Efficacy and safety of adding ipragliflozin to insulin in Japanese patients with type 1 diabetes mellitus: a retrospective study

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Abstract. Advances in insulin preparations and administration methods have produced a gradual improvement in glycemic control in patients with type 1 diabetes mellitus (DM). Nevertheless, glycated hemoglobin (HbA1c) levels in patients with type 1 DM are still poor compared to those in patients with type 2 DM. Here, we sought to assess the efficacy and safety of the sodium-glucose cotransporter 2 (SGLT2) inhibitor ipragliflozin (IPRA) in patients with type 1 DM. This study was retrospectively conducted with data from type 1 DM patients who had a history of IPRA therapy. The primary endpoint was HbA1c level at 24 weeks. The baseline characteristics of a total of 12 subjects were as follows: age, 50.1 ± 13.2 years; diabetes duration, 17.3 ± 10.5 years; body mass index (BMI), 22.9 ± 2.1 kg/m2; HbA1c, 8.8 ± 1.3%; and daily insulin dose, 0.60 ± 0.21 units/kg. IPRA decreased HbA1c levels to 8.2 ± 1.2% (p < 0.05) and reduced insulin dose to 0.52 ± 0.17 units/kg (p < 0.01) after 24 weeks. HbA1c value was particularly reduced in subjects with preserved C-peptide index. IPRA significantly reduced body weight by –1.4 ± 1.4 kg (p < 0.01) 16 weeks after starting treatment, with no further weight loss after 24 weeks. There were no instances of diabetic ketoacidosis or severe hypoglycemia. IPRA exerted beneficial effects on glycemic control without any severe adverse effects, and should be safe and effective when used in patients with type 1 DM with understanding of correspondence in sick day.

Key words: Sodium-glucose co-transporter 2 inhibitor, Ipragliflozin, Type 1 diabetes
Here, we conducted a retrospective observational study to confirm the efficacy and safety of ipragliflozin (IPRA) in Japanese patients with type 1 DM on MDI therapy.

Materials and Methods

Study design

This study was retrospectively conducted among patients with type 1 DM who had received IPRA during the period from April 1, 2019, to August 21, 2020, at the Division of Diabetes, Endocrinology and Metabolism in Kawasaki Medical School Hospital. Inclusion criteria were 1) patients with insulin-dependent type 1 DM, 2) age ≥20 years, and 3) IPRA therapy. Exclusion criteria were cases with 1) slowly progressive type 1 DM, 2) type 2 DM, 3) diabetes due to other causes, and 4) eGFR <30 mL/min/1.73 m². We collected data on patient characteristics, treatment, and adverse events, as well as biochemical data. The registration flow of subjects is shown in Supplementary Fig. 1. We used an “efficacy analysis group” (EAG) of 12 cases receiving continuous treatment with IPRA for 24 weeks to estimate the drug’s efficacy. We also used a “safety analysis group” of 16 subjects with early discontinuation of IPRA to investigate the drug’s safety. The study protocol was approved by the institutional review board of Kawasaki Medical School (No. 5029-00), and the study was carried out in accordance with the Declaration of Helsinki. The procedure for informed consent regarding this research was via opt-out through the homepage of our hospital.

Statistical analysis

All analyses were carried out using commercial software (JMP version 12, SAS Institute, Inc., Cary, NC, USA). The results are expressed as the mean ± standard deviation. The paired t-test was used to compare mean values from two related samples. Analysis in the paired multi-group test was by one-way repeated measures ANOVA followed by multiple comparisons with Holm’s method. Correlations between variables were tested with Pearson’s correlation coefficient. Continuous variables with a non-normal distribution were analyzed after logarithmic transformation. \( p < 0.05 \) was considered statistically significant.

Results

The EAG consisted of normal-weight middle-aged type 1 DM patients with a long medical history and difficulty in controlling blood glucose levels. Clinical background before IPRA administration is shown in Table 1. Fig. 1 and Fig. 2 show changes in HbA1c values and insulin dose before and after IPRA therapy. The daily dose of IPRA was 50 mg in all cases, based on the recommendations of the Japan Diabetes Society, with adjustment of insulin dose in the range of 0% to 20% according to HbA1c levels [17]. On the other hand, in some cases where the insulin dose was excessive due to excessive energy intake, insulin dose was reduced by up to 20% at the start of SGLT2 inhibitor at the judgement of the attending physician. In this study, the percentage reduction of insulin dose at the start of IPRA administration was as follows: 0%–9% reduction, 8%; 10%–19% reduction, 58%; ≥20%, 33%. HbA1c levels at 8 weeks after the start of IPRA administration were decreased by \(-0.78 \pm 0.72\%\) (Fig. 1A and 1B), and the daily insulin dose was reduced by 18.2 ± 8.5% (Fig. 2A, 2B). The quantity of bolus insulin needed to be increased slightly after 8 weeks of IPRA therapy (Fig. 2C), but the daily insulin dose at 24 weeks was significantly lower than that at baseline (Fig. 2A, 2B). Nevertheless, HbA1c levels at 24 weeks were significantly lower than those at baseline (Fig. 1A). As shown in Supplementary Table 1, the change in HbA1c value at 24 weeks after administration was significantly negatively correlated with C-peptide index and tended to be negatively correlated with baseline HbA1c level. In three cases in which blood ketone bodies could be tested, the maximum value of total ketone bodies was 602.4 μmol/L and the total ketone bodies remained at approximately 50–120 μmol/L. The results of urinary qualitative tests performed continuously during the observation period in all cases are shown in Supplementary Table 2. IPRA significantly reduced body weight by \(-1.4 \pm 1.4 \text{ kg}\) at 16 weeks after treatment; no further weight loss was confirmed after 24 weeks of administration (Fig. 3). The change in body weight value at 24 weeks after administration was significantly negatively correlated with diabetes duration (Supplementary Table 3). The variables related to lipid metabolism, hepatic damage, and renal function were not altered by IPRA administration (Supplementary Table 4).

As shown in Supplementary Table 5, there were no serious adverse events. Three patients had hypoglycemia. There were no patients with severe hypoglycemia or ketoacidosis. Vulvar pruritus, genital candidiasis, cystitis, thirst, and gastroenteritis were observed in one subject each.

Discussion

In general, it is difficult to maintain meticulous glycemic control in subjects with type 1 DM compare to those with type 2 DM, because type 1 DM is characterized by absolute insulin deficiency. In this study, we showed that the SGLT2 inhibitor IPRA exerted beneficial effects on
## Table 1  Baseline characteristics in 12 subjects with type 1 diabetes before IPRA prescription

| Parameters                        | Mean ± Standard deviation |
|-----------------------------------|---------------------------|
| Age (yrs)                         | 50.1 ± 13.2               |
| Gender, male (%)                  | 42                        |
| Diabetes duration (yrs)           | 17.3 ± 10.5               |
| Body weight (kg)                  | 59.0 ± 7.0                |
| Body mass index (kg/m²)           | 22.9 ± 2.1                |
| Casual serum C-peptide (ng/mL)    | 0.13 ± 0.11               |
| C-peptide index                   | 0.09 ± 0.1                |
| HbA1c (%)                         | 8.8 ± 1.3                 |
| Casual plasma glucose (mg/dL)     | 253 ± 93                  |
| Total cholesterol (mg/dL)         | 187 ± 34                  |
| Triglycerides (mg/dL)             | 93 ± 59                   |
| HDL-cholesterol (mg/dL)           | 63 ± 13                   |
| LDL-cholesterol (mg/dL)           | 109 ± 23                  |
| Non-HDL-cholesterol (mg/dL)       | 128 ± 29                  |
| ALT (U/L)                         | 16 ± 8                    |
| AST (U/L)                         | 17 ± 6                    |
| γ-GTP (U/L)                       | 20 ± 12                   |
| Creatinine (mg/dL)                | 0.67 ± 0.20               |
| Uric acid (mg/dL)                 | 3.6 ± 1.2                 |

### Pre-existing Diabetic Complications

|                  |                             |
|------------------|-----------------------------|
| Neuropathy, no. (%) | 5 (42%)                    |
| Retinopathy, no. (%)| 3 (25%)                    |
| Nephropathy, Stage, number (%) | Stage 1, 10 (83%), Stage 2, 3 (17%) |
| Ischemic heart disease, no. (%) | 0 (0%)                     |
| Stroke, no. (%)    | 1 (8.3%)                    |
| Peripheral arterial disease, no. (%) | 0 (0%)                     |
| Dyslipidemia, no. (%) | 5 (42%)                    |
| Hypertension, no. (%) | 2 (17%)                    |
| Hyperuricemia, no. (%) | 0 (0%)                     |

### Insulin therapy (before IPRA prescription)

|                          |                             |
|--------------------------|-----------------------------|
| Multiple daily injection, no. (%) | 13 (100%)                |
| CSII, no. (%)            | 0 (0%)                      |
| Total insulin dose (U)   | 35.2 ± 11.3                 |
| Insulin dose per body weight (U/kg) | 0.60 ± 0.21                |
| Dose of long-acting insulin analog (U) | 14.4 ± 4.8                |
| Dose of rapid-acting insulin analog (U) | 20.8 ± 8.1                |

Data are indicated as mean ± standard deviation unless otherwise noted. C-peptide index was calculated by using the results of casual blood sampling. Abbreviations: HbA1c = hemoglobin A1c, HDL = high density lipoprotein, IPRA = ipragliflozin, LDL = low density lipoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, γ-GTP = γ-glutamyl transpeptidase, CSII = continuous subcutaneous insulin injection.
**Fig. 1** Change of HbA1c levels after the addition of IPRA to insulin therapy.
A) HbA1c level before and after IPRA therapy. B) Change in HbA1c level after IPRA therapy. Data are presented as average ± standard deviation. * $p < 0.05$, ** $p < 0.005$; vs. baseline.

**Fig. 2** Change in insulin dose after the addition of IPRA to insulin therapy.
A) Reduction rate in insulin dose per body weight after IPRA therapy. B) Total insulin dose before and after IPRA therapy. C) Bolus insulin dose before and after IPRA therapy. D) Basal insulin dose before and after IPRA therapy. Data are indicated as the mean ± standard deviation. ** $p < 0.005$, *** $p < 0.001$, **** $p < 0.0001$; vs. baseline.
glycemic control in subjects with type 1 DM. This result was consistent with the results of Phase 2 and 3 studies [10-16], meta-analyses [18-20], and clinical reports [21, 22]. Our results indicate that HbA1c values were reduced, especially in subjects where higher insulin secretory capacity remained (Supplementary Table 1). Previous human and animal studies reported that SGLT2 inhibitors improve residual beta-cell function in subjects with type 2 DM by reducing glucose toxicity [23-25]. Similarly, we speculated that recovery of residual pancreatic beta-cell function may have contributed to improvement of blood glucose in patients with type 1 DM. Our present data confirm that SGLT2 inhibitors are useful in patients with poorly-controlled type 1 DM.

IPRA significantly reduced body weight at 16 weeks after treatment, but no further weight loss was confirmed after 24 weeks of administration. We consider it beneficial that the reduction in body weight with IPRA treatment was not continuous, because such body weight reduction could lead to muscle atrophy or sarcopenia. We therefore think that the benefit of using SGLT2 inhibitors would outweigh their potential risk, such as the progression of sarcopenia. Given that body weight was particularly reduced in elderly subjects with longer duration of diabetes in this study, additional caution might be required when using SGLT2 inhibitors in such patients.

Daily insulin dose during the 24-week observational period was significantly lower (by approximately 15%–18%) than that at baseline, which we speculate would likely lead to a reduction in hypoglycemia risk and prevention of body weight gain. Given the risk of severe hypoglycemia and ketoacidosis with SGLT2 inhibitors in patients with type 1 DM, adjustment of insulin dose is critically important. Although the degree of reduction in insulin dose in our subjects was consistent with previous reports [10-16], an international consensus report on risk management of diabetic ketoacidosis in patients with type 1 DM treated with SGLT inhibitors showed that reducing insulin by >10%–20% can be a risk for diabetic ketoacidosis [26]. The limited number of patients in our study prevents any prediction of the rate of insulin dose reduction with SGLT2 inhibitor use in patients with type 1 DM, and our confirmation of our findings in a larger number of subjects is required. One of our subjects experienced gastroenteritis, but this resolved without problems with use of the STICH (Stop SGLT inhibitor, inject bolus Insulin, consume 30 g Carbohydrates, Hydrate) protocol [27]. We consider that IPRA can be introduced without severe adverse effects in patients with type 1 DM as long as vigilance is maintained against possible adverse effects, and their treatment.

There are limitations to this study. First, the number of subjects was limited. Second, we did not evaluate changes in body composition such as skeletal muscle mass. Evaluation of the effect of SGLT2 inhibitors on body composition in subjects with type 1 DM is an important future task.

Taken together, our results show that the SGLT2

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**Fig. 3** Change in body weight after the addition of IPRA to insulin therapy.

A) Body weight before and after IPRA therapy. B) Change in body weight after IPRA therapy. Data are presented as mean ± standard deviation. * p < 0.05, # p < 0.01; vs. baseline
inhibitor IPRA exerts beneficial effects on glycemic control and body weight without any severe adverse effects. Since the importance of good glycemic control and body weight reduction in preventing complications in chronic diabetes, we consider that the benefit of using SGLT2 inhibitors outweighs its potential risks in subjects with type 1 DM.

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