The Canadian ACE-inhibitor trial to improve renal outcomes and patient survival in kidney transplantation—study design

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Abstract

Background. In non-transplant patients with chronic kidney disease and proteinuria, inhibition of the renin–angiotensin system with an ACE-inhibitor or an angiotensin receptor blocker has been shown to delay the progression of renal disease. Observational studies in the kidney transplant population have produced conflicting results with some studies showing benefit and others no benefit of renin–angiotensin system blockade.

Methods. This report describes the design and methodological issues of a randomized controlled trial evaluating the effect of ramipril in a renal transplant population. This study has been funded by a peer-reviewed grant from the Canadian Institutes of Health Research and is registered on the International Standard Randomised Controlled Trial Number Registry (ISRCTN-78129473).

Results. The study will randomize 528 kidney transplant patients (11 Canadian centers) with proteinuria and an estimated GFR between 20 and 55 ml/min/1.73 m² to either ramipril (5 mg BID) or placebo. Patients, clinical staff and investigators will be blinded to treatment allocation. The primary outcome will be a composite measure incorporating doubling of serum creatinine, end stage renal disease or death. Principal secondary outcomes include: decline in GFR using a radioisotopic method, change in proteinuria, change in blood pressure, incidence of adverse events (e.g. hyperkalemia, anemia), incidence of cardiovascular events and health-related quality of life assessed by the Short Form-36 and the EuroQol-5D.

Conclusions. Upon completion, this trial will provide clinically meaningful evidence about whether treatment with an ACE-inhibitor will reduce patient mortality and prolong allograft survival in renal transplant recipients.

Keywords: ACE-inhibitor; kidney transplantation; ramipril; randomized trial

Introduction

Kidney transplantation is the treatment of choice for end-stage renal disease as it prolongs survival [1], improves quality of life [2,3] and is less costly when compared to dialysis [2]. However, we are not realizing the full potential of this treatment because many renal transplants fail prematurely due to progressive chronic kidney disease or premature patient death with a functioning graft [4–6].

In non-transplant patients with chronic kidney disease and proteinuria, inhibition of the renin–angiotensin system with angiotensin receptor blockers or ACE-inhibitors has been shown to delay the progression of renal disease. This benefit has been seen in both diabetics [7,8] and non-diabetics [9]. In kidney transplant recipients, ACE-inhibitors and angiotensin receptor blockers have been used for blood pressure control and the treatment of post-transplant erythrocytosis [10], however, their use in
delaying the progression of chronic kidney disease has not been well established [11]. Observational studies to date have had conflicting findings with some studies showing benefit [12] and others showing no benefit [13] with respect to allograft survival. There have been several small randomized trials evaluating the use of ACE-inhibitors and angiotensin receptor blockers in kidney transplantation, but most of these studies were of short duration and did not examine clinical endpoints such as graft loss and death [14].

The purpose of this current trial is to determine whether the ACE-inhibitor ramipril, independent of its blood pressure lowering effect, will reduce the progression of clinically significant renal disease and mortality in renal transplant recipients with chronic kidney disease. Our hope is that treatment with ramipril will improve the health of kidney transplant patients, reduce the number requiring to resume dialysis and be cost-effective for the health care system.

Trial design and methods

The trial is a randomized, prospective, double-blind, placebo-controlled, multicentre, parallel arm trial. The trial will recruit patients over a 2-year period and follow each participant for a minimum of 2 years. Following a screening visit to confirm eligibility, patients will have one randomization visit and study visits at 1 month, 2 months, 6 months, 12 months and then every 6 months until the trial is completed. In addition to these visits, the patients will have the serum creatinine measured every 3 months. The total trial duration will be 4 years. This study has been funded by a peer-reviewed grant from the Canadian Institutes of Health Research (grant # MCT-78844). The trial has been registered on the International Standard Randomised Controlled Trial Number Registry (ISRCTN-78129473).

Study population

We are studying renal transplant recipients with chronic kidney disease as defined by impaired renal function and proteinuria [15] who are at risk for progressive renal decline, end-stage renal disease [4,6] and death [16–19]. We have chosen to study a chronic kidney disease population rather than patients without renal impairment or proteinuria because: (i) the higher number of clinical events in this population will allow us to detect a difference with the intervention; (ii) chronic kidney disease is present in 75–90% of kidney transplant recipients [20]; and (iii) previous trials of ACE-inhibitors in non-transplant patients have enrolled patients with proteinuria and significant renal disease. Specific inclusion and exclusion criteria are listed in Table 1.

### Table 1. Inclusion and exclusion criteria for the trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>(i) Estimated glomerular filtration rate between 20 and 55 ml/min/1.73 m² using the Modification of Diet in Renal Disease study equation</td>
<td>(i) Unable to provide informed consent</td>
</tr>
<tr>
<td>(ii) Proteinuria ≥ 0.2 g/day</td>
<td>(ii) &lt;18-years old</td>
</tr>
<tr>
<td>(iii) ≥ 6 months post-transplantation</td>
<td>(iii) Pregnant</td>
</tr>
<tr>
<td>(iv) Angioedema from an ACE-inhibitor or angiotensin receptor blocker or other known reaction to an ACE-inhibitor (such as rash, neutropenia or cough)</td>
<td>(iv) from an ACE-inhibitor or angiotensin receptor blocker</td>
</tr>
<tr>
<td>(v) Serum potassium &gt; 5.5 mmol/l on two or more occasions in the preceding 3 months for those not on an ACE-inhibitor or angiotensin receptor blocker or serum potassium &gt; 5.9 mmol/l on two or more occasions in the preceding 3 months for those on an ACE-inhibitor or angiotensin receptor blocker</td>
<td>(v) Severe comorbid conditions (e.g. malignancy, disabling stroke) with life expectancy &lt;3 months</td>
</tr>
<tr>
<td>(vi) Left ventricular dysfunction that requires an ACE-inhibitor or an angiotensin receptor blocker</td>
<td>(vi) New immunosuppressive agent started or previous immunosuppressant stopped in the 3 months prior to study entry or plan to switch immunosuppressive agents within next 3 months</td>
</tr>
<tr>
<td>(vii) Severe comorbid conditions (e.g. malignancy, disabling stroke) with life expectancy &lt;3 months</td>
<td>(ix) Acute coronary syndrome, stroke or transient ischaemic attack in the 3 months prior to study entry</td>
</tr>
<tr>
<td>(viii) Serum potassium &lt; 3 months</td>
<td>(x) Currently on an ACE-inhibitor or an angiotensin receptor blocker and patient or physician unwilling to stop the medication</td>
</tr>
<tr>
<td>(ix) Acute coronary syndrome, stroke or transient ischaemic attack in the 3 months prior to study entry</td>
<td>(xi) Acute rejection episode in the 3 months prior to study entry</td>
</tr>
<tr>
<td>(x) Acute rejection episode in the 3 months prior to study entry</td>
<td>(xii) Are currently on four or more blood pressure pills and have an average blood pressure over three visits &gt;150/100</td>
</tr>
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### Intervention

Patients are randomized to receive the ACE-inhibitor, ramipril or an identical appearing placebo capsule. Ramipril is given at a dose of 5 mg po daily for 2 weeks and then 5 mg po BID thereafter. The target dose of 10 mg daily was based on positive results from non-transplant trials that used this dosing regimen [21–23].

### Randomization and treatment allocation

The randomization process consists of a computer-generated random listing of treatment allocation in permuted blocks of 4 and 6 stratified by centre and glomerular filtration rate (above or below 40 ml/min/1.73 m²). An independent biostatistician prepared the randomization schedule. Only the independent study statistician and a designated research pharmacist at the coordinating centre have knowledge of the randomization codes. After screening the patient for eligibility and obtaining informed consent, the study nurse will randomize the patient using the number in the next chronological order from the randomization lists provided ahead of time by the coordinating centre. The study nurse will then obtain the corresponding numbered bottle from storage containing either drug or placebo, which has been prepared ahead of time by the designated research pharmacist at the coordinating centre and then shipped to each clinic site.
**Blinding**

In order to minimize selection and ascertainment biases, physicians, nurses, investigators, research staff and members of the Data Safety and Monitoring Committee will be blinded to the randomization schemes and treatments administered. The trial statistician will designate another statistician to prepare all randomization schemes and interim analyses. Only the designated research pharmacist at the coordinating centre has knowledge of the treatment allocation for individual patients.

**Medical management**

In addition to the primary trial intervention, blood pressure and dyslipidaemia will be controlled according to published guidelines [11,24]. Other co-interventions that might influence study outcome such as aspirin use, smoking cessation, weight control, glycaemic control in diabetics and immunosuppressive medication use will be monitored but not controlled. All participants will have strict blood pressure control based on the 2004 Canadian Recommendations for the Management of Hypertension [25] and the K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease [11]. In both of these reports, the target blood pressure for patients with chronic kidney disease is below 130/80. Abnormal lipid profiles will be managed according to published guidelines that have been specifically written for renal transplant recipients [24].

**Primary outcome measure**

The primary outcome measure is a composite measure incorporating the following clinically important endpoints: doubling of serum creatinine, end-stage renal disease or death. Doubling of serum creatinine will be confirmed by two consecutive tests at least 4 weeks apart in a central laboratory [26]. End-stage renal disease is defined as the date the patient undergoes repeat kidney transplantation or starts dialysis. The composite outcome of doubling creatinine, end-stage renal disease or death was chosen because it encompasses well-defined, clinically relevant outcomes to both patients and physicians [27]. This composite outcome has also been used in major randomized trials evaluating the use of ACE-inhibitors or angiotensin receptor blockers in non-transplant patients [8,26,28,29].

**Secondary outcomes**

The following secondary endpoints will be evaluated: (i) rate of decline in the glomerular filtration rate as determined using a radioisotopometric method; (ii) change in urine protein excretion; (iii) systolic and diastolic blood pressure; (iv) incidence of adverse events such as early rise in serum creatinine (>30% increase from baseline [11], hyperkalaemia, anaemia and hypotension (systolic blood pressure <100 mmHg [11]; (v) incidence of cardiovascular events such as acute coronary syndrome, congestive heart failure, stroke, transient ischaemic attack, amputation; cardiac, cerebral or peripheral revascularization procedure; (vi) total number of hospitalizations; and (vii) health-related quality of life assessed by the Short Form-36 and the EuroQol-5D [30].

**Sample size**

Based on data from the literature [17,18,31–35] we estimated the 4-year survival rate (freedom from endpoint doubling creatinine, end-stage renal disease or death) in the placebo arm to be 70%. In a trial assessing cardiac disease in the renal transplant population (mean creatinine clearance 60 ml/min), the proportion of patients surviving without graft failure, doubling of creatinine, or death was estimated to be 80% after 4 years [31,32,35,36]. In patients with a serum creatinine >143 umol/l at baseline, only 67.1% survived 4 years without graft failure, doubling of creatinine or death [37]. Similarly, in a study involving 601 renal transplant recipients (mean creatinine clearance 62 ml/min), the freedom from doubling creatinine, end-stage renal disease or death was 68.4% after 4.2 years of follow-up [38]. Given that our study population will have more advanced kidney disease (proteinuria and a maximum glomerular filtration rate of 55 ml/min), we believe an estimate of 70% survival is reasonable. In terms of benefit, we expect that ramipril will further increase the 4-year survival rate to 82%. The 12% absolute difference translates into a 17% relative increase in survival. An absolute difference of 12% was justified on the basis of a survey we conducted involving Canadian transplant nephrologists. In this survey, an absolute difference of 12% was the dominant minimal clinically important difference that the respondents wanted to observe for ramipril to be considered an improvement over current practice. Assuming a 12% absolute difference in 4-year survival, a 2-year accrual period, a 4-year study duration, a two-sided α-error of <0.05, a β-error of 0.20 and a 5% non-compliance rate, we require 264 patients per arm or 528 patients in total.

**Statistical analysis**

All statistical analyses will be based on an intention-to-treat approach. The principal analysis will compare the time from randomization to the development of our primary outcome (doubling of serum creatinine, end-stage renal disease or death) between patients allocated to ramipril and placebo. The dates of death and end-stage renal disease will be well documented. Due to logistics and feasibility, the exact date of doubling of creatinine cannot be ascertained, as patients will be tested at 3-month intervals. Therefore, if the creatinine is found to be doubled,
the date for the survival analysis will be considered as the midpoint between the dates of the last two creatinine measurements. Unadjusted survival rates with 95% confidence intervals will be compared using log-rank tests. In addition, Cox proportional hazards regression models will be used to further elucidate the measure of effect while adjusting for possible confounding variables. The continuous secondary endpoints (glomerular filtration rate, urine protein excretion, blood pressure) will be analysed using either parametric (independent t-test) or non-parametric procedures (Wilcoxon rank sum) followed by generalized linear regression models that adjust for important risk factors. The secondary endpoints that are categorical variables will be analysed using an unadjusted log-rank test followed by Cox proportional hazard model procedures to adjust for important prognostic risk factors. An interim analysis of the primary outcome will be performed once 50% of subjects with at least 1-year of follow-up have been accrued to determine if ramipril is beneficial or harmful. The group sequential test has been generated using the O’Brien and Fleming spending function to determine the test boundary. A 5% non-compliance factor has been incorporated. These results assume symmetrical significance boundaries with $\alpha = 0.003$ for the interim analysis.

**Trial committees**

The Steering Committee will consist of all members of the Executive Committee, all site principal investigators and research staff. The committee will review and implement all aspects of this trial. The Data Safety and Monitoring Committee (DSMC) has responsibility for the interim analyses and monitoring of adverse events throughout the study. The DSMC works independently from the trial and serves in an advisory role to the Executive Committee and Study Chair. The DSMC consists of four individuals with expertise in clinical trials, biostatistics and nephrology. The DSMC will recommend termination or continuation of the study after the interim analysis.

**Enrollment to date**

The trial has started recruiting at several of the sites. As of May 2007, 41 patients have provided consent. Thirty patients have been randomized and the other 11 are undergoing screening. The 11 trial sites include the University of British Columbia, Vancouver; University of Calgary, Calgary; University of Alberta, Edmonton; University of Western Ontario, London; McMaster University, Hamilton; Queen’s University, Kingston; University of Toronto, University Health Network and St Michael’s Hospital, Toronto; University of Ottawa, Ottawa; McGill University, Montreal and Dalhousie University, Halifax.

**Conclusion**

At the end of recruitment there will be over 500 kidney transplant recipients enrolled in this trial. This will be far greater than any of the previously published randomized trials examining renin–angiotensin blockade following kidney transplantation. The results of this trial will provide evidence for both patients and clinicians, which will be clinically meaningful. That is, whether treatment with an ACE-inhibitor will reduce patient mortality and allograft failure. In addition to these hard outcomes, the trial will determine whether health-related quality of life is improved and if the decline in glomerular filtration rate is delayed with ACE-inhibitor use.

**Conflict of interest statement.** None declared.

**References**

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