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Improving transplant opportunities for patients who are sensitised

Submission date
17/09/2018

Recruitment status
Suspended

Registration date
29/10/2018

Overall study status
Completed

Last Edited
18/07/2022

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Antibodies against non-self tissue types may result from previous pregnancy, blood transfusion or transplantation. An individual in whom tissue type antibodies are detected is considered “sensitised”. At the time of transplant, if an antibody is present that is directed against the new kidney, it can recognise the kidney and cause immediate rejection.
Highly sensitised patients are those who have antibodies directed against more than 85% of their potential donors, and are difficult to transplant. Due to the risk of immediate rejection, they may not be able to receive a kidney directly from their living donor, and may wait a long time for the offer of a deceased donor transplant. This study will determine the effectiveness of a treatment regimen to reduce the antibodies causing sensitisation.

Who can participate?
People aged 18-65 awaiting a kidney transplant who fit any of the following criteria:
1. Highly sensitised and have been on the deceased donor waiting list for at least 3 years, OR
2. Have antibodies directed against their living donor and have not been offered a transplant after three runs in the UK Living Kidney Sharing Scheme, OR
3. Have antibodies directed against their living donor and are very highly sensitised (antibodies to more than 95% of the population). In this situation the chance of a match in the UK Living Kidney Sharing Scheme is small, and participants can be enrolled in the trial without any prior runs.

What does the study involve?
The study will include two groups of patients, one of which will receive treatment to reduce sensitisation, and a second control group which will receive no intervention. The control group will have their antibodies measured every three months, as is the case for routine monitoring. All patients in both groups will remain eligible throughout the study for any compatible transplants that are offered.
The treatment includes a technique to remove antibodies (plasmapheresis) together with a combination of drugs to prevent their re-synthesis (rituximab, dexamethasone and bortezomib). Rituximab is given first. After three weeks, plasmapheresis followed by bortezomib and dexamethasone is given twice weekly on four occasions. In this treatment group, the change in antibodies is measured after 1, 2, 4, 8 and 12 weeks, then every 4 weeks to one year. If there is

only a small reduction in the level of sensitisation, a second course of treatment will be carried out after three months.
The fall in antibody levels is predicted to increase the chance of a transplant offer being received from either a deceased donor or through the National Living Donor Kidney Sharing Schemes (NLDKSS).

What are the possible benefits and risks of participating?
There is no guarantee that the treatment will be beneficial; however, we expect some patients will have a significant fall in their tissue type antibodies, and hence it becomes easier to identify a suitable transplant. Information from the scientific sub-study may also help us understand why some patients respond differently to others, and hence enable better prediction of this in the future.
The possible risks are in relation to the intervention group. During plasmapheresis, blood pressure can occasionally fall, leading to light-headedness, or there may be an allergic reaction to the replacement fluid. When plasma exchange treatments such as this are given frequently, blood clotting factors can fall, leading to a risk of bleeding. Calcium levels can also fall, which may cause pins and needles.
Rituximab may have side effects at the time of infusion, including fever, chills, nausea and occasionally vomiting, low blood pressure and allergic reactions (rash, itchiness, shortness of breath). Rituximab may lead to participants becoming more susceptible to infections (a particular type of pneumonia), although this is rare. The immune system's memory for previous infections may be affected by rituximab, causing an overall reduction in antibody levels, which could potentially lead to an increased rate of serious infections. Very rarely, this could lead to developing a fatal viral infection in the brain called progressive multifocal leucoencephalopathy, caused by the JC virus.
Bortezomib can reversibly affect blood counts, causing anaemia, low white blood cells and platelets. It can also cause gastrointestinal side effects, including decreased appetite, nausea, vomiting and diarrhoea. Bortezomib can occasionally cause numbness and tingling in the hands and feet (peripheral neuropathy). There may be reactivation of viral infections, such as those that cause chicken pox and cold sores.
Dexamethasone may irritate the lining of the stomach, causing indigestion. It may also cause changes in mood, insomnia and an increase in blood sugar levels.
These possible side effects will be monitored closely and managed as required. All participants in the intervention group will receive prophylaxis against pneumocystic jirovecii infection for 6 months after rituximab, and against herpes simplex virus for 3 weeks after bortezomib.

Where is the study run from?
Clinical Trials Unit NHS Blood and Transplant, John Radcliffe Hospital, Oxford (UK)

When is the study starting and how long is it expected to run for?
March 2018 to April 2022

Who is funding the study?
Kidney Research UK

Who is the main contact?
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Contact information

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Clinical Trials Information System (CTIS)
2017-002602-12

Protocol serial number
16/SEP/6613E

Study information

Scientific Title
Improving Transplant Opportunities for Patients who are Sensitised (ITOPS): a feasibility, randomised, controlled phase III trial

Study objectives
Does combination treatment with rituximab, plasma exchange and bortezomib result in a durable fall in HLA antibodies in highly sensitised patients awaiting renal transplantation?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales Research Ethics Committee 1, 02/11/2017, 17/WA/0313

Study design
Randomised; Interventional; Design type: Not Specified, Not Specified

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Kidney transplantation

Interventions
The allocation sequence will be produced by the trial statistician using SAS statistical software. The allocation sequence will have a varying undisclosed block size and will be stratified by site. Participants will be allocated to a 1:1 ratio to the trial intervention (rituximab, plasmapheresis, bortezomib and dexamethasone) versus control (standard care) group. Participants will be randomised using an online central randomisation service (www.sealedenvelope.com). Allocation concealment will be ensured, as participant's screening log number and initials will need to be provided to Sealed Envelope to obtain randomisation code and treatment group.
The study will include two groups of patients, one of which will receive treatment to reduce sensitisation, and a second control group which will receive no intervention. The control group will have their antibodies measured every three months, as is the case for routine monitoring. All patients in both groups will remain eligible throughout the study for any compatible transplants that are offered.
The treatment includes a technique to remove antibodies (plasmapheresis) together with a combination of drugs to prevent their re-synthesis (rituximab, dexamethasone and bortezomib). Rituximab is given first (day 0) at a dosage of 1 g through intravenous injection. After three weeks, plasmapheresis (1.5 plasma volumes) followed by bortezomib (1.3 mg/m^2 via subcutaneous injection) and dexamethasone (total dose 20 mg via oral tablets) is given twice weekly on four occasions. Serum for assessment of HLA antibodies is collected 4, 8 and 12 weeks post treatment and tested as a batch at 12 weeks. Any specificities that have fallen below an MFI of 2000 when tested by luminex SAB analysis are removed from the unacceptable antigen profile registered with NHSBT, and the reaction frequency recalculated. If the reaction frequency has fallen by at least 10%, monitoring of HLA antibodies will continue 4 weekly to 48 weeks (with batch testing at 24, 36 and 48 weeks), with further adjustment of the unacceptable antigen profile at each time point. If the reaction frequency has not fallen by at least 10%, a second cycle of treatment with plasmapheresis, bortezomib and dexamethasone will be given, with subsequent monitoring as above.
The fall in antibody levels is predicted to increase the chance of a transplant offer being received from either a deceased donor or through the National Living Donor Kidney Sharing Schemes (NLDKSS).
The control group will have no intervention, and antibody monitoring every 12 weeks (as current standard care).

Intervention Type
Other

Primary outcome(s)
The proportion of patients achieving an absolute reduction in calculated reaction frequency (cRF) of at least 10% at 12 weeks following their last intervention, compared to control group who have received no intervention.

Key secondary outcome(s))
1. The proportion of eligible participants who consent to the trial, assessed at the point of consent
2. Confirmation that at 12 weeks post-final intervention there has been an absolute fall in cRF of least 10% in at least 50% of the participants treated, compared to cRF at enrolment.
3. The proportion of patients in the intervention and control groups achieving an absolute reduction in cRF of at least 10% at 24 weeks following their last intervention or on routine monitoring, as compared to cRF at enrolment. If the MFI of an HLA A, B or DR antibody rises above an MFI of 2500 following previous de-listing, they will be listed again. A cut off of 2500 is used for re-listing as there is greater variability in antibody level at these relatively low concentrations.
4. The proportion of patients in the intervention and control groups achieving an absolute reduction in cRF of at least 10% at 48 weeks following their last intervention or on routine monitoring, as compared to cRF at enrolment.
5. Compared to cRF at enrolment, the percentage decrease in cRF at 12, 24, and 48 weeks following final treatment in intervention group or on routine monitoring.
6. The percentage of participants in the intervention group with B cell depletion at 12 weeks after the first cycle of treatment. B cell depletion is defined as an absolute reduction in B cell count to equal to or less than 5% the B cell count at enrolment for that individual participant.
7. Patient acceptability, assessed using the EQ-5D and Kidney Disease Quality of Life Instrument (KDQoL-SF) at recruitment and 18 months after enrolment for both intervention and control groups (or 90 days after transplantation, whichever is earlier) either face to face or by post.
8. The number of participants receiving a transplant during the study period from either a deceased or a living donor (with confirmation that any increase in offer rate was as a result of change in cRF).
9.The number of participants developing any grade neuropathy following each cycle of treatment.

Completion date
01/04/2022

Eligibility

Key inclusion criteria
1. Aged 18 – 65 years
2. Able to give informed consent and willing to fulfil trial requirements
3. Completed the necessary assessments to receive a renal transplant
4. In stable health, as determined by the Investigator based on medical history and laboratory tests during the screening period
5. Negative serological test for hepatitis B (surface antigen and core antibody) and hepatitis C within the last 6 months, and HIV within the last 12 months
6. Documented immune status to varicella zoster virus (VZV) (at any time)
7. Female participant of childbearing potential must be willing to use a highly effective method

of contraception for one year following rituximab (this period will also include the recommended 3 month period for avoidance of pregnancy following bortezomib). Male participants must be willing to use a highly effective form of contraception for 3 months post last dose of bortezomib
8. Persistent (for at least one year) and stable (tested on at least three occasions over the preceding year) circulating HLA antibodies defined by Luminex Single Antigen Bead analysis at the time of recruitment
9. Recipients awaiting deceased donor transplantation must have cRF >85% and at least 3 years on the transplant waiting list
10. Recipients with an HLA incompatible living donor who have been considered for enrolment in the UK Living Kidney Sharing Scheme must fit either of the following:
10.1. cRF is >95%
10.2. cRF is ≥85% and they have received no offers after three runs in the NLDKSS

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Pregnancy, planned pregnancy during the trial period, or current breast feeding
2. Active viral, bacterial or fungal infection precluding immunosuppression
3. Active malignant disease
4. Listed for transplantation of any organ other than kidney alone
5. History of active or clinically significant respiratory, gastrointestinal (including pancreatitis), hepatic, cardiac,
neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorder that, in the Investigator's
opinion, could affect the conduct of the trial
6. History of non-adherence, alcohol or substance abuse that, in the judgment of the Investigator, may impair or risk the subject's full participation in the trial
7. Positive serological test for hepatitis B, C or HIV
8. Negative serological test for VZV
9. Previous graft loss to recurrent primary disease within 2 years of transplantation
10. Documented intolerance of bortezomib, rituximab or their exipients, or dexamethasone
11. Persistent thrombocytopaenia, platelet count <100 X 109/L for the past 3 consecutive months
12. Persistent neutropaenia, absolute neutrophil count < 2 X 109/L for the past 3 consecutive months
13. Hypogammaglobulinaemia, serum IgG less than local laboratory lower limit of normal at screening

14. Peripheral neuropathy of any grade (reported by symptoms or on clinical examination)
15. Currently involved in any other clinical trial of an IMP or have taken an IMP within 30 days prior to trial entry

Date of first enrolment
24/09/2018

Date of final enrolment
23/03/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Clinical Trials Unit NHS Blood and Transplant, John Radcliffe Hospital
Headley Way
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Sponsor information

Organisation
Cardiff and Vale University Health Board

ROR
https://ror.org/0489f6q08

Funder(s)

Funder type
Government

Funder Name
Kidney Research UK (KRUK); Grant Codes: ITOPS

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No