Losartan, an Angiotensin-II Receptor Antagonist, Retards the Progression of Advanced Renal Insufficiency

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Chronic renal disease often progresses to end-stage renal disease (ESRD) requiring renal replacement therapy. Angiotensin-II plays a central role in the progression to ESRD in various kinds of renal diseases through the hemodynamic and non-hemodynamic mechanisms (Wolf 1998;
Narita et al. 1999). Angiotensin-II increases intraglomerular pressure by constriction of efferent arteriole (Keane et al. 1989). This peptide stimulates proliferation and extracellular matrix protein synthesis of mesangial cells (Wolf 1998; Yamabe et al. 2000). Tubulointerstitial lesion is also induced by angiotensin-II in some experimental models (Johnson et al. 1992; Klahr et al. 1995).

Although antagonism of renin-angiotensin system by angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II type 1 receptor antagonist (AIIA) has been shown to exert renoprotective effects (Lewis et al. 1993; Maschio et al. 1996; Brenner et al. 2001; Lewis et al. 2001), it is not fully investigated whether such treatment is effective and safe in patients with chronic renal failure. Administration of AIIA in patients with moderate to severe renal function impairment may have some benefit as they did not require dose adjustment because of their prevalent hepatic metabolism (Sica et al. 1995).

The purpose of the present study was to examine the effect of AIIA losartan on the progression of advanced renal insufficiency including patients with serum creatinine level more than 3.0 mg/dl.

**Subjects and Methods**

**Subjects**

Eight hypertensive patients with chronic renal disease, who had baseline serum creatinine (Cr) level > 2.0 mg/dl before initiation of losartan and were followed-up for more than 24 weeks after introduction of losartan, were retrospectively analyzed. All patients had been followed-up at our outpatient clinic before the initiation of losartan for more than 24 weeks. All patients gave a written informed consent, in accordance with the Helsinki Declaration of the World Medical Association. This study was approved by ethic committee of Hirosaki University. Characteristics of these 8 patients are shown in Table 1. There were 6 males and 2 females with a mean age of 55.6 ± 12.3 years. The etiology of chronic renal disease was IgA nephropathy in 2 patients, anti-neutrophil cytoplasmic antibody related nephropathy in one, membranoproliferative glomerulonephritis in one, membranous nephropathy in one, nephrosclerosis in one, adult-onset polycystic kidney disease (APKD) in one and diabetic nephropathy in the remaining one. Mean serum

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Diagnosis</th>
<th>Body weight (kg)</th>
<th>Serum Cr (mg/dl)</th>
<th>MBP (mmHg)</th>
<th>Medications before the treatment of losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>ANCA related nephropathy</td>
<td>62.6</td>
<td>3.8</td>
<td>131.7</td>
<td>Calcium channel blocker, methylprednisolone</td>
</tr>
<tr>
<td>2</td>
<td>68/M</td>
<td>MPGN</td>
<td>60.0</td>
<td>3.0</td>
<td>94.7</td>
<td>Calcium channel blocker, ACE-I, predonisolone, allopurinol</td>
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<tr>
<td>3</td>
<td>48/F</td>
<td>IgA nephropathy</td>
<td>48.0</td>
<td>2.2</td>
<td>94.7</td>
<td>β-blocker</td>
</tr>
<tr>
<td>4</td>
<td>69/M</td>
<td>Membranous nephropathy</td>
<td>64.5</td>
<td>2.5</td>
<td>128.0</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>5</td>
<td>51/M</td>
<td>Nephrosclerosis</td>
<td>67.6</td>
<td>3.0</td>
<td>129.3</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>6</td>
<td>51/F</td>
<td>APKD</td>
<td>47.8</td>
<td>5.2</td>
<td>111.3</td>
<td>Calcium channel blocker, α-blocker</td>
</tr>
<tr>
<td>7</td>
<td>34/M</td>
<td>IgA nephropathy</td>
<td>59.5</td>
<td>2.3</td>
<td>91.7</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>8</td>
<td>68/M</td>
<td>Diabetic nephropathy</td>
<td>57.5</td>
<td>3.0</td>
<td>90.0</td>
<td>Calcium channel blocker, α-blocker</td>
</tr>
<tr>
<td>Mean</td>
<td>55.6 ± 12.3</td>
<td></td>
<td>3.1 ± 0.9</td>
<td>108.9 ± 18.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasmic antibody; APKD, adult onset polycystic kidney disease; Cr, creatinine; MBP, mean blood pressure; M, male; F, female; MPGN, membranoproliferative glomerulonephritis.
Cr level at baseline was 3.1 ± 0.9 mg/dl. Mean blood pressure (MBP) at baseline was 108.9 ± 18.4 mmHg. Body weight of each patient was also shown. All patients did not have edema and episodes that would affect their muscle mass, including infection and malnutrition, had not occurred during the study. Each patient received 25 to 50 mg of losartan daily to decrease the blood pressure (Table 2). Medication before the treatment of losartan was continued and the dosage was not altered during follow-up period. As antihypertensive treatment, 7 patients received calcium channel blocker, two \( \alpha \)-blocker, two ACE-I and one \( \beta \)-blocker. Only 2 out of 8 patients were treated with ACE-I, despite the beneficial effects of ACE-I therapy in patients with chronic renal disease (Maschio et al.), because there are responders and non-responders to ACE-I or ARB, depending on individual (patient) factors in diabetic and non-diabetic renal disease (Bos et al. 2000). Two patients received maintenance dosage of steroid. Allopurinol was given in 1 patient.

**Table 2. Effect of losartan on slopes of reciprocal serum creatinine (sCr) plot in each patient**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dosage of losartan (mg/day)</th>
<th>sCr (mg/dl)</th>
<th>Slope of reciprocal sCr plot (dl/mg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before losartan</td>
<td>After losartan</td>
<td>Before losartan</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>5.2</td>
<td>7.2</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Mean Cr</td>
<td>3.1 ± 0.9</td>
<td>3.5 ± 1.6</td>
<td>-0.004 ± 0.03</td>
</tr>
</tbody>
</table>

\* \( p < 0.05 \) vs pretreatment period.

Statistics

Data are expressed as mean ± s.d. A software program (StatView 5.0, Abacus Concept Inc., Berkeley, CA, USA) was used for the statistical analysis. Paired Student \( t \)-test was used to compare the values between before and after the losartan treatment. Linear regression analysis was used to determine the relationship between degree of MBP change and \( 1/sCr \) slope change. A \( p \) value of 0.05 used to determine significance.

**Results**

MBP was decreased in 5 patients, but mean value of all patients did not change significantly after the treatment for 24 weeks (108.9 ± 18.4 mmHg before and 101.3 ± 12.1 mmHg after losartan, \( p = 0.21 \), Fig. 1A). Although serum Cr level was increased after 24 weeks from the initiation of losartan in 5 cases, the mean value difference was not significant (3.1 ± 0.9 mg/dl before and 3.5 ± 1.6 mg/dl after losartan, \( p = 0.18 \), Fig.
Fig. 1. Changes in mean blood pressure, serum levels of creatinine, potassium and uric acid before and after losartan therapy. A: Changes in mean blood pressure (MBP). B: Changes in serum creatinine (Cr). C: Changes in serum potassium (K). D: Changes in serum uric acid (UA).

Fig. 2. Reciprocal serum creatinine (1/sCr) plot before and after introduction of losartan therapy in each patient. Each line was constructed by plotting reciprocal values of serum Cr against time. The slope of each line indicates the rate of progression of renal dysfunction.

Fig. 3. Relationship between degree of mean blood pressure change (ΔMBP) and slope of reciprocal serum creatinine plot change (Δ1/sCr) in patients treated with losartan for 24 weeks. ΔMBP was defined as baseline MBP value minus MBP value after 24 weeks and Δ1/Cr was defined by value of 1/sCr slope before losartan treatment minus 1/sCr slope value after introduction of losartan.
Slope of $1/sCr$ was decreased in 6 out of 8 patients, and was unchanged in remaining 2 (Fig. 2 and Table 2). The slope of $1/sCr$ was reduced significantly after losartan ($-0.004 \pm 0.002$ dl/mg/week before and $-0.001 \pm 0.002$ dl/mg/week after losartan, $p < 0.05$, Fig. 2 and Table 2). There was a trend that improvement of slope of $1/sCr$ was related to the degree of MBP change ($p = 0.056$, Fig. 3).

Data of proteinuria before and after the losartan treatment were available in 4 patients (Table 3). Reduction of proteinuria as expressed by urinary protein-to-creatinine ratio was observed 3 out of 4 patients. Baseline proteinuria level was low in the remaining patient in whom losartan did not reduce the amount of urinary protein excretion. Serum K levels increased in 6 cases, but the mean value did not change significantly after the treatment for 24 weeks (4.7 $\pm$ 0.3 mEq/l before and 5.3 $\pm$ 0.6 mEq/l after losartan, $p = 0.06$, Fig. 1C). Mean serum UA level was unchanged after the treatment for 24 weeks (7.9 $\pm$ 1.0 mg/dl before and 7.7 $\pm$ 1.0 mg/dl after losartan, $p = 0.67$, Fig. 1D). No adverse effect of losartan was observed during the 24 weeks of treatment.

**DISCUSSION**

In most of clinical trials to explore the beneficial effects of ACE-I or AIIA on chronic renal diseases, levels of serum Cr at the entry were less than 3.0 mg/dl. In addition, there is a concern about worsening of renal function by pharmacological interruption of renin-angiotensin system in patients with chronic renal failure because such treatment may decrease intraglomerular pressure inadequately. Initial increase of serum Cr within 30% after ACE-I treatment may reflect adequate intraglomerular pressure reduction (Bakris and Weir 2000), however, upper limit of serum Cr until which this indication is applied remains undetermined. Ruggeneti et al. (2001) showed that treatment of ACE-I was renoprotective for those with mean serum Cr > 3.0 mg/dl in the post hoc analysis of the ramipril efficacy in nephropathy trial. RENAAL study showed that losartan retard the progression of nephropathy of type 2 diabetes whose serum Cr at baseline was between 1.3 and 3.0 mg/dl (Brenner et al. 2001). These results suggest pharmacological inhibition of renin-angiotensin system with ACE-I or AIIA is effective in patients with advanced renal insufficiency. However, current available results of large-scale clinical studies are limited in diabetic nephropathy (Brenner et al. 2001).

In the present study, we found that the initiation of losartan resulted in a significant reduction of mean 1/sCr slope in 8 patients with chronic renal failure with various etiologies and with serum Cr level > 2.0 mg/dl. The velocity of progressive impairment of renal function as defined by 1/sCr slope was not accelerated by the treatment of losartan in the all patients but rather was slowed. Our subjects included 4 cases with serum Cr level $\geq$ 3.0 mg/ml. Even in such patients, slope of 1/Cr was decreased in 3 and was not changed in remaining 1.

The mechanism by which losartan retarded the progression of renal dysfunction and the reason why losartan failed to improve the 1/sCr slope in 2 patients in the present study remains to be unknown. Adequate blood pressure control was not achieved after the initiation of losartan. A renoprotective effect of losartan seems to be blood pressure-independent in one hand (Brenner
et al. 2001), but hypertension is known to be an independent risk factor for ESRD (Peterson et al. 1995). There was a trend that the improvement of the slope of 1/sCr was related to the changes of MBP by losartan. Blood pressure lowering effect, at least in part, may account for the reduction of 1/Cr slope by losartan. If blood pressure had been strictly controlled, losartan may have exerted its renoprotective effect more dramatically and improved the 1/sCr slope in all of our patients. It is acknowledged that reduction of proteinuria is closely associated with renoprotective effect of AIIA (de Zeeuw et al. 2004). Although proteinuria was not assessed quantitatively in all the patients, reduction of proteinuria was observed 3 out of 4 patients. Thus antiproteinuric effect of losartan may also account for the improvement of 1/sCr slope. Taken together, both control of blood pressure and reduction of proteinuria may be prerequisite condition for the AIIA treatment of advanced renal insufficiency. Further study is needed to clarify the optimal dose of losartan to achieve adequate blood pressure control and reduction of proteinuria in patients with advanced renal insufficiency.

There were various etiologies of chronic renal diseases in the present study. Angiotensin-II has shown to be involved in the formation of common pathological features such as glomerulosclerosis and interstitial fibrosis (Johnson et al. 1992; Klahr et al. 1995; Wolf 1998; Yamabe et al. 2000). These suggest that blockade of renin-angiotensin system may delay the progression of various types of chronic renal disease. Our study included a patient with APKD. The effect of ACE-I on the progression of APKD is inconclusive (Jafar et al. 2005) and decline in renal function by ACE-I treatment has been reported (Chapman et al. 1991). We did not exclude a patient with APKD in the present study because such patients are also considered to be candidates for AIIA treatment to prevent cardiovascular disease that is a leading cause of death in patients with ESRD. Losartan did not worsen natural course of renal function in our APKD patient as 1/sCr slope was not changed by losartan treatment.

There was a trend of increase in serum K after losartan. Although AIIA may induce hyperkalemia to a lesser extent than ACE-I (Bakris et al. 2000), caution is still needed when it is given to patients with advanced renal insufficiency. Our patients did not reveal hyperkalemic electrocardiographic changes (not shown). It seems beneficial to keep serum K level above 4.5 mEq/l in acute myocardial infarction and heart failure (Macdonald and Struthers 2004). Optimal level of serum K in patients with chronic renal failure treated with AIIA is yet to be determined.

Losartan is known to increase renal UA excretion (Roch-Ramel et al. 1997). We were not able to find reduction of serum UA after losartan. This may suggest UA-lowering effect of losartan is restricted to patients whose renal function is preserved.

Although the present study is a short-term retrospective one done in a small number of patients, losartan seems to retard the progression of advanced renal insufficiency and monitoring of 1/sCr slope may be recommended when AIIA is given to patients with renal failure to confirm its effect and safety. A large randomized controlled study is needed to confirm this preliminary result and clarify the optimal dose of losartan for these patients.

References


Renoprotective Effect of Losartan in Advanced Renal Insufficiency


