Everolimus in de Novo Liver Transplantation: a Multicentre Randomized Study (EPOCAL)

Study Type: Interventional
Study Design: Allocation: Randomized
   Intervention Model: Parallel Assignment
   Masking: None (Open Label)
   Primary Purpose: Treatment

Title: Terapia Con Everolimus Nel Trapianto de Novo di Fegato: Uno Studio Multicentrico Randomizzato

ClinicalTrials.gov Identifier: NCT01423708

Primary Outcome Measures:
- Biopsy-proven rejection episodes (BPAR) [Time Frame: 3 months]
- Graft survival [Time Frame: 3 months]
- Patient post-Liver Transplantation survival [Time Frame: 3 months]
- Everolimus monotherapy [Time Frame: 30 days]; patients not requiring calcineurin inhibitors (CNI)

Secondary Outcome Measures:
- Renal function evaluation [Time Frame: 24 months]; impact of therapy on renal function, evaluated by creatinine clearance according to the Modification of Diet in Renal Disease (MDRD) Study.
- Requests for dialysis [Time Frame: 24 months]
- Incidence of Adverse Events [Time Frame: 24 months]; evaluation of common post Liver Transplantation Adverse Events: wound healing, bone marrow depression, hyperlipidemia, proteinuria, diabetes mellitus, diagnosed hypertension, infections, levels of HCV.

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- **No Intervention: Control**
  Standard immunosuppression protocol with Tacrolimus, maintaining trough levels between 6 and 12 ng/ml in the first month, in association with steroids (20 mg/day with subsequent weaning within 3 months after transplantation

- **Experimental: Everolimus**
  Administration of Everolimus in association with Tacrolimus and steroids.

Administration of Everolimus within 24 hours from the time of randomization (7 days from the time of transplantation) in association with Tacrolimus and steroids. The first dose level of the trough will be performed at day 7 after initiation of therapy. After the reaching an Everolimus trough level of >5ng/ml (final target 6-12 ng/ml), there will be a gradual weaning of tacrolimus (bringing Tacrolimus blood levels <5 ng/ml)
with discontinuation of Tacrolimus within 30 days after transplantation when possible.

**Criteria**

Ages Eligible for Study: 18 Years to 70 Years (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

**Inclusion Criteria:**
- Male or female patients between 18 and 70 years of age,
- Patients undergoing de novo liver transplantation from cadaveric donor with a functional graft at the time of randomization,
- Transplantation from cadaveric donor whole or split liver,
- Patients able to communicate properly with the study investigators, to understand and respond to the needs of the protocol and who have given written consent
- Cold ischemia time <12 hours

**Exclusion Criteria:**
- Physical or laboratory abnormalities or mental illness within 2 weeks before randomization such that, in the opinion of the investigator, may interfere with participation in the study
- Women who are pregnant (positive test with hCG values > 5mUI/ml) or breast feeding
- Women of childbearing potential, with the following exceptions: a) women in menopause (spontaneous amenorrhea for at least 12 months, spontaneous amenorrhea for at least 6 months with FSH levels >40 mIU/ml, surgical bilateral oophorectomy at least 6 weeks before baseline, with or without hysterectomy) b) women who use one or more reliable and approved methods of contraception for the duration of the study and for the three months following discontinuation of study treatment.
- Patients who undergo transplantation or multivisceral transplantation of pancreatic islets, or who have previously undergone organ transplantation or tissue.
- Patients who undergo combined liver-kidney transplantation
- Patients who undergo living donor liver transplantation
- Patients who undergo ABO-incompatible liver transplantation
- Patients who undergo transplantation from donors positive for HBV surface antigen or HIV
- History of malignant disease at any site in the 3 year period prior, regardless of whether or not there is evidence of recurrence or metastasis. (Except non-metastatic skin cancers such as basal cell or squamous cell carcinoma of the skin, or hepatocellular carcinoma)
• Patients receiving other investigational drugs within 4 weeks before baseline or who are currently enrolled in other clinical trials
• Patients who show hypersensitivity to the drug (or drugs similar to Everolimus - Former macrolides) or class or pharmaceutical excipients. Also, when there are contraindications
• A history of coagulopathy or the presence of any medical condition that requires long-term anticoagulant therapy after transplantation (The use of low-dose ASA is admissible)
• Platelet count <=40,000/mm3 or WBC count <2000/mm3 or hemoglobin <=7g/dl at the time of randomization
• Severe systemic infections
• High cholesterol levels (>350mg/dl) or severe hypertriglyceridemia (>500mg/dl). Patients with compensated hyperlipidemia are eligible.
• Diagnosis of pre-transplant autoimmune liver disease (PBC, sclerosing cholangitis)
• Acute Liver Failure