DIABETES RESEARCH AND CLINICAL PRACTICE 116 (2016) 244–252

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Efficacy and safety of saxagliptin, a dipeptidyl peptidase-4 inhibitor, in hemodialysis patients with diabetic nephropathy: A randomized open-label prospective trial ☆

Masanori Abe [a,*], *Terumi Higuchi* [b], *Masari Moriuchi* [a], *Masahiro Okamura* [a], *Ritsukou Tei* [a], *Chinami Nagura* [a], *Hiroyuki Takashima* [a], *Fumito Kikuchi* [c], *Hyoe Tomita* [d], *Kazuyoshi Okada* [a]

[a] *Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan*

[b] *Department of Nephrology, Keiai Hospital, Tokyo, Japan*

[c] *Department of Nephrology, Meirikai Chuo General Hospital, Tokyo, Japan*

[d] *Department of Nephrology, Yujin Clinic, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form
4 April 2016
Accepted 18 April 2016
Available online 26 April 2016

Keywords:
Saxagliptin
Hemodialysis
Type 2 diabetes
Glycated albumin

ABSTRACT

Aims: Saxagliptin is a dipeptidyl peptidase-4 inhibitor that was approved in Japan for the treatment of type 2 diabetes in 2013. We examined its efficacy and safety in Japanese hemodialysis patients with diabetic nephropathy.

Methods: In this prospective, open-label, parallel-group study, Japanese hemodialysis patients were randomized to receive either oral saxagliptin (2.5 mg/day) or usual care (control group) for 24 weeks. Before randomization, patients received fixed doses of conventional antidiabetic drugs (oral drugs and/or insulin) for 8 weeks; these drugs were continued during the study. Endpoints included changes in glycated albumin (GA), hemoglobin A1c (HbA1c), postprandial plasma glucose (PPG), and adverse events.

Results: Both groups included 41 patients. Mean GA, HbA1c, and PPG decreased significantly in the saxagliptin group (−3.4%, −0.6% [−7 mmol/mol], and −38.3 mg/dL, respectively; all $P < 0.0001$) but not in the control group (0%, −0.1% [−1 mmol/mol], and −3.7 mg/dL, respectively) ($P < 0.0001$, $P < 0.001$, and $P < 0.0001$, respectively). In saxagliptin-treated patients, the reduction in GA was significantly greater when saxagliptin was administered as monotherapy than in combination therapy (−4.2% vs. −3.0%, $P = 0.012$) despite similar baseline values (24.5% vs. 23.3%). Reductions in GA, HbA1c, and PPG were greater in patients whose baseline values exceeded the median (23.8% for GA,

☆ Previously presented at: 60th Annual Meeting of the Japanese Society for Dialysis Therapy (Yokohama, Japan, June 26–28, 2015).

* *Corresponding author at:* Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, 30-1 Oyaguchi Kami-chou, Itabashi-ku, Tokyo 173-8610, Japan. Tel.: +81 3 3972 8111; fax: +81 3 3972 8311.

E-mail addresses: abe.masanori@nihon-u.ac.jp (M. Abe), thiguchi@keiai-hospital.jp (T. Higuchi), mi.piace.hayden.v@gmail.com (M. Moriuchi), patrickemboma@yahoo.co.jp (M. Okamura), haru_li_huang@yahoo.co.jp (R. Tei), nagura.chinami@nihon-u.ac.jp (C. Nagura), craftsmanship.t.h@gmail.com (H. Takashima), kikuchi5308@air.ocn.ne.jp (F. Kikuchi), yjntomita@gmail.com (H. Tomita), okada.kazuyoshi@nihon-u.ac.jp (K. Okada).

http://dx.doi.org/10.1016/j.diabres.2016.04.034

6.6% for HbA1c, and 180 mg/dL for PPG). There were no adverse events associated with saxagliptin.

Conclusions: Saxagliptin (2.5 mg/day) was effective and well tolerated when used as monotherapy or combined with other antidiabetic drugs in Japanese hemodialysis patients with type 2 diabetes.

Clinical Trial Registration number: UMIN000018445.

1. Introduction

In patients with type 2 diabetes on hemodialysis, the accumulation of antidiabetic drugs or their metabolites between hemodialysis sessions and their rapid clearance during hemodialysis make it difficult to predict the pharmacological effects of these drugs, hampering efforts to achieve and maintain glycemic control. For these reasons, sulfonylureas are unsuitable owing to the risk of prolonged hypoglycemia, while metformin is contraindicated in patients with moderate to advanced chronic kidney disease, including hemodialysis [1]. Patients on hemodialysis are also at high risk of hemodialysis-induced hypoglycemia, and low and high glucose levels are associated with poor outcomes, including a high risk of death [2].

Insulin is considered to be the most effective treatment for type 2 diabetes in hemodialysis patients, but the risk of hypoglycemia remains a significant concern necessitating careful dosing and monitoring of blood glucose concentrations [1]. α-Glucosidase inhibitors and glinides were reportedly effective in improving glycemic control and had low risks of hypoglycemia in hemodialysis patients [3,4]. However, these drugs are not available in all countries, and the original National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended that α-glucosidase inhibitors should be avoided in patients with advanced stage chronic kidney disease (CKD) and on dialysis [5]. Several novel classes of antidiabetic drugs have been introduced since the original KDOQI guidelines, including dipeptidyl peptidase-4 (DPP-4) inhibitors, and these classes of drugs have been incorporated into the updated guidelines [6].

In Japanese hemodialysis patients, prior studies have shown favorable efficacy and safety profiles of the DPP-4 inhibitors alogliptin, teneligliptin, and vildagliptin [7–9]. Saxagliptin is a newer member of the DPP-4 class that was approved in Japan for the treatment of type 2 diabetes in 2013. Accordingly, studies are needed to verify the efficacy and safety of saxagliptin in Japanese hemodialysis patients with type 2 diabetes. Therefore, we performed a randomized controlled study to verify the efficacy and safety of saxagliptin in these patients.

For the purpose of this study, the major glycemic endpoint was the change in glycated albumin (GA), rather than the change in hemoglobin A1c (HbA1c), because the former is a better marker for glycemic variability in hemodialysis patients and is less likely to be affected by factors such as erythropoiesis stimulating agent (ESA) dose, anemia, and iron administration [10–12].

2. Materials and methods

2.1. Ethics

The study protocol was approved by the Ethics Committee of Keiai Hospital, and all patients provided written informed consent (Clinical Trial Registration number: UMIN000018445; ethics board approval number: RK-20140701-02). The study protocol was designed in accordance with the Declaration of Helsinki.

2.2. Subjects

Enrollment criteria for the study were as follows: (1) age ⩾ 20 years and ⩽80 years, (2) hemodialysis duration >6 months at enrollment, (3) type 2 diabetes mellitus, and (4) poor glycemic control which was defined as a glycated albumin (GA) level exceeding 20.0% after 8 consecutive weeks of daily administration of conventional therapy (dietary therapy alone, oral antidiabetic agents and/or insulin). Exclusion criteria were as follows: (1) age < 20 years or >80 years; (2) a history of severe heart failure, angina, myocardial infarction, or stroke within the past 6 months; (3) the presence of infectious disease, liver dysfunction, thyroid disease, malignant tumors, or treatment with steroids or immunosuppressants; (4) current hospitalization; and (5) treatment with any DPP-4 inhibitor within the past 6 months.

2.3. Study design and treatments

This study was designed similarly to our prior studies of alogliptin and vildagliptin [7,8]. This prospective, open-label, parallel-group, multi-center study was conducted between June 2014 and October 2015, and eligible patients were randomized to receive oral saxagliptin (2.5 mg/day) or usual care for 24 weeks. Before randomization, patients received fixed doses of conventional antidiabetic drugs (oral hypoglycemic agents and/or insulin) for 8 weeks, and these drugs were continued during the 24-week treatment period. If the GA value remained ⩾20.0% after 12 weeks of treatment in either group, the dose(s) of other antidiabetic drugs could be increased. If the investigator believed that saxagliptin presented a safety problem, its administration was to be interrupted. Patients continued their regular medications, such as antihypertensive drugs, ESAs, phosphate binders and lipid-lowering agents, during the study period.

The randomization of subjects was monitored by an independent investigator with no previous knowledge of the subjects. Dynamic balancing randomization was applied, taking into account age, sex, hemodialysis duration, and hemoglobin concentration to minimize potential differences in baseline characteristics between the groups. The details of the assignment were then given to seven independent investigators, who provided patient care at the four hemodialysis centers involved in this study.

2.4. Hemodialysis

In all patients, hemodialysis was performed for 4 h at a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min. Hemodialysis was performed using dialyzers containing high-flux membranes. The surface area of the dialyzer membrane was selected according to the patient's body weight. The glucose concentration of the dialysate was 100 mg/dL. Heparin was administered at a dose of 2600–5000 units per 4-h hemodialysis session for anticoagulation. The volume of ultrafiltration was maintained on the basis of clinical dry weight during each session.

Blood samples were obtained before the start of each hemodialysis session. All patients received recombinant human erythropoietin (epoetin alpha). The erythropoietin responsiveness index (ERI) was defined as the mean weekly ESA dose divided by the clinical dry weight and mean blood hemoglobin [i.e., ERI = weekly ESA dose (units)/dry weight (kg)/hemoglobin (g/dL)] to normalize the ESA dose according to the severity of anemia [13].

2.5. Study evaluations and endpoints

The primary efficacy endpoint was the change in GA. Secondary endpoints included changes in vital signs and laboratory/biochemical tests during the study, and safety. GA and HbA1c levels were measured every month as indices of glycemic control. Postprandial plasma glucose (PPG) levels were measured three times per week before each hemodialysis session, and results are expressed as the mean PPG values of 12 measurements per month. Vital signs, including body weight, interdialytic weight gain, body mass index (BMI), cardiothoracic ratio on chest X-ray, and predialysis systolic and diastolic blood pressures were recorded every month. Hemoglobin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase, total cholesterol, high-density lipoprotein, triglyceride, total protein, and albumin concentrations were measured by routine clinical chemistry procedures using commercially available assay kits. PPG, HbA1c, and GA were measured using the same assay kits in all four centers. GA was measured by an enzymatic method using the Lucica GA-L® Kit (Asahi Kasei Pharma Co., Tokyo, Japan).

All variables were assessed every month during the 8-week pre-treatment observation period and the 24-week treatment period. Efficacy variables were analyzed in all subjects, and in patients divided into several subgroups by age, BMI, and treatment regimen (monotherapy vs. combination with oral antidiabetic drugs and/or insulin).

Subjects could be withdrawn in the event of allergy/intolerance to the drug, if either the serum transaminase concentration or creatine kinase concentration increased to more than 2× the upper limit of normal, or following an event that, in the investigator's opinion, might have posed a risk to the patient or confounded the results of the study.

At each visit, subjects were questioned with regard to study compliance (diet and medications), concomitant medications, and adverse events (AEs). Safety assessments were performed throughout the study. AEs were graded by intensity: mild, moderate, or severe. Serious adverse events were defined as medical events that resulted in death, hospitalization, or significant disability or incapacity.

2.6. Statistical analyses

Data are expressed as the mean ± standard deviation or median (interquartile range) as appropriate. Continuous variables were compared using the Student's *t*-test or the Mann–Whitney *U* test, and categorical variables were compared using the χ^2 test or Fisher's exact test. Statistical significance was set at $P < 0.05$. All analyses were performed using JMP software version 12 (SAS Institute Ltd., Cary, NC, USA).

The sample size was determined based on 80% power, assuming an effect size of a 4% difference in the change in GA from baseline between the two groups and a standard deviation of 3.0%, based on the results of a previous trial [8]. This yielded a two-sided significance level of 0.05, and an estimated number of evaluable patients of 26 (13 per group). Allowing for a dropout rate of 10% after randomization, a sample size of 30 randomized subjects (15 per group) was necessary for this study. To collect additional data on the efficacy and safety of saxagliptin, we chose to enroll approximately 40 patients per group.

3. Results

3.1. Subjects

A total of 534 patients were initially screened and 84 patients were randomly assigned to the saxagliptin group ($n = 42$) or the control group ($n = 42$). Details of patient disposition are shown in Supplementary Fig. 1. All of the patients had anuria and all had poor glycemic control. The primary renal diagnosis was diabetic nephropathy caused by type 2 diabetes mellitus. One patient in the saxagliptin group was admitted to hospital owing to pneumonia, and one patient in the control group was prescribed a DPP-4 inhibitor owing to severe hyperglycemia. Both of these patients were excluded from the final analysis, so 41 patients were analyzed in each group. Data were available for all 82 patients at all time-points. As shown in Table 1, there were no significant differences in the baseline demographic, hemodynamic, or anthropometric variables; dialysis mode; type of vascular access; cardiovascular comorbidities; or medications between the two groups. The saxagliptin dose was not changed in any patient and none

Table 1 – Patient characteristics at baseline.

Variable	Saxagliptin group	Control group	P value
N	41	41	
Males	27 (65.9)	28 (68.3)	0.816
Age (years)	66.9 ± 9.4	66.3 ± 9.4	0.282
Hemodialysis duration (m)	50.9 ± 33.7	50.2 ± 33.0	0.929
Body mass index (kg/m^2)	22.8 ± 3.7	22.9 ± 3.7	0.837
Postprandial plasma glucose (mg/dL)	186 ± 35	185 ± 47	0.832
Glycated albumin (%)	23.7 ± 2.9	23.6 ± 2.7	0.597
Hemoglobin A1c (% [mmol/mol])	6.5 ± 0.8 (48 ± 8.8)	6.5 ± 0.7 (48 ± 7.7)	0.929
Cardiovascular comorbidities			
Ischemic heart disease	7 (17.1)	6 (14.6)	0.765
Cerebral vascular events	2 (4.9)	1 (2.4)	0.562
Peripheral artery disease	3 (7.3)	2 (4.9)	0.649
Dialysis mode			0.697
Hemodialysis	38 (92.7)	37 (90.2)	
Hemodiafiltration	3 (7.3)	4 (9.8)	
Type of vascular access			0.727
Arteriovenous fistula	36 (87.8)	35 (85.4)	
Arteriovenous graft	5 (12.2)	6 (14.6)	
Catheter	0	0	
Antidiabetic therapy			
Oral antidiabetic agents	20 (48.8)	21 (51.2)	0.827
Insulin therapy	5 (12.2)	6 (14.6)	0.749
Oral antidiabetic agents + insulin	4 (9.7)	3 (7.4)	0.697
Diet alone	12 (29.3)	11 (26.8)	0.808
Use of renin-angiotensin system inhibitors	34 (82.9)	33 (80.5)	0.778
Use of statins	18 (43.9)	19 (46.3)	0.827

Values are shown as the *n* (%) or mean ± standard deviation.

of the patients in the saxagliptin group started another antidiabetic drug. One patient in the control group was prescribed a DPP-4 inhibitor during the study and was withdrawn from the study. The dose of repaglinide was increased in three patients in the control group because of poor glycemic control. Duration of diabetes was also significantly associated with hemodialysis duration (Supplementary Table 1).

3.2. *Glycemic control*

Fig. 1 shows the changes in glycemic variables during the 24-week treatment period. GA (%) decreased significantly from 23.7 ± 2.9 at baseline to 20.3 ± 2.0 at week 24 in the saxagliptin group ($P < 0.0001$) but remained unchanged in the control group, with values of 23.6 ± 2.7 and 23.6 ± 3.1 at baseline and week 24, respectively. The GA level decreased significantly at each visit in the saxagliptin group compared with baseline and the control group. Twenty-two patients in the saxagliptin group had a GA level <20% at the end of treatment. HbA1c and PPG also decreased significantly in the saxagliptin group compared with baseline levels and compared with corresponding levels in the control group. Mean GA, HbA1c, and PPG all decreased significantly in the saxagliptin group (−3.4%, −0.6% [−7 mmol/mol], and −38.3 mg/dL, respectively; all $P < 0.0001$), but not in the control group (0%, −0.1% [−1 mmol/mol], and −3.7 mg/dL, respectively) ($P < 0.0001$, $P < 0.001$, and $P < 0.0001$, respectively).

3.3. *Efficacy in subgroups of patients*

The efficacy of saxagliptin was also examined in subgroups of patients divided by the baseline variables age, BMI, and treatment regimen. As shown in Table 2, the improvements in GA, HbA1c, and PPG were comparable between subgroups of patients divided by age (<70 vs. ⩾70 years) and BMI (<23 vs. ⩾23 kg/m^2).

When patients were divided into saxagliptin monotherapy ($n = 13$) and combination therapy subgroups (saxagliptin plus oral antidiabetic agents and/or insulin) ($n = 28$), we found no significant differences in sex distribution, age, or BMI between these subgroups. Notably, the reduction in GA was significantly greater in the monotherapy subgroup than in the combination therapy subgroup (−4.2% vs. −3.0%, $P = 0.012$) despite similar baseline values (24.5% vs. 23.3%). The reduction in HbA1c was numerically greater in the monotherapy subgroup (−0.8% vs. −0.55%), albeit not significantly ($P = 0.053$). By contrast, the reduction in PPG was comparable in both subgroups (−41 vs. −37 mg/dL, $P = 0.539$).

We also calculated the reductions in GA, HbA1c, and PPG in subgroups of saxagliptin-treated patients divided by the median values of each variable at baseline (23.8% for GA, 6.6% for HbA1c, and 180 mg/dL for PPG) (Fig. 2). As shown in this figure, the reductions in each variable from baseline to week 24 were significantly greater in patients with values exceeding the median at baseline.

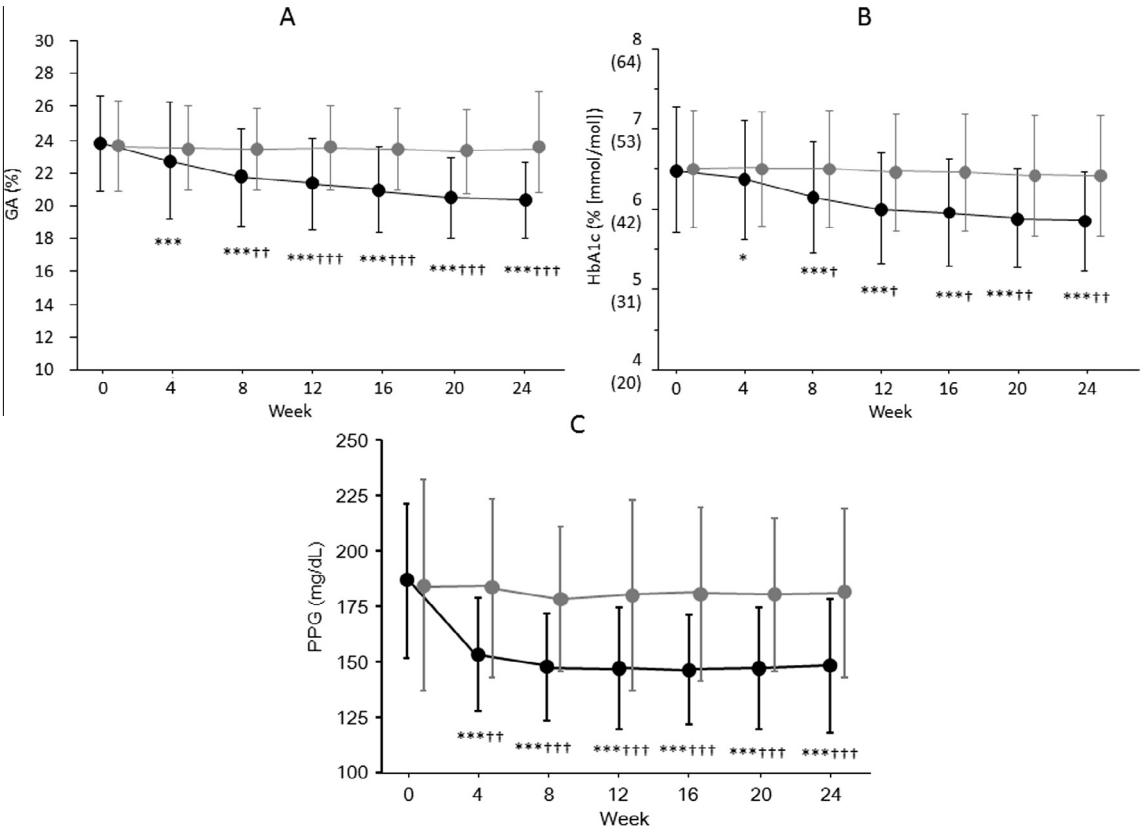

Fig. 1 – GA (A), HbA1c (B), and PPG (C) at each visit. Results are presented as the mean ±SD. Black circles, saxagliptin group; gray circles, control group. $^{*}P < 0.01$ and $^{***}P < 0.0001$ vs. Week 0. $^{\dagger}P < 0.01$, $^{\dagger\dagger}P < 0.001$, and $^{\dagger\dagger\dagger}P < 0.0001$ vs. the control group. GA, glycated albumin; HbA1c, hemoglobin A1c; PPG, postprandial plasma glucose.

3.4. *Vital signs and laboratory variables*

Table 3 shows the vital signs and laboratory variables at baseline and at the end of the study in both groups. Of note, a significant decrease in ERI was observed in the saxagliptin group. In addition, saxagliptin was associated with a significant decrease in triglyceride concentrations, which was probably secondary to its glucose-lowering effects.

3.5. *Safety*

None of the patients exhibited significant AEs such as symptomatic hypoglycemia or liver dysfunction. Saxagliptin was well tolerated, and it was not interrupted in any of the patients. Although one patient in the saxagliptin group was admitted to hospital because of pneumonia, this was not related to saxagliptin treatment.

4. Discussion

Key findings of this study are that saxagliptin significantly improved glycemic control in terms of GA, HbA1c, and PPG when added to prior therapy compared with continuing prior therapy in Japanese patients with type 2 diabetes on hemodialysis. Furthermore, saxagliptin was well tolerated and did not cause marked changes in vital signs or laboratory variables.

Earlier Japanese studies showed that other classes of drugs, including α-glucosidase inhibitors (e.g., voglibose) and glinides (e.g., mitiglinide), improved glycemic control and were associated with low risks of hypoglycemia in hemodialysis patients [3,4]. However, the current KDOQI recommendations suggest that the α-glucosidase inhibitors acarbose and miglitol should be avoided in patients with glomerular filtration rates (GFR) <30 and <25 mL/min/1.73 m^2, respectively, and that the glinides repaglinide and nateglinide should be used conservatively in patients with a GFR of <30 mL/min/1.73 m^2 [6]. Current KDOQI guidelines also mention the need to avoid metformin and some sulfonylureas, and state that the doses of DPP-4 inhibitors may need to be reduced. In addition, the guidelines highlight the need to administer saxagliptin at a lower dose (2.5 mg/day) in patients with a GFR of ⩽50 mL/min/1.73 m^2 [6]. However, these recommendations were essentially based on Western studies and for patients with stages 3–5 CKD, not necessarily those with end-stage kidney disease or on dialysis. In addition, further evidence of the efficacy of these drugs in Japanese patients was needed.

Several DPP-4 inhibitors have been approved in Japan, and prior studies have examined the efficacy and safety of alogliptin, teneligliptin, and vildagliptin in Japanese hemodialysis patients [7–9]. These studies showed significant improvements in glycemic control without an increased risk of hypoglycemia.

Table 2 – Subgroup analysis in the saxagliptin group.

	Age (years)			BMI (kg/m^2)			Treatment regimen[a]		
	<70	⩾70	*P* value	<23	⩾23	*P* value	Monotherapy	Combination	*P* value
N	21	20		21	20		13	28	
Males	14 (66.7)	13 (65.0)	0.453	12 (57.1)	15 (75.0)	0.238	10 (76.9)	17 (60.7)	0.320
Age (years)	60.6 ± 7.0	75.2 ± 3.9	<0.0001	64.4 ± 8.4	69.4 ± 10.0	0.086	66.6 ± 11.3	67.1 ± 8.1	0.846
BMI (kg/m^2)	21.6 ± 3.8	23.8 ± 3.3	0.053	20.3 ± 2.1	26.1 ± 2.1	<0.0001	22.0 ± 1.9	23.5 ± 4.0	0.093
GA (%)									
Baseline	24.5 ± 2.7	23.0 ± 3.1	0.114	24.5 ± 3.5	22.8 ± 1.9	0.056	24.5 ± 3.9	23.3 ± 2.3	0.217
Change[b]	−3.6 ± 2.1	−3.2 ± 1.4	0.484	−3.3 ± 2.0	−3.5 ± 1.6	0.792	−4.2 ± 1.8	−3.0 ± 1.6	0.012
HbA1c (% [mmol/mol])									
Baseline	6.5 ± 0.7 (48 ± 7.7)	6.5 ± 0.8 (48 ± 8.7)	0.918	6.5 ± 0.7 (48 ± 7.7)	6.5 ± 0.9 (48 ± 9.8)	0.764	6.6 ± 0.8 (49 ± 8.7)	6.4 ± 0.7 (46 ± 7.7)	0.575
Change[b]	−0.66 ± 0.41 (7.2 ± 4.5)	−0.61 ± 0.48 (6.7 ± 5.2)	0.709	−0.65 ± 0.50 (7.1 ± 5.5)	−0.62 ± 0.38 (6.8 ± 4.2)	0.870	−0.80 ± 0.58 (8.7 ± 6.3)	−0.55 ± 0.34 (6.0 ± 3.7)	0.053
PPG (mg/dL)									
Baseline	178 ± 29	195 ± 38	0.105	191 ± 32	181 ± 37	0.341	183 ± 29	187 ± 37	0.671
Change[b]	−40 ± 23	−36 ± 23	0.566	−41 ± 23	−36 ± 23	0.456	−41 ± 29	−37 ± 24	0.539

BMI, body mass index; GA, glycated albumin; HbA1c, hemoglobin A1c; PPG, postprandial plasma glucose.
Values are shown as the *n* (%) or mean ± standard deviation.
[a] Saxagliptin was administered as monotherapy or in combination with oral antidiabetic agents and/or insulin.
[b] Change from baseline to week 24.

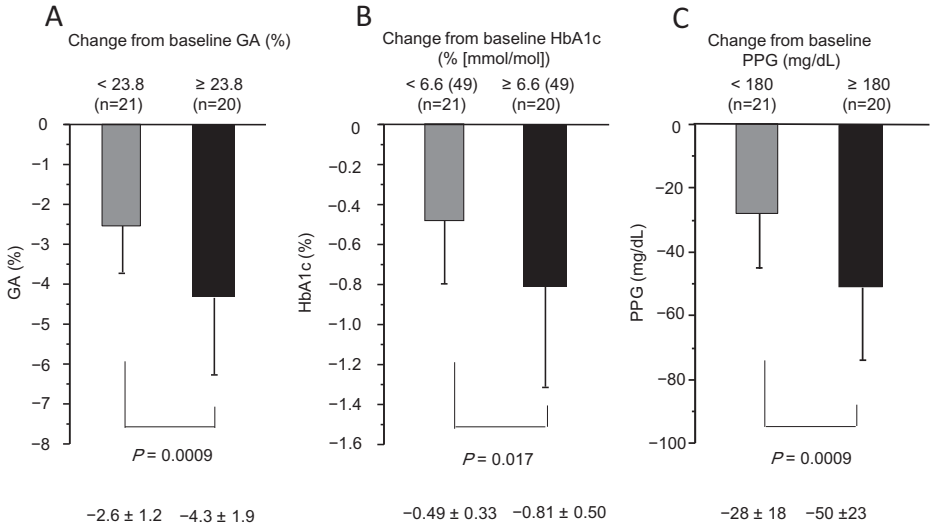

Fig. 2 – Changes from baseline to the end of treatment in GA, HbA1c, and PPG in saxagliptin-treated patients according to baseline GA (A), HbA1c (B), and PPG (C). Results are presented as the mean ± standard deviation. GA, glycated albumin; HbA1c, hemoglobin A1c; PPG, postprandial plasma glucose.

Table 3 – Changes in vital signs and laboratory variables.

Variables	Saxagliptin group			Control group			Between-group P values	
	Baseline	Endpoint	P value[a]	Baseline	Endpoint	P value[a]	Baseline	Endpoint
SBP (mmHg)	147 ± 12	146 ± 12	0.073	147 ± 12	148 ± 14	0.101	0.936	0.506
DBP (mmHg)	76 ± 9	76 ± 10	0.057	77 ± 13	77 ± 13	0.351	0.829	0.583
Heart rate (bpm)	77 ± 10	77 ± 10	0.937	77 ± 8	77 ± 8	0.509	0.971	0.925
Hemoglobin (g/dL)	11.0 ± 0.6	11.0 ± 0.7	0.392	11.0 ± 0.7	10.9 ± 0.7	0.381	0.923	0.332
ESA dose (U/week)	5902 ± 2421	4768 ± 2466	<0.0001	5926 ± 2639	5963 ± 2665	0.33	0.965	0.038
ERI	9.49 ± 4.42	7.77 ± 4.63	0.0008	9.73 ± 5.67	10.02 ± 5.15	0.847	0.829	0.041
Total protein (g/dL)	6.6 ± 0.3	6.6 ± 0.3	0.139	6.5 ± 0.5	6.5 ± 0.5	0.228	0.167	0.123
Serum albumin (g/dL)	3.6 ± 0.2	3.7 ± 0.3	0.141	3.7 ± 0.6	3.6 ± 0.3	0.157	0.477	0.184
AST (U/L)	15.3 ± 4.9	15.0 ± 4.1	0.327	15.0 ± 6.5	15.5 ± 6.9	0.47	0.802	0.699
ALT (U/L)	12.0 ± 6.3	11.8 ± 5.6	0.253	11.3 ± 6.6	12.2 ± 7.7	0.107	0.657	0.756
LDH (U/L)	183 ± 26	182 ± 25	0.224	180 ± 28	179 ± 29	0.649	0.692	0.649
ALP (U/L)	228 ± 40	230 ± 39	0.742	230 ± 61	223 ± 63	0.406	0.869	0.517
γ-GTP (U/L)	21.4 ± 11.0	20.9 ± 10.3	0.168	21.2 ± 12.3	20.6 ± 11.2	0.374	0.932	0.983
Total cholesterol (mg/dL)	154 ± 32	151 ± 29	0.173	149 ± 22	148 ± 20	0.877	0.292	0.638
HDL-cholesterol (mg/dL)	44.7 ± 12.7	45.0 ± 12.7	0.781	42.4 ± 12.1	42.1 ± 12.0	0.755	0.39	0.286
Triglyceride (mg/dL)	98 (57–140)	86 (56–124)	0.0015	118 (77–144)	112 (84–167)	0.64	0.491	0.041
BMI (kg/m^2)	22.7 ± 3.7	22.7 ± 3.6	0.813	22.9 ± 3.7	22.9 ± 3.8	0.969	0.837	0.848
Clinical dry weight (kg)	59.5 ± 13.1	59.6 ± 12.8	0.914	50.6 ± 13.4	60.6 ± 13.7	0.959	0.723	0.64
CTR (%)	49.0 ± 2.7	49.0 ± 2.6	0.222	49.9 ± 2.8	49.6 ± 3.0	0.761	0.136	0.355
Interdialytic weight gain (kg)	2.91 ± 0.99	2.77 ± 0.93	0.0015	2.93 ± 0.99	2.96 ± 1.05	0.145	0.904	0.573

SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoiesis stimulating agent; ERI, erythropoietin responsiveness index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase, γ-GTP, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; BMI, body mass index; CTR, cardiothoracic ratio.
Values are shown as the mean ± standard deviation or median (interquartile range).
[a] Within-group comparisons.

The current study was performed to evaluate the efficacy and safety of saxagliptin in the hemodialysis setting, and hence determine whether saxagliptin had similar properties to alogliptin, teneligliptin and vildagliptin. Of note, we found that saxagliptin achieved significant reductions in the glycemic variables GA, HbA1c, and PPG compared with the control group. Moreover, saxagliptin was associated with a significant reduction in triglyceride concentrations, which was probably

secondary to its glucose-lowering effects. A reduction in triglyceride concentrations was also reported in the vildagliptin study [8] but not in other studies.

Nowicki et al. examined the efficacy and safety of saxagliptin in a heterogeneous cohort of patients with renal impairment (moderate, severe, or end-stage kidney disease on dialysis) in a phase III trial [14]. However, only 19 and 20 hemodialysis patients were randomized to saxagliptin and placebo, respectively, of which 10 and 13 completed 12 weeks of treatment and 6 and 9 completed 52 weeks of treatment. Furthermore, they assessed glycemic control in terms of HbA1c, not GA. For these reasons, additional studies were necessary to provide better understanding of the efficacy and safety of saxagliptin in hemodialysis patients. Meanwhile, Nakamura et al. reported that DPP4 inhibitors decreased HbA1c and GA levels by 0.3%–1.3% and 1.7%–4.9%, respectively, in hemodialysis patients [15]. However, that report only included one saxagliptin study, the study by Nowicki et al. [14]. The effects of saxagliptin on GA have not been reported to date. Therefore, the present study was the first to evaluate the efficacy of saxagliptin in terms of the changes in both HbA1c and GA in a clearly defined cohort of hemodialysis patients.

The present study also showed that saxagliptin was effective in subgroups of patients divided by baseline characteristics, combination therapies, and baseline glycemic status. Intriguingly, however, the efficacy of saxagliptin in terms of the reduction in GA was significantly greater in patients treated with saxagliptin as monotherapy than in patients treated with saxagliptin in combination with other antidiabetic drugs.

In this study, 28.0% of patients were on dietary therapy alone and 21.9% were prescribed insulin with or without oral antidiabetic agents. In previous studies, dietary therapy alone and insulin were prescribed to 30% and 0% of patients, respectively [8], to 50% and 0%, respectively [7], and to 40% and 26.6%, respectively [9]. The proportions of patients on dietary therapy alone may be explained by the fact that at some centers, glycemic control of hemodialysis patients is only assessed in terms of HbA1c, and antidiabetic agents are not routinely prescribed to patients whose HbA1c is <7.0%. Renal anemia, ESAs, and blood loss during hemodialysis may lower HbA1c without lowering GA. Therefore, the proportion of patients prescribed dietary therapy alone was perhaps higher than might be expected in our study and in these earlier studies, and more patients might be prescribed antidiabetic therapies if glycemic control is assessed in terms of GA instead of HbA1c.

Based on the laboratory variables and AEs observed in this study, saxagliptin had no apparent safety concerns. In the present study, 21.9% of patients were prescribed insulin with or without oral antidiabetic agents, and 28.0% were prescribed dietary therapy alone. Furthermore, sulfonylureas are contraindicated in hemodialysis patients in Japan. It is possible that the low use of insulin and the prohibited use of sulfonylureas contributed to the low rate of adverse events (especially hypoglycemia) in the present study, relative to that in patients with moderate–severe renal impairment [14,16]. Intriguingly, however, there were reductions in the ESA dose, ERI, and interdialytic weight gain in the saxagliptin group relative to the control group in our study. A small reduction in interdialytic weight gain was also observed with vildagliptin [8]. To our knowledge, this is the first report to show that a DPP-4 inhibitor was associated with a reduction in ERI. It has been reported that DPP-4 inhibitors have anti-inflammatory effects and improve bone marrow function [17,18], which may have contributed to the reductions in ERI and ESA dose in the saxagliptin group observed in the present study. The reduction in ERI is likely to be clinically relevant because it may allow for lower doses of ESAs over the long term, thus reducing exposure and treatment costs, and increasing cost-effectiveness while maintaining target hemoglobin levels in hemodialysis patients. However, these possibilities will need to be addressed in future studies.

Unlike other DPP-4 inhibitors, saxagliptin is rapidly excreted via hepatic and renal pathways. Approximately 25% of the dose undergoes renal excretion and approximately 22% is excreted in feces [19]. Consequently, renal impairment increases the total bioavailability of saxagliptin with increases in the area under the concentration–time curves of 16%, 41%, and 108% in mild, moderate, and severe renal impairment, respectively, compared with normal renal function [20]. Therefore, the dose of saxagliptin should be adjusted based on the patient's kidney function. By contrast, linagliptin shows much lower renal elimination so dose adjustments are unnecessary in patients with renal impairment. Although the renal elimination profile of linagliptin suggests that it will be an ideal agent for patients on dialysis, a randomized controlled trial has not yet been conducted in this population [21].

There are some limitations to this study. In particular, it was conducted at just four centers, so might not reflect the clinical management of hemodialysis patients throughout Japan. In addition, the results may not be generalizable to non-Japanese patients. Because this trial did not have a double-blind design, the absence of masking may have introduced a bias. Finally, the study was not adequately powered for the subgroup analyses, so larger studies may be required to confirm the efficacy of saxagliptin in these subgroups.

In conclusion, the present study showed that saxagliptin at a dose of 2.5 mg/day was effective and well tolerated when used as monotherapy or in combination with other antidiabetic drugs in Japanese hemodialysis patients with type 2 diabetes. Longer-term studies are warranted to confirm the long-term efficacy and safety of saxagliptin in these patients.

Disclosure

MA has received honoraria from Kyowa Hakko Kirin Co. Ltd. The other authors have no conflict of interest to declare.

Authors' contributions

Study concept and design: MA, TH; data acquisition: MA, TH, MM, MO, RT, CN, HT, FK, HT; data analysis/interpretation: MA, TH; statistical analysis: MA; supervision or mentorship: KO. All authors contributed important intellectual content during manuscript drafting or revision, and accept accountability for the overall work, and ensured that questions pertaining to the

accuracy or integrity of the work were appropriately investigated and resolved. MA takes responsibility that this study is reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study were explained.

Acknowledgments

Publication of this report was financially supported by a grant from Kyowa Hakko Kirin Co. Ltd. (No financial support was received for implementation of this study.) Medical writing support was provided by Dr. Nicholas D. Smith (Edanz Group Ltd.) and Elsevier/ELMCOM™. Kyowa Hakko Kirin Co. Ltd. was not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2016.04.034.

REFERENCES

[1] Abe M, Okada K, Soma M. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice. Curr Drug Metab 2011;12:57–69.
[2] Abe M, Kalantar-Zadeh K. Haemodialysis-induced hypoglycaemia and glycaemic disarrays. Nat Rev Nephrol 2015;11:302–13.
[3] Abe M, Okada K, Maruyama T, Maruyama N, Matsumoto K. Efficacy and safety of mitiglinide in diabetic patients on maintenance hemodialysis. Endocr J 2010;57:579–86.
[4] Abe M, Okada K, Maruyama T, Maruyama N, Matsumoto K. Combination therapy with mitiglinide and voglibose improves glycemic control in type 2 diabetic patients on hemodialysis. Expert Opin Pharmacother 2010;11:169–76.
[5] Kidney Disease Outcomes Quality Initiative ((KDOQI)). Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49:S62–73.
[6] KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–86.
[7] Fujii Y, Abe M, Higuchi T, Mizuno M, Suzuki H, Matsumoto S, et al. The dipeptidyl peptidase-4 inhibitor alogliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis. Expert Opin Pharmacother 2013;14:259–67.
[8] Ito M, Abe M, Okada K, Sasaki H, Maruyama N, Tsuchida M, et al. The dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis. Endocr J 2011;58:979–87.
[9] Otsuki H, Kosaka T, Nakamura K, Shimomura F, Kuwahara Y, Tsukamoto T. Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes. Int Urol Nephrol 2014;46:427–32.
[10] Inoue K, Goto A, Kishimoto M, Tsujimoto T, Yamamoto-Honda R, Noto H, et al. Possible discrepancy of HbA1c values and its assessment among patients with chronic renal failure, hemodialysis and other diseases. Clin Exp Nephrol 2015;19:1179–83.
[11] Williams ME, Mittman N, Ma L, Brennan JI, Mooney A, Johnson CD, et al. The Glycemic Indices in Dialysis Evaluation (GIDE) study: comparative measures of glycemic control in diabetic dialysis patients. Hemodial Int 2015;19:562–71.
[12] Nakao T, Inaba M, Abe M, Kaizu K, Shima K, Babazono T, et al. Best practice for diabetic patients on hemodialysis 2012. Ther Apher Dial 2015;19(Suppl. 1):40–66.
[13] Higuchi T, Abe M, Yamazaki T, Okawa E, Ando H, Hotta S, et al. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: a randomized controlled trial. Am J Kidney Dis 2015;67:260–70.
[14] Nowicki M, Rychlik I, Haller H, Warren M, Suchower L, Gause-Nilsson I, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract 2011;65:1230–9.
[15] Nakamura Y, Hasegawa H, Tsuji M, Udaka Y, Mihara M, Shimizu T, et al. Diabetes therapies in hemodialysis patients: dipeptidase-4 inhibitors. World J Diabetes 2015;6:840–9.
[16] Udell JA, Bhatt DL, Braunwald E, Cavender MA, Mosenzon O, Steg PG, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 trial. Diabetes Care 2015;38:696–705.
[17] Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care 2014;37:2884–94.
[18] Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 2013;62:347–51.
[19] Anderson R, Hayes J, Stephens JW. Pharmacokinetic, pharmacodynamic and clinical evaluation of saxagliptin in type 2 diabetes. Expert Opin Drug Metab Toxicol 2016:1–7.
[20] Flynn C, Bakris GL. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. Nat Rev Nephrol 2013;9:147–53.
[21] Abe M, Okada K. DPP-4 inhibitors in diabetic patients with chronic kidney disease and end-stage kidney disease on dialysis in clinical practice. Contrib Nephrol 2015;185:98–115.