ISRCTN47808000 https://doi.org/10.1186/ISRCTN47808000

Liver immunosuppression free trial ("LIFT"), version 1

Submission date 08/07/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 08/07/2015	**Overall study status** Completed	
Last Edited 11/08/2025	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims

Following liver transplantation patients need to be given powerful drugs (known as immunosuppressive medication), to prevent organ rejection. These drugs are usually given for the rest of the patients life, which can result in important side effects. This the main reason why in the long run transplanted patients die more frequently than non-transplanted healthy individuals. Not all liver transplant patients, however, require lifelong immunosuppressive medication. Some of them develop a phenomenon known as operational tolerance and can discontinue this medication without rejecting the transplanted liver. In tolerant patients the withdrawal of anti-rejection medication could increase their survival and improve their quality of life. However, until now there have been no tests to identify tolerant patients before immunosuppression medication is stopped. Our research group recently identified a genetic test of tolerance in liver biopsies that can predict the outcome of immunosuppressive drug withdrawal. This test could radically change the long-term care of liver transplant patients.

Who can participate?

Liver transplant patients that received their new liver more than 3 years ago or more than six years ago if aged 18-49 or at least 50 years old respectively.

What does the study involve?

Participants first have a liver biopsy for the genetic test of tolerance. They are then randomly allocated to one of two groups. Patients randomized to group 1 are offered drug withdrawal regardless of the result of the genetic test. Patients randomized to group 2 undergo drug withdrawal if the genetic test is positive, and continue the immunosuppressive medication if the test is negative. By comparing the outcome of the 2 groups we will determine how much the test can benefit transplanted patients.

What are the possible benefits and risks of participating?

Chronic immuno-suppression (IS) is associated with a variety of life threatening side effects following liver transplantation, including infection, malignancy, hypertension, diabetes, nephrotoxicity and cardiovascular diseases. Calcineurin inhibitor induced nephrotoxicity, in particular, is responsible for a significant rate of chronic renal failure, need for renal replacement therapy and increased mortality. Elimination of calcineurin inhibitors may preserve

waning renal function and avoid the associated morbidity and mortality risk.Identification of a reproducible and reliable tolerance signature will allow tailoring of IS to individual patient characteristics. It may also identify critical pathways responsible for the tolerant state that can be therapeutically exploited to induce tolerance in those who do not achieve it spontaneously. While there is abundant information in the literature suggesting that in carefully selected liver recipients IS withdrawal is feasible and safe, the procedure is not without risk, as it can induce immunologically-mediated allograft rejection. In this regard, the main risks of IS withdrawal are acute and/or chronic rejection, silent development of allograft fibrosis, potential complications associated with the need to increase IS to treat rejection episodes; and graft loss or patient mortality.

Where is the study run from?
King's College London (UK)

When is the study starting and how long is it expected to run for?
August 2015 to October 2017

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Ms Jurate Wall

Contact information

Type(s)
Scientific

Contact name
Ms Jurate Wall

Contact details
King's College London
Basement
Denmark Hill
London
United Kingdom
SE5 9RS

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02498977

Clinical Trials Information System (CTIS)
2014-004557-14

Protocol serial number
19194

Study information

Scientific Title
Prospective randomised marker-based trial to assess the clinical utility and safety of biomarker-guided immunosuppression withdrawal in liver transplantation ("LIFT" Trial).

Acronym
LIFT

Study objectives
The objective of this study is to determine if a genetic test of tolerance in liver biopsies can be employed to optimize immunosuppression withdrawal, so that withdrawal is only performed in patients who have developed tolerance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London- South East, 09/02/2015, ref: 14/LO/2172

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Hepatology; Subtopic: Hepatology; Disease: All Hepatology

Interventions
Adult liver transplant recipients will undergo gradual IS withdrawal following randomisation 1:1 to either:
1. Non-Biomarker-based IS weaning (Arm A)
2. Biomarker-based IS weaning (Arm B). Participants allocated to Arm B will be offered IS withdrawal only if they are classified as tolerant on the basis of a biomarker test (Arm B+), while they will remain on maintenance IS if classified as non-tolerant (Arm B-)

Intervention Type
Other

Primary outcome(s)
To determine if the use of a liver tissue transcriptional test of tolerance to stratify liver recipients prior to IS withdrawal accurately identifies operationally tolerant recipients and reduces the incidence of rejection, as compared with a control group in whom IS withdrawal is performed without stratification.

Key secondary outcome(s))

1. To establish the safety of biomarker-guided IS withdrawal
2. To determine the health-economic impact of withdrawing IS in liver transplant recipients and to assess how much this cost is influenced by the use of a diagnostic test of operational tolerance
3. To assess the effect of IS withdrawal on the quality of life of liver transplant recipients
4. To determine the extent to which IS withdrawal improve drug-related co-morbidities
5. To investigate if liver transplant recipients under IS become operationally tolerant over time
6. To determine if the presence of donor-specific anti-HLA antibodies influence the success of IS withdrawal, and whether IS withdrawal promotes the development of anti-HLA antibodies in liver transplant recipients
7. To explore the association between operational liver transplant tolerance, iron metabolism, immunosenescence, and specific gut microbiome profiles

Completion date
31/03/2021

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 29/01/2019:
1. At the time of screening: more than 3 years post-transplant if participants are ≥50 years old, OR ≥ 6 years post-transplant if participant age is ≤50 years old.
2. Recipient of either deceased or living donor liver transplant.
3. Recipient of single organ transplant only
4. Liver function tests: direct bilirubin ≤17.1 umol/L and ALT ≤60 IU/L at the screening visit.
5. On calcineurin inhibitor (CNI) IS with or without one of the following: Low dose mycophenolic acid (≤ 1080 mg daily), mycophenolate mofetil (MMF ≤ 1500 mg daily), azathioprine (≤ 150 mg daily), sirolimus/everolimus; or on monotherapy with sirolimus/everolimus or mycophenolate /mycophenolic acid monotherapy (effective contraception must be used
before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, see Appendix 6),
6. Ability to sign informed consent.

Previous participant inclusion criteria:
1. At the time of screening: more than 3 years post-transplant if participants are ≥50 years old, OR ≥ 6 years post-transplant if participant age is 18-49 years old.
2. Recipient of either deceased or living donor liver transplant
3. Recipient of single organ transplant only
4. Liver function tests: direct bilirubin =17.1 umol/L and ALT =60 IU/L at the screening visit.
5. On calcineurin inhibitor (CNI) based maintenance IS and no more than one of the following: Low dose mycophenolic acid (= 1080 mg daily), mycophenolate mofetil (MMF = 1500 mg daily), or azathioprine (= 150 mg daily); or on mycophenolate/mycophenolic monotherapy (effective contraception must be used before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy)
6. Ability to sign informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 29/01/2019:
1. Serum positivity for HCV-RNA
2. Serum positivity for HIV-1 infection, HBV surface antigen or HBV-DNA
3. Immune-mediated liver disease in which IS discontinuation is inadvisable (autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis).
4. Acute or chronic rejection within the 52 weeks prior to screening.
5. GFR <30 mL/min (to mitigate the risk of worsening renal failure should rejection occur and high level of CNI be required).
6. The need for chronic anti-coagulation that cannot be safely discontinued to safely perform for a liver biopsy.
7. Baseline (screening) liver biopsy showing any of the following: a) acute rejection according to Banff criteria; b) early or late chronic rejection according to Banff criteria; c) inflammatory activity and/or fibrosis in excess of permissive criteria (Table 1) (25); f) any other findings that might make participation in the trial unsafe. Eligibility will be determined by the central pathologist.
8. Patient age <18 years old at the time of transplant.
9. Pregnant females and females of childbearing age not using effective contraception (See Appendix 6).
10. Current illicit drug or alcohol abuse.
11. Inability to participate in frequent monitoring of liver function (every 3 weeks) and clinical visits during IS withdrawal.
12. Inability to comply with study directed treatment.
13. Any medical condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
14. Participation in another clinical trial during the month prior to enrolment.

Previous participant exclusion criteria:
1. HCV infection (defined by serum positivity for HCV-RNA)
2. Positive serology for HIV-1, hepatitis B surface antigen, or hepatitis B DNA
3. Immune-mediated liver disease in which IS discontinuation is inadvisable (autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis)
4. Acute or chronic rejection within the 52 weeks prior to screening
5. GFR <40 mL/min (to mitigate the risk of worsening renal failure should rejection occur and high level of CNI be required)
6. The need for chronic anti-coagulation that cannot be safely discontinued for a minimum of 1 week to safely perform for a liver biopsy
7. Baseline (screening) liver biopsy showing any of the following:
7.1. Acute rejection according to Banff criteria
7.2. Early or late chronic rejection according to Banff criteria
7.3. Moderate-severe fibrosis (Ishak stage 3 or more)
7.4. Chronic hepatitis (defined as predominantly mononuclear portal inflammation with or

without plasma cells) with moderate/marked portal inflammation (Ishak 3 or more) or with mild /moderate interface hepatitis (Ishak 2 or more)
7.5. Perivenular necro-inflammatory activity in a majority of terminal hepatic venules
7.6. Any other findings that might make participation in the trial unsafe. Elligibility will be determined by the central pathologist
8. Pregnant females and females of childbearing age not using effective contraception
9. Current illicit drug or alcohol abuse
10. Inability to participate in frequent monitoring of liver function (every 3 weeks) and clinical visits during IS withdrawal
11. Inability to comply with study directed treatment
12. Any medical condition that in the opinion of the principal investigator would interfere with safe completion of the trial

Date of first enrolment
01/08/2015

Date of final enrolment
01/10/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College Hospital (lead)
London
United Kingdom
SE5 9RS

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/04/2025	11/08/2025	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 11	27/09/2019	07/10/2022	No	No