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TWO study: cell therapy trial in renal transplantation

Submission date
19/03/2018

Recruitment status
Recruiting

Registration date
28/03/2018

Overall study status
Ongoing

Last Edited
18/09/2025

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
The body's immune system is essential in fighting off infection and preventing cancers from forming. However, for kidney transplant patients, if left unchecked, the immune system will reject the transplanted kidney causing it to fail. Patients who have a kidney transplant must take daily medications to limit the immune system and prevent rejection. These medicines are very effective but long term they can have serious and life-threatening side-effects including an increased risk of infection, cancer, heart disease and diabetes. Medication side-effects can actually contribute to kidney transplants failing and reduce the life expectancy of kidney transplant patients. Finding new ways to prevent transplant rejection will reduce the amount of medication transplant patients require. This might help kidney transplants and transplant patients survive for longer. Regulatory T cells (Treg) are a group of naturally occurring white blood cells. In healthy individuals these cells help control the body's immune system and prevent excessive immune responses that might actually be harmful. This study aims to use these Treg cells to prevent the immune response that leads to transplant rejection. Treg cells will be taken from the blood of kidney transplant patients. The number of Treg cells will be increased in a laboratory and given back to the same patient through a drip into the bloodstream. It is hoped that the increased number of Treg cells will help to prevent the immune system from rejecting a kidney transplant. If successful, this treatment will reduce the medications that kidney transplant patients need to take and with it reduce the serious side-effects listed above.

Who can participate?
Patients over the age of 18 who are due to have a kidney transplant from a living donor (typically a relative or friend who is willing to give the patient one of their kidneys)

What does the study involve?
Participants are randomly allocated to one of two groups. Patients in the control group receive normal care before and after their kidney transplant. They are asked to take the usual medications used to prevent transplant rejection. Patients in the treatment group give blood before their kidney transplant to find Treg cells in the blood and increase their number in the laboratory. 5 days after kidney transplant these patients are given an increased number of Treg cells back into the bloodstream through a drip. After the cells are given the aim is to reduce the number and dose of medications these patients are taking. All patients are asked to have a

biopsy (sample) of their kidney transplant 9 months after the transplant operation to look for any signs of rejection or kidney damage. Biopsy results alongside routine and experimental blood tests are used to assess how well the Treg cell treatment is working and its effects on the immune system.

What are the possible benefits and risks of participating?
Participants may not benefit directly from this study. However, if cell therapy is successful, less medications will be needed to prevent rejection, reducing drug side-effects. The aim is to use the information provided by this study to guide future cell therapy treatments and improve the lives of patients having kidney transplants. Analysis of samples from participants in this study may allow the development of tests to predict which kidney transplant patients are at risk of rejection or medication side-effects so that doctors can intervene at an early stage. Participants need to donate blood throughout the study. There is a small risk of discomfort or bruising when the blood samples are taken and a very small risk of feeling faint or a simple faint occurring when taking this sample. For those patients who receive Treg cell infusions, there may be a reduction in the blood count after initial blood donation but this should return to normal within 4 weeks. The risk of Treg cell administration is less than a blood transfusion. There is a very small risk of an allergic reaction. Common symptoms include; a red, itchy skin rash; swelling of the hands, feet, ankles, and legs, dizziness and headaches. Any longer term risks of infusing Treg cells are unknown but early studies have shown this to be safe and have not identified any concerns to date. There is a low risk (<1%) of significant bleeding complications after a kidney transplant biopsy.

Where is the study run from?
Oxford Transplant Centre, Churchill Hospital, Oxford (UK)

When is the study starting and how long is it expected to run for?
September 2016 to September 2031

Who is funding the study?
Medical Research Council (MRC)

Who is the main contact?
1. Dr Paul Harden
2. Dr Fadi Issa
3. Dr Matt Brook
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-001421-41

Integrated Research Application System (IRAS)
227287

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
37306; 12926

Study information

Scientific Title
The TWO study: Transplantation Without Over-immunosuppression - a Phase IIb trial of regulatory T cells in renal transplantation

Acronym

TWO Study: Treg Cell Therapy Trial v1.0

Study objectives

Current study hypothesis as of 23/09/2020:
Patients receiving solid organ transplants must be maintained on drugs that suppress the immune system in order to prevent the immune system from rejecting the transplant. These medicines are highly efficacious, with one-year kidney transplant survival in the UK being > 95%. However, long-term outcomes are significantly limited by the serious and life-threatening side-effects of immunosuppressive drugs, which include enhanced rates of infection, malignancy and cardiovascular and metabolic disease such as heart attacks and diabetes. Long-term maintenance on immunosuppressive drugs together with treatment of the unwanted side effects is a huge burden not only for the patient but also for the healthcare system, in terms of resource allocation and expenditure. Thus a major goal of future transplantation is to find ways to reduce the amount of immunosuppressive drugs used, whilst protecting the kidney transplant from immune system damage.
Regulatory T cells (Treg) are a subset of white blood cells that act to prevent autoimmune disease and to limit an 'overshoot' of normal immune responses to viruses. A promising approach is to use the regulatory ability of these cells to suppress the immune response causing rejection of the transplanted kidney. Having proven the safety and feasibility of Treg-based immunotherapy in the ONE Study (trial identifier: ONETreg1; ClinicalTrials.gov number: NCT02129881; EudraCT number: 2013-002099-42, co-sponsored by King's College London and Guy's and St Thomas' NHS Foundation Trust, REC number 13/SC/0568); the TWO Study aims to demonstrate the further safety, feasibility and efficacy of this treatment on a larger scale, with the goal of allowing reduction of immunosuppression to a single drug by 48 weeks post-transplantation.

Previous study hypothesis:
Patients receiving solid organ transplants must be maintained on drugs that suppress the immune system in order to prevent the immune system from rejecting the transplant. These medicines are highly efficacious, with one-year kidney transplant survival in the UK being > 95%. However, long-term outcomes are significantly limited by the serious and life-threatening side-effects of immunosuppressive drugs, which include enhanced rates of infection, malignancy and cardiovascular and metabolic disease such as heart attacks and diabetes. Long-term maintenance on immunosuppressive drugs together with treatment of the unwanted side effects is a huge burden not only for the patient but also for the healthcare system, in terms of resource allocation and expenditure. Thus a major goal of future transplantation is to find ways to reduce the amount of immunosuppressive drugs used, whilst protecting the kidney transplant from immune system damage.
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Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 10/05/2018, Health Research Authority, South Central, Oxford A research ethics committee (Bristol Research Ethics Committee Centre, Whitefriars, BS1 2NT, UK; +44 (0)207 104 8089; oxforda.rec@hra.nhs.uk), REC ref: 18/SC/0054

Study design
Randomized; Interventional; Design type: Treatment, Cellular, Immunotherapy

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Current interventions as of 23/09/2020:
Participating living donor renal transplant recipients will be randomised on a 1:1 basis to either Treg cell infusion (intervention) or standard care (control). In the intervention arm 5 to 10xE6/kg autologous Treg cells (TR001) will be infused intravenously at 5 days post transplant. Patients receiving cell therapy will ultimately wean off mycophenolate mofetil and be maintained on low dose tacrolimus monotherapy. Patients in the control arm will receive standard maintenance immunosuppression consisting of tacrolimus and mycophenolate mofetil.

Previous interventions:
Participating living donor renal transplant recipients will be randomised on a 1:1 basis to either Treg cell infusion (intervention) or standard care (control). In the intervention arm 5 to 10xE6/kg autologous Treg cells (TR001) will be infused intravenously at 6 months post transplant. Patients receiving cell therapy will subsequently be maintained on low dose tacrolimus monotherapy. Patients in the control arm will receive standard maintenance immunosuppression consisting of tacrolimus and mycophenolate mofetil.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
TR001

Primary outcome(s)
Incidence of biopsy-confirmed acute rejection (BCAR) in the 6 to 18-month period post-transplantation. A 9 month protocol biopsy will be performed in all participants including the control arm to allow a histological comparison of the impact of Treg therapy in the treatment arm. Any other biopsies performed during follow-up will be at the discretion of the responsible clinician and will be deemed ‘for-cause’. All biopsies will be reviewed and reported by the study pathologist using the Banff criteria.

Key secondary outcome(s))

Current secondary outcome measures as of 23/09/2020:
Measured over 18 months post-transplant:
1. Time to first biopsy-confirmed acute rejection episode will be measured in days
2. Severity of acute rejection episodes will be based on histological scoring according to the Banff criteria and degree of renal recovery following treatment
3. Incidence of graft loss due to rejection
4. Renal transplant function will be assessed by estimated glomerular filtration rate (eFGR) using the CKD-EPI equation
5. Patient survival
6. Incidence of adverse events to include:
6.1. Incidence of drug-related adverse events
6.2. Incidence of identified serious and/or opportunistic infections (including CMV, EBV and polyoma (BK) virus)
6.3. Incidence of neoplasia
6.4. Incidence of autoimmune disorders
6.5. Incidence of anaemia, cytopaenia and biochemical disturbances unrelated to kidney function
7. Total immunosuppression burden at 18 months post-transplantation will be defined by number of immunosuppressive agents, dose of immunosuppressive agents and serum tacrolimus level (measured in nanograms per ml). This will include assessment of the proportion of patients taking tacrolimus monotherapy
8. Chronic allograft nephropathy on renal transplant biopsies will be measured by the degree of interstitial fibrosis and tubular atrophy (IF/TA) as assessed by the study pathologist on protocol biopsies taken at 9 months post-transplant
9. Patient-reported outcomes measured using SF-36 and EQ-5L-5D questionnaires

Exploratory outcome measures:
1. Immune monitoring will be assessed formally at 2 weeks pre-transplant, day+4 and weeks 1, 2, 4, 12, 38, 43, 51 and 78 post-transplant. Patients in the treatment arm will also be analysed at 22 weeks post-transplant. Outcomes will include:
1.1. Cell phenotype analysis of peripheral blood
1.2. T cell functional assays against donor and third-party antigens
1.3. Serum cytokine analysis and third-party antigen analysis
1.4. Gene expression and RNA sequencing analysis to include Treg-specific demethylated region and T-cell receptor sequencing
2. Analysis of immune infiltrates present in kidney transplant biopsies including cell phenotype and transcript
3. Next-generation sequencing of viruses detected in clinical specimens

Previous secondary outcome measures:
Measured over 18 months and again at 5 years post-transplantation:
1. Time to first biopsy-confirmed acute rejection episode will be measured in days
2. Severity of acute rejection episodes will be based on histological scoring according to the Banff criteria and degree of renal recovery following treatment
3. Incidence of graft loss due to rejection
4. Renal transplant function will be assessed by estimated glomerular filtration rate (eFGR) using the CKD-EPI equation
5. Patient survival
6. Incidence of adverse events to include:
6.1. Incidence of drug-related adverse events
6.2. Incidence of identified serious and/or opportunistic infections (including CMV, EBV and

polyoma (BK) virus)
6.3. Incidence of neoplasia
6.4. Incidence of autoimmune disorders
6.5. Incidence of anaemia, cytopaenia and biochemical disturbances unrelated to kidney function
7. Total immunosuppression burden at 18 months post-transplantation will be defined by number of immunosuppressive agents, dose of immunosuppressive agents and serum tacrolimus level (measured in nanograms per ml). This will include assessment of the proportion of patients taking tacrolimus monotherapy
8. Chronic allograft nephropathy on renal transplant biopsies will be measured by the degree of interstitial fibrosis and tubular atrophy (IF/TA) as assessed by the study pathologist on protocol biopsies taken at 9 months post-transplant
9. Exploratory outcomes will be assessed at 2 weeks pre-transplant and 4, 12, 24, 30, 38, 44, 52 and 78 weeks post-transplant. Patients in the treatment arm will also be analysed at 22, 26, 27 and 28 weeks post-transplant. Outcomes will include:
9.1. Cell phenotype analysis of peripheral blood
9.2. T cell functional assays against donor and third-party antigens
9.3. Serum cytokine analysis and third-party antigen analysis
9.4. Gene expression and RNA sequencing analysis to include Treg-Specific demethylated region and T-cell receptor sequencing

Completion date
30/09/2031

Eligibility

Key inclusion criteria
Kidney recipient inclusion criteria:
1. Chronic renal insufficiency necessitating kidney transplantation and approved to receive a kidney allograft from a living donor
2. Willing and able to give informed consent for participation in the trial
3. Aged 18 years or above
4. In the Investigator’s opinion, is able and willing to comply with all trial requirements
5. Able to commence the immunosuppressive regimen at the protocol-specified time point
6. Female participants of child bearing potential and male participants whose partner is of childbearing potential must be willing to ensure that they or their partner use highly effective contraception during the trial
7. Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial

Kidney donor inclusion criteria:
1. Eligible for live kidney donation
2. Aged at least 18 years
3. ABO blood group compatible with the organ recipient
4. Willing to provide personal, medical and biological data for the trial analysis
5. Willing and able to provide a blood sample for the immune monitoring assays
6. Willing and able to give informed consent for participation in the trial

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Kidney recipient exclusion criteria:
1. Patient has previously received any tissue or organ transplant
2. Known contraindication to the protocol-specified treatments or medications
3. ABO blood group incompatible with donor
4. Calculated reaction frequency (CRF) of >40% within 6 months prior to transplant
5. Previous treatment with any desensitisation procedure (with or without IVIg)
6. Concomitant malignancy or history of malignancy within 5 years prior to planned study entry (excluding successfully treated non-metastatic basal or squamous cell carcinomas of the skin)
7. Serologically positive for anti-HIV-1/2 Ab, HbsAg, anti-HBcAb, antiHCV Ab, anti-HTLV-1/2 Ab or syphilis (treponema palladium)
8. Significant liver disease, defined as persistently elevated ALT levels >3 x upper limit of normal range (ULN)
9. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
10. Participation in another clinical trial during the study or within 28 days prior to planned study entry
11. Female participant who is pregnant, lactating or planning pregnancy during the course of the trial
12. Psychological, familial, sociological, or geographical factors potentially hampering compliance with the study protocol and follow-up visit schedule
13. Any form of substance abuse, psychiatric disorder, or other condition that, in the opinion of the investigator, may invalidate communication with the investigator and/or designated personnel

Kidney donor exclusion criteria:
1. Exposure to any investigational agents at the time of kidney donation, or within 28 days prior to kidney donation
2. Any form of substance abuse, psychiatric disorder, or other condition that, in the opinion of the Investigator, may invalidate communication with the Investigator designated personnel
3. Is a paired exchange donor
4. Is an altruistic donor

Date of first enrolment
06/12/2018

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Transplant Centre
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/N027930/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United Kingdom

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 Fadi Issa (fadi.issa@nds.ox.ac.uk). Raw data supporting published outcomes will be available on reasonable request for a period of 5 years following publication for purposes of scrutiny. Where mutually agreed, further analysis of this data will be permitted subject, where required, to appropriate ethical approval. Any data provided will be fully anonymised.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/04/2022	17/05/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes