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Randomised study for immunosuppression regimen in liver transplantation

Submission date	Recruitment status	[_] Prospectively registered
09/07/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/07/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
29/10/2013	Digestive System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Prof Andrew Burroughs

Contact details
Royal Free Hampstead NHS Trust
Pond Street
London
United Kingdom
NW3 2QG
+44 (0)20 7433 0060
Andrew.Burroughs@royalfree.nhs.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
3729

Study information

Scientific Title
Randomised trial of monotherapy with tacrolimus versus triple therapy with tacrolimus azathioprine and steroids

Study objectives
Hepatitis C virus (HCV)-induced cirrhosis is a leading indication for liver transplantation. There is universal and unavoidable graft re-infection, leading to cirrhosis in 20% after 5 years. Although immunosuppression influences severity of HCV recurrence, a particular regimen which conclusively results in less severe recurrence, is not known.

A recent meta-analysis demonstrated no difference between cyclosporin and tacrolimus, but tacrolimus based immunosuppression reduced graft loss compared to cyclosporin. Another meta-analysis suggests steroids may not be beneficial contrary to a recent study. A randomised study using only calcineurin inhibitor monotherapy (MT) showed both safety and effectiveness in terms of acute and chronic rejection rates, immune graft loss, graft function and patient and graft survival.

We designed a randomised study in liver transplant recipients with hepatitis C virus (HCV) cirrhosis assessing tacrolimus monotherapy (MT) versus tacrolimus, azathioprine and prednisolone triple therapy (TT), hypothesing that the monotherapy arm would have less immunosuppressive potency and, being without maintenance steroids, have less deleterious effects on recurrent HCV.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Ethics Committee of the Royal Free Hospital in 1999 (ref: 3729)

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied

Hepatitis C virus (HCV)-induced cirrhosis

Interventions
Tacrolimus (Prograf®, Fujisawa Ltd, Ireland) 0.1 mg/kg/day was given in two divided doses in both MT and TT groups starting within 6 hours from transplantation via a nasogastric tube. Azathioprine was given initially intravenously (iv) then orally 1 mg/kg/day, and methylprednisolone(16 mg/day iv) until oral intake was established, when 20 mg/day prednisolone was used. If poor renal and/or graft function was present tacrolimus dosing (which was evaluated every other day) was adjusted according to clinical progress and occurrence of adverse effects, maintaining a whole blood level of 5 - 14 ng/mL (aiming for 5 - 10 ng/mL) by microparticle enzyme immunoassay (ImxTacrolimus II, Abbott Laboratories, USA). Azathioprine was administered at the same dose unless neutropenia developed. Prednisolone was gradually tapered from 3 weeks onwards and then stopped between 3 and 6 months, according to each centre's practice.

Randomisation took place on arrival to the operating theatre. Each centre had a separate randomisation sequence. Follow-up stopped at death, re-transplantation, or end of January 2008.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Tacrolimus, azathioprine, prednisolone

Primary outcome measure
The primary end-point was whichever of the following occurred first:
1. Progression of fibrosis, to Ishak stage 4, or
2. Graft failure requiring retransplantation or patient death, or
3. Treatment failure for immunological reasons, i.e., more than two histologically confirmed episodes of cellular rejection failing to respond to therapy

The primary endpoints were measured either in yearly intervals (biopsies) or whenever they occurred within the study period.

Secondary outcome measures
Secondary end-points included:
1. Patient survival
2. Acute cellular rejection early (less than 14 days) or not
3. Chronic rejection
4. Steroid resistant cellular rejection irrespective of further changes in immunosuppression
5. Recurrence of HCV, defined by Ishak inflammation score greater than or equal to 4
6. Withdrawal from the randomised allocation

The secondary endpoints were measured at yearly endpoints or whenever a clinical decompensation occurred.

Overall study start date

01/01/2000

Completion date
01/06/2007

Eligibility

Key inclusion criteria
From January 2000 to June 2007, in three liver transplant centres, (Royal Free Hospital, Edinburgh Royal Infirmary and St Vincents Hospital, Dublin; all using the same donor pool) consecutive transplant recipients were randomised if they:
1. Had cirrhosis
2. Were hepatitis C virus ribonucleic acid (HCV RNA) positive in serum
3. Had previous histology confirming HCV-related disease
4. Had possible or confirmed/concomitant alcoholic aetiology or hepatocellular carcinoma (HCC)
5. Were older than 18 years, either sex
6. Had given informed written consent (at listing for transplantation)
7. Received a cadaveric liver transplant

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
110

Key exclusion criteria
1. Retransplantation
2. Multi-organ, split or auxiliary transplants
3. Contraindications to tacrolimus or azathioprine
4. Refusal to participate

Date of first enrolment
01/01/2000

Date of final enrolment
01/06/2007

Locations

Countries of recruitment
England

Ireland

United Kingdom

Study participating centre
Royal Free Hampstead NHS Trust
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
Royal Free Hampstead NHS Trust (UK)

Sponsor details
Pond Street
Hampstead
London
England
United Kingdom
NW3 2QG
klara.kalu@royalfree.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.royalfree.nhs.uk/

ROR
https://ror.org/04rtdp853

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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?
Results article	results	01/03/2006		Yes	No
Results article	results	01/06/2014		Yes	No