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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*

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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,

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* *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).

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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.