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Optimized TacrolimuS and MMF for HLA Antibodies after Renal Transplantation

Submission date
26/03/2013

Recruitment status
No longer recruiting

Registration date
26/03/2013

Overall study status
Completed

Last Edited
24/01/2023

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Treatment of kidney disease accounts for a significant proportion of NHS spending. Transplantation is the best treatment for kidney failure, in terms of length and quality of life. It is also more cost-effective than dialysis. However, most transplants fail after 10-12 years and patients have to go back onto dialysis, placing a considerable burden on the NHS. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for a biomarker of chronic rejection called HLA antibodies (found in the blood). All transplant units in the UK can do this, but routine screening of patients has not been adopted because it is not clear how best to treat patients with antibodies. This study will test a screening and treatment protocol for HLA antibodies. The aim is to reduce transplant failure rates over 3 years.

Who can participate?
The trial is open to all kidney transplant recipients aged 18-70 years who have had their transplant for 12 months or more and currently have good kidney function.

What does the study involve?
Participants with antibodies will be randomly allocated to one of two groups: the biomarker-led (BLC) group or the standard care (SC) group. In the BLC group, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of three drugs, prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this treatment will be effective at preventing dysfunction and expect this to feed through to improvements in graft survival. In the SC group, screening results are not made available and participants will remain on their current treatments. Participants without antibodies will be randomly allocated to one of two groups: a group called blinded screening where results will not be given or a group called unblinded screening where results will be given. They will remain on standard treatment. Testing will continue every 8 months. Recruits in the SC group will move into the BLC group if they become antibody positive.

What are the possible benefits and risks of participating?
As well as the potential impact on transplant failure, the drugs used here are associated with better cholesterol profiles and lower blood pressures than others in common usage. There are

potential risks. Tacrolimus is associated with an increased risk of diabetes mellitus and enhanced immunosuppression in general is associated with an increased incidence of infection, especially viral and with an increased risk of malignancy. It is difficult to predict such risks in this study. The incidence of diabetes, infection and malignancy will be monitored carefully on this trial.

Where is the study run from?
The study is run and coordinated by a team from King's College London, based at Guy's Hospital (UK).

When is the study starting and how long is it expected to run for?
June 2013 to September 2020 (updated 12/05/2020, previously: Recruitment will begin in June 2013 and finish by May 2016. The study is scheduled to finish in May 2019.)

Who is funding the study?
National Institute for Health Research through an EME programme grant (UK)

Who is the main contact?
Professor Anthony Dorling
anthony.dorling@kcl.ac.uk
added 12/05/2020: Senior Trial Manager
Dr Leanne Gardner
leanne.gardner@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Anthony Dorling

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-004308-36

Protocol serial number
13990

Study information

Scientific Title
A randomized controlled clinical trial to determine if a combined screening /treatment programme can prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies

Acronym
OuTSMART

Study objectives
Current study hypothesis as of 12/05/2020:
Treatment of kidney disease accounts for a significant proportion of NHS spending. Although transplantation is the best treatment for kidney failure, most transplants do not survive for the recipient's natural lifespan, but instead fail after 10-12 years. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for 'HLA antibodies' in the blood. This application is to test a screening and treatment protocol for antibodies in a randomised controlled trial. Those with antibodies will be randomised into biomarker-led (BLC) or standard care (SC) groups. In the former, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this regime is effective at preventing graft dysfunction and expect this to double blinded and recruits will remain on their current therapies. In those without antibodies, recruits will be randomised to either blinded or unblinded screening and remain on standard treatment. Testing will continue every 8 months; recruits in the unblinded screening group will move into the BLC group if they become antibody positive. The primary outcome is to determine the time to graft
failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint will be assessed remotely when a minimum of 43 months post-randomisation has been achieved by all. Secondary outcomes include rates of deterioration, the incidence of infections, cancers and diabetes, an analysis of the role of non-adherence with medication, and a scientific study to identify new biomarkers associated with outcomes. A cost analysis will confirm whether the screening programme and treatment protocol can save money by keeping kidney transplants functioning for longer.
The recruitment target is to enroll 1900 HLA antibody-negative patients. This should allow recruitment of sufficient numbers of HLA antibody-positive patients.
More details can be found at: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=13990

Previous study hypothesis:
Treatment of kidney disease accounts for a significant proportion of NHS spending. Although transplantation is the best treatment for kidney failure, most transplants do not survive for the recipient's natural lifespan, but instead fail after 10-12 years. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for 'HLA antibodies' in the blood. This application is to test a screening and treatment protocol for antibodies in a randomised controlled trial. Those with antibodies will be randomised into biomarker-led (BLC) or standard care (SC) groups. In the former, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this regime is effective at preventing graft dysfunction and expect this to feed through to improvements in survival. In the SC group, screening results are

double blinded and recruits will remain on their current therapies. In those without antibodies, recruits will be randomised to either blinded or unblinded screening and remain on standard treatment. Testing will continue every 8 months; recruits in the unblinded screening group will move into the BLC group if they become antibody positive. The primary outcome is kidney failure rates within 3 years of randomisation in HLA antibody+ recruits, predicted to be approximately 20% in the SC but <10% in the BLC groups. Secondary outcomes include rates of deterioration, the incidence of infections, cancers and diabetes, an analysis of the role of non-adherence with medication, and a scientific study to identify new biomarkers associated with outcomes. A cost analysis will confirm whether the screening programme and treatment protocol can save money by keeping kidney transplants functioning for longer.

The recruitment target is to enroll 1900 HLA antibody-negative patients. This should allow recruitment of sufficient numbers of HLA antibody-positive patients.

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Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - Hampstead, 14/01/2013, ref: 12/LO/1759

Study design
Randomised; Interventional; Design type: Screening, Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Renal and Urogenital; Subtopic: Renal and Urogenital (all Subtopics); Disease: Renal

Interventions
Optimized Treatment protocol, The 'optimized treatment' protocol in the recruits with HLA Ab in unblinded group will be:
1. Mycophenolate mofetil bd, tds or qds, or enteric coated mycophenolic acid bd, with daily dose determined according to local unit guidelines. The patient will be stabilized on the maximum tolerated dose.
2. Tacrolimus od or bd, according to local unit preference, with dose titrated to achieve 12-hour post-dose levels of 4g/L to 8g/L (4-8 ng/ml). The patient will be stabilized on the maximumtolerated dose that achieves these levels.
3. Prednisolone od. Starting at 20mg for two weeks, then reducing by 5 mg od every two weeks down to a maintenance dose of 5mg od.
Screening for HLA antibodies, Serum prepared from 10mls of blood will be used in the commercially available 'LABScreen' tests, containing fluorescently tagged beads coated with purified HLA antigens. All participating centres have 'Luminex' equipment for analysis of these tests and the skills to process samples and interpret results. Therefore, the tests will be performed in each of the centres.

Follow-Up Length: 36 month(s)

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Mycophenolate mofetil, tacrolimus, prednisolone

Primary outcome(s)
Current primary outcome measure as of 12/05/2020:
Determine the time to graft failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint will be assessed remotely when a minimum of 43 months post-randomisation has been achieved by all.

Previous primary outcome measure:
Renal Transplant Failure Rates; Timepoint(s): 3 Years post-recruitment

Key secondary outcome(s))
Current secondary outcome measures as of 12/05/2020:
1. Analysis of adherence and perceptions of risk; Timepoint(s): 32 months
2. Change in estimated Glomerular Filtration Rate; Timepoint(s): 32 months
3. Patient Survival; Timepoint(s): 32 months
4. Proteinuria; Timepoint(s): 32 months
5. Rate of acute rejection; Timepoint(s): 32 months
6. Rates of biopsy proven malignancy; Timepoint(s): 32 months
7. Rates of Culture-positive infection; Timepoint(s): 32 months
8. Rates of Diabetes Mellitus; Timepoint(s): 32 months
9. Scientific analyses of humoral & cellular immunity and CD34+ cells; Timepoint(s): 32 months

Previous secondary outcome measures:
1. Analysis of adherence and perceptions of risk; Timepoint(s): 3 years
2. Change in estimated Glomerular Filtration Rate; Timepoint(s): 3 years
3. Patient Survival; Timepoint(s): 3 years
4. Proteinuria; Timepoint(s): 3 years
5. Rate of acute rejection; Timepoint(s): 3 years
6. Rates of biopsy proven malignancy; Timepoint(s): 3 years
7. Rates of Culture-positive infection; Timepoint(s): 3 years
8. Rates of Diabetes Mellitus; Timepoint(s): 3 years
9. Scientific analyses of humoral & cellular immunity and CD34+ cells; Timepoint(s): 3 year

Completion date
30/09/2020

Eligibility

Key inclusion criteria
1. Renal transplant recipients >1 year post transplantation
2. Aged 18-70 years, male and female
3. Estimated glomerular filtration rate (eGFR) of >=30

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Total final enrolment
2037

Key exclusion criteria
1. Recipient requiring HLA desensitisation to remove antibody for a positive XM transplant
2. Recipient known already to have HLA antibody who has received specific intervention for that antibody or for CAMR / chronic rejection
3. Recipient of additional solid organ transplants (e.g. pancreas, heart, etc).
4. History of malignancy in previous 5 years (excluding non-melanomatous tumours limited to skin)
5. HBsAg+,HBcAb+, HepC+ or HIV+ recipient (on test performed within previous 5 years)
6. History of acute rejection requiring escalation of immunosuppression in the 6 months prior to screening.
7. History of an ongoing or previous infection (no time limit) that would prevent optimization of immunosuppression, including ocular Herpes simplex.
8. Known hypersensitivity to any of the IMPs
9. Known hereditary disorders of carbohydrate metabolism
10. Patient enrolled in any other studies involving administration of another IMP at time of recruitment
11. Pregnancy or breastfeeding females (based on verbal history of recipient)
12. Pre-menopausal females who refuse to consent to using suitable methods of contraception throughout the trial.

Date of first enrolment
01/09/2013

Date of final enrolment

30/09/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Guy's and St Thomas' Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
The Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1FR

Study participating centre
St Helier Hospital
Epson
United Kingdom
KT18 7EG

Study participating centre
Bradford Royal Infirmary
Duckworth Lane

Bradford
United Kingdom
BD9 6RJ

Study participating centre
Manchester Royal Infirmary
North Road
Manchester
United Kingdom
M13 9WL

Study participating centre
St James Hospital
Beckett St.
Leeds
United Kingdom
LS9 7TF

Study participating centre
Salford Royal Hospital
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
York Hospital
Wigginton Road
York
United Kingdom
YO31 8HE

Study participating centre
University Hospitals Birmingham
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Royal Preston Hospital
Sharoe Green Lane North
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
University Hospitals Coventry and Warwickshire
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Sponsor information

Organisation
King's College London (UK)

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
NIHR (UK) - Efficacy and Mechanism Evaluation; Grant Codes: 11/100/34

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Anthony Dorling (Anthony.dorling@kcl.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		12/01/2023	24/01/2023	Yes	No
Protocol article	protocol	21/01/2014		Yes	No
Protocol article	updated protocol and statistical analysis plan	05/08/2019	07/08/2019	Yes	No
Abstract results		24/02/2016	18/11/2021	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes