Examination of the Effect of Changing to Azilsartan From Candesartan in Renal Transplant Patients

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ABSTRACT

Background. Azilsartan, an angiotensin receptor blocker (ARB), was administered to renal transplant recipients to investigate the safety and antihypertensive effect in addition to its ARB-characteristic organ-protective effect.

Methods. The subjects were 20 patients (18 males, 2 females; baseline serum creatinine 2.39 ± 1.33 mg/dL) responding poorly to candesartan, who suffered albuminuria (>0.3 g/g creatinine) and hypertension (>140/90 mm Hg) following renal transplantation. Three months after candesartan was switched to azilsartan 20 mg/d, blood pressure, creatinine-corrected urinary albumin excretion, urinary L-type acid binding protein, urinary 8-hydroxydeoxyguano-sine, serum creatinine, and estimated glomerular filtration rate were evaluated. Thirteen patients received cyclosporine (65.0%) and 7 received tacrolimus (35.0%). Another hypertensive (calcium antagonist) agent was combined in 7 (35.0%).

Results. Systolic blood pressure significantly decreased from 139.5 mm Hg (baseline) from 128.7 mm Hg (at 3 months), whereas no significant changes were observed for diastolic blood pressure. The percentage of patients achieving the target level of antihypertensive effect (blood pressure < 130/80 mm Hg) significantly improved from 30.0% (baseline) to 70.0% (at 3 months). No significant changes were observed in renal graft function, oxidative stress marker level, or biochemical examination findings.

Conclusion. Sufficient antihypertensive effect was demonstrated soon after switching to azilsartan. However, no significant change was found in renal damage markers. Long-term study must be conducted to confirm the protective effect azilsartan on the transplanted kidney, as found with candesartan. The safety of azilsartan was demonstrated. If the transplanted kidney protection is demonstrated, this drug is expected to contribute to the improved long-term prognosis of renal transplant recipients.

ANGIOTENSIN RECEPTOR BLOCKERS (ARB) are the first-line drugs of antihypertensive therapy, and azilsartan is the most recently introduced ARB in Japan. Basic and clinical research has confirmed that azilsartan has antihypertensive effects superior to other ARB. Prevention and treatment of hypertension are particularly important since cardiovascular diseases such as heart disease and cerebral vascular disturbances are associated with a poor prognosis and the death of one-third of all transplant patients in Japan. If azilsartan shows excellent antihypertensive effect in addition to the renoprotective effects of this class of drugs, it is expected to contribute to improvement in the long-term survival of patients with renal transplants. The objective of this study was to evaluate whether azilsartan has superior antihypertensive effects and renal protective effects as compared with other ARB. Of renal transplant patients who received candesartan alone or combination of calcium blockers, patients who had poor response to the antihypertensive therapy or who tested

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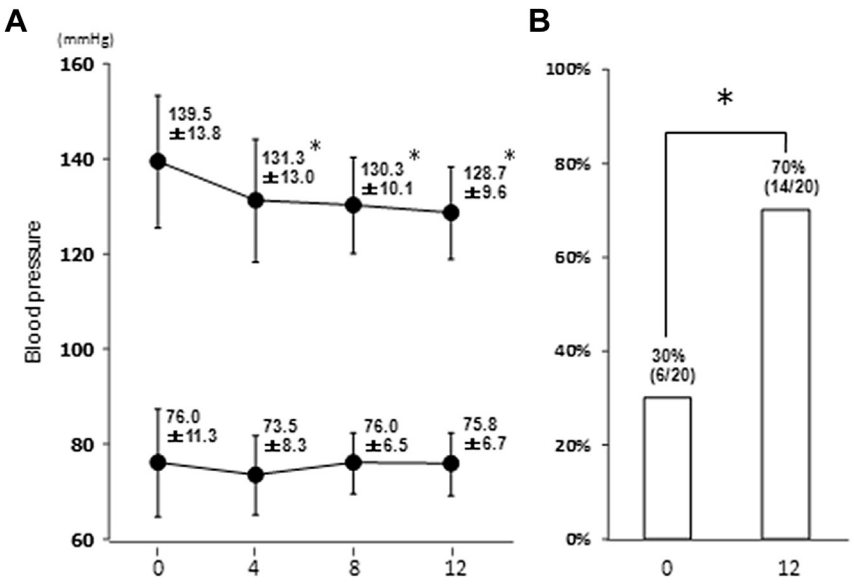

Fig 1. **(A)** Time course of blood pressure up to week 12. *$P < .01$ vs week 0. **(B)** Percentage of patients achieving the target level of antihypertensive effect (blood pressure < 130/80 mm Hg) at the week 0 and week 12. *$P < .05$ vs week 0.

positive for albuminuria were included in this study, and azilsartan was administered in place of candesartan to these patients. This study also examined the type of specific drug effects of azilsartan, namely renoprotective effects and suppressive effects on oxidative stress. The safety during treatment with azilsartan was also evaluated.

PATIENTS AND METHODS

The target of this study was 20 patients (18 males and 2 females whose serum creatinine level was 2.39 ± 1.33 mg/dL at baseline for treatment azilsartan) who presented with proteinuria, urinary albumin-to-creatinine ratio (UACR) > 300 mg/g creatinine in random spot collection, and/or hypertension (blood pressure > 140/90 mm Hg) after renal transplantation and were considered to have insufficient response to antihypertensive therapy with candesartan. With regard to calcineurin inhibitors (CNI), cyclosporine, tacrolimus, and steroid were used in 13 (65.0%), 7 (35.0%), and 19 patients, respectively. Seven patients (35.0%) received combination with calcium blockers before treatment with azilsartan. In all 20 patients, treatment was switched from candesartan to azilsartan, and azilsartan was administered at 20 mg/d for 12 weeks. Blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), UACR were measured at baseline and weeks 4, 8, and 12. As biomarkers of oxidative stress and kidney injury, 8-hydroxydeoxyguanosine (8-OHdG) and liver-type fatty acid binding protein (L-FABP) in urine were measured at baseline and week 12. Biochemical tests were performed at baseline and week 12 for evaluation of adverse events.

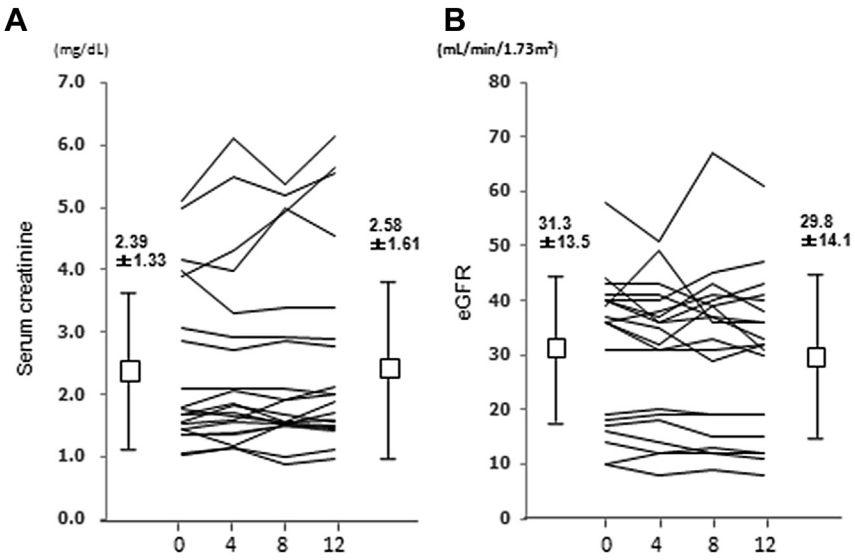

Fig 2. **(A)** Time course of serum creatinine and **(B)** the estimated glomerular filtration rate (eGFR) up to week 12. *Not significant (week 0 vs week 12).

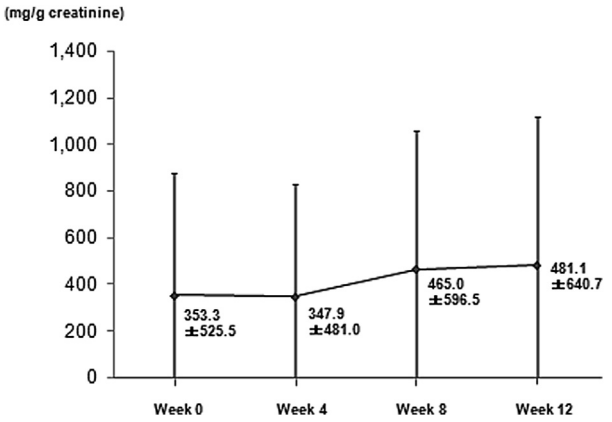

Fig 3. Time course of urine albumin-to-creatinine ratio (UACR) up to week 12. *Not significant (week 0 vs week 4, week 8, week 12).

Statistical Analysis

All data were expressed as mean values ± standard deviations. Paired *t* test was used to estimate the antihypertensive effect, renoprotective effect, suppressive effects on oxidative stress, and safety during treatment with azilsartan from baseline to week 12. McNemar test was used to estimate the blood pressure reduction effect of azilsartan during examination. Wilcoxon signed rank test was used to estimate renoprotective effect from changes in UACR.

Statistical significance was set at $P < .05$. The Statistical Package for the Social Science version 20.0 (IBM corporation, Armonk, NY, United States) was used for statistical analysis.

RESULTS

Systolic blood pressure significantly decreased from 139.5 mm Hg at baseline to 128.7 mm Hg at week 12 (Fig 1A, $P < .01$). The percentage of patients achieving the target level of antihypertensive effects (blood pressure < 130/80 mm Hg) significantly improved from 30% at baseline to 700% at week 12 (Fig 1B, $P < .05$). No significant changes were observed in renal function (serum creatinine and eGFR), UACR, 8-OHdG, L-FABP, and biochemical examination findings during the examination (Figs 2A, B, 3 and 4, and Table 1).

DISCUSSION

ARBs are considered to have a renal protective effect independent of blood pressure reduction [1]; however, the antihypertensive effect of ARB monotherapy is inadequate. A sufficient and prolonged antihypertensive effect leads to the prevention of vascular deaths [2], and therefore the administration of ARBs with a high antihypertensive effect would contribute to an improvement in the long-term survival of renal transplant recipients over and above the drugs' organ-protective effects.

We administered candesartan for a long-term period of 7 years to renal transplant recipients with hypertension and/or proteinuria, demonstrating its protective effect on renal graft function, which was considered to be due to the suppression of proteinuria. However, its efficacy in terms of blood pressure reduction was inadequate [3].

Azilsartan, developed in Japan, was designed to exert a potent and long-lasting antihypertensive effect. Azilsartan was initially synthesized from candesartan and has higher tissue penetration properties and stronger AT1 receptor binding affinity compared to other ARBs, including candesartan [4]. These physical properties of azilsartan are considered to be most important in the mechanism of its potent antihypertensive effect. Many studies have already reported the albuminuria-suppressing effect of candesartan [5], which is an important specific drug effect of ARBs; meanwhile, one basic study has shown that azilsartan also

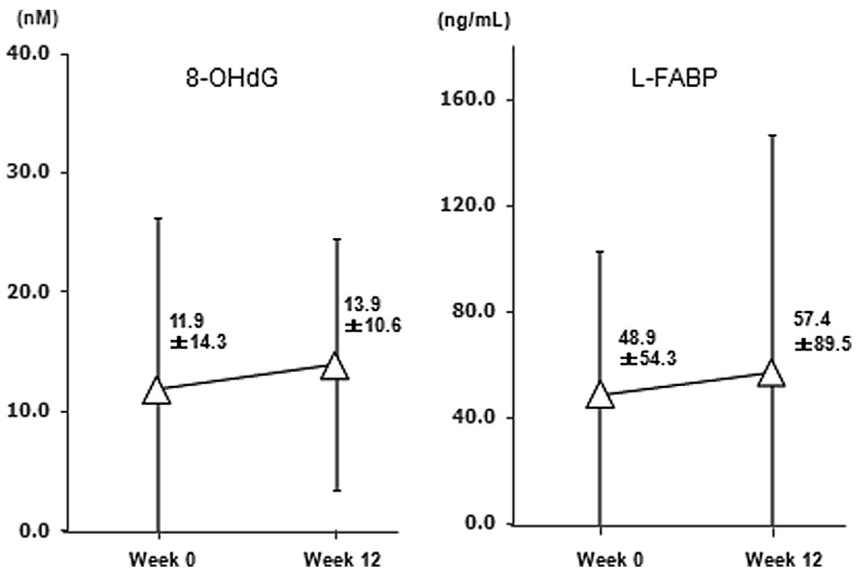

Fig 4. Changes in urine 8-OHdG and L-FABP at week 0 and week 12. *Not significant (week 0 vs week 12).

Table 1. Clinical Data at Week 0 and Week 12

	Week 0	Week 12	*P*
Na (mEq/dL)	140.2 ± 2.1	140.5 ± 3.3	NS
K (mEq/dL)	4.7 ± 0.6	5.1 ± 0.7	NS
Tcho (mg/dL)	205.8 ± 24.7	202.5 ± 17.5	NS
LDL- C (mg/dL)	117.6 ± 19.3	112.2 ± 19.5	NS
AST (IU/L)	19.0 ± 8.2	19.9 ± 10.2	NS
ALT (IU/L)	16.5 ± 8.7	16.5 ± 8.6	NS
γ- GTP (IU/L)	24.8 ± 8.6	25.4 ± 8.3	NS
HbA1c (%)	5.7 ± 0.8	5.6 ± 0.9	NS

Abbreviations: Tcho, Total cholesterol; NS, not significant.

suppressed albuminuria and that the effect is greater than with candesartan [6,7].

The objectives of our present study were primarily to evaluate the short-term antihypertensive effect of azilsartan and secondarily to evaluate the proteinuria-suppressing effect as well as the protective effect on renal graft function. All subjects of the study were renal transplant recipients who had been treated with candesartan, without a sufficient blood pressure reduction (target blood pressure of ≤130/80 mm Hg) and/or with proteinuria (≥0.3 g/g creatinine). We administered 20 mg/d of azilsartan after the cessation of candesartan, and the results showed that blood pressure was significantly reduced compared to baseline after 4 weeks of azilsartan treatment, and systolic blood pressure was significantly reduced within 12 weeks. No high diastolic blood pressures were observed from before the start of treatment, and there were no excessive reductions in diastolic blood pressure after the start of treatment.

In terms of the antihypertensive effect of azilsartan, a significant reduction in systolic blood pressure and a significant improvement (from 30% to 70%) in the percentage of patients who achieved the target blood pressure were obtained in a short period of time; we therefore consider that a favorable antihypertensive effect was demonstrated. With regard to renal graft function, there were no significant changes in serum creatinine or urine albumin levels, and there was no tendency toward improvement in these parameters; therefore, no short-term improvement in renal graft function was observed. Furthermore, there were no significant changes in markers of oxidative stress or renal damage, and therefore no protective effects on renal function were observed following the short-term administration of azilsartan.

In renal transplant recipients, renal toxicity, vascular endothelium disorders, and other pathologic conditions are persistent due to chronic exposure to CNI, and it is difficult to obtain any improvement in kidney tissue damage over a short period of time without eliminating non-immunologic factors compromising renal function. Future research should examine the renal protective effects of azilsartan in long-term administration, and if these effects can be demonstrated, azilsartan will have great potential as an agent for improving the long-term prognosis of renal transplant recipients.

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