information system developed by the Japan Diabetes Clinical Data Management Study Group (JDDM) to promote clinical research into diabetes.

METHODS

Study Design and Participants

The data for the present cohort study were extracted from the CoDiC database to incorporate patient records from 54 clinics or general/university-affiliated hospitals across Japan. The study was carried out in primary care settings on patients who visited these clinics before May 2005, and for whom diabetes was diagnosed and classified based on criteria in the Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus. Treatment goals recommended by the JDS were HbA1c levels <6.5% (JDS value, later described), with fasting and post-prandial plasma glucose levels of <130 mg/dL and <180 mg/dL, respectively. A total of 10,854 type 2 diabetes patients who were under treatment with OAD in May 2005 and whose data input were continued until July 2010 were analyzed. The clinical data were collected in the Central Analytical Center established by the JDDM on CD-R storage disks in October 2010. The clinical data were analyzed by Microsoft Access and Excel software (Microsoft Corporation, Redmond, WA, USA). The data at baseline (from May to July, 2005) at the same months in every year and at the end of the study (July 2010) were analyzed. The JDDM ethics committee approved the study protocol, and informed consent was obtained from patients at each institution participating in the study, based on the requirements stated in the Guidelines for Epidemiology Study in Japan.

Outcomes noted and analyzed were the prescription of insulin regimens and the comparison of effects on glycemic control (changes in HbA1c levels and mean decline in HbA1c) among the regimens administered during the 5-year study period. The mean decline in HbA1c was calculated by subtracting the value of the HbA1c levels measured at the end of the study from the value at baseline.

Laboratory Methods

HbA1c levels were measured using high-performance liquid chromatography in each clinic or hospital. The levels were standardized in each institution according to the criteria recommended by the JDS committee and presented as HbA1c (JDS value), with the normal range defined as 4.3–5.8%. This range is comparable with the 4.0–6.0% and 4.5–6.2% quoted by American Diabetes Association criteria and UK Prospective Diabetes Study criteria, respectively. Recently, the JDS committee recommended that HbA1c (%) be estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS;%) + 0.4%22,23 and in the present study, HbA1c values are presented as a NGSP value calculated by the same formula. Other variables were determined by standard methods, including body mass index (BMI), blood pressure, plasma glucose, low-density lipoprotein-cholesterol and other biochemical markers.

Statistical Analysis

Statistical analyses were carried out using the SPSS version 20 software package (IBM, Armonk, NY, USA). Clinical and biochemical characteristics were compared among the patients by using Student’s t-test and one-way analysis of variance (ANOVA), and then by Tukey’s honestly significant difference. Changes in BMI and HbA1c were tested using repeated measures ANOVA with Greenhouse Geisser correction. To reduce the effect of treatment selection bias and potential confounding effects, we carried out adjustments for differences in baseline characteristics by means of propensity score matching. Patients were selected based on this score calculated using the Greedy 5-to-1 digit-matching algorithm for baseline characteristics; that is, age, age at onset, duration of diabetes, and BMI and HbA1c at baseline in patients. The chi square test was used to compare patient number distributions in the treatment groups, as well as the prescribed OAD and insulin regimens. The data were presented as the mean ± standard deviation.

RESULTS

Patients and Clinical Characteristics

Of the 10,854 patients prescribed with OAD at baseline (2005), the number of patients introduced to insulin therapy increased every year, and 1,253 patients (11.5%) were treated with insulin at the end of the study (2010). Of these, 2.9% were transferred from OAD to insulin and 8.6% were given insulin in addition to OAD (Figure 1a). Patients changed to LSI increased from 2005 to 2009 and decreased in 2010. The number of patients prescribed with sulfonylureas decreased, whereas the number of
patients prescribed with metformin or pioglitazone increased (data not shown). Dipeptidyl peptidase-4 inhibitors were prescribed from 2010. The number of patients prescribed with one species of OAD decreased, and the number of patients prescribed with multiple species increased (data not shown). Of 317 patients receiving insulin therapy in 2010, 37.9% were treated with twice-daily MIX, and 28.4% were treated with basal–bolus therapy using RA plus LA (Figure 1b). Of 936 patients receiving the combination therapy of OAD plus insulin in 2010, 37.6% were treated with basal LA and 34.6% were treated with twice-daily MIX.

Table 1 lists the clinical characteristics at baseline for patients who in 2010 were treated with OAD, LSI, insulin therapy or combination therapy. Patients receiving combination therapy were younger than those in the other patient groups ($P < 0.001$). The age at onset was lower in the patients receiving insulin and combination therapy ($P < 0.001$), and the duration of the disease was longer ($P < 0.001$). BMI was lower in the patients receiving insulin therapy ($P = 0.001$), whereas the HbA1c level was higher in patients receiving insulin and combination therapy than in patients receiving LSI and OAD ($P < 0.001$).

Changes in Bodyweight and Glycemic Control in All Patients
In the patients receiving OAD and LSI in 2010, BMI had decreased over the 5 years (repeated measures ANOVA, $P < 0.001$; Figure 1c). In contrast, BMI gradually increased in the patients receiving insulin therapy ($P < 0.001$), although the values were lower at baseline in the patients receiving insulin therapy than in those receiving OAD and LSI ($P < 0.05$ and $P < 0.01$, respectively), and reached the levels in the patients on OAD and LSI at the end of the study. BMI at baseline in the patients receiving combination therapy did not differ from that in the patients receiving OAD and LSI, although it gradually increased to be more than baseline by the end of the study ($P < 0.01$ and $P < 0.01$, respectively).
HbA1c levels at baseline were higher in the patients receiving insulin therapy and combination therapy than in those receiving OAD and LSI (P < 0.001; Table 1 and Figure 1d). The levels in the patients receiving insulin therapy and combination therapy gradually decreased; however, they did not reach the levels in the patient groups receiving OAD and LSI (repeated measures ANOVA, P < 0.05). The levels from 2008 to 2010 were higher in the patients receiving combination therapy than in the patients receiving insulin therapy (P < 0.01, from 2008 to 2010). Mean HbA1c levels were higher than 8.0% in the patients receiving combination therapy during the study.

Changes in Bodyweight and Glycemic Control in the Patients Receiving Insulin

In the patients transferred to insulin therapy, the numbers of patients introduced to twice-daily MIX were highest at the end of the study followed by those of patients treated with basal–bolus insulin with RA plus LA (RA + LA; Figure 1b). In these patients, we therefore analyzed changes in BMI and HbA1c levels (Figure 2). In the patients treated with twice-daily MIX, mean BMI and HbA1c levels at baseline were 23.5 ± 3.3 and 8.40 ± 1.11%, respectively, with most of this group started on twice-daily MIX as the initial insulin regimen, and only a small proportion of patients changed from other insulin regimens (Figure 2a upper panel). BMI increased gradually, but not significantly, during the term (P = 0.158). HbA1c levels significantly decreased (repeated measures ANOVA, P < 0.001), although the mean HbA1c did not reach 7.0% (Figure 2b). In the patients receiving RA + LA, the mean BMI and HbA1c levels at baseline were 24.0 ± 4.6 and 8.63 ± 1.27%, respectively. A total of 23 patients (36.5%) had originally started this regimen, and 40 patients (63%) had changed from other insulin regimens (Figure 2a lower panel). BMI increased gradually, but not significantly (P = 0.205). Although HbA1c levels gradually decreased, the mean HbA1c was higher than 8.0% (Figure 2b). Basal–bolus insulin was introduced to more patients as a change from another insulin regimen, compared with twice-daily MIX (P < 0.01).

From the 103 and 63 patients, respectively, treated with twice-daily MIX and basal–bolus insulin, 96 patients were included in a propensity score matched analysis (48 from each group). In the cohort before propensity score matching, BMI did not differ between the groups at baseline or during the term. HbA1c levels from 2008 were lower or tended to be lower in the patients receiving twice-daily MIX than in the patients receiving basal-bolus insulin (Figure 2b upper panel), although the mean decline in HbA1c did not differ between patient groups at the end of the study (lower panel). In the propensity score-matched cohort, there were no differences in age, age at onset, duration of diabetes, BMI or HbA1c level at baseline (60.3 ± 7.6 vs 61.8 ± 8.3 years, 47.4 ± 9.3 vs 48.8 ± 9.8 years, 13.0 ± 8.0 vs 13.0 ± 6.7 years, 23.9 ± 3.3 vs 23.7 ± 4.5, 8.42 ± 1.15 vs 8.71 ± 1.26%, respectively). HbA1c levels gradually and significantly decreased in the patients on twice-daily MIX and basal–bolus insulin (repeated measures ANOVA, P < 0.001 and P < 0.001, respectively), and there were no significant differences in HbA1c levels between the groups during the term (Figure 2c upper panel) and in the mean decline in HbA1c at the end of the study (Figure 2c lower panel).

Changes in Bodyweight and Glycemic Control in the Patients Receiving Insulin Plus OAD

In the patients treated by adding insulin therapy to OAD, the numbers added to the basal LA were highest at the end of the study followed by those treated with twice-daily MIX (Figure 1b), thus we analyzed changes in BMI and HbA1c levels in those patients (Figure 3). In the patients receiving basal LA, mean BMI and HbA1c levels at baseline were 24.3 ± 3.9 and 8.09 ± 1.02%, respectively. A total of 271 patients (87.7%) had started basal LA as the initial insulin regimen, and 38 patients (12.2%) changed from another insulin regimen (Figure 3a upper panel). BMI increased slightly, but not significantly (P = 0.294). HbA1c levels changed during the term; however, they did not improve compared with the level at baseline (P = 0.767), and the mean HbA1c was over 8.0% (Figure 3c upper panel). In the patients treated by twice-daily MIX, mean

Table 1 | Clinical characteristics of the patients at baseline

| Variables                      | LSI (8.3) | OAD (80.2) | INS (2.9) | Comb (8.6) | P-value |
|--------------------------------|-----------|------------|-----------|------------|---------|
| Age (years)                    | 61.9 ± 109| 61.8 ± 103| 61.5 ± 106| 59.1 ± 109| <0.001  |
| Age at onset (years)           | 51.6 ± 121| 51.6 ± 117| 48.9 ± 113| 47.6 ± 117| <0.001  |
| Duration of disease (years)    | 10.0 ± 85 | 98 ± 87   | 123.3 ± 85| 11.2 ± 85  | <0.001  |
| BMI                            | 24.8 ± 39 | 24.6 ± 39 | 23.7 ± 36 | 24.7 ± 43  | 0.001   |
| Systolic BP (mmHg)             | 133 ± 17  | 130 ± 14  | 134 ± 15  | 130 ± 15   | <0.001  |
| LDL-cholesterol (mg/dL)        | 115 ± 28  | 116 ± 27  | 119 ± 30  | 120 ± 31   | 0.034   |
| HbA1c (%)                      | 7.44 ± 1.11| 7.41 ± 0.95| 8.32 ± 1.25| 8.33 ± 1.23| <0.001  |

Data are mean ± standard deviation. P-value: Variables are compared among the patient groups by analysis of variance. LSI, lifestyle intervention; OAD, oral antidiabetic drug therapy; INS, insulin therapy; Comb, combination therapy with oral antidiabetic drug plus insulin. BMI, body mass index; BP, blood pressure; LDL-cholesterol, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.
BMI and HbA1c levels at baseline were 24.6 ± 4.3 and 8.50 ± 1.29%, respectively. A total of 191 patients (69.7%) had initially started this insulin regimen, and 83 patients (30%) had changed from another insulin regimen (Figure 3a lower panel). BMI increased gradually, but not significantly (P = 0.064), and it tended to be higher in the patients receiving twice-daily MIX than in the patients receiving basal LA (P < 0.05 in 2008). HbA1c levels decreased (repeated measures ANOVA, P < 0.001), and the mean HbA1c reached levels below 8.0% at the end of the study. Basal LA was introduced to more patients as the original insulin regimen, compared with twice-daily MIX (P < 0.01).

Although basal LA and twice-daily MIX were introduced in 309 and 274 patients, respectively, 418 patients were included in a propensity score matched analysis (209 from each group). In the cohort before propensity score matching, BMI was higher or tended to be higher in the patients receiving twice-daily MIX than in the patients receiving basal LA (P < 0.05 in 2008). HbA1c at baseline was higher in the patients receiving twice-daily MIX than in the patients receiving basal LA (P < 0.01); however, the mean HbA1c was lower or tended to be lower in the former patients than in the latter group from 2008 to 2010 (Figure 3b upper panel). The mean decline in HbA1c at the end of the study was larger in the patients receiving twice-daily MIX than in the patients receiving basal LA (P < 0.01). In the propensity score-matched cohort, there were no differences in age, age at onset, duration of diabetes, BMI or HbA1c levels at baseline between the groups (59.7 ± 9.8 vs 59.6 ± 11.6 years, 47.7 ± 10.5 vs 47.6 ± 11.6 years, 12.0 ± 7.6 vs 11.9 ± 8.0 years, 24.4 ± 4.2 vs 24.5 ± 4.0, 8.29 ± 1.00 vs 8.25 ± 1.00%, respectively). HbA1c levels gradually and significantly decreased in the patients on twice-daily MIX (repeated measures ANOVA, P < 0.001; Figure 3c upper panel). In contrast, although HbA1c levels changed in the patients receiving basal LA (P = 0.001), the levels at the end of the study did not differ from those at baseline (P = 0.497). HbA1c levels were lower in the patients receiving twice-daily MIX than in the patients receiving basal LA from 2008 to 2010. The mean decline in HbA1c was therefore larger in the patients receiving twice-daily MIX than in the patients receiving basal LA (P < 0.05; Figure 3c lower panel).

**DISCUSSION**

Propensity score matching to control for baseline characteristics of individual patients is a useful approach to avoid selection bias and confounding effects in evaluating the efficacy of a treatment in cohort studies. Indeed, such a method was
recently used successfully to minimize or eliminate selection biases and confounding effects related to diabetes treatment selection\textsuperscript{11}. Our current analysis of the CoDiC\textsuperscript{16} database collected from multiple institutions across Japan using propensity score matching showed that basal LA was added for many patients who had poor glycemic control despite concurrent treatment with OAD. However, it showed that this treatment approach induced no significant reduction of HbA1c levels over the long term, while the levels gradually and significantly decreased in patients from the same cohort introduced to a twice-daily MIX and basal–bolus insulin regimen.

In the patients introduced to insulin in the present study, approximately 80\% were prescribed twice-daily MIX, basal LA and basal–bolus insulin with RA plus LA. Biphasic insulin accounts for the majority of insulin prescriptions, based on worldwide figures showing greater consumption of biphasic insulin than either short- or long-acting insulin\textsuperscript{25}. In the consensus algorithm for the medical management of type 2 diabetes regarding the second medication added to metformin, insulin can be initiated with a basal (intermediate- or long-acting) insulin\textsuperscript{6}. Once-daily basal insulin, LA plus OAD has been regarded as an effective option for glycemic control in type 2 diabetes\textsuperscript{7}. This algorithm and the associated report could thus have affected the introduction of basal LA in many patients. The basal–bolus insulin was considerably changed compared with other insulin regimens, possibly because glycemic control was not attained by the original regimen. In the 4-T trial, 73.7\% of the original prandial RA recipients, and 81.6\% of those given basal insulin were transferred to a basal–bolus regimen\textsuperscript{26}. In our previous study, just 7\% of the patients were started on basal–bolus therapy, whereas 93\% were transferred to this therapy from other insulin regimens\textsuperscript{12}.

Randomized, control trial studies showed greater HbA1c reduction in type 2 diabetes patients when insulin was initiated using biphasic or prandial insulin rather than basal insulin\textsuperscript{8,26}. In our previous short-term observational study, HbA1c reduction was greater in the patients receiving prandial RA and twice-daily MIX, compared with basal LA\textsuperscript{12}. Type 2 diabetes is a progressive disease in which poor glycemic control is exacerbated over time and pancreatic β-cell function declines\textsuperscript{1,2}. Thus, attaining no significant improvement in the patients prescribed additional basal LA was attributed to the small reduction in HbA1c, and this might be overcome by the progressive exacerbation of glycemic control in the longer term. Alterna-
tively, because the number of patients given basal LA added to OAD increased from 2008 onward, as did those given added twice-daily MIX from 2007, a delay in basal LA initiation might fail to induce further significant improvement of glycemic control. As it has been shown that HbA1c reduces to a nadir 3–6 months after the addition of basal insulin, the different timing of insulin initiation could only in part contribute to the different improvements in glycemic control. The present study did not examine changing the dose of OAD as an additional treatment to insulin. Such an approach might affect the glycemic control, although it seems unlikely that only one patient group would be affected.

Many groups have reported that basal LA is safe and effective in improving glycemic control. These studies were randomized trials carried out over a relatively short term; that is, <1 year. Another RCT also showed that the addition of basal insulin reduced HbA1c levels for 1 year. However, in a RCT with 3-year follow up, following the aforementioned trial, prandial insulin was added in 81.6% of patients initiated with basal LA, because hyperglycemia became unacceptable. Twice-daily MIX and basal–bolus insulin might therefore have longer-term efficacy for decreasing HbA1c than basal LA. Although the present results did not include hypoglycemic data, previous meta-analyses showed that biphasic and basal-bolus insulin might increase the incidence of hypoglycemia to a greater extent than basal insulin, and RCTs have shown that the hypoglycemia rates were highest in prandial groups and lowest in the basal groups. Because hypoglycemia is an important issue for insulin injection, studies with longer follow-up terms are required. In the present study, each insulin regimen was associated with a non-significant increase in BMI. In addition, recent meta-analyses showed that compared with basal insulin, biphasic and basal–bolus insulin were associated with greater weight gain with stronger heterogeneity, including several trials reporting no overall change in weight. Thus, further studies of changes in bodyweight in patients on insulin regimens are required.

In the Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), all treatment decisions should be made in conjunction with the patient, focusing on his/her preferences, needs and values. Evidence both from RCTs and from well-designed observational studies can and should be used to find the optimal treatment regimen. The data both from our propensity score-matched cohort study and from the RCTs, including a review of RCTs that found that a greater proportion of type 2 diabetes patients achieve the HbA1c goal of <7% with biphasic or prandial insulin compared with basal insulin potentially apply to all clinical situations of diabetes care. Thus, doctors and patients should be aware of these findings before prescription of basal insulin as the initial insulin regimen in addition to OAD.

The present cohort study had some limitations. The possibility that unmeasured confounding factors affecting the effect of insulin treatment could not be ruled out. Therefore, the propensity score-matching method used in the present study might not have adequately matched the clinical characteristics of the patient groups. Also, because we did not analyze the patients whose data input had stopped during the studied period, the possibility of selection bias cannot be completely excluded. We did not take account of complications, including micro- and macrovascular diseases and accidental diseases, and such factors could affect the choice of insulin regimens and motivation to treatment of both patients and providers. Furthermore, the present study had insufficient standardization of treatment regimens and glycemic goals, although insulin therapy was initiated according to JDS guidelines for the management of diabetes. Also, the different supporting system of the providers and the different proficiency of the clinicians in insulin therapy could affect the choice of insulin regimens and the targets of glycemic control, with the unmeasured clinical and social interactions possibly influencing the efficacy of the treatment. Because the initiation rate of insulin therapy in patients treated with OAD was low, 2.2 out of 100 per year, in the present study, the numbers in each studied group were limited. Larger and longer-term studies are required to draw firm conclusions.

In conclusion, the present cohort study using the propensity score-matching method to adjust for baseline factors showed that basal LA was initiated in many type 2 diabetes patients who had poor glycemic control despite existing treatment with OAD, but that such an approach did not achieve adequate improvement in glycemic control over the long term. This finding might suggest the potential loss of opportunity for many patients initiated with basal insulin to have received other insulin regimens that could deliver better glycemic control. Thus, doctors and patients should be aware of the evidence before prescribing basal insulin as the initial insulin regimen in type 2 diabetes patients who had poor glucose control despite OAD therapy.

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APPENDIX 1

The following members of JDDM participated in the present study: Dr Nobuyuki Abe, Dr Keiko Arai, Dr Azuma Kanatsuka, Dr Hiroshi Fujiya, Dr Yoshihide Fukumoto, Dr Koichi Hirao, Dr Fumihiko Dake, Dr Tomohiro Iizumi, Dr Masaaki Ito, Dr Koichi Iwasaki, Dr Akira Kanamori, Dr Sumio Kato, Dr Masakazu Kato, Dr Koichi Kawai, Dr Akira Kawara, Dr Kenichi Kimura, Dr Kazumasa Chikamori, Dr Kotaro Iemitsu, Dr Shigetake Kou, Dr Mikihiko Kudo, Dr Yoshio Kurihara, Dr Gendai Lee, Dr Akira Tsuruoka, Dr Naoki Manda, Dr Kiyokazu Matoba, Dr Hiroshi Hayashi, Dr Masa Minami, Dr Nobuichi Kuribayashi, Dr Kazuhiro Miyazawa, Dr Yasuko Chiba, Dr Takeshi Osono, Dr Shin Nakamura, Dr Hideo Sasaki, Dr Katsutoshi Komori, Dr Mariko Oishi, Dr Akira Okada, Dr Fuminobu Okuguchi, Dr Morifumi Yanagisawa, Dr Hidekatsu Sugimoto, Dr Hiromichi Sugiyama, Dr Masahiko Takai, Dr Masato Takaki, Dr Hiroshi Takamura, Dr Hiroshi Takeda, Dr Kokichi Tanaka, Dr Takashi Miwa, Dr Osamu Tomonaga, Dr Madoka Taguchi, Dr Katsuya Yamazaki, Dr Takako Wada, Dr Noriharu Yagi, Dr Kuniko Yamaoka and Dr Atsuyoshi Yuhara.