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BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention Trial

Submission date
29/01/2010

Recruitment status
No longer recruiting

Registration date
02/02/2010

Overall study status
Completed

Last Edited
27/10/2014

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Almost everyone in the population has been exposed to a virus called BK virus, often when they were children. This virus infects the persons kidneys, but does not cause disease in people with a normal immune system. In the past few years, it has become known that BK virus can reactivate in transplant patients, and cause inflammation and scarring in the transplanted kidney. This reactivation occurs within the first year after transplant in about 40% of people, and is found by testing the patients urine. About 20% of transplant recipients will develop a more severe form of reactivation, where the virus actually gets into the bloodstream. Once the virus is in the bloodstream, the chances of the virus causing scarring in the kidney are 50-80%. In the past, when left untreated, most patients with active BK virus in their kidney lost their transplant and returned to dialysis. Physicians have treated BK virus in the kidney by reducing immunosuppression, to allow the immune system to fight the virus. Immunosuppressants prevent your body's immune system from attacking the new kidney, which would cause the transplanted kidney to be rejected. Some of the people entering this study will be put into the lower immunosuppression group (Group 1). We have designed a drug combination (leflunomide and sirolimus) that is expected to have antiviral activity and reduce scarring. . Leflunomide has been shown to interfere with virus infection in the laboratory, and there are many patient cases reported where it has been helpful in BK virus infection. Sirolimus (also known as Rapamune) is an immunosuppressive agent used in many transplant centres. It may protect against scarring, although this is not proven. Some patients in this study will be randomized to receive the leflunomide/sirolimus combination therapy (Group 2). The purpose of this study is to determine whether reduction of immunosuppression or combination therapy (leflunomide/sirolimus) is a better treatment for patients who develop reactivation of BK virus in their bloodstream.

Who can participate?
The study is open to both male and female kidney transplant recipients over 18 years of age with stable kidney function, who have BK in their blood, have a kidney only transplant (not multi-organ), are not pregnant or breastfeeding, and do not already have liver diseases such as Hepatitis B or C.

What does the study involve?
Patients entering this study will be randomly assigned to either the group with lowered

immunosuppression or the combination therapy group. Patients allocated to lowered immunosuppression (Group 1), will have their mycophenolic acid (CellCept or Myfortic) lowered, and then the calcineurin inhibitor (ProGraf or Neoral) will be reduced. Patients allocated to the combination therapy group (Group 2), will have mycophenolic acid and calcineurin inhibitor stopped, and they will be started on sirolimus and leflunomide. Levels of the drugs will be monitored with blood tests and adjusted to ensure patients levels are in the correct range. Patients will be asked to undergo a biopsy initially when they become positive for BK virus in blood, and again after 1 year of therapy. Kidney function, blood counts, and liver function tests will be monitored monthly. Blood will continue to be monitored for the BK virus throughout the study. Blood and urine samples will be tested to see how well the patients kidneys and other body systems are working. These samples will then be frozen and stored for future research on kidney disease. At baseline, 3, 6, 12 months, yearly and if patients withdraw from the study they will be asked to fill out questionnaires that ask about quality of life.

What are the possible benefits and risks of participating?
Patients who agree to participate in this study may or may not get a direct medical benefit. BK virus infection may be improved during the study but there is no guarantee that this research will help every patient. The information we get from this study may help us to provide better treatments in the future for patients with BK infection.Participation in the study is voluntary, and patients may withdraw at any time without jeopardizing their health care. In addition, the physician or the researcher may withdraw a patient from the study if they develop complications or side effects that necessitate other treatments. The risks associated with reduced immunosuppression include a potential increased risk of rejection. There are risks associated with any immunosuppressive medications, but they are necessary to protect the kidney from rejection. There is a potential risk of increased liver injury in patients taking leflunomide who drink alcohol. Patients are advised to adhere to the Low Risk Drinking Guidelines (http://www.lrdg.net/guidelines.html) which are endorsed by public health agencies. All immunosuppressive medications, including the ones used in this study, may pose a risk to developing fetuses or to babies who are being breastfed. All patients on any immunosuppressive medication are advised to seek expert consultation prior to becoming pregnant, to determine the medications with the least risk to the baby. Pregnancy must be avoided if either partner is receiving leflunomide, and in women receiving sirolimus, mycophenolate sodium or mycophenolate mofetil. Adequate contraception during the treatment period is required. Tacrolimus should only be used during pregnancy when the potential benefits to the mother justify the potential risk to the baby.

Where is the study run from?
The study will be conducted at approximately 15 Transplant Centers across Canada and the United States with the main center being at the University of Calgary in Calgary, Alberta, Canada

When is the study starting and how long is it expected to run for?
This study started in July of 2010 and it is estimated that it will continue until December 2017. The study is currently recruiting and will continue to recruit until the approximately 300 patients have entered in the study.

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

Who is the main contact?
Dr. Lee Anne Tibbles
tibbles@ucalgary.ca

Contact information

Type(s)
Scientific

Contact name
Dr Lee Anne Tibbles

Contact details
University of Calgary
Health Research Innovation Centre, Office 4A12
3280 Hospital Drive NW
Calgary
Canada
T2N 4Z6
+1 403 220 2064
tibbles@ucalgary.ca

Additional identifiers

Protocol serial number
MCT-99787; UC-NEPH-2009001

Study information

Scientific Title
BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention - a phase III multicentre randomised parallel group trial

Acronym
The BK: KIDNI Trial

Study objectives
The primary hypothesis is that treating human polyomavirus (BK) infection with an anti-viremia /anti-fibrosis approach based on leflunomide plus sirolimus will translate into lower rates of multiple hard outcomes as compared to standard reduction of immunosuppression.

On 17/08/2010 this trial record was updated in response to amendments to the trial protocol, approved by the ethics board. All changes can be found in the relevant field with the above update date.

On 27/10/2014 the anticipated end date was changed from 31/03/2014 to 31/03/2018.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Calgary Conjoint Health Research Ethics Board, 18/02/2010, ref: E-22933
An amendment to the protocol was approved by the local IRB, 24/06/2010 and by Health Canada

on 23/06/2010
Amendment #3 to the protocol was approved by Health Canada on 18/12/2012

Study design
Phase III multicentre randomised parallel-group assessor-blind (outcome assessors, statistician) trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
BK nephropathy

Interventions
Amended as of 17/08/2010:
De novo transplant patients will have monthly measurements of urine or plasma BK virus at their centre. Once either urine or plasma is positive for BK, plasma will be sent to the central reference laboratory to measure BK by polymerase chain reaction. Patients with positive PCR for plasma BK (viremia) will be randomised to either standard therapy (control) or sirolimus /leflunomide (treatment).

The control group (standard therapy: reduction of immunosuppression) will have the antimetabolite (mycophenolate mofetil, mycophenolate sodium or azathioprine) either discontinued or reduced at first occurrence of viremia. If the initial quantification of viremia is 10,000 copies or greater per ml of plasma, the antimetabolite will be discontinued. This level of viremia has been retrospectively associated with increased risk of BK nephropathy, and significant reduction of immunosuppression, such as complete withdrawal of one agent, is now accepted practice. Plasma quantitative PCR of less than 10,000 BK viral copies per ml will initially be treated with reduction of the dose of antimetabolite by 50%. This is consistent with the current practice of most Canadian centres. Plasma BK PCR will be performed monthly during the trial, and any quantitative value of greater than 10,000 copies per ml will lead to permanent discontinuation of the antimetabolite. If after one month the viremia has not reduced by 1 log unit, the calcineurin inhibitor will be reduced to target levels of 4-8 ng/ml for tacrolimus, or 50-100 ng/ml for cyclosporine. Patients will continue to be monitored for BK DNA in plasma.

In the treatment arm (sirolimus and leflunomide), the calcineurin inhibitor will be discontinued, the antimetabolite will be discontinued, and the prednisone dose will be reduced to 5 mg per day. The patient will be treated with sirolimus, initially 4 mg per day, with dosage adjustment to attain trough levels of 6 - 8 ng/ml. Leflunomide, the investigational product, will be started using 100 mg per day for 5 days, followed by 40 mg per day, with dosage adjustments to keep levels of the active metabolite A77 1726 between 40 and 100 ug/ml. Biopsies will be taken at first viremia and one year follow-up. Biopsy proven rejection will be treated according to site-specific guidelines.

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Initial information at time of registration:
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The control group (standard therapy) will have the antimetabolite, either mycophenolic acid, mycophenolate sodium or azathioprine discontinued. If after one month the viremia has not reduced by 1 log unit, the calcineurin inhibitor will be reduced to target levels of 4 - 8 ng/ml for tacrolimus, or 50 - 100 ng/ml for cyclosporin. Patients will continue to be monitored for BK DNA in plasma. Biopsies will be taken at first viremia and one year follow-up. Biopsy proven rejection will be treated according to site specific guidelines.

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Biopsies will be taken at first viremia and one year follow-up. Biopsy proven rejection will be treated according to site specific guidelines.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Leflunomide, sirolimus

Primary outcome(s)
Amended as of 17/08/2010:
Multiple failure times per subject will represent the primary study outcome. Failure events will be:
1. Doubling of serum creatinine or an increase of at least 100 umol/L
2. Need for renal replacement therapy for graft end-stage failure
3. Death

Binary change in serum creatinine will be defined as 100% increase (relative change) or 100 umol /L increase (absolute change) as compared to the lowest value between randomisation and the first 2 months; the change must persist for at least one month, with the event date being the initial assessment date.

This multiple event approach is implied by design as patients may experience further events once the first has occurred. The likelihood of these further events may change after the first has occurred and as a result of BK infection providing clinical and biological support to the existence of correlation in the competing risks data arising from the present study. The competing risks of these further events may change as a result of treatment.

Initial information at time of registration:
Multiple failure times per subject will represent the primary study outcome. Failure events will be:
1. Doubling of serum creatinine
2. Need for renal replacement therapy for graft end-stage failure, and
3. Death

This multiple event approach is implied by design as patients may experience further events once the first has occurred. The likelihood of these further events may change after the first has occurred and as a result of BK infection providing clinical and biological support to the existence of correlation in the competing risks data arising from the present study. The competing risks of these further events may change as a result of treatment.

Key secondary outcome(s))

Amended as of 17/08/2010:
1. Rate of decline in renal function: based on decline in eGFR in mL/min/1.73 m2 using the MDRD prediction equation
2. Time to 50% increase in serum creatinine (relative change) or 50 umol/L increase (absolute change) as compared to the lowest value between randomization and the first 2 months (the change persisting for at least one month, with the event date being the initial assessment date)
3. Time to clearance of viremia, which will be defined as 2 sequential monthly measurements with undetectable BK viral DNA by PCR.
4. Biopsy proven acute rejection using the Banff 2007 criteria
5. Grade of BK nephropathy on biopsy at 12 months as defined by Nickeleit and Mihatsch in Transplant International (2006)
6. Chronic allograft nephropathy at 12 months based on the Banff 2007 and CADI scoring systems
7. Change in selected health related quality of life measures between treatment groups. HRQOL will be assessed using a spectrum of HRQOL instruments including a generic questionnaire (Short-Form 36 [SF-36]), and a preference-based questionnaire (Euroqol [EQ-5D]). The primary HRQOL measure will be the change in the Euroqol EQ-5D index score.
8. Differences in health care costs between the two strategies. Costs to be assessed will include the direct costs associated with each of the interventions (i.e. drug costs, laboratory monitoring costs), and the cost of other relevant transplant medications. In addition to collecting intervention-specific costs, we will also collect information for all patients on associated health care costs including the cost of hospitalization, the cost of outpatient day care visits (i.e. for non-protocol renal biopsies, medication infusions, etc), the cost of diagnostic imaging, and the cost of dialysis, for those patients requiring dialysis.

Initial information at time of registration:
1. Rate of decline in renal function: based on decline in estimated glomerular filtration rate (eGFR) in mL/min/1.73^m2 using the Modified Diet in Renal Disease (MDRD) prediction equation
2. Time to clearance of viremia, which will be defined as two sequential monthly measurements with undetectable BK viral DNA by PCR
3. Biopsy proven acute rejection using the Banff 2007 criteria
4. Grade of BK nephropathy on biopsy at 12 months as defined by Nickeleit and Mihatsch in Transplant International (2006)
5. Chronic allograft nephropathy at 12 months based on the Banff 97 and CADI scoring systems
6. Change in selected health related quality of life measures between treatment groups. Health-Related Quality of Life (HRQOL) will be assessed using a spectrum of HRQOL instruments including a disease specific questionnaire (Kidney Transplant Questionnaire [KTQ]), a generic

questionnaire (Short-Form 36 [SF-36]), and a preference-based questionnaire (Euroqol [EQ-5D]). The primary HRQOL measure will be the change in the Euroqol EQ-5D index score.
7. Differences in health care costs between the two strategies. Costs to be assessed will include the direct costs associated with each of the interventions (i.e. drug costs, laboratory monitoring costs), and the cost of other relevant transplant medications. In addition to collecting intervention-specific costs, we will also collect information for all patients on associated health care costs including the cost of hospitalisation, the cost of outpatient day care visits (i.e. for non-protocol renal biopsies, medication infusions, etc), the cost of diagnostic imaging, and the cost of dialysis, for those patients requiring dialysis.

Completion date
31/03/2018

Eligibility

Key inclusion criteria
Current inclusion criteria as of 01/02/2013:
1. All adults (aged greater than or equal to 18 years, either sex) de novo renal transplant patients with grafts from both living donors and deceased donors and up to two renal transplants prior to the current transplant
2. Presence of BK viremia based on a positive BK virus deoxyribonucleis acid polymerase chain reaction (DNA PCR) in plasma, of any degree
3. Greater than 1 month post-kidney transplant
4. Provision of informed consent (self or legal representative)

Previous inclusion criteria:
1. All adults (aged greater than or equal to 18 years, either sex) de novo renal transplant patients with grafts from both living donors and deceased donors and up to two renal transplants prior to the current transplant
2. Presence of BK viremia based on a positive BK virus deoxyribonucleis acid polymerase chain reaction (DNA PCR) in plasma, of any degree
3. Greater than 2 months post-kidney transplant
4. Provision of informed consent (self or legal representative)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

Current exclusion criteria as of 05/02/2013:
1. Fourth or subsequent renal transplant
2. Multiorgan transplant
3. Cold ischemia time for current transplant exceeding 36 hours
4. Pregnancy, breastfeeding , or women of child bearing potential not willing to use a reliable method of contraception
5. Current involvement in another interventional trial (observational follow-up is permitted)
6. Known allergy to sirolimus or leflunomide
7. Pre-existing liver disease including Hepatitis B or C
8. Poor renal function due to causes other than BK virus, as determined by the site Qualified Investigator

Previous exclusion criteria:
1. Fourth or subsequent renal transplant
2. Multiorgan transplant
3. Cold ischemia time for current transplant exceeding 36 hours
4. Patients with BK viremia less than 2 months after transplant
5. Pregnancy or breastfeeding
6. Involvement in another drug trial
7. Known allergy to sirolimus or leflunomide
8. Pre-existing liver disease including hepatitis B or C
Added 17/08/2010:
9. Persistent estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2 for a period of at least 2 weeks in duration

Date of first enrolment
01/03/2010

Date of final enrolment
31/03/2018

Locations

Countries of recruitment
Canada

Study participating centre
University of Calgary
Calgary
Canada
T2N 4Z6

Sponsor information

Organisation
University of Calgary (Canada)

ROR
https://ror.org/03yjb2x39

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (CIHR) (Canada) - http://www.cihr-irsc.gc.ca (ref: MCT-99787)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration