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Angiotensin Converting Enzyme (ACE) inhibition for the preservation of renal function and patient survival in kidney transplantation

Submission date
12/07/2006

Recruitment status
No longer recruiting

Registration date
13/07/2006

Overall study status
Completed

Last Edited
18/07/2016

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Kidney transplantation is the treatment of choice for end-stage kidney disease as it has been shown to improve quality of life, prolong survival and is less expensive than dialysis. However, over 50% of kidney transplants fail because of kidney disease or the patient dies with a functioning transplant. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are drugs that are mainly used to treat high blood pressure and heart failure. Studies in non-transplant patients have shown that an ACE-inhibitor or ARB can delay the progression of kidney disease. It is unclear whether these medications are beneficial in kidney transplant recipients because the studies to date have been small. The aim of this study is to determine whether the ACE-inhibitor ramipril, independent of its blood pressure lowering effect, reduces the progression of kidney disease in kidney transplant recipients.

Who can participate?
Kidney transplant recipients with kidney disease

What does the study involve?
Participants are randomly allocated to be treated with either ramipril or placebo (dummy drug) capsules. All participants have their blood pressure strictly controlled as per recommended guidelines. The incidence of kidney disease and death is measured in the two groups, along with blood pressure, heart disease, stroke, hospitalizations, quality of life and costs of care.

What are the possible benefits and risks of participating?
If ramipril is found to decrease the progression of kidney disease, kidney transplant failure or death, its use in kidney transplantation will be strongly endorsed. Since transplantation improves quality of life and is less expensive than dialysis, a positive result from this study will improve the health of kidney transplant recipients and likely save money for the health care system.

Where is the study run from?
The Ottawa Hospital (Canada)

When is the study starting and how long is it expected to run for?
July 2006 to December 2014

Who is funding the study?
Canadian Institutes of Health Research (Canada)

Who is the main contact?
Debora Hogan
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Contact information

Type(s)
Scientific

Contact name
Dr Gregory Knoll

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
MCT-78844

Study information

Scientific Title
Angiotensin Converting Enzyme (ACE) inhibition for the preservation of renal function and patient survival in kidney transplantation: a randomised, double blind, placebo-controlled trial

Study objectives
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.

Ethics approval required

Old ethics approval format

Ethics approval(s)
1. Ottawa Health Science Network Research Ethics Board, Ottawa, Ontario, Canada (21/02/2006, 15/03/2006, 05/06/2006)
2. Further amendments added on 16/07/2008: 14/09/2006, 24/05/2007, 25/04/2008
3. Further amendments added on 12/11/2009: 01/02/2008, 01/10/2009

Study design
Randomised double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Chronic kidney disease in renal transplant patients

Interventions
Experimental arm: ramipril (ALTACE®) will be given as follows: 5 mg (one capsule) daily for two weeks, then 10 mg (two capsules) daily thereafter.

Control arm: placebo capsules filled with lactose monohydrate and encapsulated into gelatin. Placebo capsules will match over-encapsulated Ramipril 5 mg (also encapsulated into gelatin with lactose monohydrate as a filler). One capsule daily for two weeks, then two capsules daily thereafter.

Added as of 18/01/2010:
Each participant will have an aliquot (approximately 1 cc per study visit) of serum stored for up to 15 years for:
1. Possible recalculation of creatinine
2. Quality assurance (calibration of cystatin C), and
3. Potential future testing for novel markers of kidney disease

Serum samples will be stored at -80C at the EORLA Research Lab (The Ottawa Hospital General Campus). Any future testing would be submitted to a Research Ethics Board (REB) for approval.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ramipril

Primary outcome measure
1. A composite measure incorporating the following clinically important endpoints:
1.1. Doubling of serum creatinine
1.2. End-stage renal disease or death
2. Time points of measurement:
2.1. Doubling of serum creatinine will be confirmed by two consecutive tests at least four weeks apart in a central laboratory. The base creatinine for the primary outcome will be the creatinine performed at the time of randomisation.
2.2. End-stage renal disease will be defined as the date the patient undergoes repeat kidney transplantation or starts dialysis
2.3. Death defined as the date the patient dies

Secondary outcome measures
1. Rate of decline in glomerular filtration rate (radioisotopic method), measured at baseline and then every six months thereafter
2. Urine protein excretion (24 hour urine), measured at baseline and then every six months thereafter
3. Systolic and diastolic blood pressure, measured at screening, baseline, one month, two months (only if BP is 130/80 mmHg at one month), six months and every six months thereafter. Amended as of 12/11/2009 to: Patients will return one month after the study visit to either their family physicians or transplant clinic for follow-up blood pressure monitoring each time their blood pressure is greater than 130/80 mmHg.
4. Incidence of adverse events: early rise in serum creatinine (greater than 30% increase from baseline), hyperkalemia (potassium = 5.5 mmol/l), and anemia (haemoglobin less than 110 g/l in women and less than 120 g/l in men), serum creatinine (Cr) and potassium will be measured at screening, baseline, two weeks, one month, six months, and every six months thereafter. At each visit, the serum Cr compared to the baseline sample taken at randomisation to determine if a doubling in Cr has occurred. Haemoglobin will be measured at baseline, two weeks, one month, six months, and every six months thereafter.
5. Incidence of cardiovascular events, documentation will be gathered for review by a blinded adjudication committee.
6. Total number of hospitalisations, will be measured at each follow-up visit (every six months) and well documented on case report forms
7. Health-related quality of life, generic (SF-36 v2 health survey) and utility measure (EuroQOL-5D). Quality of life questionnaires will be completed by patients at baseline, six months, 12 months and then annually.
8. Health care resource utilisation, will be measured at each visit - baseline and every six months thereafter

Added as of 16/07/2008:
9. Clinically meaningful diagnostic characteristics of serum Cystatin C and beta trace protein will be measured at each visit-baseline and every 6 months thereafter

Added as of 12/11/2009 (latest ethics amendment in October 2009):
10. Serum storage: each participant will be asked to allow any serum remaining after every 6-

month testing, to be stored for up to 15 years for:
10.1. Possible recalculation of creatinine
10.2. Quality assurance (calibration of Cystatin C)
10.3. Potential future testing for novel markers of kidney disease
Serum samples will be stored at -80°C at the EORLA Research Lab (The Ottawa Hospital General Campus). Any future testing would be submitted to a REB for approval. Serum will eventually be destroyed using standard operating laboratory procedures at The Ottawa Hospital.

Overall study start date
01/07/2006

Completion date
31/12/2014

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/07/2008:
Patients, either sex, who underwent the kidney transplantation and who:
1. Have an estimated glomerular filtration rate greater than or equal to 20 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease study (MDRD) equation which has been validated in renal transplant patients
2. Have proteinuria = 0.2 grams/day
3. Are at least three months post-transplantation
4. Have signed informed consent

Previous inclusion criteria:
Patients, either sex, who underwent the kidney transplantation and who:
1. Have an estimated glomerular filtration rate between 20 and 55 ml/min using the Modification of Diet in Renal Disease study (MDRD) equation which has been validated in renal transplant patients
2. Have proteinuria = 0.2 grams/day
3. Are at least six months post-transplantation
4. Have signed informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
528 (212 by end of recruitment)

Key exclusion criteria
1. Unable to provide informed consent
2. Less than 18 years old

3. Pregnant (ramipril contraindicated)
4. Angioedema from an ACE inhibitor or angiotensin receptor blocker or other known reaction to an ACE inhibitor (such as rash, neutropenia or cough)
5. Serum potassium greater than 5.5 mmol/l on two or more occasions in the preceding three months for those not on an ACE inhibitor or angiotensin receptor blocker
6. Serum potassium greater than 5.9 mmol/l on two or more occasions in the preceding three months for those on an ACE inhibitor or angiotensin receptor blocker
7. Left ventricular dysfunction that requires an ACE inhibitor or an angiotensin receptor blocker
8. Other severe co-morbid conditions (e.g. malignancy, disabling stroke) with life expectancy less than three months
9. New immunosuppressive agent was started or previous immunosuppressant stopped in the three months prior to study entry or plan to switch immunosuppressive agents within next three months
10. Had an acute coronary syndrome, stroke or transient ischaemic attack in the three months prior to study entry
11. Were previously enrolled in this study
12. Currently enrolled in another interventional trial
13. Currently on an ACE-inhibitor or an angiotensin receptor blocker and patient or physician unwilling to stop medication
14. Had an acute rejection episode in the three months prior to study entry
15. Currently on four or more blood pressure pills and have an average blood pressure over three visits greater than 150/100

Date of first enrolment
01/07/2006

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
Canada

Study participating centre
The Ottawa Hospital
Ontario
Canada
K1H 7W9

Sponsor information

Organisation
Ottawa Hospital Research Institute (OHRI) (Canada) - formerly Ottawa Health Research Institute

Sponsor details

501 Smyth Road
Ottawa
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Sponsor type
Government

Website
http://www.ohri.ca/home.asp

ROR
https://ror.org/03c62dg59

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (ref: MCT 78844)

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/01/2008		Yes	No
Results article	results	01/04/2016		Yes	No