ISRCTN42322435 https://doi.org/10.1186/ISRCTN42322435

Induction of operational tolerance in stable liver graft recipients

Submission date	Recruitment status	[X] Prospectively registered
26/08/2012	Stopped	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
11/09/2012	Stopped	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
16/01/2019	Surgery	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Continuing immune suppression lifelong following liver transplant has long been held as essential to ensure the best outcome for our patients. However, these immunosuppressive drugs are associated with side effects. These include increased risk of infection, cancer and heart disease. A recent study of UK liver transplants showed that for patients surviving longer than 1 year after transplant the survival rate was half that of the general population. There was no sign that this outcome had improved between 1994 and 2007. These issues have led to a focus on drug weaning strategies, with a view to stopping immune suppression if stable transplant function can be maintained. Early studies have shown this so-called operational tolerance is possible in around 20% of patients, although it is believed this could be a lot higher at late time points following transplant.

Our aim is to identify:
1. The proportion of stable liver transplant patients that develop operational tolerance with physician-directed reduction or withdrawal of immunosuppression at a late point after transplantation.
2. Whether the development of operational tolerance leads to a reduction in illness and improvement in life expectancy.
3. Whether a two-step strategy of reduction of immune suppression followed by withdrawal is safe and effective.

Who can participate?
Liver transplant recipients more than 5 years from transplantation.

What does the study involve?
Participants will be randomly assigned to either the immunosuppression weaning group or the control group. In the immunosuppression weaning group, doses of immunosuppressive drugs will be halved. The control group will continue receiving their current immunosuppression dose. Patients will undergo protocol liver biopsies at time of recruitment, after 1 year and after 3 years.

If after 3 years on half-dose immune suppression the patient's liver function tests are stable and liver biopsy satisfactory they will be offered the opportunity to stop immune suppression altogether. It is understandable that they might feel uncomfortable about stopping immune suppression drugs completely and we therefore stress that this aspect of the study is optional. The study will run for 4 years and clinic follow-up will take the same form it does at present.

What are the possible benefits and risks of participating?
If we are able to successfully stop immune suppression it will mean the participants are not exposed to the potential side effects of the drugs. We expect this to lead to a reduction in illness and longer life expectancy.
Clearly, developing rejection on weaning immune suppression is a concern. Reassuringly, previous studies have demonstrated that those patients who fail to become tolerant and develop rejection are not exposed to a higher risk of loss of their transplanted liver or death. Episodes of rejection appear to be mild in most patients and generally settle without requiring high-dose steroids. If they do develop rejection they will be withdrawn from the study and recommenced on their previous treatment.

Where is the study run from?
Addenbrooke's Hospital Cambridge (lead centre), Queen Elizabeth Hospital Birmingham and King's College Hospital London (UK).

When is the study starting and how long is it expected to run for?
Recruitment will take place over a 12-month period and it is envisaged that the study will start in January 2013 and will end in December 2018.

Who is funding the study?
Cambridge University Hospitals NHS Trust (UK).

Who is the main contact?
Dr Roger McCorry
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Towards operational tolerance. A randomised prospective controlled trial to compare a planned reduction (and subsequent withdrawal) of immune suppression with no change in immune suppression in selected stable liver graft recipients.

Study objectives
Operational tolerance is defined as the state wherein a liver graft retains function and lacks histological signs of rejection in the absence of immune suppression, but the recipient remains immune competent capable of responding to all other immune challenges, including infection.
We aim to identify:
1. The proportion of stable liver transplant recipients that develop operational tolerance with physician directed reduction or withdrawal of immunosuppression at a late point after transplantation.
2. Whether the acquisition of operational tolerance leads to reduction in morbidity or mortality.
3. Whether a two-step strategy of reduction of immune suppression followed by withdrawal is safe and effective.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cambridge Central Research Ethics Committee, 01 October 2012

Study design
Randomised controlled multicentre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Liver transplant recipients; immunosuppression; operational tolerance

Interventions
In the intervention group immunosuppression shall be weaned, with reduction of drug doses by half for first 3 years of the study.

The control group shall continue full dose immunosuppression.

If after three years patients with reduced immune suppression have stable biochemistry then they will be offered a follow up liver biopsy and if that remains compatible with operational tolerance they will be offered the opportunity to stop immune suppression altogether.

Intervention Type
Procedure/Surgery

Phase
Not Applicable

Primary outcome(s)
To determine the proportion of stable liver transplant recipients that develop operational tolerance with physician directed reduction or withdrawal of immunosuppression at a late point after transplantation

Key secondary outcome(s))
1. To determine whether the acquisition of operational tolerance leads to reduction in morbidity or mortality
2. To determine whether a two-step strategy of reduction of immune suppression followed by withdrawal is safe and effective

Completion date
31/12/2018

Eligibility

Key inclusion criteria
1. Age over 40 and regarded as competent to make informed decisions
2. More than 5 years from transplantation
3. No episodes of steroid resistant acute rejection or acute rejection beyond one year post-transplant
4. Transplantation for non-auto-immune liver disease
5. Stable liver biochemistry with an ALT less than 30 IU/L and serum immunoglobulins
6. Prepared to have a liver biopsy prior to entry as well as 1 and 3 years after study entry
7. An adequate liver biopsy with minimal inflammation restricted to the portal tract, at worst minimal fibrosis, without bile duct damage or arteriopathy
8. On monotherapy with a calcineurin inhibitor or Sirolimus
9. Prepared to enter a randomised controlled trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Not competent to make a decision regarding enter into the study
2. Current malignancy

Date of first enrolment
01/01/2013

Date of final enrolment
31/12/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Department of Hepatology
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
National Health Service (UK)

Results and Publications

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes