PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

Post-LTPL Organ Dysfunction - Non-invasive diagnostic with aid of plasmatic apoptosis markers

Trial Acronym

CaspAct-LTPL (=Caspase Activation in Liver Transplantation)-Trial

URL of the trial

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Brief Summary in Lay Language

Within the last decades, liver transplantation has matured from an experimental treatment to the therapeutical choice in patients with incurable liver diseases. However, in some cases there are still transplantation failures with extensive consequences for the patients, such as a necessary re-transplantation or death of the individual patient. The causes might be reject reactions, infections (e.g. viruses), surgical problems (e.g. difficult vascular circumstances with subsequent perfusion problems), and furthermore, limited quality of donor organs.

In order to recognise these problems, graft function has to be monitored extensively. In some cases invasive and hazardous diagnostic has to be performed. Despite these measures, present estimation of transplant survival prognosis is still very limited.

Aim of the present study is therefore to define prospective prognosis for patients undergoing liver transplantation and to enable estimation of transplant survival in the first postoperative days. In the process, the prognostic value of newly developed cell death biomarkers as well as inflammation markers in blood plasma of patients undergoing liver transplantation from deceased donors should be investigated. An early and non-invasive recognition of transplant dysfunction would enable targeted diagnosis and initiation of causal therapy in patients with transplant failure.

Brief Summary in Scientific Language

Orthotopic liver transplantation from deceased donors (LTPL) is a routinely used therapeutically option in patients with end stage liver disease. Due to improvements in organ allocation, immunosuppressive therapy regimes and antiviral prophylaxis, long term outcome of patients following LTPL became more favorable within the last decades.

Nevertheless, due to several factors (e.g. reduced quality of liver graft, prolonged

phases of ischemia, etc.), failure or impaired function of liver transplant can be observed. Moreover, cases of rejections, infectious complications, perfusion disorders as well as insufficiencies of the biliary, arterial or venous vessels, may lead to a complicated course.

Therefore an extensive monitoring including clinical, laboratory, microbiological, virological and ultra-sound-based diagnostic measures has to be performed. In the case of doubt, more invasive diagnostic tools such as liver biopsy or angiographic diagnostics have to be recommended but are associated with a greater risk for the individual patient. Despite these diagnostic options, there is still a lack in valid prognostic factors for early identification of patients at high risk for a complicated course following LTPL.

The aim of the present study is therefore to define prospective prognosis for patients undergoing liver transplantation from deceased donors and to enable estimation of transplant survival in the first postoperative days. In the process, clinical-chemical parameters, such as transaminases or markers of graft´s synthetic capability (e.g. INR), as well as disease severity scoring (MELD, SOFA, APACHE II) should be investigated. Moreover, the prognostic value of cell death biomarkers (total keratin 18, keratin 18 fragments), inflammation markers (IL-6, TNF-alpha, sICAM-1), reactive metabolites (RNS: L-arginine, asymmetric dimethylarginine, RCS: methylglyoxal) as well as markers for AGE/RAGE-interaction (sRAGE/AGE-CML) should be evaluated.

Early and non-invasive identification of liver graft dysfunction would accelerate the causative therapy as well as simplify the decision for re-transplantation.

In a prospective, non-randomized clinical study, 150 patients following orthotopic liver transplantation from deceased donors were enrolled (L1-L150). Patients following living donor liver transplantation were not included in the present investigation. The management of LTPL-patients was performed according to “Heidelberg Manual for Liver Transplantation”. Relevant baseline data, clinical data as well as routine blood parameters were collected. Patients were reevaluated for short term complications for 10 days after LTPL. Complications were recorded as follows: (a) infectious complications (pneumonia, cholangitis, urinary tract infection, sepsis, severe sepsis, septic shock), (b) cases of rejection (signs for rejection in liver biopsy, clinical suspicion of rejection with application of a corticosteroid bolus), (c) vascular complications (thrombosis or stenosis of hepatic artery, portal vein or supra-/ infrahepatic venocaval vein) inclusively major bleeding (with the need for invasive diagnostics or re-operation/-transplantation), or (d) biliary complications (insufficiency, stenosis or ischemia of bile duct or bilio-digestive anastomosis). Patients who did not reveal any complication within the 10-day observation period served as a control group. Moreover, a long-term follow-up was performed 180 days after LTPL.
Blood samples (EDTA) from LTPL-patients were collected prior to transplantation (Pre), immediately after the surgical procedure (T0), as well as 1 day (T1), 2 days (T21), 3 days (T3), 4 days (T4), 5 days (T5), 6 days (T6) and 7 days (T7) later. Plasma of all study participants was immediately obtained by centrifugation, transferred into cryotubes, and stored at -80°C until further processing.

Part 1 (total keratin 18, keratin 18 fragments, IL-6, TNF-alpha, sICAM-1):
Due to financial feasibility, measurements of these parameters were performed in patients L1-L100 at the following timepoints: prior to transplantation (Pre), immediately after the surgical procedure (T0), as well as 1 day (T1), 3 days (T3), 5 days (T5), and 7 days (T7) later.
For the quantitative determination of total K18 in plasma, we used the M65

enzyme linked immunosorbent assay (ELISA) kit (Peviva AB, Bromma, Sweden) according to the manufacturer's instructions. For the quantitative determination of the caspase-generated neoepitope of K18, we used the M30-Apoptosense ELISA kit (Peviva AB, Bromma, Sweden) according to the manufacturer's instructions. Furthermore, different plasma biomarkers were measured in order to determine the ongoing inflammatory response (IL-6, TNF-alpha) and cellular activation (sICAM-1) using ELISA kits according to the manufacturer's instructions (IL-6: R&D Systems, Minneapolis, MN, USA / TNF-alpha: R&D Systems, Minneapolis, MN, USA / sICAM-1: Bender MedSystems, Vienna, Austria). All assays were performed in duplicate.

Part 2 (RCS: methylglyoxal, RNS: l-arginine, asymmetric dimethylarginine, AGE/RAGE-interaction: AGE-CML, sRAGE):
Due to financial feasibility, measurements of these parameters should be performed in patients L1-L150 at the following timepoints: prior to transplantation (Pre), immediately after the surgical procedure (T0), as well as 1 day (T1), 3 days (T3), 5 days (T5), and 7 days (T7) later.
For the quantitative determination of l-arginine, asymmetric dimethylarginine, AGE-CML and sRAGE in plasma, enzyme linked immunosorbent assay (ELISA) kits will be used (l-arginine: Immundiagnostik, Bensheim, Germany / asymmetric dimethylarginine: Immundiagnostik, Bensheim, Germany / sRAGE: R&D Systems, Minneapolis, MN, USA / AGE-CML: MicroCoat, Bernried, Germany) according to the manufacturer's instructions. For the quantitative determination of methylglyoxal in plasma, HPLC-based measurements will be performed. All assays will be performed in duplicate.

Do you plan to share individual participant data with other researchers?

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Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00003434**
- Date of Registration in DRKS: **2012/01/11**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **S-055/2009 , Ethik-Kommission I der Medizinischen Fakultät Heidelberg**

Secondary IDs

Health condition or Problem studied

- Free text: **Patients undergoing orthotopic liver transplantation from deceased donors**
- ICD10: **C22.0 - Malignant neoplasm: Liver cell carcinoma**
- ICD10: **K74.6 - Other and unspecified cirrhosis of liver**

Interventions/Observational Groups

- Arm 1: **Control group: No complication within the 10-day observation period**
- Arm 2: **Vascular complication within the 10-day observation period**
- Arm 3: **Biliary complication within the 10-day observation period**
- Arm 4: **Patients with an infection within the 10-day observation period**
- Arm 5: **Patients with a rejection within the 10-day observation period**

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Observational study**
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control**
- Purpose: **Prognosis**
- Assignment: **Parallel**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

Development of a complication (vascular complication, biliary complication, rejection, infection) within 10 days after transplantation

Secondary Outcome

Development of a complication (vascular complication, biliary complication, rejection, infection) within 180 days after transplantation

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Klinik für Anaesthesiologie, Heidelberg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2009/05/12**
- Target Sample Size: **150**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Liver transplantation from deceased donors

Exclusion criteria

Not meeting the inclusion criteria, refusing study participation

Addresses

- **Primary Sponsor**

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■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

■ **Institutional budget, no external funding (budget of sponsor/PI)**

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Institutional budget, no external funding (budget of sponsor/PI)

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Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2011/11/17**

Trial Publications, Results and other documents

- Paper **[---]***

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*