A Five-year Comparison of the Renal Protective Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients with Non-Diabetic Nephropathy

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Abstract

Objective Evidence suggests that the effectiveness of angiotensin-converting enzyme (ACE) inhibition diminishes with time, resulting in increasing angiotensin II levels, the action of which can be inhibited by the addition of an angiotensin receptor blocker (ARB). In the present study, the renal protective effects of ACE inhibitors and ARBs were compared over a five-year period in a prospective, randomized, open-blind study in 68 non-diabetic Japanese patients with elevated serum creatinine levels.

Patients and Methods Japanese patients with renal insufficiency were randomly assigned to receive either an ACE inhibitor (benazepril 1.25 to 5 mg daily or trandolapril 0.5 to 4 mg daily) or ARB (candesartan 2 to 8 mg daily or losartan 25 to 100 mg daily) at the Kidney Disease Center at Saitama Medical School Hospital. The primary study endpoint was a change in glomerular filtration rate (GFR) between the baseline value and the last available value obtained during the five-year treatment period, as estimated by the Cockcroft-Gault equation. Secondary endpoints included the annual changes in GFR, serum creatinine level, urinary protein excretion, and blood pressure, as well as the rate of development of end-stage renal disease.

Results There were no significant differences in the primary endpoint between the two groups. However, after 4 years, the decline in GFR in patients treated with ARBs was significantly greater than that seen in patients treated with an ACE inhibitor (p<0.05). Furthermore, the rate of introduction of dialysis therapy was also significantly greater in the ARB-treated patients (52.7% in ACE inhibitor and 81.2% in ARB group at year 5, p<0.01).

Conclusion While our data suggested that ARB, like ACE, treatment might slow the progression of renal dysfunction, it also pointed to the necessity to be alerted to the progression to end-stage renal disease with long-term medication.

Key words: angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blocker (ARB), glomerular filtration rate (GFR), non-diabetic renal disease

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Introduction

The renin-angiotensin system (RAS) plays an important role in regulating blood pressure (BP). Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) inhibit the RAS and have been shown to be effective treatments for hypertension (1, 2). Independent of their ability to lower BP, these compounds have also been reported to reduce the progression of nephropathy in patients with diabetes mellitus (DM) and chronic renal failure (CRF) (3). The acute administration of ACE inhibitors reduces plasma angiotensin II (Ang II) concentrations to undetectable levels though interestingly, there is some evidence that their chronic administration results in partial escape i.e., incomplete suppression of Ang II levels,
which may reduce their effectiveness as BP-lowering agents (4). On the other hand, ARBs block the high affinity type 1 receptor binding site of angiotensin II, which is constitutively expressed in all vascular tissues as well as in the kidney and is responsible for mediating nearly all of the known biological effects of angiotensin II (5). The results from a couple of clinical trials suggested that ACE inhibitors did not completely inhibit the RAS and as such, their ability to prevent and reduce the progression of non-diabetic chronic renal insufficiency is dubious (6). In contrast, several studies suggested that ARBs slowed the progression of renal dysfunction in patients with type 2 diabetes (7, 8) as well as non-diabetic nephropathy (9, 10). Relatively few studies have examined the efficacy of monotherapy with ARBs in patients with non-diabetic nephropathy. Moreover, no direct comparison of the long term effectiveness of ACE inhibitors and ARBs has been carried out in non-diabetic patients (11). Thus, there is a need for a head-to-head comparison of the effectiveness of ACE inhibitors and ARBs in long-term non-diabetic nephropathy. To that end, in this study, we compared the effects of ARBs and ACE inhibitors on glomerular filtration rate (GFR) and the initiation of dialysis therapy over a five-year period.

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Study Design
This prospective, randomized, open-blind, parallel-group study was conducted at the Kidney Disease Center at Saitama Medical School Hospital. All subjects provided written informed consent. Financial support was provided by Saitama Medical School Foundation alone-no funds were provided by any government-related administrative office or pharmaceutical company. All patients were primarily under the care of Dr. H. Suzuki, while Drs. J. Shoda and Y. Kanno assisted in the preparation of this manuscript.

Patients and Methods

Patients
Study participants were selected by screening their laboratory data, medical history, and current medical status. Sixty-eight subjects who met our inclusion and exclusion criteria were ultimately selected for this study. Inclusion criteria included the following: age between 35 and 70, a history of hypertension, and a calculated creatinine clearance of between 25 and 59 mL/min, as estimated by the Cockcroft and Gault equation (12). The exclusion criteria included unstable renal function or active renal disease, peripheral vascular disease, valvular disease, malignancy, hepatitis or severe liver disease, and a recent history of a severe cardiovascular accident such as a myocardial infarction, stroke, or congestive heart failure. Our 68 subjects with non-diabetic renal insufficiency were randomly (randomization was carried out using the envelop method i.e., the physician picked up an envelope in which the allocated group was indicated) ass-
Changes in serum creatinine. Serum creatinine, which was used as a criterion for the initiation of dialysis therapy, showed a gradual tendency to increase in both groups; there were no significant differences between groups. Numbers under the time course express the number of surviving patients in each group.

Changes in creatinine clearance. Creatinine clearance, another criterion for the determination of a patient’s entry into dialysis treatment, similarly showed a gradual tendency to increase. * p<0.05 versus the ACE inhibitor group

signed to receive an ACE inhibitor (benazepril, 1.25 to 5 mg daily or trandolapril, 0.5 to 4 mg daily) or an ARB (candesartan, 2 to 8 mg daily or losartan, 25 to 100 mg daily). Our subjects took their medications between April 1999 and March 2004.

Patients that were already receiving ACE inhibitors or ARBs stopped taking these medications but did not discontinue taking their other antihypertensive drugs. These patients were then randomly assigned to a treatment group. No run-in period was incorporated into our study design.

Evaluation of Biochemical Data

At the beginning of each 4-month period, the following parameters were measured in each subject: body weight, sitting blood pressure, heart rate, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes, and hemoglobin. Blood pressure was monitored at regular intervals throughout the study by measuring sitting blood pressure with an automated arm-cuff device (Nippon Colin, Nagoya, Japan) in our outpatient clinic.

End Points

The primary study endpoint was a change in GFR after 5 years. Secondary endpoints included annual changes in GFR, urinary protein excretion, serum creatinine level, and blood pressure, the rate of development of end-stage renal disease and adverse events, and other laboratory abnormalities.

Patients were followed for 5 years with regular visits. Their target blood pressure was less than 130/80 mmHg which was maintained with calcium antagonists, diuretics, and alpha1 blockers in addition to either an ACE inhibitor or ARB. The criteria that were used to determine if it was time to place a patient on dialysis therapy included untreatable hyperkalemia, pulmonary edema, and uremic symptoms that were not controllable by pharmacological and dietary intervention. In addition to these criteria, a patient might also have been placed on dialysis if they exhibited intractable anemia, massive edema, etc.

Lipid lowering drugs i.e., primarily statin derivatives were administered if serum cholesterol levels exceeded 200 mg/dl or low density lipoprotein (LDL) cholesterol levels exceeded 120 mg/dl.

Patients were instructed to follow a diet with a daily protein and salt intake of less than 0.7 g/kg body weight and 9 g, respectively.

Statistics

Quantitative data were expressed as the mean ±SEM. An unpaired, Student’s t-test or Mann-Whitney test was used to compare values between groups. An analysis-of-covariance model was used to evaluate GFR differences. The changes in GFR after 5 years were determined based on year 5 values for subjects who completed the study, and based on the last available value for subjects who dropped out before year 5. An ANOVA was used to compare the serial changes between the two group means. A p-value of <0.05 was considered to be significant. Patient survival and cumulative renal survival were calculated using the Kaplan-Meier life-table analysis method, and differences between the groups were evaluated by the log-rank test. It was determined that data would be required from 32 subjects in each treatment group in order to achieve a power of 95 percent at a one-sided alpha level of 5 percent.

Results

Patient Profiles

The demographic and clinical characteristics of our patients are shown in Table 1. Patients’ underlying renal disease was diagnosed on the basis of examination of their medical history, as well as on the results of their urine analysis, blood test, and renal biopsy. Chronic glomerulonephritis was diagnosed by renal biopsy or when the patient had a history of proteinuria/hematuria before the onset
of hypertension. At the start of study, the mean ±SEM blood pressures in the ACE inhibitor and ARB groups were 138.9/84.5±14.7/10.5 mmHg and 140.0/81.0±10.3/8.9 mmHg, respectively, while their urinary protein excretion was 2.08±0.20 g/day and 2.55±1.32 g/day, respectively; these values were not statistically significant.

**Changes in GFR**

Changes in estimated GFR and serum creatinine are shown in Fig. 1 and Fig. 2, which do not include the data of subjects that had begun dialysis treatment at each time point. Serum creatinine levels increased gradually throughout the study in all patients, regardless of treatment. Estimated creatinine clearances fell significantly from 43.6±5.9 ml/min to 5.2±1.2 ml/min (p<0.001) in the ACE inhibitor group, and from 37.8±6.5 ml/min to 8.8±1.8 ml/min (p<0.001) in the ARB group. At year 3, the level of estimated creatinine clearance in the ACE inhibitor group was significantly higher than in the ARB group (p<0.05), though there were no differences between these groups at any of the other time points.

**Changes in Blood Pressure**

Changes in systolic and diastolic blood pressure are shown in Fig. 3 and Fig. 4. Systolic/diastolic blood pressure fell from 138.9±2.7/84.5±2.0 mmHg to 127.6±2.0/76.9±2.6 mmHg (p<0.05) in the ACE inhibitor group, and from 140.0±2.6/81.0±2.3 mmHg to 130.0±5.7/76.7±3.3 mmHg (p<0.05) in the ARB group, respectively; these differences between the 2 groups were not statistically significant, nor were there any differences in blood pressure between these groups throughout the study. At 1 year, systolic blood pressure was decreased to 93.8±1.1% in the ARB group and 92.3±1.0% in the ACE inhibitor group.

**Changes in Urinary Protein Excretion**

Urinary protein excretion decreased significantly from 2.08±0.20 g/day to 1.76±0.17 g/day in the ACE inhibitor group and from 2.56±0.34 g/day to 2.16±0.29 g/day in the ARB group. At 1 year, urinary protein excretion was decreased to 83.6±4.5% in the ARB group and 93.1±5.5% in the ACE inhibitor group. There were no significant differences in urinary protein excretion between groups at any point in the study (Fig. 5).

**Rates of End-Stage Renal Disease**

By year 5, 19 (52.7%) of 36 patients in the ACE inhibitor group had begun dialysis therapy, while 26 (81.2%) of 32 patients in the ARB group had done so. Kaplan-Meier survival curve analysis showed no significant differences in the rate of introduction of dialysis therapy between groups until year 3. During the last 2 years, there was a significant increase in the need for dialysis therapy in patients treated with an ARB (Fig. 6).

**Average ACE inhibitor, ARB, and other Antihypertensive Agent Doses**

Twenty-four patients were treated with losartan at an average dose of 45.8±7.2 mg daily while 8 patients were treated with an average candesartan dose of 6.8±1.2 mg daily. The dosage of ACE inhibitors temporally exceeded the authorized dose in Japanese health insurance coverage in some of the patients with the agreement of the patient and pharmaceutical section. Twenty-six patients were treated with an average benazepril dose of 2.2 mg ±0.8 mg daily and 10 patients were treated with 3.1 mg ±0.6 mg of trandolapril daily. Overall, 80% of patients were concomitantly treated with a calcium channel blocker. Furosemide was employed in 24% and 28% of patients in the ACE inhibitor group and the ARB group, respectively. There was no significant difference in the frequency of use.

**Adverse Events and Safety Profile**

Candesartan and losartan were better tolerated with fewer overall and drug-related discontinuations; only 1 patient discontinued use of losartan. Two patients discontinued ACE inhibitor treatment because they developed a dry cough. No serious, drug-related adverse events occurred during the study. Finally, no deaths or major cardiac events occurred.
Our data showed that ARBs were not inferior to ACE inhibitors in their ability to prevent the progression of renal dysfunction in subjects with non-diabetic renal disease. However, the ultimate requirement for dialysis therapy was higher in subjects treated with ARBs than in those who took ACE inhibitors, at years 4 and 5.

While it was anticipated that we would witness a high incidence of cardiovascular events in our patients because of the strong association of such events with chronic renal insufficiency (13, 14), no cardiovascular events were observed over the 5-year course of the study in either group. A similar observation was made by Nakao et al (9) who reported very few cardiovascular events in non-diabetic patients with renal disease that were treated with an ACE inhibitor or ARB, or both. Compared to previous studies (15, 16), the blood pressures of the patients in the trial of Nakao et al (9) as well as in our study were low, which likely accounted for the relative cardio-protection in these individuals (17). In addition to their ability to lower blood pressure, ACE inhibitors and ARBs also block the RAS, which may afford cardio-renal protection by a mechanism that is independent of their ability to lower blood pressure. Moreover, the majority of study participants had already begun treatment with an ACE inhibitor, which might also have accounted for their reduced incidence of cardiovascular disease and dry cough, as well as their lower basal levels of urinary protein excretion. The foregoing notwithstanding, we can not rule out roles for aspirin and statins (18), one of which was taken by more than half of our patients.

In the present study, the rate of decline of GFR was similar between groups over the course of the study. Recently, the DETAIL study examined the effects of telmisartan, an ARB and enalapril, an ACE inhibitor on GFR in patients with type 2 diabetes in a head-to-head comparison over 5 years and found that telmisartan was not inferior to enalapril in providing long-term renoprotection (11). While ACE inhibitors and ARBs inhibit the RAS by different mechanisms, they were found to have similar cardio- and renal-protective effects in large-scale clinical trials (19). In our study, the blood pressure lowering and antiproteinuric effects of ACE inhibitors and ARBs were found to be similar, though renal survival was better in patients in the ACE inhibitor group during the latter part of the study. This unexpected finding may have been due to the fact that the ACE inhibitor and ARB doses used were insufficient to provide renoprotection. It has been recommended that the dose of an ACE inhibitor be adjusted in patients with renal dysfunction to avoid hyperkalemia and the immediate progression to renal failure (20). The prescribed dose of the ARBs used by the patients in the present study resulted in ARB excretion in their urine, a finding that has important negative implications for the long-term use of these compounds in patients with chronic renal insufficiency (21); such a deleterious effect was also reported with the long-term use of ACE inhibitors.

It has been suggested that ACE inhibition increases serum and tissue bradykinin levels, the latter of which may help to mediate the ability of ACE inhibitors to reduce blood pressure and proteinuria, induce natriuresis, and inhibit glomerulosclerosis. On the other hand, ARBs lack the ability to activate the bradykinin system (19), which, in light of our findings, supports the notion that bradykinin mediates renoprotection. The angiotensin type 2 receptor is known to antagonize angiotensin-associated functions such as vasoconstriction, aldosterone release, and the stimulation of tubular transport, which are mediated by the angiotensin type 1 receptor (22). However, it was recently reported that the activation of angiotensin type 2 receptors alone conferred a degree of renal protection (23). Thus, it is still unclear as to whether an angiotensin type 1 receptor antagonist is as good as, better, or worse than an ACE inhibitor vis-à-vis its ability to delay the progression of renal disease.

Some limitations of our study need to be mentioned. First, the fact that only one physician was involved might have resulted in inadvertent selection bias. Second, the num-

Discussion

Figure 5. Changes in urinary protein excretion. Patients in the ARB group excreted more protein than those in the ACE inhibitor group from the very beginning of the study. In both groups, urinary protein excretion was significantly decreased. ** denotes p<0.01 vs. each basal value.

Figure 6. Kaplan-Meier survival curves for patients treated with an ACE inhibitor or ARB. At year 3, there were no significant differences in the rate of introduction into dialysis therapy between the two groups. However, during the last 2 years, there was a significant increase in the rate of introduction of dialysis therapy in ARB patients.

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ber of participants was very small, which may have contributed to the lack of significance in certain comparisons. Third, the study was not carried out in a double-blinded manner; thus, bias may have been introduced into the study. This being said, however, there were no significant differences in the levels of serum creatinine and blood pressure in patients with mild renal dysfunction between the two groups. It therefore appears that our assessment of the effects of ACE inhibitors and ARBs on GFR was nonetheless valid. Fourth, while we had originally planned to carry out head-to-head comparisons, this became difficult in light of the fact that two types of ACE inhibitors and ARBs were used in the study. Nonetheless, there were no significant baseline differences in blood pressure or serum creatinine in patients who took benazepril and trandolapril or losartan and candesartan.

In conclusion, while our data suggested that ARB, like ACE, treatment might slow the progression of renal dysfunction, it also pointed to the possibility that there is a constant necessity to be aware of progression to end-stage renal disease with long-term medication.

A part of this study was presented at the 37th annual meeting of the American Society of Nephrology (San Diego, 2004) and at the 102nd annual meeting of the Japanese Society of Internal Medicine (Osaka, 2005).

References


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