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The addition of simvastatin portal venous infusion to cold storage solution of explanted whole liver grafts for facing ischemia /reperfusion injury in an area with low rate of deceased donation

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Registration date 22/12/2015	**Overall study status** Completed	
Last Edited 04/01/2023	**Condition category** Surgery	

Plain English summary of protocol

Background and study aims
Liver transplantation is the best treatment for end-stage liver disease. The interruption of the blood supply to the donor liver during cold storage damages the liver, affecting how well the liver will function after transplant. The drug simvastatin may help to protect donor livers against this damage and improve outcomes for the transplant recipients. The aim of this study is to evaluate the benefits of treating the donor liver with simvastatin compared with the standard transplant procedure.

Who can participate?
Adults with chronic liver disease on the waiting list for their first liver transplantation from a deceased donor.

What does the study involve?
Patients are randomly allocated to receive either a donor liver that has been treated with simvastatin or a donor liver that has not been treated with simvastatin. All participants are routinely evaluated with a liver biopsy (sample), intensive care monitoring, daily laboratory and ultrasound examinations for the first week after the operation and when required during their hospital stay. Participants also visit the outpatient clinic for ultrasound scans and laboratory liver function tests 15 and 30 days and 3, 6, 9, 12 and 18 months after the operation.

What are the possible benefits and risks of participating?
The use of simvastatin could reduce donor liver damage, and decrease the length of hospital stay and rate of complications. There is a remote probability of liver damage with the use of statins, but simvastatin is a well-known drug with a minimal reported risk of liver damage compared with the other statins.

Where is the study run from?
Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT) (Italy)

When is the study starting and how long is it expected to run for?
April 2016 to July 2020

Who is funding the study?
Ministry of Health, Italian Government

Who is the main contact?
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Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2015-004755-49

Protocol serial number
GR-2013-02357764

Study information

Scientific Title
The addition of simvastatin portal venous infusion to cold storage solution of explanted whole liver grafts for facing ischemia/reperfusion injury in an area with low rate of deceased donation

Acronym
SimvaLT

Study objectives
Liver transplantation (LT) is the treatment of choice for end-stage liver disease. Ischemia /reperfusion (I/R) injury during the conventional cold storage and preservation of donated livers is a key determinant of graft function after LT. Simvastatin suppresses inflammatory effect in

vascular endothelial cells, protecting the liver against I/R injury and its effects on graft from extended-criteria donors, including donor age (>60 years old), amine requirements, hypernatremia, prolonged intensity care stay, African race, and graft steatosis. As recently suggested, we hypothesize that simvastatin's protective effects may occur in the liver during the harvesting procedure from deceased donor and could significantly ameliorate post-LT outcomes. We propose a prospective, double-blinded, randomized phase 2 study of 2 parallel groups designed to include 106 consecutive subjects who will undergo LT for the first time with portal infusions of simvastatin during liver procurement.

LT is the only life-saving therapy for most types of end-stage liver disease. In Italy, the overall rate of cadaver donation is 22.2 donors per million per year, and in some regions, as Sicily, the rate is 12.6 donors per million per year. In the past years, ISMETT, a transplant hospital in Sicily, has been committed to face this organ shortage and over the years, the number of transplants has steadily increased thanks to marginal donors, living donors and split LT. ISMETT has implemented techniques and strategies to make the best use of valuable resources, maintaining a high level of liver transplantation: from July 1999 till May 2014, we performed 902 LTs for adults: 755 (84%) were performed by using 601 whole livers (80%), 99 (13%) were living-related LTs and 55 (7%) were split LTs. The one-year survival rate (cadaveric liver transplantation) is 85.4%. The shortage of organs led to the use of steatotic liver grafts from extended-criteria donors, even if these livers are much susceptible to I/R injury and have poorer outcome than non-steatotic livers. It has been demonstrated by preclinical studies that these negative effects of I/R can be prevented by adding simvastatin to the cold preservation solution shortly before procurement to protect both parenchymal and endothelial components of the liver after warm reperfusion. The proposed project aims to be the first prospective randomized clinical trial to prove the efficacy of simvastatin in preventing I/R injury and expand the donor pool.

Specific Aims:
The hypothesis behind the present study is that a single intravenous injection of simvastatin will be more effective in improving liver graft metabolism than the alone physical reduction of temperature obtained with the cold storage. This early clinical trial might represent a crucial bridge between preclinical drug study and the definitive regulatory hurdle for drug approval in multi-organ harvesting procedures from deceased donors. The incorporation of scientifically and analytically validated clinical effects of simvastatin into this rationally designed hypothesis-testing clinical trial could offer a promising way forward to achieve prevention I/R injury and expand the donor pool.

Aim 1. To evaluate the efficacy of simvastatin addition to cold-storage in preventing ischemia /reperfusion injuries.
Aim 2. To study whether the simvastatin, which is a very cheap vaso-protective compound, might be a rapid and useful pharmacological support to donor surgeons for increasing the viability of harvested organs from deceased donors.
Aim 3. To provide evidence-based research to demonstrate which strategies might reduce healthcare costs and prevent primary organ failure, retransplantation in urgency, and any complications related to high mortality.

Experimental Design Aim 1: Simvastatin procurement protocol will be evaluated in terms of post-reperfusion liver biopsy, liver function tests and hepatic Doppler ultrasonography during very early post-LT phase and in the intermediate follow-up period.
Experimental Design Aim 2: We will compare 3-month, 6-month and 12-month graft survival after LT with organs from conventional and marginal donors, with or without portal venous infusion of simvastatin.
Experimental Design Aim 3: We will investigate hospitalization stays and all transplant-related

complications in terms of the multi-tier Clavien grading system, in order to identify a significant relation into two homogenous groups of liver transplanted patients, only different for simvastatin infusion regimen; using the same procedure, with identical surgical instruments, and medical and nursing skilled staff.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved by the institutional review board on 14/09/2014
2. IRCCS ISMETT ethics committee, 10/10/2017, ref: IRRB/72/14

Study design
Prospective double-blinded randomized phase II study of two parallel groups

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Current interventions as of 09/02/2018:
Patients will be randomized in a 1:1 ratio to receive an organ perfused or not perfused with a single dose of simvastatin immediately before the donor hepatectomy (80 mg PO once, through naso-gastric tube) in addition to cold storage Celsior Solution (CS). The other explanted whole liver grafts will be treated solely with Placebo associated with CS. LTs with standard technique will be performed and all recipients will be routinely evaluated during hospitalization with an intraoperative post-reperfusion liver biopsy, intensive care monitoring ,daily laboratory and Doppler ultrasound examinations for the first postoperative week and subsequently when they will be clinically indicated during the hospital stay. Outpatient clinic visits with liver Doppler ultrasound examinations and laboratory examination of liver function tests will be performed on POD15 and POD30, and 3, 6, 9, 12, 18 months after LT, for having maximal adherence to our normal clinical practice. We will perform protocol-specific post-reperfusion biopsy at the time of LT for ruling out early histologic damage, but we will perform liver biopsy during the follow-up period only when it will be clinically indicated. An accrual period of 30 months will be assumed and a minimum follow-up period of 6 months will be utilized for living enrolled patients.

Previous interventions:
Patients will be randomized in a 1:1 ratio to receive an organ perfused or not perfused with a single dose of portal venous infusion of simvastatin immediately after the donor hepatectomy (1 mg/kg) in addition to cold storage Celsior Solution (CS). The other explanted whole liver grafts will be treated solely with the simvastatin solvent (dimethyl sulfoxide) associated with CS. LTs with standard technique will be performed and all recipients will be routinely evaluated during hospitalization with an intraoperative post-reperfusion liver biopsy, intensive care monitoring , daily laboratory and Doppler ultrasound examinations for the first postoperative week and subsequently when they will be clinically indicated during the hospital stay. Outpatient clinic visits with liver Doppler ultrasound examinations and laboratory examination of liver function

tests will be performed on POD15 and POD30, and 3, 6, 9, 12, 18 months after LT, for having maximal adherence to our normal clinical practice. We will perform protocol-specific post-reperfusion biopsy at the time of LT for ruling out early histologic damage, but we will perform liver biopsy during the follow-up period only when it will be clinically indicated. An accrual period of 30 months will be assumed and a minimum follow-up period of 6 months will be utilized for living enrolled patients.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Graft survival

Key secondary outcome(s))
1. Patient survival
2. The incidence of primary no function (PNF)
3. Differences in transaminases, INR and bilirubin values on POD 2, 7, 15, 30, 90, 180, 270, 360, 540
4. Lengths of hospital stays and intensive care unit stays
5. Clavien classification will be used to evaluate postoperative events in the first 6 months after transplantation (surgical and medical complications, including infections)
6. 1-year patient and graft-rejection-free survival

Completion date
06/07/2020

Eligibility

Key inclusion criteria
Adult patient on waiting-list for liver transplantation from deceased donors at Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
58

Key exclusion criteria
1. Recipients with acute liver disease
2. Pediatric patients or pediatric donors
3. Patients undergoing re-LT
4. Patients undergoing split or living donor LT

Date of first enrolment
30/06/2018

Date of final enrolment
06/04/2020

Locations

Countries of recruitment
Italy

Study participating centre
Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT)
Via Ernesto Tricomi, 5
Palermo
Italy
90127

Sponsor information

Organisation
Ministry of Health, Italian Government

ROR
https://ror.org/00789fa95

Funder(s)

Funder type
Government

Funder Name
Ministero della Salute

Alternative Name(s)
Italian Ministry of Health, Italy Ministry of Health, Ministry of Health of Italy, Ministry of Health - Italy, Ministry of Health, Italy

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Italy

Results and Publications

Individual participant data (IPD) sharing plan
The data that support the findings of this study are available from RI.MED Foundation and ISMETT but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Salvatore Gruttadauria and Duilio Pagano (dpagano@ismett.edu).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/12/2022	04/01/2023	Yes	No
Protocol article	protocol	27/12/2018	06/01/2021	Yes	No
Other publications	Transplant Trial Watch	01/12/2022	04/01/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes