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Safety and Efficacy of Imeglimin for Type 2 Diabetes in Patients Undergoing Dialysis

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Abstract. *Background/Aim: Imeglimin is a novel small molecular tetrahydrotriazine that has been shown to improve hyperglycemia in clinical trials among patients with type 2 diabetes. Nevertheless, its pharmacokinetics in patients with renal dysfunction remain unclear. The objective of this study was to elucidate the safety and effects of imeglimin in patients with type 2 diabetes undergoing dialysis. Patients and Methods: Six patients with type 2 diabetes undergoing hemodialysis (HD) or peritoneal dialysis (PD) received imeglimin 500 mg/day. The observation period was 3.3±2.3 months. Results: Fasting blood glucose was significantly decreased, compared to baseline after imeglimin treatment (126.2±32.0 mg/dl, p=0.037, vs. baseline). Furthermore, levels of alanine aminotransferase were decreased (10.3±6.3 IU/l, p=0.006, vs. baseline). Glycated hemoglobin A1c and triglyceride tended to be decreased, albeit without statistical significance. Levels of total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and aspartate aminotransferase were not changed compared to baseline values. Conclusion: Despite the small sample size, imeglimin was found to be an effective and relatively well-tolerated agent for the treatment of patients with type 2 diabetes undergoing both HD and PD. During the observation period, adverse events such as hypoglycemia, diarrhea, nausea, or vomiting were not recognized in any patient.*

Diabetic kidney disease (DKD), a major diabetic vascular complication, is increasing global disease burden, whilst being the leading cause of end-stage renal disease (ESRD) (1, 2). Blood glucose control is basically important for the prevention of DKD; there is a relationship between the degree of glucose control and the development of DKD. Furthermore, the control of blood pressure using renin-angiotensin-aldosterone (RAAS) inhibitors seems to have renoprotective effects.

Incretin-related drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon like peptide-1 (GLP-1) elicit vasotropic effects and decrease diabetes-induced inflammation and oxidative stress, ameliorating DKD. Recent large clinical trials clearly indicated that sodium-glucose cotransporter-2 (SGLT2) inhibitors delayed DKD progression. Despite significant advances, limited progress has been made regarding for the prevention and treatment of DKD and residual risk still exists (3).

Imeglimin is a novel oral anti-diabetic agent that is being tested in clinical trials as monotherapy or add-on therapy to lower fasting blood glucose or glycated hemoglobin A1c (4). Recently, it has been reported that imeglimin prevents endothelial dysfunction by reducing the size of mitochondrial permeability transition pore, which plays a pivotal role in cell death, without inhibiting mitochondrial respiration (5). Thus, imeglimin. Therefore, imeglimin can be promising as a therapeutic agent to reduce residual risks related to DKD progression. However, the efficacy and safety of imeglimin in CKD patients, especially in patients undergoing dialysis, has not been reported. This is the first study to examine the efficacy and safety of imeglimin in dialysis patients.

Patients and Methods

Patients. This study included a retrospective cohort of 6 cases who underwent dialysis as outpatients in the Nagai Hospital (Tsu, Japan) or the Seiwadai Clinic (Nara, Japan). All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of the Nagai Hospital and the Seiwadai Clinic approved this study (approval number: 2022-01 and 2022-02, respectively). This is a retrospective medical record

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review study. The patients were treated as per protocol, the requirement to obtain informed consent was waived, and ethical review was not performed by the institutional (Nagai Hospital and Seiwadai Clinic) review board rule because the patient number in this study was less than nine.

Data analysis. Data were collected and analyzed retrospectively by using electronic medical records maintained at the Nagai Hospital and Seiwadai Clinic. Fasting blood glucose, glycated hemoglobin A1c (HbA1c) aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and patient characteristics (*e.g.*, underlying diseases, duration of dialysis, age, sex, and body mass index) were searched in the electronic medical records.

Statistical analysis. Statistical significance for differences was determined by the interquartile range and Wilcoxon test. All analyses were performed using StatView (SAS Institute) and Excel software. Statistical significance was defined as $p<0.05$.

Results

Six male patients were finally enrolled in the study. The age at onset was 55.2±7.0 years. The observation period was 3.3±2.3 months. Six patients were treated with imeglimin 500 mg/day. Concomitant medications for diabetes were as follows: Glinide (50%), Glucagon like peptide-1 receptor agonist (100%), insulin (67%), α-Glucosidase inhibitor (17%) (Table I).

Fasting blood glucose was significantly decreased, compared with baseline after imeglimin treatment (baseline *vs*. on therapy: 140.8±81.3 mg/l and 126.2±32.0 mg/l, respectively, $p=0.037$, Figure 1A). HbA1c tended to be decreased, albeit without significance (baseline *vs*. on therapy: 7.2±1.7 mg/l and 6.7±0.8 mg/l, respectively, $p=0.114$, Figure 1B). Furthermore, levels of ALT were decreased (14.5±9.5 IU/l and 10.3±6.3 IU/l, respectively, $p=0.006$, Figure 1C), although AST was not changed during the observation period (9.2±5.2 IU/l and 8.0±4.8 IU/l, respectively, $p=0.916$, Figure 1D).

Lastly, we analyzed the effect of imeglimin in patient lipid profile. Administration of imeglimin did not change triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol (triglyceride, baseline *vs*. on therapy: 173.5±97.0 mg/dl and 139.5±49.5 mg/dl ($p=0.249$, Figure 2A); total cholesterol, baseline *vs*. on therapy: 165.3±28.6 mg/dl and 165.0±26.6 mg/dl ($p=0.753$, Figure 2B); HDL cholesterol, baseline *vs*. on therapy: 43.5±11.4 mg/dl and 44.6±13.1 mg/dl ($p=0.463$, Figure 2C); LDL cholesterol, baseline *vs*. on therapy: 89.1±20.1 mg/dl and 92.5±22.3 mg/dl ($p=0.917$, Figure 2D), respectively).

During the observation period, adverse events such as hypoglycemia, diarrhea, nausea, or vomiting were not recognized.

Table I. *Patient characteristics*.

N	6
Male:female	6:0
Age (years)	55.2±7.0
HD:PD	5:1
BMI (kg/m^2)	27.4±6.8
Duration of diabetes (years)	15.5±5.4
Duration of dialysis (years)	4.0±3.0
Observation period (months)	3.3±2.3
Anti-diabetic agents (n)	14
Glinide (n)	3
Glucagon like peptide-1 receptor agonist (n)	6
Insulin (n)	4
a-Glucosidase inhibitor (n)	1
Anti-hypertensive agents (n)	8
ARBs (n)	1
ARNI (n)	1
Ca-Blockers (n)	4
β-Blockers (n)	1
Anti-dyslipidemia agents (n)	4
Statins (n)	4
Anti-uric acid agents (n)	3
Febuxostat	3

HD, Hemodialysis; PD, peritoneal dialysis; BMI, body mass index; ARBs, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor.

Discussion

Due to the paucity of real-world data on imeglimin, this is the first study to confirm the efficacy and safety of this agent in Japanese patients with type 2 diabetes undergoing dialysis. Our results showed that imeglimin decreased fasting blood glucose and HbA1c tended to be decreased, although the difference was not statistically significant. Furthermore, levels of ALT were decreased, although AST was not changed during the observation period. However, administration of imeglimin did not change triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol. In addition, no adverse events were observed during the study.

The availability of diabetes medications for use in dialysis is limited. Therefore, our results are significant despite the small sample size, as they demonstrate the safety of imeglimin in dialysis patients.

Imeglimin is a novel oral anti-diabetic agent, the first of a new class of molecules called glimins, for which the mechanism of action has been studied (4). The Trials of Imeglimin for Efficacy and Safety 1 (TIMES 1) study was conducted to determine the efficacy, safety, and tolerability of imeglimin monotherapy in Japanese patients with type 2 diabetes. This study showed imeglimin significantly improved HbA1c compared to placebo, with a change in HbA1c from baseline of –0.87% at week 24 (95%CI=–1.04 to –0.69, $p<0.0001$) (6).

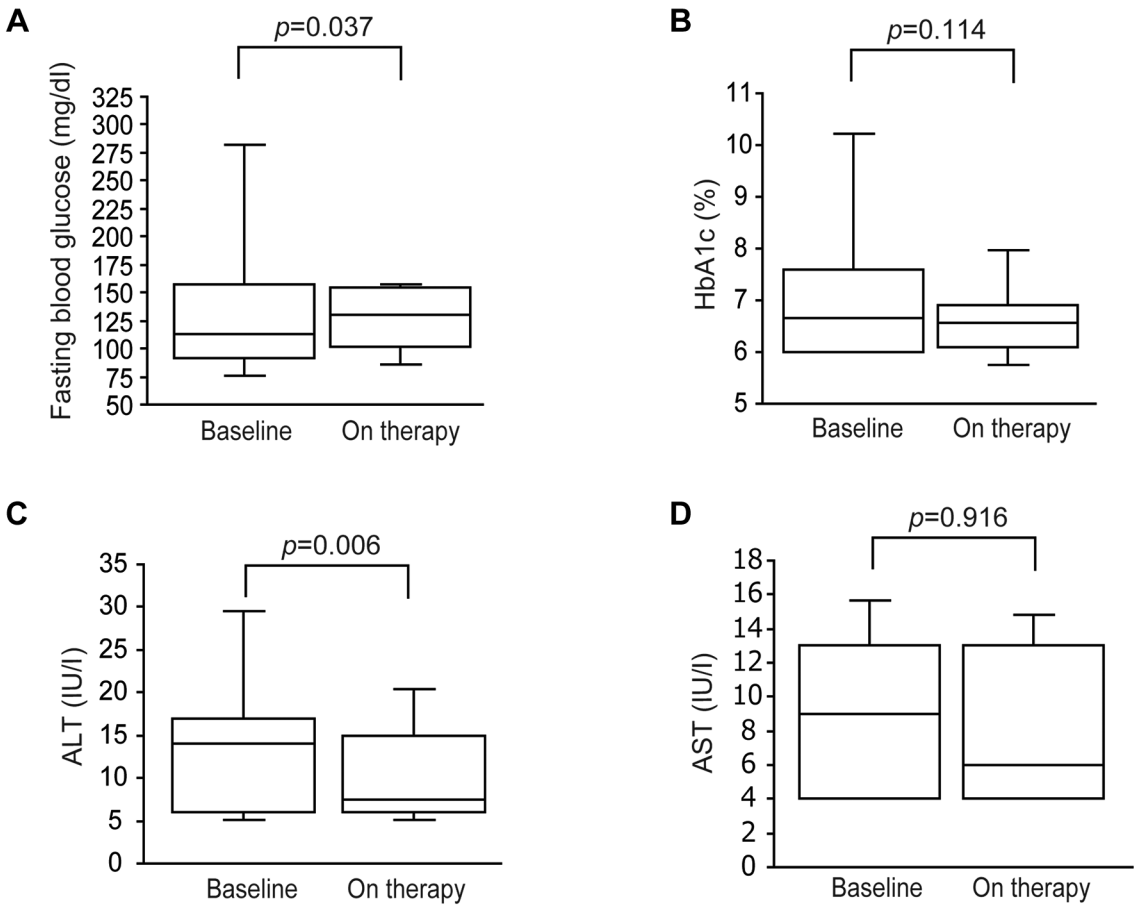

Figure 1. *Box plots showing changes in levels of fasting blood glucose, HbA1c, ALT, and AST upon imeglimin treatment during the observation period. (A) Fasting blood glucose, (B) HbA1c, (C) ALT, (D) AST. HbA1c, Hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase.*

Several studies including ours clearly demonstrated that both diabetic status and insulin resistance play a significant role in the generation of oxidative stress; free glucose activates glucose aldose reductase activity and polyol pathway, decreasing NADPH/$NADP^+$ ratio (7). Increases in intracellular glucose can activate protein kinase C (PKC) *via de novo* synthesis of diacylglycerol (DAG) (8). Activation of DAG-PKC signal transduction pathway in the glomerulus is associated with processes such as mesangial expansion, basement membrane thickening, endothelial dysfunction, and activation of cytokines and transforming growth factor-β (TGF-β) in DKD (9). Studies using rodents indicated that increased oxidative stress may be a cause of DKD (10-12). Inhibition of the polyol pathway with an aldose reductase inhibitor showed the possibility of reducing the effects of hyperglycemia on DKD (13).

It is reported that imeglimin decreased oxidative stress by acting on the liver, muscle, and pancreas, involving in the pathogenesis of type 2 diabetes, through a mechanism that targets the mitochondria. Our results showed levels of ALT were significantly decreased. Interestingly, imeglimin reduced lipid parameters and hepatic steatosis in the livers of high fat feeding mice.

A recent study indicated that metformin at therapeutic concentrations (1 mM) decreased glucogenesis by inhibiting mitochondrial glycerol 3-phosphate dehydrogenase action in a redox-dependent manner (14). Activation of NF-κB is involved in developing DKD and metformin can act on NF-κB signaling, suppressing inflammatory cytokines in the plasma of non-diabetic patients (15, 16). However, metformin cannot be used in CKD patients with impaired renal function, such as undergoing dialysis, due to the risk of lactic acidosis (17). On the other hand, since imeglimin has not been shown not to produce lactic acidosis in a rodent model of CKD, it has been considered for use in dialysis patients. Our results are very significant in that imeglimin improves glycemic control in dialysis patients and also lowers ALT, a marker of fatty liver without side effects.

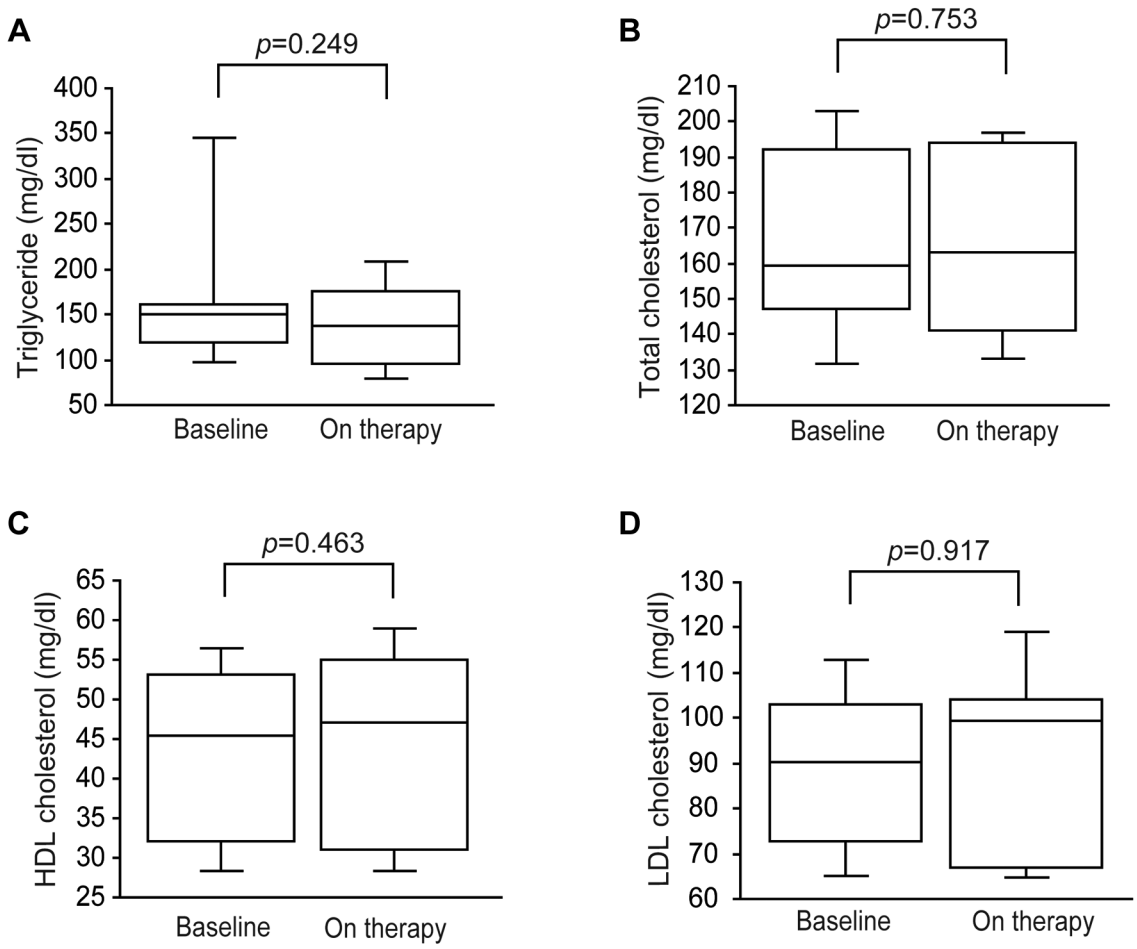

Figure 2. *Box plots showing changes in levels of triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol upon imeglimin treatment during the observation period. (A) Triglyceride, (B) total cholesterol, (C) HDL cholesterol, (D) LDL cholesterol. HDL, High density lipoprotein; LDL, low density lipoprotein.*

Imeglimin is not metabolized and is eliminated unchanged in the urine. Therefore, dosage reduction might be necessary in patients with renal impairment. Previous study using a population pharmacokinetics analysis suggested 500 mg q.d. of imeglimin would be an appropriate dosing regimen for patients with type 2 diabetes with renal impairment when the estimated glomerular filtration rate is below 15 ml/min/1.73 m^2 (18).

This study had several limitations. A retrospective analysis was performed on a small cohort from two medical institutions. Although the study had a small number of patients, it was necessary to report the effects of imeglimin in dialysis patients in real-world data as soon as possible.

Our study showed that oral imeglimin decreases fasting blood glucose and ALT in patients with type 2 diabetes undergoing dialysis. During the observation period, adverse events were not recognized. Further, we have demonstrated that administration of imeglimin could be useful to improve the prognosis of patients with type 2 diabetes undergoing dialysis.

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Conflicts of Interest

Akira Mima received a speaker honorarium from Otsuka, Kyowa Kirin, Mitsubishi Tanabe, Torii, Kowa, Bayer, Eli Lilly, Mochida, Sumitomo Pharma and Boehringer Ingelheim.

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