ACE Inhibitor Versus β-Blocker for the Treatment of Hypertension in Renal Allograft Recipients

Martin Hausberg, Michael Barenbrock, Helge Hohage, Susanne Müller, Stefan Heidenreich, Karl-Heinz Rahn

Abstract—Angiotensin-converting enzyme (ACE) inhibitors have been shown to slow the progression of chronic renal failure. However, the value of ACE inhibitors for the treatment of hypertension in renal allograft recipients has not been established. ACE inhibitors dilate the efferent glomerular arteriole, an effect that may aggravate the decrease in glomerular filtration rate resulting from cyclosporine-induced vasoconstriction at the afferent glomerular arteriole. Therefore, the goal of this double-blind, randomized study was to compare the antihypertensive and renal effects of the ACE inhibitor quinapril with those of the β-blocker atenolol in renal allograft recipients in whom hypertension developed 6 to 12 weeks after transplantation. All patients received cyclosporine as an immunosuppressant and had stable graft function (serum creatinine concentration, <220 μmol/L) at entry into the study. Twenty-nine patients who received quinapril (daily dose titrated between 2.5 and 20 mg) and 30 patients who received atenolol (daily dose titrated between 12.5 and 100 mg) completed the 24-month study. The two groups did not differ in age, sex ratio, height, and weight before entry into the study. Quinapril decreased diastolic blood pressure from 96±1 to 84±1 mm Hg (average throughout treatment period), and atenolol decreased diastolic blood pressure from 96±1 to 83±1 mm Hg. The serum creatinine concentration did not change significantly in either group after 24 months (129±8 μmol/L at entry and 148±19 μmol/L after 24 months in the quinapril group and 131±6 μmol/L at entry and 152±15 μmol/L after 24 months in the atenolol group; P=NS for both groups). After 24 months, the change in urinary albumin excretion from baseline was −10±15 mg/d in the quinapril group and 52±32 mg/d in the atenolol group (P=0.03). These results show that quinapril and atenolol are effective antihypertensive drugs when used after renal transplantation. Moreover, compared with atenolol, quinapril has no adverse effects on graft function. The relative reduction in albuminuria observed with quinapril as compared with atenolol could indicate a beneficial effect of quinapril on long-term graft function. (Hypertension. 1999;33:862-868.)

Key Words: transplantation, renal hypertension β-adrenergic receptor blockers angiotensin-converting enzyme inhibitors cyclosporine

Use of cyclosporine in the immunosuppressive therapy of renal allograft recipients has been shown to improve early outcome and short-term1-2 and long-term graft survival.3 However, use of cyclosporine after renal transplantation is associated with a high prevalence of hypertension.4,5 Posttransplant hypertension in cyclosporine-treated renal allograft recipients generally develops within the first year after transplantation.6-7 Hypertension is a major cause of chronic allograft failure.8,9 It is characterized by sodium retention and volume expansion,9,10 enhanced sympathetic nerve activity,11 and renal vasoconstriction related in part to endothelin,12 which preferentially affects the afferent arterioles and causes a decrease in glomerular filtration rate and renal plasma flow.13

In patients with chronic renal disease, therapy for hypertension slows the progression of renal insufficiency.14 Angiotensin-converting enzyme (ACE) inhibitors seem to be particularly effective in slowing the deterioration of renal function in patients with diabetic15,16 and non-diabetic glomerular disease.17,18 ACE inhibitors induce vasodilation preferentially at the efferent glomerular arterioles, thereby reducing intraglomerular capillary pressure, correcting glomerular hypertension, and preventing hyperfiltration.19,20 These mechanisms may be responsible for the reduction in proteinuria, decrease in glomerular hypertrophy, and prevention of glomerular sclerosis observed with use of ACE inhibitors in chronic renal disease.6,14,20 As in chronic renal parenchymal disease, hypertension is often associated with progressive deterioration of renal function, glomerular capillary hypertension, and proteinuria in renal transplant recipients.21-26 Therefore, it may be hypothesized that ACE inhibitors preserve glomerular morphology and function in renal allograft recip-
patients.27 On the other hand, by their vasodilator effect at the efferent glomerular arteriole,19 ACE inhibitors may potentiate the reduction of glomerular filtration rate caused by cyclosporine.13

The aim of this study was to compare the effects of the ACE inhibitor quinapril on blood pressure and renal allograft function with those of the β-blocker atenolol, which does not have overt direct renal vascular effects28 but which is a standard antihypertensive drug used after kidney transplantation.4

Methods

Patients

Patients were eligible for the study if they were 18 to 60 years old and had received a renal allograft 6 to 12 weeks earlier. Patients had sitting diastolic blood pressures (DBPs) of >90 mm Hg in the absence of antihypertensive medication on 3 measurements obtained on different days. Renal allograft function was stable (serum creatinine concentration, <220 μmol/L).

Exclusion criteria were renal allograft artery stenosis; more than 1 renal transplantation; myocardial infarction within the previous 6 months; history of stroke, liver disease (alanine aminotransferase and aspartate aminotransferase more than twice the upper normal range), malignancies, diabetes mellitus, and lupus erythematosus; known intolerance of ACE inhibitors, β-blockers, or diuretics; obstructive pulmonary disease; bradycardia (heart rate of <52 bpm); heart failure; serious arrhythmias; history of hereditary angioedema; pregnancy or desire to become pregnant; known noncompliance; participation in other studies within the 30 days before inclusion in this study; and inability to give informed consent. The study was approved by the Institutional Review Board on Human Investigation, and written informed consent was obtained from all patients.

Study Design

Antihypertensive Treatment

Patients were randomly selected to receive either atenolol or quinapril for a total of 24 months. Study medication was taken between 7 and 10 AM. The initial dosage was 12.5 mg of atenolol once daily or 2.5 mg of quinapril once daily (dosage step 1). If DBP values of <90 mm Hg were not obtained, the dosage was titrated in 3 additional steps (step 2, to 25 mg of atenolol or 5 mg of quinapril; step 3, to 50 mg of atenolol or 10 mg of quinapril; and step 4, to 100 mg of atenolol or 20 mg of quinapril). If with step 4 the target DBP of <90 mm Hg was not reached, 40 to 80 mg of furosemide once daily was added in an open way. If this was still insufficient for blood pressure control, other antihypertensive agents were added.

Immunosuppressive Treatment

Immunosuppressive treatment consisted of either cyclosporine and prednisolone (5 to 15 mg/d) or cyclosporine, azathioprine (1 to 2 mg/d per kg of body weight), and prednisolone (5 to 15 mg/d). Cyclosporine whole-blood trough levels were individually adjusted between 7 and 10 AM. The initial dosage was 12.5 mg of atenolol, which does not have overt β-blocker atenolol, which does not have overt

Protocol

During the first month, patients were seen weekly; thereafter, they were seen once every 2 weeks for up to 6 months. Then, follow-up visits were scheduled monthly for the next 6 months and thereafter once every 3 months up to month 24. Patients attended the outpatient department between 7 and 10 AM before the antihypertensive drugs were taken. At each visit, a physical examination (including measurements of blood pressure, heart rate, and body weight) and laboratory analyses were performed. At entry into the study, after 12 months, and after 24 months, ultrasound examinations of the renal allografts were performed. The results of all measurements, concomitant medications, adverse events, and patient compliance (including pill counts) were reported on case report forms.

Measurements

Systolic blood pressure (SBP), DBP, and heart rate were measured with the patient sitting after 10 minutes of rest using an automatic sphygmomanometer (Dinamap, model 1846 SX). The average of 3 measurements taken in intervals of 3 minutes was calculated. Blood pressure was measured at the arm without an arteriovenous fistula. If patients did not have a patent brachial arteriovenous fistula, the arm with higher blood pressure readings was determined at entry into the study and used for all additional measurements.

Ultrasound examinations of the renal allografts were performed using a Picker CS9500 ultrasonic diagnostic instrument with a 3.5-MHz probe. Allograft length and width and cortex thickness were measured. Allograft volume was estimated using the rotational ellipsoid formula: $V = \frac{4}{3} \pi d_{\text{diameter}} \times d_{\text{transversal}}^3$. Allograft sinus volume was estimated using the following formula: $V = \frac{1}{2} \pi d_{\text{diameter}} (2d_{\text{cortex}} - 2d_{\text{cortex}}^2)$. Allograft cortex volume was calculated as allograft volume minus allograft sinus volume. At entry and at months 12 and 24, creatinine clearance and 24-hour urinary excretion of total protein (biuret method), albumin, and α-microglobulin (turbidimetric method) were measured.

Outcome Measures

Primary outcome measures were changes in serum creatinine concentration and DBP in patients treated with atenolol as compared with patients treated with quinapril. Secondary outcome measures were the proportion of patients with increases in serum creatinine concentration of ≥45 μmol/L (≥0.5 mg/dL) during the study; development of allograft failure; changes in urinary excretion of protein, albumin, and α-microglobulin; and changes in creatinine clearance in patients treated with atenolol as compared with quinapril.

Statistical Analysis

Data are mean±SEM. For continuous variables, an average value while receiving treatment was calculated (average of values at months 3, 6, 9, 12, 15, 18, 21, and 24 or every 3 months up to the last value for the intention-to-treat analysis). Statistical comparison between the atenolol and quinapril groups was performed by using the Wilcoxon rank-sum test for continuous variables. The influence of treatment on the course of continuous variables was tested with the Wilcoxon signed-rank test. Qualitative variables were compared using Fisher’s exact test. Statistical significance was assumed at $P<0.05$. All analyses were performed using SAS software.

Sample size was calculated to detect a difference in serum creatinine concentrations between treatment groups of 45 μmol/L (0.5 mg/dL). Considering a type I error of 0.05, a type II error of 0.2, and an average standard deviation of serum creatinine concentrations of 62 μmol/L (0.7 mg/dL), a sample size of 29 patients completing the study in each treatment group was estimated.

Results

Patients Entered Into Study and Withdrawals

Between September 1992 and January 1995, 70 patients were entered into the study, on average 68±3 days after renal transplantation. Causes of renal failure were chronic glomerulonephritis in 30 patients, rapid progressive glomerulonephritis in 7, polycystic kidney disease in 7, chronic pyelonephritis in 12, renal vascular disease in 3, hemolytic uremic syndrome in 2, Alport’s syndrome in 1, medullary sponge kidney in 1, and unknown in 7.

Of these 70 patients, 35 were randomly selected to receive atenolol and 35 were selected to receive quinapril. Demographic data of the 2 treatment groups are shown in Table 1. There were no differences between groups.

Thirty patients in the atenolol group and 29 in the quinapril group completed the 24-month study. Five patients in the
TABLE 1. Demographic Data of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quinapril</th>
<th>Atenolol</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
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<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>43±2</td>
<td>43±2</td>
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<td>Sex, male/female</td>
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<td>26/9</td>
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<tr>
<td>Weight, kg</td>
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<td>69±2</td>
<td>NS</td>
</tr>
<tr>
<td>Patients who completed the study</td>
<td>43±2</td>
<td>43±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Intention-to-Treat Analysis

The data of 69 patients in whom at least 1 follow-up visit was performed were subjected to an intention-to-treat analysis. Reasons for withdrawal in the quinapril group were unwillingness to continue in 3 patients, switch from cyclosporine to tacrolimus in 1, death resulting from septicemia in 1, and acute hepatitis C in 1. Reasons for withdrawal in the atenolol group were unwillingness to continue in 3 patients, bradycardia in 1, and switch from cyclosporine to tacrolimus in 1. Except for the patient who died of septicemia, all patients who withdrew lived for at least 2 years after inclusion in the study. In 2 of the patients who withdrew, 1 in each group, terminal graft failure developed within 1 year after withdrawal, and both resumed hemodialysis treatment.

In both groups, there was a significant reduction in SBP and DBP. Heart rate decreased in atenolol-treated patients and did not change significantly in quinapril-treated patients. There was no significant change in serum creatinine concentrations or creatinine clearance in either group. Five patients in the quinapril group and 8 in the atenolol group had an increase in serum creatinine concentration of >45 \(\mu\text{mol/L}\) (>0.5 mg/dL) after 24 months or at withdrawal (P=NS). Twenty-four-hour urinary protein excretion significantly decreased in quinapril-treated patients and did not change significantly in atenolol-treated patients. Twenty-four-hour urinary albumin excretion tended to decrease in the quinapril group and to increase in the atenolol group. Changes in 24-hour urinary albumin excretion in the quinapril group differed significantly from those in the atenolol group (P=0.03). Twenty-four-hour urinary \(\alpha_1\)-microglobulin excretion significantly decreased in quinapril-treated patients and did not change significantly in atenolol-treated patients. However, the changes in \(\alpha_1\)-microglobulinuria did not differ significantly between groups.

According-to-Protocol Analysis

The according-to-protocol analysis was performed for 30 patients treated with atenolol and 29 patients treated with quinapril who completed the 24-month study. The average dose of study medication at month 24 was 16±1 mg/d in quinapril-treated patients and 67±7 mg/d in atenolol-treated patients. Twenty-two quinapril-treated patients and 19 atenolol-treated patients required furosemide (average final doses were 37±3 mg/d for quinapril-treated patients and 38±3 mg/d for atenolol-treated patients). Twenty-one patients in the quinapril group and 14 in the atenolol group received calcium antagonists (21 versus 14 patients). However, the average time on treatment with calcium antagonists was higher in the atenolol group (597±41 days versus 412±53 days in the quinapril group; P=0.006). \(\beta\)-Blockers were...
TABLE 3. According-to-Protocol Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quinapril</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td>Blood pressure, mm Hg</td>
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<td></td>
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<td>145±3</td>
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<tr>
<td>Diastolic</td>
<td>96±1</td>
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<tr>
<td>Heart rate, bpm</td>
<td>81±2</td>
<td>76±2</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL‡</td>
<td>129±8</td>
<td>148±19</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min§</td>
<td>87±9</td>
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</tr>
<tr>
<td>Urinary protein excretion, g/d</td>
<td>0.7±0.1</td>
<td>0.4±0.1*</td>
</tr>
<tr>
<td>Urinary albumin excretion, mg/d</td>
<td>53±12</td>
<td>42±11</td>
</tr>
<tr>
<td>Urinary α1-microglobulin excretion, mg/d</td>
<td>48±12</td>
<td>21±5*</td>
</tr>
<tr>
<td>Cyclosporine trough level, μg/L</td>
<td>103±6</td>
<td>91±9</td>
</tr>
<tr>
<td>Prednisolone dose, mg/d</td>
<td>15.0±2.1</td>
<td>7.8±0.3*</td>
</tr>
</tbody>
</table>

*P<0.05 vs baseline value. †P<0.05, quinapril vs atenolol. Baseline values did not differ significantly between groups for any variable.

To convert from micromolar concentration to milligrams per deciliter, multiply by 0.0113.

†To convert from milliliters per minute to milliliters per second, multiply by 0.01667.

administered to 15 patients in the quinapril group (replacing calcium antagonists in 9 patients and in addition to calcium antagonists in 6) and to 9 patients in the atenolol group (replacing calcium antagonists in 3 and in addition to calcium antagonists in 6).

Both atenolol-treated and quinapril-treated patients had significant reductions in SBP and DBP (Table 3 and Figure 1). The reduction in DBP did not differ between groups. The average reduction in SBP during the 24-month treatment period tended to be more pronounced in atenolol-treated patients (−9±2 and −15±3 mm Hg in the quinapril and atenolol groups, respectively; P=0.06). However, average SBP and DBP values during the 24-month treatment period were similar in both groups (Figure 1).

Heart rate did not change significantly in quinapril-treated patients at any time, whereas atenolol-treated patients had a significant reduction in heart rate by an average of 10±2 bpm during the entire study.

At entry, serum creatinine concentrations and creatinine clearances did not differ between the atenolol and quinapril groups. Neither serum creatinine concentrations nor creatinine clearances changed significantly in either group during the study (Table 3 and Figure 2). Furthermore, there were no statistically significant differences between groups in serum creatinine levels at any time.

However, a subgroup analysis of patients with serum creatinine concentrations above the median value of 124 μmol/L at entry (n=13 for quinapril and n=19 for atenolol) showed after 24 months a significant reduction in serum creatinine concentrations from 166±8 to 140±9 μmol/L (P<0.01) in quinapril-treated patients, which was significantly different (P=0.02) from the evolution in atenolol-treated patients (from 150±6 to 174±18 μmol/L; P=NS). At termination of the study, 4 quinapril-treated patients and 6 atenolol-treated patients had an increase in serum creatinine concentrations of >45 μmol/L (>0.5 mg/dL) above baseline values (P=NS). There was a significant correlation between DBP and serum creatinine concentration in the atenolol group (Spearman coefficient=0.227; P=0.0001) but not in the quinapril group (Spearman coefficient=0.04; P=0.314). Se-
rum creatinine concentrations were not lower in patients who received calcium antagonists as compared with patients who did not in either group.

Total allograft volume and allograft cortex volume decreased significantly in both groups after 12 months. In the quinapril group, allograft volume decreased from 154±11 to 118±5 mL (P<0.0001) and cortex volume decreased from 131±8 to 106±6 mL (P<0.0005). In the atenolol group, allograft volume decreased from 141±8 to 117±8 mL (P<0.005) and cortex volume decreased from 128±8 to 104±6 mL (P<0.005). However, there were no significant differences between atenolol-treated and quinapril-treated patients. Also, after 24 months, total allograft volume and allograft cortex volume tended to be lower than at entry in both groups, but this did not reach statistical significance in either group.

Twenty-four-hour urinary protein excretion significantly decreased in quinapril-treated patients but remained unchanged in the atenolol group (Table 3). Twenty-four-hour urinary albumin excretion tended to decrease in the quinapril group and to increase in the atenolol group after 24 months of treatment. Changes in the quinapril group differed significantly from changes in the atenolol group. Twenty-four-hour urinary α1-microglobulin excretion significantly decreased in quinapril-treated patients and tended to decrease in the atenolol group. Changes in α1-microglobulinuria did not differ between groups.

In both treatment groups, patients gained weight. At month 24, the average increase in body weight from baseline values was 6±1 kg in the quinapril group and 8±1 kg in the atenolol group (P<0.0001 vs baseline for all values). There were no significant differences between groups.

Cyclosporine whole-blood trough levels were similar in atenolol-treated and quinapril-treated patients and did not change significantly throughout the study. Prednisolone dosage did not differ significantly between groups at entry. In both groups, there were progressive but similar reductions of prednisolone dosages during the 24-month study (Table 3).

**Discussion**

This study shows, first, that the ACE inhibitor quinapril and the β-blocker atenolol are effective in the treatment of posttransplant hypertension in renal allograft recipients receiving cyclosporine. Second, renal transplant function did not differ between patients treated with quinapril and those treated with atenolol. A significant deterioration of renal allograft function was not observed in either group at the end of the 24-month treatment period. Third, when compared with the changes in atenolol-treated patients, quinapril-treated renal allograft recipients had a significant reduction in proteinuria and urinary albumin excretion at the end of the 24-month observation period.

Hypertension develops in the majority of renal allograft recipients treated with cyclosporine. Possible mechanisms of cyclosporine-induced hypertension include activation of the sympathetic nervous system and renin-angiotensin system and disturbance of the balance between vasodilator and vasoconstrictor pathways. Importantly, each dose of cyclosporine causes renal vasoconstriction, affecting the arterial pressure with lisinopril of approximately 3 g/d.
and observed a significant reduction in proteinuria without deterioration of renal function after 3 months of treatment.

This study is the first to compare an ACE inhibitor with a β-blocker in hypertensive renal allograft recipients receiving cyclosporine. The above-mentioned studies comparing calcium antagonists and ACE inhibitors in renal transplantation did not show a clear advantage of either drug. We also did not observe an obvious advantage of the β-blocker atenolol or the ACE inhibitor quinapril in terms of blood pressure control and renal allograft function. In both groups, good blood pressure control was achieved, and in neither group was renal allograft function significantly deteriorated during the 24-month treatment period. However, we speculate that, compared with the changes in the atenolol group, the significant reductions in proteinuria and albuminuria with quinapril may be beneficial for the further development of renal allograft function in our patients. In support of this, Hohage et al. observed a negative influence of even mild proteinuria (<1 g/d) on long-term graft survival in renal transplant patients.

Limitations of the study include, first, patient selection. Only patients with good, stable graft function and no severe comitant disease were included. This may explain the excellent outcome for both groups and may be in part responsible for the lack of differences between groups. The subgroup analysis of patients with serum creatinine concentrations above the median value at entry, despite the limitations of such a retrospective analysis, suggests a beneficial effect of quinapril on renal function in this subgroup. Second, no measurements of glomerular filtration rate were made. However, measured changes in serum creatinine concentrations and creatinine clearance reflect changes in glomerular filtration rate because neither quinapril nor atenolol interfere with tubular creatinine secretion. Third, the observation period of 2 years may have been too short. It is conceivable that after a longer treatment period, differences in allograft function between treatment groups may appear.

**Conclusion**

The β-blocker atenolol and ACE inhibitor quinapril are effective for the treatment of hypertension in renal allograft recipients treated with cyclosporine. When compared with atenolol, quinapril has no adverse effects on graft function. The significant reduction in proteinuria observed with quinapril but not atenolol could indicate a beneficial effect of quinapril on long-term graft function.

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**References**


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