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ORIGINAL ARTICLE

Metformin monotherapy in children and adolescents with type 2 diabetes mellitus in Japan

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Abstract

Objective To evaluate the safety and effectiveness of metformin monotherapy for 52 weeks, including 24 weeks of treatment and a 28-week extension period for evaluation of long-term safety, in 37 Japanese pediatric patients with type 2 diabetes mellitus.

Research design and methods This study design was an open-label, non-randomized, multicenter trial. The primary effectiveness endpoint was the changes from baseline to the final visit at 24 weeks in HbA1c. The secondary endpoints were the rate for achieving the treatment goal, and the changes in glycated albumin, fasting blood glucose, fasting insulin, HOMA-IR, and fasting serum lipids. Metformin was administrated at the dose of 500 mg/day up to a maximum of 2000 mg/day taken in two or three divided doses.

Results The mean change of HbA1c at the final visit at 24 weeks for 20 metformin-naïve patients (Group A) was $-0.66 \pm 0.95\%$ and that of 17 already-on metformin patients (Group B) was $-0.98 \pm 1.62\%$. These figures proved the effectiveness of metformin as defined before the study. Secondary effectiveness endpoints were also improved. The improvement of blood glucose, fasting insulin and serum lipid levels proved the effectiveness of metformin without increasing body weight. Adverse effects such as nausea and diarrhea were observed in 35 of the 37 subjects and drug-related adverse events were observed in 19 patients. However, these events were not serious and did not increase with long-term treatment.

Conclusions Metformin is safe and effective for Japanese pediatric patients with T2DM.

Keywords Metformin · Metformin monotherapy · Childhood and adolescent T2DM · Safety · Adverse effects

Nobuo Matsuura and Shin Amemiya are co-first authors and chairpersons of the first and second trials, respectively.

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Abbreviations

T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
HbA1c	Hemoglobin A1c
FPG	Fasting plasma glucose
GA	Glycated albumin
HOMA-IR	Homeostasis model assessment for insulin resistance
FAS	Full analysis set
CI	Confidence interval
BMI-SDS	Body mass index standard deviation score
ISPAD	International Society for Pediatric and Adolescent Diabetes
GCP	Good clinical practice
SU	Sulfonylurea
α-GI	α-Glucosidase inhibitor
NGSP	National Glycohemoglobin Standardization Program
AEs	Adverse events

ADRs Adverse drug reactions
M/F Male/female

Introduction

The incidences of obesity and type 2 diabetes mellitus (T2DM) have been increasing globally due to changes in lifestyles, decreased physical activity, and increased stress in children and adolescents [1–3]. Moreover, the long-term prognosis of T2DM is not satisfactory compared with type 1 diabetes mellitus (T1DM) [4]. Youth onset T2DM carries a higher risk of progressive diabetic kidney disease than adult-onset T2DM [5] and involves hypertension and hyperlipidemia, as well as health risk behaviors [3, 6].

The first choice for treatment of T2DM is thought to be metformin [7–9]. Clinical trials performed in the USA [10] and Europe [11] that proved the effectiveness and safety of metformin in children and adolescents with T2DM were reported previously. Metformin therapy has beneficial treatment effects for reduction of the body mass index standard deviation score (BMI-SDS) and fasting glucose, improves insulin sensitivity, and reduces the risk of T2DM in obese children and adolescents [12]. According to the clinical practice guidelines from the American Academy of Pediatrics, and the International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines 2009 and 2014, insulin or metformin is the preferred first-line treatment for children and adolescents with T2DM, together with lifestyle modification and education [7–9].

Before the present clinical trial, we conducted a clinical study for the first time in Japan for the purpose of evaluating the efficacy and safety of metformin monotherapy for Japanese pediatric patients with T2DM from September 2004 through June 2006, supported by Ministry of Health, Labor and Welfare Research grants for clinical research on pediatric disease [13]. In that study, a total of 47 patients with T2DM (aged from 10 years to less than 20 years, M/F 21/26) were enrolled and administrated either 750 mg/day or 1500 mg/day of metformin for 24 weeks. The primary objective was the effectiveness of metformin, comparing the baseline hemoglobin A1c (HbA1c) value with that at the 24-week visit. Thirty-eight patients completed the clinical study. Treatment was discontinued for 5 patients because of worsening of metabolic control and the remaining 4 patients discontinued for various other reasons. Before we started the first clinical study, we hypothesized that metformin could be considered to be effective when the lower limit of the two-sided 95% confidence interval (CI) was more than 0.80. The primary effectiveness variable was 0.7895 (patients in whom metformin was effective/total patients who had completed the study protocol) which did not satisfy the hypothesized criterion for effectiveness, and metformin was judged to have no effectiveness for Japanese pediatric patients even though it showed a tendency to be effective in the first study [13]. However, the 24:0 week ratio of HbA1c was 0.938 ± 0.148 and the 95% CI of the 24:0 week ratio of HbA1c ranged from 0.890 to 0.988, which showed improvement between 0 and 24 weeks [13].

We conducted the second study for the purpose of evaluating the additional effectiveness and safety in the case of long-term metformin use for Japanese pediatric T2DM patients.

Materials and methods

Study design and methods of second clinical trial

The second clinical trial, supported by Sumitomo Dainippon Pharma Co., Ltd., was performed from May 2011 through March 2014. The multicenter, open-label, uncontrolled study was conducted at 21 sites across Japan, in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP) and other relevant notifications. The clinical trial examined whether doses from 500 mg/day up to a maximum of 2000 mg/day of metformin could be used for Japanese pediatric patients with T2DM for 24 weeks (treatment phase) and examined the long-term safety up to 52 weeks (extended treatment phase).

Pediatric and adolescent patients with T2DM from 6 to 17 years old were enrolled in the following 4 groups: (a) only stable diet–exercise therapy for more than 8 weeks before the trial, (b) sulfonylurea (SU) at a fixed dose added to stable diet–exercise therapy for more than 12 weeks before the trial, (c) an α-glucosidase inhibitor (α-GI) at a fixed dose added to the stable diet–exercise therapy for more than 12 weeks before the trial, and (d) metformin at a fixed dose of less than 750 mg without any other anti-diabetic medication taken for more than 12 weeks before the trial. Treatment groups, a, b and c, were patients naïve for metformin (Group A) and treatment group d was an already-on metformin group (Group B).

The criteria for enrollment immediately before the trial followed those of the National Glycohemoglobin Standardization Program (NGSP), i.e., the HbA1c level should be ≥ 7.0 and $< 12.1\%$ and the percent degree of obesity should be $> 0\%$ by age and sex when compared to the school health statistics compiled by the Ministry of Education, Culture, Sports Science and Technology of Japan in 2000. The rate of variability in HbA1c among the 37 patients was less than 15%. Patients with impaired renal function (creatinine level at 4 weeks before enrollment ≥ 1.0 mg/dL or renal replacement therapy), liver dysfunction (AST [GOT] and ALT [GPT] levels at 4 weeks before enrollment ≥ 3 times the study site's upper limit of normal), impaired cardiovascular

function (cardiac failure or myocardial dysfunction), or impaired pulmonary function (respiratory failure or chronic respiratory acidosis) were excluded.

In group A, metformin was taken orally, either immediately preprandially or postprandially, at a starting dose of 500 mg/day in two or three divided doses and the dose was increased to 1500 mg/day stepwise. In group B, metformin was started at 1000 mg/day and increased in the same manner. The dose could be increased up to 2000 mg/day based on blood glucose control and safety. In detail, metformin was increased 500 mg/day if the HbA1c was over 7.0% or GA was over 20% and the safety of trial was verified at every visit in both groups.

Statistics

Statistical analysis was conducted using SAS version 9.2. Summary statistics (e.g. mean, SD, 95% confidential interval and percentage) are used to present the study results. As summary statistics for the primary endpoint, the results for each time point are provided as mean ± SD, and the change from baseline of each time point is provided as mean ± SD (95% confidential interval). Since this was a study with a small number of subjects, the significance level is not given in this study. If the two-sided 95% CI of HbA1c at the final visit of 24 weeks did not include zero and the point estimate was less than − 0.3%, the treatment was defined as "effective" for pediatric T2DM patients in this report.

Results

Patient characteristics

All 37 subjects were eligible for analysis by FAS. Among these, 20 were naïve for metformin treatment (14 had received no medication, 4 were treated with SU, and 2 were treated with α-GI) (group A), and the remaining 17 patients were already on metformin at less than 750 mg/day (group B) (Table 1). Thirty-one patients were under 16 years of age. The patients enrolled in this trial were comparable with the patients with T2DM in our previous study [16]. The average

Table 1 Patients' characteristics at baseline

	Group A Naïve patients ($N=20$)	Group B Already-on patients ($N=17$)	Total ($N=37$)
Male/female	7/13	4/13	11/26
Age (years)	13.7 ± 2.1	13.4 ± 1.7	13.5 ± 1.9
< 10	1 (5.0)	0 (0.0)	1 (2.7)
≥ 10 to < 12	1 (5.0)	2 (11.8)	3 (8.1)
≥ 12 to < 14	7 (35.0)	7 (41.2)	14 (37.8)
≥ 14 to < 16	7 (35.0)	6 (35.3)	13 (35.1)
≥ 16	4 (20.0)	2 (11.8)	6 (16.2)
Diabetes duration (years)	0.9 ± 1.1	1.2 ± 1.7	1.0 ± 1.4
BMI (kg/m^2)	27.69 ± 5.87	28.67 ± 4.62	28.14 ± 5.29
< 25	7 (35.0)	3 (17.6)	10 (27.0)
≥ 25	13 (65.0)	14 (82.4)	27 (73.0)
Percent overweight (%)	39.00 ± 30.31	44.54 ± 23.07	41.55 ± 27.00
< 20	6 (30.0)	2 (11.8)	8 (21.6)
≥ 20	14 (70.0)	15 (88.2)	29 (78.4)
HbA1c (NGSP) (%)	8.34 ± 1.61	8.64 ± 1.59	8.47 ± 1.58
≥ 6.05 to < 7.5	6 (30.0)	4 (23.5)	10 (27.0)
≥ 7.5 to < 9.0	10 (50.0)	8 (47.1)	18 (48.6)
≥ 9.0	4 (20.0)	5 (29.4)	9 (24.3)
GA (%)	19.68 ± 6.51	19.99 ± 4.71	19.82 ± 5.68
FPG (mg/dL)	165.5 ± 55.1	171.1 ± 51.8	168.1 ± 53.0
IRI (μU/mL)	22.264 ± 13.813	33.317 ± 51.458	27.342 ± 36.177
HOMA-IR	8.569 ± 5.718	13.602 ± 21.344	10.881 ± 15.039
eGFR(ml/min/1.73 m^2)	143.14 ± 31.05	146.57 ± 33.86	144.72 ± 31.96

Data are mean ± standard deviation or *n* (%)

BMI body mass index, *HbA1c* hemoglobin A1c, *NGSP* National Glycohemoglobin Standardization Program, *GA* glycoalbumin, *FPG* fasting plasma glucose, *IRI* immunoreactive insulin, *HOMA-R* homeostasis model assessment insulin resistance

weight was 69.72 (44.4–112.0) kg, the average body mass index (BMI) was 28.14 (19.5–40.9), and the average percent overweight was 41.55% (−3.1 to 106.6%). The average duration of T2DM was 1.0 year (0–5 years). Finally, 37 patients were enrolled and all patients completed the clinical study for 52 weeks.

Primary effectiveness

The definition of effective treatment is described in the methods section.

As shown in Table 2, HbA1c levels (mean ± SD) in Group A at 0, 24, and 52 weeks were 8.34 ± 1.61%, 7.68 ± 1.80% and 7.97 ± 2.13%, respectively. The changes in HbA1c (95% CI) at the final visit at 24 weeks and at 52 weeks were −0.66 ± 0.95% (−1.11, −0.21) and −0.37 ± 1.09% (−0.88, 0.15). The HbA1c levels (mean ± SD) in Group B at 0, 24, and 52 weeks were 8.64 ± 1.59%, 7.66 ± 1.38% and 8.07 ± 1.35%, respectively. The changes in HbA1c (95% CI) at the final visit at 24 weeks and at 52 weeks were −0.98 ± 1.62% (−1.81, −0.14) and −0.56 ± 1.19% (−1.18, −0.05). These findings proved the effectiveness and dose increment effect of metformin.

In the 37 patients, HbA1c (mean ± SD) levels at 0, 24 and 52 weeks of study were 8.47 ± 1.58%, 7.67 ± 1.60% and 8.02 ± 1.79, respectively. The changes in HbA1c (95% CI) at the final visit at 24 weeks and at 52 weeks were −0.81 ± 1.29% (−1.24, −0.37) and −0.46 ± 1.13% (−0.83, −0.08), respectively. HbA1c at 52 weeks was elevated little bit than at 24 weeks.

Secondary effectiveness

The secondary effectiveness variables of 9 characteristics at baseline, 24 weeks and 52 weeks are shown in Table 3. Eight secondary efficacy values (but not HDL-Cho) showed decreases in the final evaluations at 24 weeks and 52 weeks from the baseline in Groups A and B together.

Table 2 Changes in HbA1c levels at the final evaluation (24 weeks and 52 weeks)

FAS					
Groups	Evaluation time	*n*	HbA1c (%)	Changes in HbA1c (%)	
			Mean (SD)	Mean (SD)	95% CI
Group A	At baseline	20	8.34 ± 1.61	–	–
	24 weeks	20	7.68 ± 1.80	−0.66 ± 0.95	(−1.11, −0.21)
	52 weeks	20	7.97 ± 2.13	−0.37 ± 1.09	(−0.88, 0.15)
Group B	At baseline	17	8.64 ± 1.59	–	–
	24 weeks	17	7.66 ± 1.38	−0.98 ± 1.62	(−1.81, −0.14)
	52 weeks	17	8.07 ± 1.35	−0.56 ± 1.19	(−1.18, 0.05)
Total	At baseline	37	8.47 ± 1.58	–	–
	24 weeks	37	7.67 ± 1.60	−0.81 ± 1.29	(−1.24, −0.37)
	52 weeks	37	8.02 ± 1.79	−0.46 ± 1.13	(−0.83, −0.08)

Data are mean ± standard deviation or (lower limited, upper limited). The final evaluation (24 weeks) was calculated from the final value during the treatment phase and the final evaluation (52 weeks) was calculated from the final value during the continuous treatment phase

Table 3 Secondary efficacy summarized for Groups A and B together

Parameters	At baseline	Change from baseline at 24 weeks	95% CI	Change from baseline at 52 weeks	95% CI
Degree of obesity (%)	41.55 ± 27.00 (37)	−1.23 ± 6.09 (37)	(−3.26, 0.80)	−2.22 ± 5.84 (37)	(−4.17, −0.27)
IRI (μU/mL)	27.869 ± 36.546 (36)	−10.437 ± 32.382 (35)	(−21.561, 0.687)	−9.818 ± 31.827 (36)	(−20.587, 0.950)
HOMA-R	11.120 ± 15.181 (36)	−4.961 ± 13.033 (35)	(−9.438, −0.484)	−4.366 ± 12.877 (36)	(−8.723, −0.009)
GA (%)	19.82 ± 5.68 (37)	−3.29 ± 3.76 (37)	(−4.55, −2.04)	−2.35 ± 3.20 (37)	(−3.42, −1.28)
FPG (mg/dL)	169.7 ± 52.8 (36)	−24.3 ± 42.3 (36)	(−38.6, −9.9)	−12.0 ± 34.9 (36)	(−23.8, −0.2)
T-Cho (mg/dL)	194.5 ± 34.0 (36)	−12.4 ± 23.2 (36)	(−20.3, −4.6)	−7.7 ± 20.2 (36)	(−14.5, −0.9)
TG (mg/dL)	160.6 ± 105.1 (36)	−10.2 ± 83.1 (36)	(−38.3, 17.9)	−8.4 ± 80.9 (36)	(−35.7, 19.0)
HDL-Cho (mg/dL)	48.3 ± 11.7 (36)	0.3 ± 6.5 (36)	(−1.9, 2.5)	1.1 ± 6.8 (36)	(−1.2, 3.3)
LDL-Cho (mg/dL)	126.3 ± 34.7 (36)	−97 ± 23.1 (36)	(−17.5, −1.8)	−5.1 ± 21.2 (36)	(−12.3, 2.0)

Data are means ± standard deviation (*n*) or (lower limit, upper limit)

Adverse events (AEs) and adverse drug reactions (ADRs)

There were 146 AEs such as diarrhea, nausea, vomiting, anorexia, and abdominal pain in 35 of the 37 patients (94.6%) and 36 ADRs in 19 patients (19/36, 52.8%), including serum lactic acid levels elevated to more than twofold the standard upper value (3.0–17.0 mg/dL), atopic dermatitis, etc. However, no adverse event such as hypoglycemia or lactic acidosis serious enough to discontinue the trial was observed. There was no serious AE leading to death. Dose reduction and interruption caused by AEs occurred for 4 patients (10.8%) and 5 patients (13.5%), respectively. More gastrointestinal AEs tended to occur in Group A patients (13/20, 65%) during the early phase of metformin treatment than in those of Group B (5/17, 29.4%) but these events did not increase with long-term treatment. These AEs improved after dose reduction and interruption.

Discussion

The incidence of obese children has increased globally together with an increase of T2DM in children [1–3]. The recent guidelines from the American Academy of Pediatrics for newly diagnosed T2DM in children and adolescents and the ISPAD guidelines suggest integrating lifestyle modification in concert with medication with either insulin or metformin [7–9].

These third (our first) and fourth (our second) clinical trials of metformin for pediatric use ever performed in the world again proved metformin to be safe and effective for children and adolescents with T2DM. The effectiveness of metformin in our first clinical trial was 63.8%, which was not lower than previously reported [10, 11]. The secondary endpoint of lower fasting blood glucose was also observed in both trials. The effectiveness of metformin was observed in patients who were naïve for metformin (group A) as well as in patients already on metformin (group B). The latter suggested a dose–response effect of metformin in pediatric patients with T2DM. A dose–response effect has been observed up to 2000 mg/day in adult patients [14].

In a large cohort study of adult patients with T2DM initiating metformin monotherapy, gastrointestinal intolerance and increased lactic acid in the bloodstream was reported in roughly 23–35% of patients [15]. In a recently published study on metformin monotherapy in Japanese adult patients with T2DM, AEs were observed in 91.1% of the patients (154/169) and ADRs in 67.5% (114/169) [16]. These figures were similar to those in our first and second clinical trials [13].

Our study proved that it was safe to use up to 2000 mg/day of metformin for pediatric patients, which was more than double the previously approved upper limit dose of 750 mg/day, and close to the upper limit of 2250 mg/day for adult patients with T2DM in Japan at present [16].

Since the prevalence of type 2 diabetes in children and adolescents is small in comparison with that in adults, the number of participants was limited in this study. Furthermore, many children and adolescents with type 2 diabetes mellitus have some social and familial burdens, so most pediatricians have noted that they often have difficulty in adhering to therapy. Even with these limitations, large-dose metformin therapy for children and adolescents with type 2 diabetes mellitus had already been recommended as the first choice of medication by international diabetes societies such as ISPAD, ADA and EASD at the time of this study. Therefore, the approval for children and adolescents in Japan has focused on the safety of large-dose metformin therapy.

The first clinical trial of metformin for pediatric patients with T2DM was conducted as a double-blind, placebo-control trial in the USA in 1998–1999 [10]. The mean HbA1c and FPG levels decreased in the metformin groups significantly more than in the placebo groups and no serious side effects were observed [10].

The second clinical trial was conducted in Europe using glimepiride versus metformin as a monotherapy for pediatric patients with T2DM [11]. The mean HbA1c and FPG levels were improved significantly in both the metformin and glimepiride groups; however, BMI was improved only in the metformin group [11]. Thereafter, further studies were done in adolescents.

The Treatment Options for Type 2 Diabetes in Adolescents and Youths (TODAY) study, sponsored by the NIH, was designed to test three approaches: metformin alone, metformin plus rosiglitazone, and metformin plus lifestyle intervention [3, 17]. The 3.9-year clinical trial showed that metformin plus rosiglitazone was the most effective treatment for T2DM, followed by metformin plus lifestyle intervention and then metformin alone [3, 17]. A more recent TODAY study showed the effectiveness of metformin plus short-term diabetes education in a large ethnically/racially and geographically diverse population of adolescents with recent-onset T2DM who completed at least 8 weeks of treatment. This study provided short-term improvements in glycemic control and cardiometabolic risk factors in a large adolescent T2DM population [18].

Judging from our two clinical trials and previous reports, metformin monotherapy is effective and safe for treatment of children and adolescents with T2DM, at least up to 52 weeks. We have to consider two points when beginning metformin monotherapy. The first is the patient's condition at the time of diagnosis. In most patients in Japan, T2DM is detected by urine glucose screening [1]. Many of these patients have elevated blood glucose, HbA1c and mild acidosis, which cause insulin resistance and exhaustion of

endogenous insulin. The American Academy of Pediatrics [6] and ISPAD guidelines [8, 9] recommend using intermediate-acting insulin or long-acting insulin together with metformin for T2DM. In our first trial, we found that the treatment was effective for metformin-naïve patients with lower HbA1c and lower fasting plasma glucose levels, and higher plasma IRI, C-peptide and HOMA-β levels at entry (unpublished data) [13]. Metformin plus lifestyle intervention and intensive short-acting or ultrashort-acting insulin therapy for a short period of time will be an alternative therapy at entry to reduce glucose toxicity and insulin resistance, and restore endogenous plasma insulin levels. Naturally, care should be taken to ensure that insulin therapy does not cause hypoglycemia.

Another point for metformin monotherapy will be good metabolic control sustained for a long period of time. According to the TODAY study, metformin alone is effective for short-term glycemic control in the majority of youths with T2DM [18]. However, metformin monotherapy is inadequate for sustained glycemic control in the majority of youths with T2DM after a long period of time [7–9]. In our study, HbA1c at 52 weeks was also elevated slightly compared to the level at 24 weeks. The addition of rosiglitazone to metformin is superior to metformin alone for glycemic control [3]. However, rosiglitazone is not approved in our country and is reported to have serious side effects in adults. Other anti-diabetic drugs will be necessary after a long period of time as suggested in various guidelines [7–9] and the TODAY studies [3, 17]. The most adequate pharmacologic agents after long-term metformin monotherapy have to be considered in the future.

In conclusion, we reported our clinical trials of metformin monotherapy for patients with pediatric T2DM in Japan. Our results proved the effectiveness and safety of the drug, at least up to 52 weeks, for pediatric patients as reported previously. Thus, metformin monotherapy is safe and effective for childhood and adolescent T2DM.

In the future, it may also be possible to use metformin therapy to reduce BMI for preventing T2DM in obese non-diabetic adolescents [12].

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Compliance and ethical standards

Conflicts of interest This clinical trial was funded by Sumitomo Dainippon Pharma Co., Ltd. NM and SA are co-first authors and the chairpersons of the first and second trials, respectively, and contributed to the discussion and wrote the manuscript. SS and SA were members of the coordinating committee for the first trial and SA, SS and TU for the second trial. NM and NK are members of the safety evaluation committee for the second trial. All of these members have received honoraria from Sumitomo Dainippon Pharma. No other potential conflicts of interest relevant to this article were reported. HK and YY are employees of Sumitomo Dainippon Pharma and managed the second trial and carried out statistical analysis, respectively.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or a substitute for it was obtained from all patients included in the study.

Ethical approval This study was approved by the ethics committee of the Sumitomo Dainippon Pharma (approval no. D3004001, approval date: 19 April 2011) and by the ethics committee of Saitama Medical University (approval no. 918, approval date: 24 May 2011).

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