ORIGINAL

Comparison of the efficacy and safety of 10-mg empagliflozin every day versus every other day in Japanese patients with Type 2 Diabetes Mellitus : a pilot trial

Fumiaki Obata[1)2)], Kenji Tani[3)], Harutaka Yamaguchi[3)], Ryo Tabata[2)3)], Hiroyasu Bando[2)], and Issei Imoto[4)]

[1)]*Naka-cho National Health Insurance Kito Clinic, Tokushima, Japan,* [2)]*Department of Internal and General Medicine, Tokushima Prefectural Kaifu Hospital, Tokushima, Japan,* [3)]*Department of General Medicine, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan,* [4)]*Department of Human Genetics, Graduate School of Biomedical Sciences, Tokushima Univrisity, Tokushima, Japan*

Abstract : The terminal elimination half-life (t1/2) of empagliflozin is 13.1 hours. Accordingly, we hypothesized that the administration of empagliflozin every other day might improve glycemic control in patients with type 2 diabetes mellitus, not being inferior to the therapy every day. We investigated the clinical effects and safety of the addition of empagliflozin every day or every other day to type 2 diabetic patients with a poor control in glycemia. Thirteen Japanese patients diagnosed as type 2 diabetes mellitus recruited to this study. Subjects were divided into two groups ; one was treatment with 10 mg of empagliflozin every day (Group A), the other was 10 mg of empagliflozin every other day (Group B). The comparable study of multiple clinical indexes between the 2 groups was made before and 8, 16, and 24 weeks after the treatment. After the treatment for 24 weeks, the HbA1c level was decreased both in group A (from 7.5%±1.1% to 6.5%±0.8%) and in group B (from 7.6%±0.8% to 7.2%±0.5%). This pilot trial suggested the possibility of 10-mg every other day administration with empagliflozin for Japanese patients with type 2 diabetes mellitus. J. Med. Invest. 64 : 50-57, February, 2017

Keywords **:** *sodium-glucose transporter 2 inhibitors, type 2 diabetes mellitus, every other day, empagliflozin, weight reduction*

INTRODUCTION

Sodium-glucose transporter 2 (SGLT2) inhibitors have been recently developed as oral hypoglycemic drugs for type 2 diabetes mellitus that prevent the reabsorption of glucose from primary urine at the proximal renal tubules by targeting SGLT2 (1-3). Therapy with these medicines offers us multiphasic effects attributable to weight loss including improvement of insulin resistance, reduction in blood pressure, dyslipidemia, and nonalcoholic fatty liver disease (4). Their unique extra-pancreatic glucuretic mode of action has encouraged their usage in type 1 diabetes as well (5). The favorable clinical profile of SGLT2 inhibitors has increased an interest in these medicines by health care providers. Especially in Asian patients with glycated haemoglobin (HbA1c) < 8.5%, body mass index (BMI) < 30.0, and ≥ 65 years old, stratified analyses of EMPA-REG OUTCOME study have indicated that SGLT2 inhibitors are more effective than other medicines (6). Six SGLT2 inhibitors (dapagliflozin, tofogliflozin, empagliflozin, ipragliflozin, canagliflozin, and luseogliflozin) are now available in Japan, although the cost of these medicines are relatively high because they were recently developed. Since the medication with these medicines promotes glucosuria, it may cause a greater incidence of urinary tract infections, genital mycotic infections in female patients and sepsis of urinary origin (7, 8). Empagliflozin has the highest selectivity for SGLT2 over SGLT1 (> 2,500-fold) compared with other SGLT2 inhibitors (> 1,875-fold in tofogliflozin, > 1,200-fold in dapagliflozin, > 550-fold in ipragliflozin and > 250-fold in canagliflozin) (9). Since the terminal elimination half-life (t1/2) of empagliflozin up to 13.1 hours (10), it is effective by one administration in a day. These facts give us a hypothesis that the administration of empagliflozin every other day might improve glycemic control in patients with type 2 diabetes mellitus, not being inferior to the therapy every day. Many reports have been published that the use of SGLT2 inhibitors for long time are safe, efficacy and cost-effective as a primary treatment or in combination with conventional therapies (11, 12). However, there were no reports shown whether continuous administration of low-dose empagliflozin offers a sustainable benefit to patients with type 2 diabetes mellitus after discontinuation of the treatment with other medicines or changing the medication interval. Thus, the objective of this pilot study is to investigate the sustainable effectiveness and safety of 10-mg every other day empagliflozin, comparing to results of 10-mg every day empagliflozin for 24 weeks beyond the treatment period.

Received for publication September 16, 2016 ; accepted October 16, 2016.

Address correspondence and reprint requests to Fumiaki Obata, MD, Department of Internal and General Medicine, Tokushima Prefectural Kaifu Hospital, Tokushima, Japan, 75-1, Nakamura, Mugi-cho Kaifu-gun, Tokushima, 775-0006, Japan and Fax : +81-884-72-2383.

MATERIALS AND METHODS

Design Overview

We conducted a prospective, open-label pilot study by the simple alternate randomization under no restrictions at a single clinic and investigated the clinical effects and safety of the addition of empagliflozin every day or every other day to type 2 diabetic patients with a poor control in glycemia. We obtained informed consent from patients for participation in this study, and the study was performed according to the procedure approved by the ethical and research committee of Tokushima Prefectural Kaifu Hospital. Patients were enrolled between February 2015 and January 2016 from Naka-cho National Health Insurance Kito Clinic, Japan.

Setting and Participants

Japanese patients with type 2 diabetes mellitus aged 30-70 years

old, who were in inappropriate control of blood glucose levels (HbA1c≥6.2%) in spite of diet and exercise therapies or with other hypoglycemic agents such as biguanides, sulfonylureas, pioglitazone, α-glucosidase inhibitors, insulin, glucagon-like peptide-1 (GLP-1) agonists, and/or dipeptidyl peptidase 4 (DPP-4) were recruited from our outpatient clinic. Patients kept exercise and diet therapy during the study like before. The prescribed hypoglycemic medicines were not changed during the course of the study. The exclusion criteria for the study entry were as follows : 1) patients with serious infection, pre- or postoperative condition, or severe trauma ; 2) pregnancy, possible pregnancy, or lactating patients ; 3) moderate or severe renal impairments by estimated glomerular filtrating ratio [mL/min/1.73 m^2] < 50 mL/min, serum creatinine level > 1.5 mg/dL in men or > 1.3 mg/dL in women ; 4) alanine aminotransferase and/or aspartate aminotransferase levels 2.5-fold more than the upper limit of normal range ; 5) patients diagnosed as having cancer ; 6) patients medicated with corticosteroids ; 7) having experienced symptoms of hypoglycemia ; 8) in severely poor control or unstable state with ketoacidosis or with an increase in HbA1c > 3% in the 12 weeks before screening ; 9) presence of a severe health problem not suitable for the study ; 10) inability to participate in the study due to psychiatric or psychosocial status as assessed by the investigators.

Assignment and Interventions

Subjects were divided into two groups ; one was treatment with 10 mg of empagliflozin every day (Group A), the other was 10 mg of empagliflozin every other day (Group B).

Measurement of Baseline Characteristics and Clinical Indices

Baseline characteristics data were recorded at the enrollment including : age, gender, past medical history, personal history, family history, body mass index (BMI), disease course, etc. The comparable study of multiple clinical indexes between the 2 groups was made before and 8, 16, and 24 weeks after the treatment, including hematocrit (Ht), systolic and diastolic blood pressures (SBP/DBP), BMI, HbA1c, triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and uric acid (UA). Three to five milliliter of blood samples were collected from the antecubital vein into fluoride tubes containing sodium citrate and ethlene-diamine-tetraacetic and or heparin for the analysis in spite of meal time. Blood pressure was measured by automatic sphygmomanometer at each visit. The measurement of blood pressure was performed in the same way for all patients. The data of HbA1c was expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the following formula : HbA1c (NGSP value) (%) = 1.02×HbA1c (Japan Diabetes Society value) (%) + 0.25 (13). Safety evaluation throughout the study included physical examination, taking medial history and recording of side effects. The relation between the usage of empagliflozin and side effects was investigated. The number of all patients with side effects such as urinary tract infections, genital mycotic infections, tremor, anxiety, nausea, palpitation, hyperhidrosis, hunger and headache, adverse drug reactions and serious side effects, and the incidence rates and number of these events, were recorded.

Statistical Analysis

Data are shown as the mean±standard deviation and categorical variables are expressed as percentages and data were analyzed to identify any differences in HbA1c and other serum indices improvement. The differences in variables between the two different treatment regimens were compared before and after the use of empagliflozin. The data did not follow normal distribution and the data were analyzed by non-parametric statistical methods. Intergroup comparison was determined using the Mann-Whitney test. The intragroup comparison was determined using the Wilcoxon signed rank test. All statistical analyses were performed by StatView version 5.0 (Abacus Concepts, Inc., Berkeley, CA) and P-values < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics of the Research Subjects

Thirteen Japanese patients diagnosed as type 2 diabetes mellitus recruited to this study. Mean age was 52.8±8.4 years old and the percentage of male was 76.9%. The patients were randomly divided into the 2 groups. Twelve patients completed the treatment regimen, but a patient in group B dropped out of the study because of adverse events. Group A consisted of 6 patients treated with 10 mg of empagliflozin every day ; Group B consisted of 6 patients treated with 10 mg of empagliflozin every other day. Table 1 shows the baseline characteristics of patients in group A and Group B. No significant difference was found between two groups in age, height, weight, BMI, SBP, and DBP, and biochemical parameters including Ht, HbA1c, TG, HDL, LDL, and UA, whereas AST and ALT were significantly higher in group A than in group B. Hypoglycemic agents which subjects used during the studied period are shown in Table 2. After the treatment for 24 weeks, the HbA1c level was decreased both in group A (from 7.5%±1.1% to 6.5%±0.8%) and in group B (from 7.6%±0.8% to 7.2%±0.5%) when compared with results at the baseline but there was no significant difference in both groups (Table 1, Fig. 1). Overall results in HbA1c are shown in Fig. 4 in the Supplementary Appendix. A significantly decreased TG was found in group A, but LDL tended to be increased after the 24 weeks treatment in two groups (Table 1, Fig. 2, 3). Increased level of AST and ALT found in patients of Group A at the baseline was decreased to normal range after 24 weeks (Table 1). In Group B, there was no significant difference in TG between baseline and week 24. The levels of HDL, LDL or TG at 24 weeks were not significantly different between the two groups (Fig. 3). Overall results in LDL, HDL and TG are shown in Fig. 6 in the Supplementary Appendix.

SBP and DBP at 24 weeks were low when compared with those at baseline, though there was not significant (Table 1, Fig. 2). There was no significant difference in SBP and DBP at 24 weeks between the two groups. Overall results in SBP and DBP also tended to be decreased in Fig. 5 in the Supplementary Appendix. Body weight and BMI were significantly decreased in 24 weeks in group B though there was no significant difference in group A. There was no significant difference in body weight and BMI at 24 weeks between the two groups (Table 1, Fig. 1).

Adverse Events

Adverse events were monitored throughout the study. Safety and tolerability results are shown as follows : Overall, 4 (30.8%) of the 13 subjects experienced AEs : two patients in group A (constipation, pollakisuria, thirst) and 2 in group B (constipation, insomnia, pollakisuria). A total of 6 AEs were detected in these subjects, 4 of which were mild and improved without treatment before study end. A patient discontinued the treatment due to AEs. Hypoglycemia was not detected in two groups. There were no clinically related changes in laboratory dates, vital signs or ECG recordings.

DISCUSSION

Empagliflozin is available as tablets (10 and 25 mg) and can only be obtained with a prescription. The recommended starting dose

Table 1. Mean±SD of the variables assessed in the examined subjects

	Group A (n=6) (empagliflozin 10 mg every day)		Group B (n=6) (empagliflozin 10 mg every other day)	
	baseline	24 weeks later	baseline	24 weeks later
Age (years)	51.5 ± 10.5	52.0 ± 10.7	53.9 ± 6.7	54.4 ± 6.6
BMI (kg/m^2)	31.1 ± 4.0	29.4 ± 3.9	26.7 ± 4.6	26.3 ± 4.2*
Weight (kg)	81.2 ± 11.2	78.3 ± 11.2	70.4 ± 17.0	70.1 ± 15.8*
SBP (mmHg)	153.3 ± 14.3	136.5 ± 10.6	144.3 ± 20.1	127.0 ± 20.2
DBP (mmHg)	95.5 ± 11.3	83.5 ± 8.8	86.1 ± 15.1	76.0 ± 19.6
AST (IU/L)	53.7 ± 24.5§	43.8 ± 20.4	26.7 ± 6.3	27.7 ± 9.4
ALT (IU/L)	72.3 ± 35.0§	52.0 ± 33.6	26.4 ± 10.3	23.0 ± 9.2
Ht (%)	44.6 ± 1.1	46.6 ± 5.2	42.3 ± 2.8	45.7 ± 0.9
HbA1c (%)	7.5 ± 1.1	6.5 ± 0.8	7.6 ± 0.8	7.2 ± 0.5
TG (mg/dL)	190.8 ± 121.7	99.6 ± 33.7*	145.0 ± 63.4	110.3 ± 37.4
HDL (mg/dL)	44.0 ± 8.3	54.8 ± 17.9	49.9 ± 16.6	50.5 ± 9.9
LDL (mg/dL)	97.5 ± 12.5	128.0 ± 17.5	95.3 ± 25.8	125.8 ± 25.0
UA (mg/dL)	6.0 ± 0.6	4.4 ± 0.7	6.0 ± 1.3	5.1 ± 1.3

BMI, body mass index ; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; Ht, hematocrit ; PG, plasma glucose ; TG, triglyceride ; HDL, high density lipoprotein cholesterol ; LDL, low density lipoprotein cholesterol ; UA, uric acid

*$p < 0.05$ vs. baseline values. None of the intergroup differences reached statistical significance.

§ $p < 0.05$ vs. baseline values between empagliflozin 10 mg every day (Group A) versus every other day group (Group B).

Table 2. Hypoglycemic agents which the subjects had taken before and after the treatment with empagliflozin

Medications	Group A		Group B	
	baseline (n=6)	24 weeks later (n=6)	baseline (n=7)	24 weeks later (n=6)
Biguanides	4	4	5	4
Thiazolidinediones	0	0	0	0
DPP-4 inhibitors	1	1	3	3
Sulfonylurea	0	0	0	0
α-GI	0	0	0	0
Glinides	1	1	4	3
GLP-1 analogues	1	1	0	0
Insulin	0	0	0	0

α-GI, alpha-glucosidase inhibitor ; DPP-4, dipeptidyl peptidase 4 ; GLP-1, glucagon-like peptide-1

is 10 mg once a day. In the present study, we examined that the administration of 10 mg of empagliflozin every other day had the availability and safety when compared with every day administration. Slightly but not significantly improved HbA1c level was seen in the same extent in both groups after the treatment for 24 weeks. No distinct differences in AEs were seen between the two groups during this study.

There have been several previous reports showing that every other day treatment with 20-mg tofogliflozin was used as add-on treatment to patients with type 2 diabetes who were unable to achieve adequate glycemic control. Takegoshi *et al.* reported that the add-on treatment for 24 weeks decreased the level of HbA1c to some extent (14, 15). These findings are compatible with results in this study, indicating that 10-mg every other day empagliflozin is potentially useful in improving glycemic control.

It has been showed that SGLT2 inhibitors including empagliflozin may improve other metabolic abnormalities, such as dyslipidemia, hyperuricemia and arterial hypertension (16-20). Our pilot study had that a statistically significant decrease of TG from the baseline was found with 10 mg of empagliflozin every day. These lowering effect of SGLT2 inhibitors may be related to several mechanisms, including improved glycemic control, decreases in body weight, or other causes. In a few studies about the efficacy of SGLT2 inhibitors on serum lipid profile, Matthaei *et al.* reported that 52-week treatment of dapagliflozin significantly increased serum HDL-C levels with no significant change of serum LDL-C and TG levels (21). Monami *et al.* also showed that SGLT-2 inhibitors significantly increased HDL-C levels with no change of TG and LDL-C levels (22). In our pilot study, a tendency toward a decrease in serum AST and ALT levels was observed at week 24 from baseline in group A. Further studies will be needed to elucidate the effects of SGLT2 inhibitors on improvement of hepatic steatosis and liver function.

Systolic blood pressure also tended to be decreased after the treatment in two groups. The mean changes in systolic blood pressure were -16.8 mmHg in group A, and the other group was -17.3 mmHg.

Medication compliance and adherence is the essential relation between prescribing a medication and treatment success and is important in achieving maximum effectiveness for favorable outcomes of prescribed regimens (23-25), but increasing the frequency of medication and treatment cost could be barrier particularly in

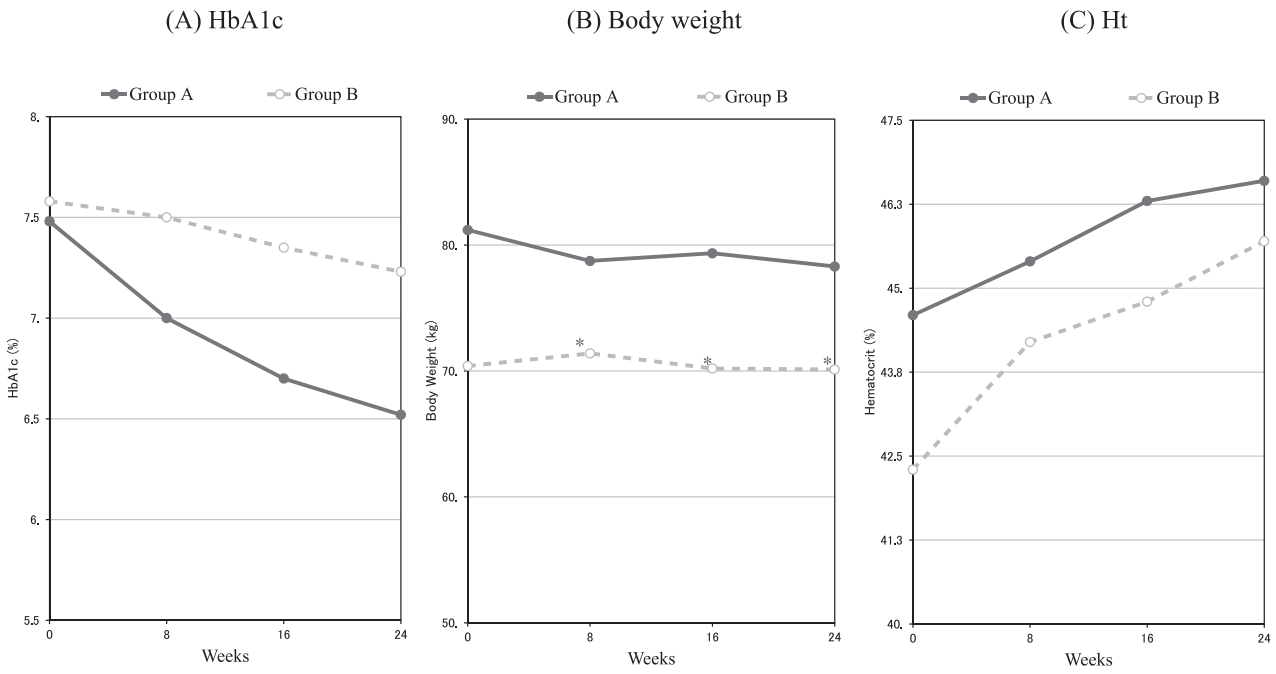

Fig. 1
Change in HbA1c (A), Body weight (B) and Ht (C) from baseline to 24 weeks. The data are presented as the mean values. The patients number is 6 in group A (black circles) and 6 in group B (white circles).
*p< 0.05 vs. baseline values in each group. Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

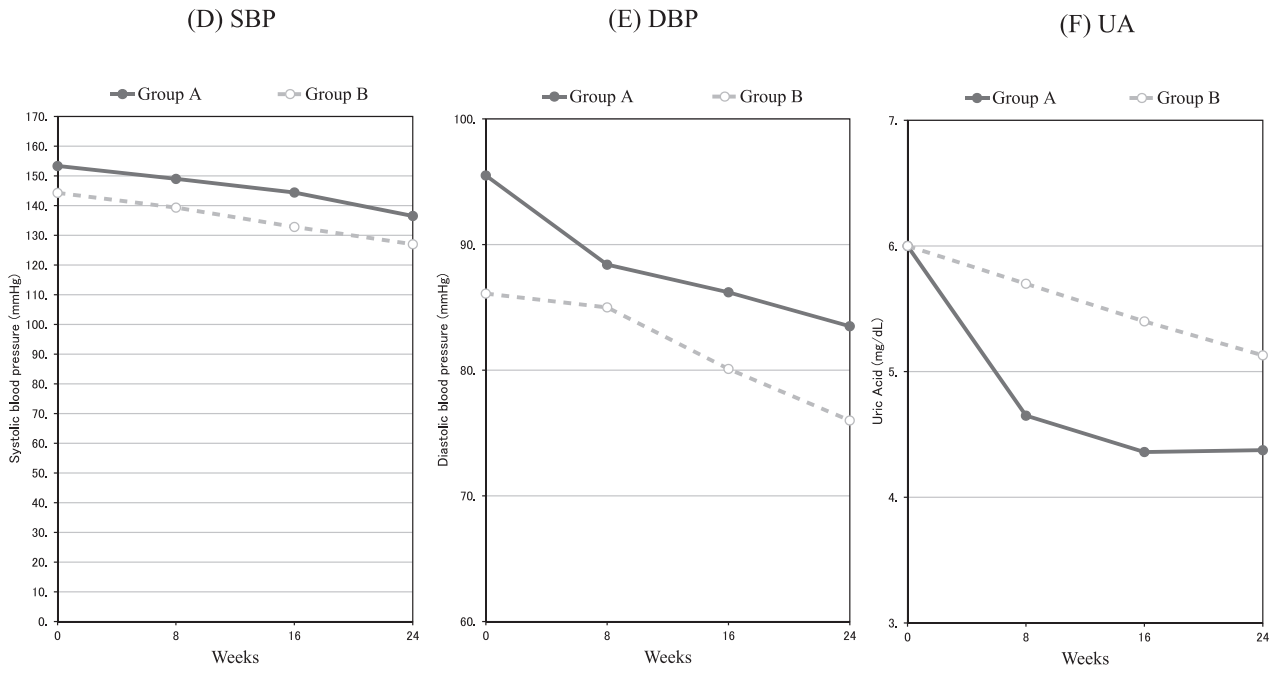

Fig. 2
Change in SBP (D), DBP (E) and UA (F) from baseline to 24 weeks. The data are presented as the mean values.
The patients number is 6 in group A (black circles) and 6 in group B (white circles).
*p< 0.05 vs. baseline values in each group. Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

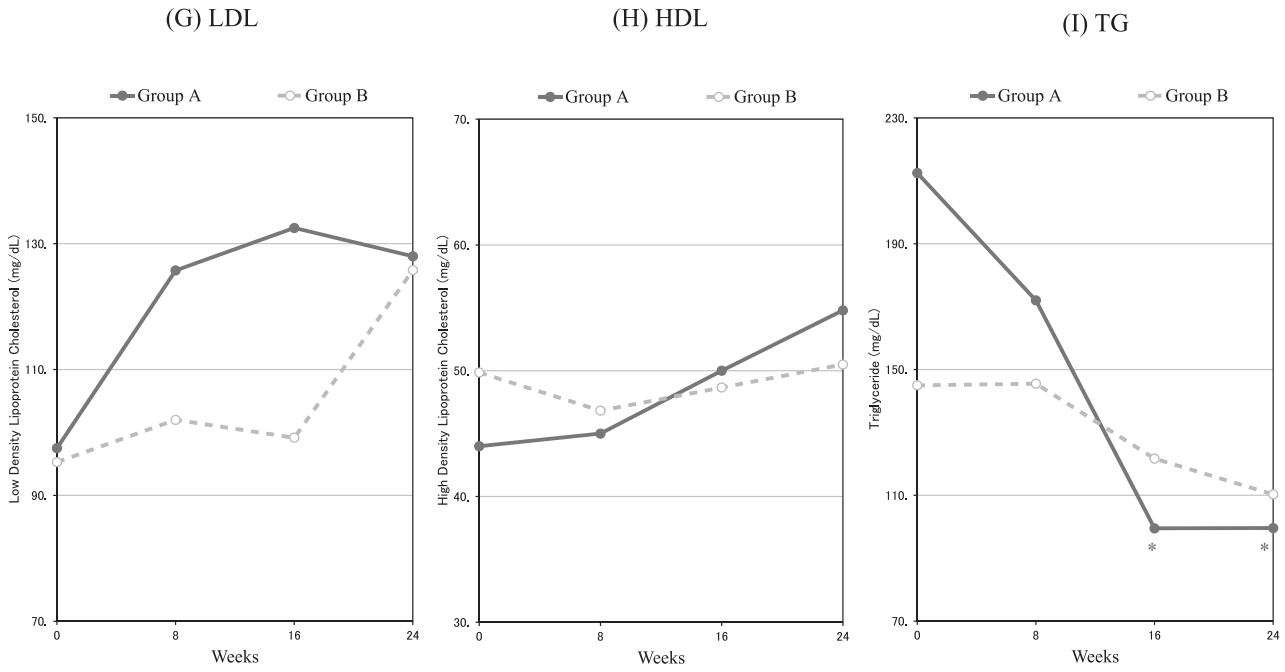

Fig. 3
Change in LDL (G), HDL (H) and TG (I) from baseline to 24 weeks. The data are presented as the mean values.
The patients number is 6 in group A (black circles) and 6 in group B (white circles).
*$p < 0.05$ vs. baseline values in each group. Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

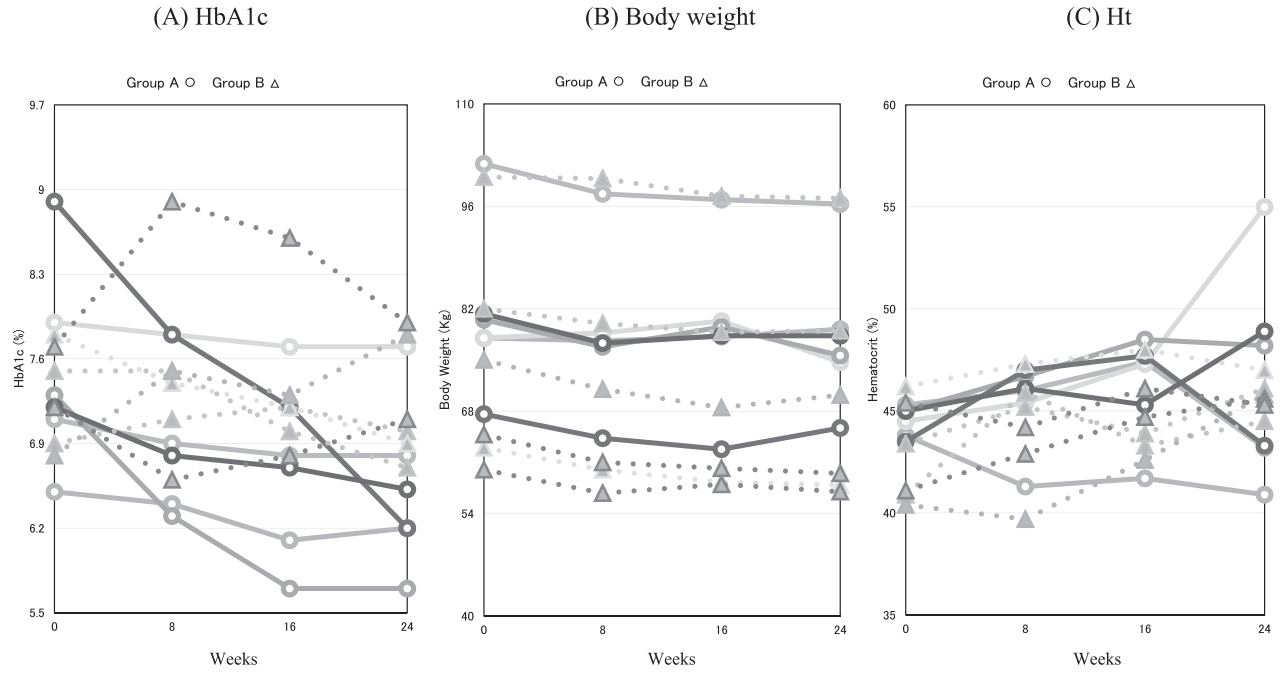

Fig. 4
Overall results in HbA1c (A), Body weight (B) and Ht (C) from baseline to 24 weeks. The patients number is 6 in group A (circles) and 6 in group B (triangles).
Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

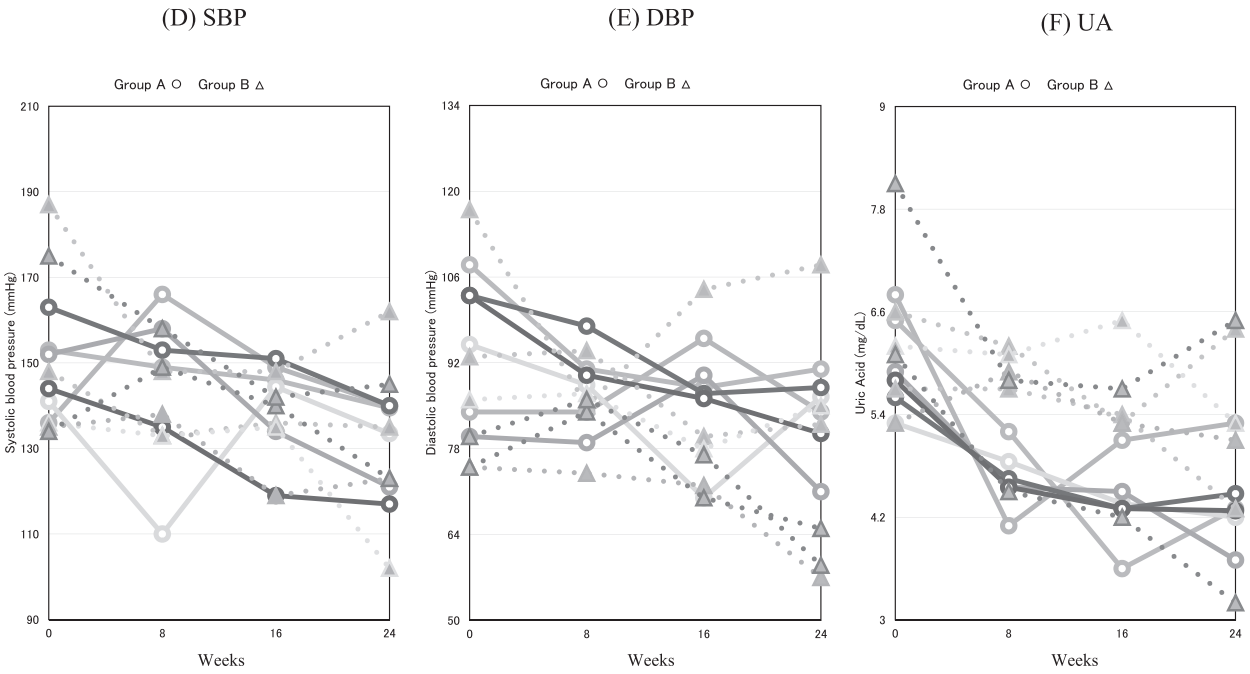

Fig. 5
Overall results in SBP (D), DBP (E) and UA (F) from baseline to 24 weeks. The patients number is 6 in group A (circles) and 6 in group B (triangles). Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

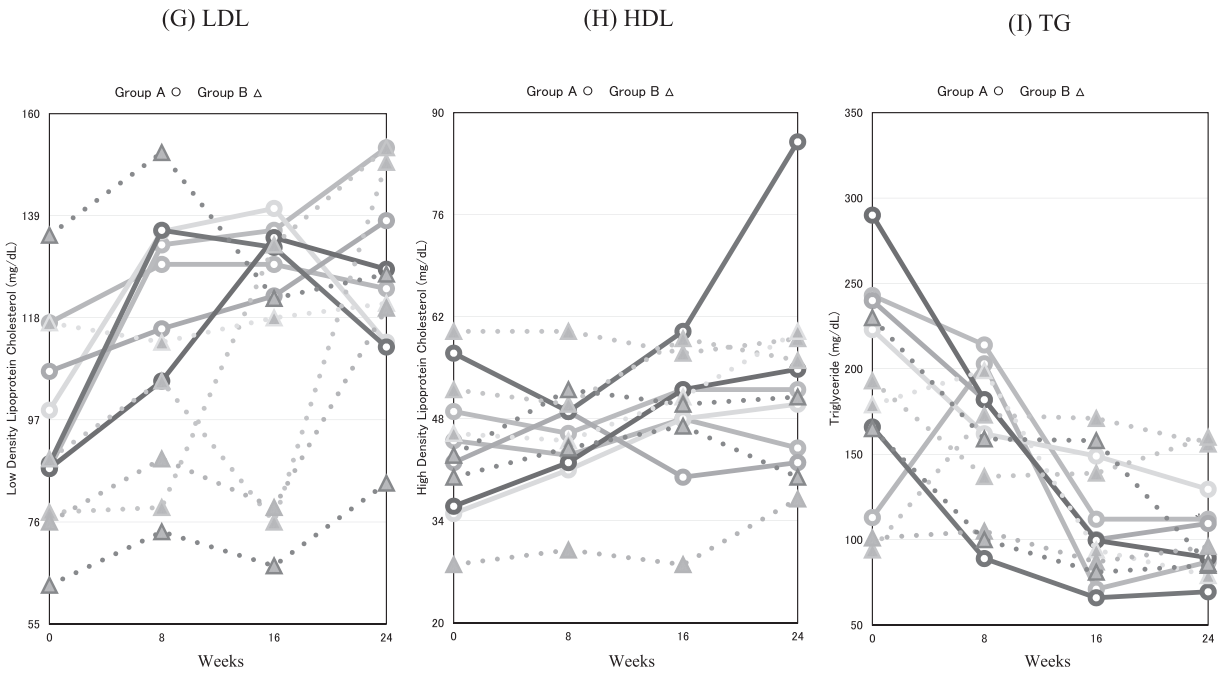

Fig.6
Overall results in LDL (G), HDL (H) and TG (I) from baseline to 24 weeks. The patients number is 6 in group A (circles) and 6 in group B (triangles). Group A consists of patients who received 10 mg of empagliflozin every day, and Group B consists of patients who received 10 mg of empagliflozin every other day.

low-income patients and may decrease patient compliance and adherence (26). Regimen of long-term recommended treatment among patients with a chronic disease has been showed that medication compliance may be as low as 50% (27) and in literature reports, 20% to 50% of patients do not adhere to their prescribed regimens, and the problem is more prominent in older adults, with 40% to 86% of elderly patients reported to be non-adherent (23, 25, 28), as they often use more medications, suffer a more number of illnesses, and are at risk of age-related cognitive decline (24, 29). In light of this, decreasing medication frequency may improve patient compliance and adherence. Taken together, the every other day administration of empagliflozin may be a practical solution for those patients with limited financial resources without compromising the clinical benefits of HbA1c lowering and among patients with previous empagliflozin intolerance.

The present study had several limitations. There was no placebo or control group to compare with two groups that received treatment. In addition, the duration of treatment was relatively short, and the number of subjects was relatively small and insufficient. Therefore, large-scale studies in which SGLT2 inhibitors are performed to patients with type 2 diabetes mellitus for longer terms should be need in the future.

CONCLUSIONS

In this small prospective, open-label pilot trial of empagliflozin as a treatment in type 2 diabetes mellitus, every other day administration with 10 mg of empagliflozin was sufficiently effective in the improvement of HbA1c and TG when compared with data of the every day administration. This pilot trial suggested the possibility of 10-mg every other day administration with empagliflozin for Japanese patients with type 2 diabetes mellitus.

A STATEMENT OF ALL FUNDING SOURCES

none

ETHICAL APPROVAL

The study was approved by the hospital ethical review committee and written informed consent was obtained before a respondent completed the questionnaire.

CONFLICTS OF INTEREST DISCLOSURES

The authors declare that there is no conflict of interest.

CONTRIBUTORS

Fumiaki O wrote the paper. All authors read, edited and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We are grateful to Professor Kenji Tani for his contribution to part of the study and to Professor Issei Imoto for his administrative support.

REFERENCE

1. Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, Millington D, Vercruysse F, Canovatchel W, Meininger G : Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin : a randomized, double-blind, phase 3 study. Diabetes Care 38 : 355-364, 2015
2. Ghosh RK, Ghosh SM, Chawla S, Jasdanwala SA : SGLT2 inhibitors : a new emerging therapeutic class in the treatment of Type 2 diabetes mellitus. J Clin Pharmacol 52 : 457-463, 2012
3. Bailey CJ : Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci 32 : 63-71, 2011
4. Virginia V : The Role of the Kidney and Sodium-Glucose Cotransporter-2 Inhibition in Diabetes Management. Clinical Diabetes 30 : 151-155, 2012
5. Henry RR, Rosenstock J, Edelman S, Mudaliar S, Chalamandaris AG, Kasichayanula S, Bogle A, Iqbal N, List J, Griffen SC : Exploring the Potential of the SGLT2 Inhibitor Dapagliflozin in Type 1 Diabetes : A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Diabetes Care 38 : 412-419, 2015
6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE : EMPA-REG OUTCOME Investigators : Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373 : 2117-2128, 2015
7. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR : Management of hyperglycemia in Type 2 diabetes, 2015 : a patient-centered approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 38 : 140-149, 2015
8. Nauck MA : Update on developments with SGLT2 inhibitors in the management of Type 2 diabetes. Drug Des Devel Ther 8 : 1335-1380, 2014
9. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, Bakker RA, Mark M, Klein T, Eickelmann P : Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor : characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 14 : 83-90, 2012
10. Seman L, Macha S, Nehmiz G, Simons G, Ren B, Pinnetti S, Woerle HJ, Dugi K : Empagliflozin (BI 10773), a potent and selective SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Drug Dev 2 : 152-161, 2013
11. Musso G, Gambino R, Cassader M, Pagano G : A novel approach to control hyperglycemia in type 2 diabetes : sodium glucose co-transport (SGLT) inhibitors : systematic review and meta-analysis of randomized trials. Ann Med 44 : 375-393, 2012
12. Clar C, Gill JA, Court R, Waugh N : Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2 : e001007, 2012
13. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H : International clinical harmonization of glycated hemoglobin in Japan : from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Investig 3 : 39-40, 2012
14. Takegoshi S, Miyata Y, Ogata N, Saito T : Availability and efficacy of 20-mg tofogliflozin administered every other day to

195 type 2 diabetic patients. Prog Med 35 : 1077-1088, 2015 (Abstract in Japanese)
15. Takegoshi S, Miyata Y, Ogata N, Saito T : Availability and efficacy of 20-mg tofogliflozin administered every other day to type 2 diabetic patients. Prog Med 35 : 141-148, 2015 (Abstract in Japanese)
16. Kaku K, Maegawa H, Tanizawa Y, Kiyosue A, Ide Y, Tokudome T, Hoshino Y, Yang J, Langkilde AM : Dapagliflozin as monotherapy or combination therapy in Japanese patients with type 2 diabetes : an open-label study. Diabetes Ther 5 : 415-433, 2014
17. Oliva RV, Bakris GL : Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens 8 : 330-339, 2014
18. List JF, Whaley JM : Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int 120 : S20-S27, 2011
19. List JF, Woo V, Morales E, Tang W, Fiedorek FT : Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 32 : 650-657, 2009
20. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G : Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. Diabetes Obes Metab 17 : 426-429, 2015
21. Matthaei S, Bowering K, Rohwedder K, Sugg J, Parikh S, Johnsson E : Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes. Diabetes Obes Metab 17 : 1075-1084, 2015
22. Monami M, Nardini C, Mannucci E : Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes : a meta-analysis of randomized clinical trials. Diabetes Obes Metab 16 : 457-466, 2014
23. Butler RJ, Davis TK, Johnson WG, Gardner HH : Effects of nonadherence with prescription drugs among older adults. Am J Manag Care 17 : 153-160, 2011
24. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA : Assessing medication adherence in the elderly : which tools to use in clinical practice?. Drugs Aging 22 : 231-255, 2005
25. Foreman KF, Stockl KM, Le LB, Fisk E, Shah SM, Lew HC, Solow BK, Curtis BS : Impact of a text messaging pilot program on patient medication adherence. Clin Ther 34 : 1084-1091, 2012
26. Reginster JY, Rabenda V, Neuprez A : Adherence, patient preference and dosing frequency : understanding the relationship. Bone 38 : S2-6, 2006
27. Chung JH, Kang DH, Oh CY, Chung JM, Lee KS, Kim TH, Moon KH, Lee W, Cho JM, Lee SW : Safety and efficacy of once daily administration of 50 mg mirodenafil in patients with erectile dysfunction : a multicenter, double-blind, placebo controlled trial. J Urol 189 : 1006-1013, 2013
28. Kripalani S, Yao X, Haynes RB : Interventions to enhance medication adherence in chronic medical conditions : a systematic review. Arch Intern Med 167 : 540-550, 2007
29. Murray MD, Morrow DG, Weiner M, Clark DO, Tu W, Deer MM, Brater DC, Weinberger M : A conceptual framework to study medication adherence in older adults. Am J Geriatr Pharmacother 2 : 36-43, 2004