ISRCTN15775356 https://doi.org/10.1186/ISRCTN15775356

Analysis of immunological and genetic factors implicated in operational tolerance in liver transplant patients

Submission date
20/07/2017

Recruitment status
No longer recruiting

Registration date
25/07/2017

Overall study status
Completed

Last Edited
06/09/2023

Condition category
Surgery

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Organ transplantation has saved many lives in recent decades. However, patients need to take lifelong medication to prevent that their immune system from rejecting the new organ. This medication, known as immunosuppression, has increased the life expectancy of transplants, but at the same time it is the major cause of death in these patients due to its side effects (problems with the kidneys, tumours). Because of this, one strategy is to get these patients to not reject the transplant without needing to take medication, which in medical terms is known as "operational tolerance". It was observed that some patients who stopped taking the medication accidentally or voluntarily had no problem of rejection and could have a normal life. In addition, it was observed that the liver is a privileged organ that allows a higher rate of tolerance than other organs. In this way, researchers tested stopping the medication in a controlled way in selected groups of patients. With these processes there is a 40% chance of successful immunosuppression withdrawal, while the other 60% that fail to stop the medication are considered "non-tolerant" patients. The aim of this study is to look for molecular markers that can indicate whether patients would be part of the 40% able to achieve "operational tolerance".

Who can participate?
Patients aged over 18 who underwent liver transplantation more than three years ago and are being treated with immunosuppression

What does the study involve?
Immunosuppression is gradually withdrawn at 1-month intervals as long as liver function is stable, and the patients are monitored monthly for liver problems. Participants who suffer a rejection episode during the immunosuppression withdrawal process are treated by reintroducing the immunosuppressive treatment. Other participants complete the withdrawal process and become tolerant. Blood samples are collected every month during the immunosuppression withdrawal to measure different types of blood cells and molecular markers. Participants are followed up for 1 year.

What are the possible benefits and risks of participating?
Participants may benefit from a lower risk of immunosuppression side effects (e.g., kidney failure, cancer). No serious side effects have been reported in previous studies (i.e., transplant loss, death).

Where is the study run from?
Hospital Universitario Virgen de la Arrixaca (Spain)

When is the study starting and how long is it expected to run for?
January 2013 to December 2016

Who is funding the study?
Instituto de Salud Carlos III (Spain)

Who is the main contact?
Dr José Antonio Pons-Miñano
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
PI12/02042

Study information

Scientific Title
Prospective study of immunological factors and genetic expression implicated in operational tolerance in liver transplant patients

Study objectives
Numerous experimental data ex vivo and/or in animal models have provided clues on the immunological bases of transplant tolerance, involving different cell populations (Treg, dendritic, B ...), cytokines, transcription factors (Foxp3), extracellular ATP degradation and T lymphocyte signaling through adenosine, etc. Several "retrospective" studies performed among transplant patients (mainly liver and kidney) who have tolerated the graft versus non-tolerant patients have described differential patterns of lymphocyte populations or gene expression in peripheral blood and tissue between both groups. In this way, patients with a liver transplant, with at least 3 years of immunosuppressive regimen and with a stable function of the organ, have a capacity to achieve greater operational tolerance than other transplant patients, being described in the literature a acceptance rate of the transplant after withdrawn of the IS around 30-40 %. Although some "prospective" study has been done, a clear profile of biomarkers has yet to be established to predict with higher precision those patients with liver transplantation being good candidates to tolerate the graft. Therefore, the trialists hypothesized that the study and analysis of multiple immunological or genetic parameters described so far in the literature in an individualized and mostly retrospective way in a group of patients with stable liver transplantation who undergo progressive IS withdrawal will allow them, after an exhaustive statistical analysis, to determine a combination of specific markers that indicate with the highest possible reliability that patients with liver transplantation may be tolerant after a progressive IS withdrawal process. In addition, the study of these markers at different points throughout the IS withdrawal process may shed some light on which phenomena are most important for achieving an immunologically favorable state of graft tolerance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Comité Ético de Investigación Clínica - Hospital Universitario Virgen de la Arrixaca, 10/03/2012, ref: PI12/02042

Study design
Interventional single-group open-label treatment single-center study

Primary study design
Interventional

Study type(s)
Quality of life

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

Interventions
Immunosuppression will be gradually withdrawn in ≥ 10 % decrements at 1-month intervals as long as the liver function is stable, and the patients will be monitored monthly for liver graft dysfunction. Some of the patients will suffer a rejection episode during the IS withdrawal process and will be treated by reintroducing the immunosuppressive therapy that they had been receiving before the beginning of the weaning protocol (non-tolerant patients; non-Tol); other patients will complete the withdrawal process and will become tolerant (Tol; no IS and normal allograft function at least one year after IS withdrawal). Liver rejection will be indicated by high serum levels of aspartate aminotransferase or alanine aminotransferase and confirmed by liver

biopsy. The diagnosis of cellular rejection will be based on the presence of predominantly mononuclear portal infiltrate plus non-suppurative ductal cholangitis with or without endothelitis. Patients will be follow-up for 1 year after rejection or tolerance.

Intervention Type
Other

Primary outcome(s)
PBMCs, plasma and mRNA will be collected every month during the IS withdrawal. Most of the outcomes will be measured at these five timepoints:
1. Immunophenotyping in peripheral blood of different cell subpopulations including regulatory T cells, NK, B, dendritic and other specific markers, using flow cytometry
2. Level of serum inflammatory cytokines, measured using multiplex ELISA
3. Gene expression pattern of a pre-established cohort of genes and miRNAs, measured using qPCR
4. The methylation level of the TSDR zone of the FOXP3 gene in peripheral blood, measured pyrosequencing
5. The concentration in plasma of ferritin, hepcidin-25 (measured by ELISA) ATP and adenosine (measured by UPLC-MS-UV)
6. Gene expression (mainly genes related to iron homeostasis), miRNAs, FOXP3 methylation and immunohistochemical analysis of Foxp3 at tissue level, measured using liver biopsies taken prior to the start of the IS withdrawal study and in the rejection episode

Key secondary outcome(s))
The diagnostic accuracy of one or more of these biomarkers of tolerance in blood or hepatic tissue, together or separately, for predicting as accurately as possible the result of protocolized withdrawal of immunosuppressive medication

Completion date
30/12/2016

Eligibility

Key inclusion criteria
1. Older than 18 years
2. Liver transplantation more than three years ago
3. Treatment with IS that includes cyclosporine or tacrolimus
4. Have a normal liver function in the last year (defined as normal transaminases and alkaline phosphatase in all laboratory controls performed during the last year)
5. Not acute rejection in the last year and not chronic rejection
6. Normal hepatic biopsy according the Banff Working Group criteria for IS withdrawal
7. Etiology of the underlying disease: cirrhosis (with or without hepatic tumour) of any cause (except autoimmune etiopathogeny diseases): alcoholic B virus, C virus cirrhosis, cryptogenetic, ..., metabolic diseases, familial amyloid polyneuropathy; biliary atresia, fulminant hepatitis no A, no B, no C
8. Patients who offer sufficient guarantees of adherence to the protocol; I. Patients who give written informed consent to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
17

Key exclusion criteria
1. Transplantation of another non-hepatic organ
2. Liver transplantation due to a disease of autoimmune etiopathogenesis (primary biliary cholangitis, primary sclerosing cholangitis or autoimmune hepatitis)
3. Patients with hepatic retransplantation
4. Active infection with hepatitis C virus or hepatitis B virus
5. Patients with chronic rejection, or acute rejection in the last year
6. Inability to understand informed consent; e: liver biopsy with significant portal or lobular inflammation
7. Patients with rheumatic/autoimmune disease requiring sustained immunosuppressive treatment

Date of first enrolment
25/03/2013

Date of final enrolment
15/07/2015

Locations

Countries of recruitment
Spain

Study participating centre
Hospital Universitario Virgen de la Arrixaca
Ctra. Madrid-Cartagena s/n
Murcia
Spain
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Sponsor information

Organisation
FFIS-Región de Murcia

ROR
https://ror.org/05m5has32

Funder(s)

Funder type
Government

Funder Name
Instituto de Salud Carlos III

Alternative Name(s)
SaludISCIII, InstitutodeSaludCarlosIII, Instituto de Salud Carlos III | Madrid, Spain, Carlos III Institute of Health, Institute of Health Carlos III, Carlos III Health Institute, La misión del Instituto de Salud Carlos III (ISCIII), ISCIII

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Spain

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 Dr José Antonio Pons (joseapons.imib.arrixaca@gmail.com). Data to be shared: principally clinical and demographic data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		17/07/2018	06/09/2023	Yes	No