A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period

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Abstract

Background. Blockade of the renin–angiotensin–aldosterone system in the early post-transplant period remains controversial. Angiotensin II-receptor blockers (ARB) have many benefits to the patient with chronic kidney disease and these benefits may also apply to the renal transplant recipient (RTR). Additionally, there are theoretical benefits of ARB use in RTR. This study was designed to investigate the safety of early ARB use after renal transplantation.

Methods. RTR with serum creatinine levels < 3.0 mg/dl were randomized to receive either ARB (n = 29) or calcium-channel blocker (CCB; n = 27) as initial therapy for post-transplant hypertension. Differences in potassium, creatinine and haemoglobin concentrations were compared at baseline, 3, 6 and 12 months after transplantation.

Results. Withdrawal from the assigned treatment was high: 12 in the ARB group (due to hyperkalaemia in six) and 17 in the CCB group (due to intractable oedema in seven and post-transplant erythrocytosis requiring an angiotensin-converting enzyme inhibitor in seven). There were no differences in blood pressure, haemoglobin or creatinine concentration at any time-points. Mean potassium concentrations were only slightly higher in the ARB vs CCB group (range: 4.2–4.3 vs 3.7–3.8 mEq/l, respectively, but clinically significant) and the number of patients with potassium values > 6.0 mEq/l was higher in ARB (n = 7) vs CCB (n = 1).

Conclusions. These data suggest that hyperkalaemia is the major complication that occurs with the use of ARB in the immediate post-transplant period. ARB use does not affect renal function or complicate the post-transplant management of RTR. Other than reducing the incidence of post-transplant erythrocytosis, ARB use does not cause an excess incidence of anaemia. Strategies to reduce the risk of hyperkalaemia may allow increased use of ARB immediately after kidney transplantation.

Keywords: angiotensin II-receptor blocker; calcium-channel blocker; hyperkalaemia; hypertension; kidney transplantation

Introduction

The potential benefits of angiotensin II-converting enzyme inhibitors (ACEI) and angiotensin II-receptor blockers (ARB) in renal transplant recipients (RTR) are numerous and include treatment of blood pressure [1] and post-transplant erythrocytosis [2,3], decrease in proteinuria [4,5] and prevention of cardiovascular disease [6]. Blockade of the renin–angiotensin system leading to decreased glomerular hypertension and transforming growth factor-β-induced collagen formation may also have renoprotective effects [7]. Lastly, improved patient and graft survival has been reported in patients with chronic allograft nephropathy who are treated with these agents [8,9]. Despite these potential benefits, controversy surrounds the use of these agents because of the concern of side effects, such as hyperkalaemia, renal dysfunction and anaemia.

In previous studies examining the role of ACEI/ARB in RTR to treat hypertension or proteinuria, the agents have been found to be quite effective [4,10–13]. However, in these studies, the agents were not initiated in the early post-transplant period but later on, usually after >1 year [2–5]. In only one previous prospective randomized study in transplant patients have ACEI been started in the immediate post-transplant period [14]. There is no prospective study examining ARB use in this period. In the study of ACEI use in the immediate post transplant period there was only one
patient reported to be withdrawn from therapy due to hyperkalemia. This patient was treated with lisinopril. However, there was no analysis of serum creatinine concentration and no mention of whether or not a priori strategies were put into place to prevent hyperkalemia. We believed that safety concerns were limiting the use of this class of medication and examined our own data retrospectively. We reported that ACEI/ARB drugs appeared to be safe when used in the early post-transplant period [15]. These initial findings seemed to confirm those of Midvedt et al. [14]. In order to confirm these observations and examine the safety of ARB in the early post-transplant period, the following prospective randomized study was performed.

The objective of this trial was to assess the safety of ARB use, with regards to hyperkalemia and renal function, in the immediate post-transplant period and to do so in a manner that would replicate average clinic practice. Therefore, after randomization, no special interventions were made to enhance retention in either treatment group. We also wished to determine if these agents caused clinically significant anaemia in patients with good allograft function.

Subjects and methods

Patient selection and randomization

Between 15 April 2001 and 14 April 2003, all patients receiving deceased donor or living donor kidney transplants at Yale University School of Medicine were screened for eligibility in this study. Eligibility criteria for the study were a willingness to participate, the ability to give informed consent, recipient of a deceased donor, living renal transplant, requiring therapy for hypertension in the early post-transplant period, with a serum creatinine of 3 mg/dl or declining at a rate of 1 mg/dl per day and with a serum potassium of ≤5.5 mEq/l. For the purposes of this study, the early post-transplant period is defined as days 0-30. Patients were ineligible to participate if they did not meet one of the above inclusion criteria, had a previous anaphylactic reaction to ACEI, were normotensive, had any clinical evidence of volume depletion, were pregnant (positive human chorionic gonadotrophin screen) were the attending physician refused enrolment by the patient.

Patients were randomized in blocks of five using a random number table. Treatment group assignment was placed in sealed envelopes and opened after the patient gave informed consent.

Study protocol

At the time of randomization, patients were assigned to a calcium-channel blocker (CCB; amlodipine) or ARB (losartan) as initial therapy for hypertension. The dose of the study medication was titrated to effect with regards to blood pressure control or a maximum dose of amlodipine 20 mg per day and losartan 100 mg per day. As clinically indicated, additional antihypertensive medications were added for blood pressure control. These medications included labetolol, selective beta-1 blocker (atenolol or metoprolol), non-selective or selective alpha-blocker (clonidine, terazosin or doxazosin) and, finally, a diuretic if needed. These medications, either individually or in combination, represent the standard of practice in the treatment of post-transplant hypertension. Two trained individuals in the transplant clinic obtained the blood pressure measurements at baseline, 3, 6 and 12 months. The central laboratory at Yale–New Haven Hospital was used for all laboratory studies. The following laboratory values were collected at enrolment and on a monthly basis thereafter: serum potassium, creatinine, and haemoglobin concentration, haematocrit and calcineurin inhibitor level.

Patients were considered to be protocol failures if they developed medication side effects requiring termination of the assigned medication or if they required the medication to which they were not randomized (e.g. the need for an ACEI for post-transplant erythrocytosis). Because the treating physicians were not blinded to the assigned treatment group, a priori the following indications were set for patient withdrawal from the study. These were patient choice or pregnancy for both groups. If randomized to CCB, the development of oedema refractory to diuretic administration or the development of post-transplant erythrocytosis or haematocrit >50%, was considered a protocol stop point. If randomized to ARB, the development of a serum potassium level >5.5 mg/dl and requiring dietary potassium restriction, diuretic or sodium polystyrene sulphonate (Kayexalate®) for treatment was a protocol stop point.

Patients were followed in the renal transplant clinics of Yale University School of Medicine for the duration of the study period. In addition to their immunosuppressive regimen per protocol, all patients received single-strength trimethoprim sulphamethoxazole daily as prophylaxis for Pneumocystis carinii pneumonia, 3 months of valgancyclovir or acyclovir as prophylaxis for viral infection, and nystatin swish and swallow as fungal prophylaxis until prednisone was tapered to 10 mg per day.

The decision to withdraw a patient was made by two of the investigators, R.N.F. and M.J.B., after review of the data. All data were extracted from the transplant flow sheet and electronic medical record. Retrospectively, information on the number of hospitalizations and biopsies performed on the patients enrolled and the patients who met the eligibility criteria but were not enrolled was collected and analysed to assess whether or not being a study participant created bias in the care delivered that may have affected the results. For example, did physician knowledge that a patient was on ARB lead them to attribute an elevated creatinine to haemodynamic effects of the medication and miss an episode of rejection?

Statistical analysis

All data in this study were analysed as intention to treatment. Data expressed as means±SD were analysed using the two-sided Student’s t-test assuming equal variance of the mean. Categorical data were analysed using the chi-squared test of significance.

Patients’ rights and protection

This study protocol was approved by the Human Investigations Committee of Yale University School of Medicine.
All patients were given detailed information about the rationale for the study and its risks. All patients gave written informed consent.

Results

Of the 146 renal transplants performed between 15 April 2001 and 14 April 2003, 95 (65%) met the eligibility criteria and 51 (35%) did not. Fifty-seven (60%) of the eligible patients were enrolled in the study. The reasons for not enrolling an eligible individual were patient refusal to participate or investigator not identifying a patient as potential enrollee in 33 (87%), patient refusal of losartan therapy in four (10%) and patient refusal of amlodipine therapy in one (3%). Randomization was successful, resulting in both groups having similar demographics (Table 1). At 3 months after randomization, 17/29 remained in the ARB group and 23/27 in the CCB group. For 6 and 12 months after randomization, the corresponding numbers of patients remaining in the study were ARB 17/29 and CCB 17/27 and ARB 17/29 and CCB 10/27, respectively. Immunosuppression was also similar in both groups. In the first 6 months of the protocol, immunosuppression was achieved with anti-CD 25 given intra-operatively and on post-operative day 4 and full-dose calcineurin inhibitor, rapamycin or mycophenolate mofetil and prednisone. During the final 18 months of enrolment, immunosuppression was achieved with anti-CD 25 induction, reduced-dose calcineurin inhibitor, rapamycin with or without prednisone. Similar numbers of patients in each group were in each immunosuppressive protocol.

Withdrawal from the study

Twelve of 29 patients (41%) in the ARB group and 17 of 27 patients (63%) in the CCB group were withdrawn from the study ($\chi^2 = 2.06$, NS). The main reason for withdrawal (Table 2) for patients in the ARB group was hyperkalaemia ($n = 6$), while patients in the CCB group were withdrawn because of intractable oedema ($n = 7$) or because of the development of post-transplant erythrocytosis requiring treatment with ACEI or ARB ($n = 7$). Of the patients in the ARB group withdrawn due to hyperkalaemia, 5/6 were withdrawn during the first month after transplantation.

Blood pressure

There was no difference in the average systolic and diastolic blood pressure between the two groups at any time period during the study. Furthermore, the average number of blood pressure medications did not differ between the two groups at 1 year (1.9±0.3 in ARB; 2.3±0.5 in CCB).

Serum potassium concentration

Although mean serum potassium concentrations were similar at enrolment, there was a slight, but statistically significant increase in levels at 3, 6 and 12 months in patients on ARB (Table 3). There was no difference in the number of patients from each group having serum potassium between 5.5 and 5.9 mEq/l (six in ARB group and nine in CCB group). However, seven patients in the ARB group developed a serum potassium level ≥6.0 mEq/l compared with one patient in the CCB group. Hyperkalaemia was the reason for withdrawal from the ARB group in six patients (Table 2).

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### Table 1. Demographics of enrolled patients

<table>
<thead>
<tr>
<th></th>
<th>ARB ($n = 29$)</th>
<th>CCB ($n = 27$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>CRT</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>LRT</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>49 (11.2)</td>
<td>46.9 (10.0)</td>
</tr>
<tr>
<td>Post-transplant day when randomized</td>
<td>4.6±4.7</td>
<td>4.5±4.7</td>
</tr>
</tbody>
</table>

### Table 2. Reasons for withdrawal from assigned study group

<table>
<thead>
<tr>
<th>Reason for withdrawal from study</th>
<th>ARB ($n = 29$)</th>
<th>CCB ($n = 27$)</th>
<th>$\chi^2 = 2.06$ (NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalaemia</td>
<td>12 (41)</td>
<td>17 (63)</td>
<td></td>
</tr>
<tr>
<td>Rejection</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No need for BP medication</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Post-transplant erythrocytosis</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Moved</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intractable oedema</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Need for ARB/ACEI for BP control</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes systemic lupus erythematosis, mesangiopcapillary glomerulonephritis type 1, IgA nephropathy and focal segmental glomerulosclerosis.
The study was specifically designed to examine the early use of ARB post-transplant, because recent data suggest that these agents may be protective against renal transplant ischaemic injury and improve recovery from delayed graft function when started early [16]. Possible mechanisms for this effect include a decrease in angiotensin-mediated vasoconstriction perpetuating delayed graft function [17], potential immunosuppressive effects that result from angiotensin II blockade [18] and an inhibition of apoptosis [19]. These data suggest that the traditional practice of avoiding agents in the ACEI/ARB category in the early post-transplant period should be re-examined.

The results of this randomized, prospective study suggest that the use of ARB in the early post-transplant period is not associated with worsening renal dysfunction or lower haematocrit. However, in distinction from the only other randomized trial to examine this question [14] we encountered a significant incidence of hyperkalaemia. Six patients discontinued ARB because of hyperkalaemia with serum potassium levels ≥6 mEq/l. The reason for the different finding is not immediately clear. Our medication protocol requires the use of single-strength trimethoprim sulphamethoxazole daily as prophylaxis for *P. carinii* pneumonia. All of the study participants had exposure to calcineurin inhibitors. It is well established that the hyperkalaemia associated with the use of ACEI or ARB is multifactorial. Furthermore, transplanted kidneys are believed to have tubular dysfunction, making them resistant to the action of aldosterone [20]. In addition to this observation, calcineurin inhibitors predispose patients to hyperkalaemia by suppressing aldosterone secretion and directly interfering with the secretion of potassium in the collecting duct [17]. A plausible explanation is that in our study population the hyperkalaemia was the result of the addition of trimethoprim sulphamethoxazole to the medication regimen in a patient population already predisposed to hyperkalaemia.

Five of these six patients developed the hyperkalaemia within the first post-transplant month while renal function was still improving and calcineurin inhibitor levels were being adjusted. In hindsight, the study should have been designed to restrict dietary potassium, especially in patients receiving ARB, during this early post-transplant period in which the risk of hyperkalaemia is highest in all patients. Further study is needed to determine whether the frequency of hyperkalaemia would be diminished significantly if dietary potassium were restricted at the onset. Nevertheless, while six patients were dropped from the ARB group because of hyperkalaemia, 17 patients were able to continue, reaping all the potential cardiac and renal benefits.

Use of ARB in the immediate post-transplant period did not result in higher serum creatinine levels with consequent need for biopsy or hospitalization. The mean serum creatinine concentration at all time-points, number of patients with a creatinine value between 1.5 and 2.0 mg/dl and number of patients with a creatinine value >2.0 mg/dl were the same in both groups. These results differ somewhat with those of Midvedt et al. [14]. The authors found a slightly but significantly lower glomerular filtration rate after 1 year.

### Table 3. Mean serum potassium concentrations (mEq/l)

<table>
<thead>
<tr>
<th>Time</th>
<th>Enrolment</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>4.5±0.5</td>
<td>4.3±0.4</td>
<td>4.3±0.5</td>
<td>4.2±0.4</td>
</tr>
<tr>
<td>CCB</td>
<td>4.3±0.6</td>
<td>3.7±0.4</td>
<td>3.8±0.4</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td><em>P</em>-value</td>
<td>0.26</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 4. Serum creatinine (mg/dl) and haemoglobin concentrations (g/dl)

<table>
<thead>
<tr>
<th>Time</th>
<th>Creatinine mg/dl (SD)</th>
<th>Haemoglobin mg/dl (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARB</td>
<td>CCB</td>
</tr>
<tr>
<td>Enrolment</td>
<td>1.9 (0.5)</td>
<td>2.0 (0.7)</td>
</tr>
<tr>
<td>3 months</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>6 months</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.5)</td>
</tr>
<tr>
<td>12 months</td>
<td>1.5 (0.6)</td>
<td>1.6 (0.03)</td>
</tr>
<tr>
<td>ARB</td>
<td>10.5 (1.2)</td>
<td>10.0 (1.5)</td>
</tr>
<tr>
<td>CCB</td>
<td>11.9 (1.3)</td>
<td>12.4 (1.8)</td>
</tr>
<tr>
<td></td>
<td>11.9 (2.3)</td>
<td>12.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>12.2 (2.2)</td>
<td>13.9 (1.3)</td>
</tr>
</tbody>
</table>

**Serum creatinine and haemoglobin concentrations**

The serum creatinine concentrations were not statistically different between the two groups at any time-point (Table 4). Between 1 and 3 months, there were six patients in the ARB group and seven in the CCB group with a serum creatinine level of 1.5–2.0 mg/dl and two patients in each group with a level of >2 mg/dl. Mean haemoglobin concentrations were also similar in both groups at all time periods. However, seven patients in the CCB group had to be withdrawn from that group because of the development of post-transplant erythrocytosis requiring treatment with an ACEI or ARB (Table 2). Analysis of the data with patients in the CCB group were developed post-transplant erythrocytosis and were removed does not alter the outcome with respect to differences in haemoglobin concentration.

In an effort to assess whether or not patients within the study received care or attention that was outside of usual practice, the sentinel events of hospital admission and renal allograft biopsy were tracked in the group of patients who were eligible for the study but not enrolled and compared with the two study groups. The average number of hospital admissions during the first 12 months following transplantation was similar for the ARB group (1.3±2.4), for the CCB group (0.9±1.1) and for eligible patients not in the study (1.7±3.0). There was also a similar number of allograft biopsies performed (between six and nine) in each group in the first 12 months post-transplant.

**Discussion**

The study was specifically designed to examine the early use of ARB post-transplant, because recent data suggest that these agents may be protective against renal transplant ischaemic injury and improve recovery...
in renal transplant patients initially treated with lisinopril vs nifedipine, a finding that may be explained by the haemodynamic effects of these agents [21]. The potential long-term benefits of these agents, such as the decrease in both proteinuria [4], and in interstitial scarring [13], as well as potential renal preservation [22] and cardiovascular risk reduction [6], compel us to become more comfortable with the haemodynamic increases in serum creatinine that may be observed with use of these agents. Our data do show that early blockade of the renin–angiotensin–aldosterone axis does not lead to more biopsies or hospitalizations for elevated serum creatinine concentration.

We did not find an increase in the incidence of anaemia or erythropoietin use to maintain haemoglobin concentrations >11 mg/dl in patients on ARB. A possible explanation is that these agents have less of an effect on haematocrit than ACEI [23]. It does appear that ARB use for hypertension is protective against post-transplant erythrocytosis. One patient in the ARB group developed post-transplant erythrocytosis compared with seven in the CCB group. The 26% incidence of post-transplant erythrocytosis in the CCB group is higher than would be expected in the general renal transplant population. We hypothesize that the increased incidence is an artefact of the study protocol. By design, and as it turned out, the protocol selected patients with better allograft function. It is possible that although post-transplant erythrocytosis is not correlated with erythropoietin concentrations, higher endogenous levels may potentiate post-transplant erythrocytosis in a predisposed individual. Conversely, poorer graft function for the same reason may be protective. The high incidence of oedema in the CCB group is also an artefact of the study design. Because patients in the CCB group could not receive an ACEI or ARB, higher dosages (up to 20 mg per day) of amlodipine were used. Our experience is that at this dosage-dependent lower extremity oedema is common. These findings are similar to those of Stigant et al. [5], who described hyperkalaemia, not renal dysfunction or anaemia, as the most common complication of ACEI started in RTR at a mean of 9 months post-transplant.

Potential problems with this study include the small numbers of patients in each group. This was due to the large number of patients dropped from each study arm, because of the strict design of the study protocol that required discontinuation of the ARB in patients with hyperkalaemia instead of first attempting dietary potassium restriction or diuretic use. Statistically, our sample size was large enough to detect a difference in the frequency of hyperkalaemia between groups. We detected no difference in renal function, assessed by serum creatinine, and anaemia, assessed by haemoglobin concentrations, but while we believe this to be a true finding, we concede that studies with a larger number of patients will be needed for corroboration.

It is tempting to extrapolate on the known benefits of ARB and the hypothesized advantages of ARB in RTR to routine clinical practice; however, hyperkalaemia is a potentially life-threatening complication and additional study is needed to determine if it can be avoided with the use of dietary potassium restriction or, possibly, the use of hydrochlorothiazide. Until the time such data become available, ARB should be used with caution and with close monitoring of serum potassium concentration in the immediate post-transplant period.

Conflict of interest statement. None declared.

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