

Protection of renal function after liver transplant using Everolimus monotherapy as the immunosuppression regimen.

Principal Investigator

Chandrashekhar Kubal, MD, PhD

Surgical Director, Liver Transplant Program (adult) Indiana University, School of Medicine

IU Health University Hospital

550 North University Boulevard

Indianapolis, IN 46202

1.0 Background

Tacrolimus is the standard immunosuppressive drug used to prevent organ rejection post liver transplant. One side effect of Tacrolimus is nephrotoxicity. Everolimus does not have the nephrotoxicity side effects of Tacrolimus. Replacement of Tacrolimus by Everolimus may have a reduced incidence of renal dysfunction in liver transplant patients who have near normal kidney function prior to liver transplantation. Other investigators have already shown a benefit in terms of renal function with introduction of Everolimus with reduced-exposure tacrolimus at 1 month after liver transplantation, this benefit has been shown was maintained to 3 years in patients who continued Everolimus therapy with comparable efficacy and no late safety concerns. [1-3] In this trial we are proposing to advance this approach further by completely eliminating Tacrolimus from patients' immunosuppression protocol. The rationale for this approach is based on our unique induction immunosuppression protocol.

Our liver transplant patients receive potent induction immunosuppression in the form of rabbit anti thymocyte globulin. We believe that in conjunction with this induction regimen, patients can be maintained on Everolimus monotherapy without the risk of rejection. By completely eliminating Tacrolimus, we believe that there may be further benefit in terms of renal function. Additionally, Everolimus is known to induce tolerance in transplant recipients. Tolerant patients do not require immunosuppression to accept transplant organs.

2.0 Rationale and Specific Aims

The long-term efficacy and safety of Everolimus monotherapy as the maintenance immunosuppression in patients receiving rATG induction is unknown.

Primary Aim

Assess the effect of Everolimus monotherapy versus Tacrolimus monotherapy on long term renal function measured by Glomerular Filtration Rate (GFR).

Secondary Aims

Compare the efficacy and safety of Everolimus monotherapy versus Tacrolimus monotherapy, as measured by the following:

- Biopsy-confirmed acute rejection
- Hyperlipidemia
- Proteinuria
- NODAT [New Onset Diabetes mellitus After Transplant], hypertension and malignancy

3.0 Study Plan, Experimental Design, and Methodology

The proposed investigation will be a single-center, randomized, open-label, active control comparison of tacrolimus as the maintenance immunosuppression (control arm) versus Everolimus (study arm).

4.0 Inclusion/Exclusion Criteria

List Inclusion criteria:

- Liver transplant recipients ≥ 18 years old
- Normal baseline renal function (GFR > 60 mL/min)
- Rabbit anti-thymocyte globulin (rATG) induction (at least one dose)
- Indication for transplant: ethanol, hepatitis C, nonalcoholic steatohepatitis or any combination of these

List Exclusion criteria:

- Increased risk of rejection: autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, positive crossmatch, retransplantation
- Incompletely healed incision or other wound healing issues at time of randomization
- Multiple or previous organ transplantation
- Severe, uncontrolled hypercholesterolemia (> 9 mmol/L) or hypertriglyceridemia (> 8.5 mmol/L) in the 6 months prior to transplantation
- Insurance company unwilling to pay for the cost of the everolimus or patient does not qualify for the Novartis Patient Assistance Program.
- Pregnant women
- Unable to provide informed consent.

5.0 Enrollment/Randomization

Following transplant, prior to the one month post-transplant visit, all eligible subjects will be approached either in the transplant unit in the hospital or at the transplant clinic in the hospital for study participation. A random permuted block design will be used to generate random assignments to the groups. This method will ensure balance across the groups over the course of the study period. The biostatistician at the Center for Outcomes Research in Surgery will prepare the master randomization assignment list. The surgery clinical research coordinator will then administer randomization. Since this is an open label study, care providers will not be blinded to the randomization. We do not believe this will interfere with the results of the study or patient care.

Following enrollment, subjects will be randomized at one month post-transplant to Tacrolimus (control) or to Everolimus (study) as maintenance immunosuppression.

A previous Phase III study (Baboolal, 2003) showed that the mean creatinine clearance rate – a measure to assess the kidney function post-transplant – in the treatment group (those receiving Sirolimus and a CNI (Cyclosporine or Tacrolimus) with planned withdrawal of the CNI) was 65mL/min (SD=14) and in the control group (those who continued to receiving Sirolimus and a CNI) it was 57mL/min (SD=13). Therefore, using the two independent-groups and two-tail t-tests, we will need to recruit 46 patients in each group. With an attrition rate of 11% (Baboolal, 2003), we approximately need 104 participants in this study (52 subjects in each arm) to achieve a statistical power of 80% at 0.05 level of significance. Power analysis and sample size calculation were done using G*Power 3.1.9.2.

6.0 Study Procedures

After liver transplant, all patients will receive the standard induction regimen and Tacrolimus monotherapy.

INDUCTION:

Rabbit anti-thymocyte globulin (rATG) 1.5 mg/kg of actual body weight rounded to nearest 25 mg and capped at 150 mg for up to three doses given IV on post-operative day (POD) 1, 3, and 5. Some patients may receive only one dose if they are considered too frail to need all three doses.

30 minutes prior to infusion, pre-medicate with the following:

Daily steroid dose

Acetaminophen (Tylenol®) 650 mg PO or per NG x 1 dose

Diphenhydramine (Benadryl®) 25 mg IV push x 1 dose

Steroids:

Methylprednisolone (Solu-Medrol®) 250 mg IV push x 1 dose on POD 1 (given 30 minutes prior to rATG) and 125 mg IV push x 1 dose on POD 3.

Maintenance:

Tacrolimus (FK / Prograf®) (titrated to a goal trough of 6 - 8 ng/mL).

RANDOMIZATION:

On POD 30, patients meeting study criteria will be randomized to either the study arm or control arm. Patients randomized to the study arm will be converted to Everolimus (target trough levels 4 - 8 ng/mL) + low dose Tacrolimus (target trough levels 3-5 ng/mL) (study arm). The control arm will be maintained on the Tacrolimus monotherapy (target trough levels 6-8 ng/mL).

At 3 months, patients in the study arm will be gradually weaned off of Tacrolimus over a period of one month to remain on Everolimus monotherapy (target trough levels 4-8

ng/mL). Patients in the control arm will remain on tacrolimus monotherapy (target trough levels 6-8 ng/mL).

Complete blood counts, liver function panels, and drug levels will be monitored as done Standard of Care [SOC]: initially twice per week for first month, once per week for next two months, once every other week for next three weeks, and then once monthly. Ultrasound, ERCP, biopsy as needed by clinical situation as SOC.

7.0 Data to be Collected

Target Population: Liver-only transplant patients

Baseline Information: Demographics (age, race, sex, BMI), pre-treatment medical history, pre-treatment concomitant medication.

Intervention: The treatment period starts at 30 days post-transplant. Subjects will be followed for up to a total of 36 months post-transplant.

During the treatment period relevant concomitant medications, adverse events, complete blood counts, liver function panels, and immunosuppression drug levels will be collected.

Follow-up: Data will be collected at 6 month, 12 month, 24 month, and 36 month timepoints. GFR will be measured at these time points. Any biopsy confirmed rejection that occurs on or before the 36 month timepoint will be recorded. See Table 1 for timeline for data collection.

Occurrence or change in NODAT [New Onset Diabetes mellitus After Transplant], hypertension, malignancy, and tolerance will be recorded throughout the length of the study. Results of any ultrasound, ECRP, or biopsy performed for clinical reasons will be recorded throughout the study.

Study follow up will be conducted per standard of care. Patients will not undergo any additional visits for study purposes during treatment or follow up.

Table 1

| | days | | | | | 30 days | Months +/- one week | | | | | | | | | |
|----------------------|------|---|---|----|----|------------|---------------------|---|---|---|---|---|----|----|----|----|
| | 0 | 1 | 7 | 14 | 21 | | 2 | 3 | 4 | 5 | 6 | 9 | 12 | 18 | 24 | 36 |
| Sr Creatinine | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Creatinine Clearance | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| MDRD GFR | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Sr Glucose | x | | | | | x | x | x | x | x | x | x | x | x | x | x |
| Urine Protein | x | | | | | x | x | x | x | x | x | x | x | x | x | x |
| Total Cholesterol | x | | | | | x | | x | | | x | x | x | x | x | x |
| BP | x | | | | | x | x | x | x | x | x | x | x | x | x | x |
| LFT | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Everolimus level | | | | | | | x | x | x | x | x | x | x | x | x | x |
| Tacrolimus level | | x | x | x | x | x | # | # | # | # | # | # | # | # | # | # |

control patients

Used for study only if available per patient standard of care.

8.0 Drug Information

Please see the “Prograf-Tacrolimus” and the “Zortress Package Insert” attachments.

9.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Definitions of Adverse Events

Adverse Event (AE)

An **adverse event** is defined as untoward medical occurrence associated with the use of a drug or procedure in humans, whether or not considered drug or procedure related. An adverse event can be **ANY** unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal (investigational) product or procedure, whether or not considered related to the medicinal (investigational) product or procedure (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’). Examples of Adverse Events that will be recorded in this study are:

- Concomitant illness
- Physical injury
- Events possibly related to medication
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- Drug interactions
- A laboratory or diagnostic test abnormality occurring shortly after the start of the study that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant

Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
 - NOTE: Hospitalizations that are not considered SAEs are:
 - Hospitalization for elective treatment of a pre-existing condition unrelated to study participation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Unexpected Adverse Event

An adverse event not mentioned in the package insert or the specificity or severity of which is not consistent with the package insert.

Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily “*caused by a therapeutic intervention*”. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

| Relationship | Attribution | Description |
|---|-------------|--------------------------------------|
| Unrelated to investigational agent/intervention | Unrelated | The AE is clearly NOT related |
| | Unlikely | The AE is doubtfully related |
| Related to investigational agent/intervention | Possible | The AE may be related |
| | Probable | The AE is likely related |
| | Definite | The AE is clearly related |

Adverse Event (AE) Reporting

Adverse events (AEs) will be reported to the principal investigator immediately and will be recorded from the time of randomization (approximately 30 days after surgery), regardless of whether or not the event(s) are considered related to trial procedures or medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Reporting to the IRB:

1. Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:
 1. were unexpected;
 2. were related or possibly related to study participation; AND
 3. suggests that the research places subject(s) or others at greater risk of harm than was previously known.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it will be reported at the time of continuing review.

2. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 business days of the study team becoming aware of the event.

10.0 Study Withdrawal/Discontinuation

Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for any reason. If the patient withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The investigator may retain and continue to use any data collected before such withdrawal of consent.

11.0 Statistical Considerations

Univariate analysis will be done to describe the distribution of the sample in terms of demographics (age, race, sex, BMI), pre-treatment medical history, pre-treatment concomitant medication. The distribution of the sample will be described in terms of mean (\pm SD), median (Inter-quartile range), or percentage depending upon the type of variable (continuous or categorical). Bivariate analysis comparing the sociodemographic variables of the treatment groups will be conducted using chi squared, student T tests, Mann U Whitney tests as appropriate.

Intent-to-treat analysis of the data from the baseline and follow-up visits will be analyzed in order to compare the renal functions after liver transplant between the study arm (those receiving Everolimus + low dose Tacrolimus) and the control arm (those maintained on the Tacrolimus monotherapy (target trough levels 6-8 ng/mL). Repeated measures analysis will be conducted to analyze measures of renal function across the treatment groups using multivariable generalized linear model (GLM) over time accounting for the correlation of the measurements obtained for each patient over time.

For the secondary end-points, bivariate analysis will be done to compare the outcomes between the treatment and the control groups. Pearson's chi-square, student T tests, and Mann U Whitney tests as appropriate. Adjustment for the correlated variance due to repeated measures will be made throughout the analysis. All analysis will be conducted at 0.05 level of significance using Stata/SE version 14.2 (StataCorp., 2015).

12.0 Data Management

Primary Data will be collected directly from the Electronic Medical Record databases CERNER, OTTR, and UNOS. Records requests from third party hospitals will be collected as needed primarily for, but not limited to, Adverse Event reporting and medical history. Adverse Events will be recorded on paper CRFs. Each Adverse Event will be reviewed and attributed by the PI. The Adverse Event CRFs will be signed by the PI. Any lab values,

drug levels, or other data not recorded in the Electronic Medical Record will be recorded by study personnel on paper CRFs and signed.

Signed consents and HIPAA authorizations will be stored in study binders. Paper copies of record requests, paper CRFs, and any Notes To File will also be stored in these study binders. Source material from the Electronic Medical Record will be printed only if needed for data quality control checks and stored in the study binders. Study binders will be stored in a HIPAA compliant, locked room.

Data will be stored electronically in REDCap. The REDCap data file will be backed up manually at least every month on a separate, HIPAA-compliant IU Box Health folder. The database will be built and tested by a biostatistician prior to the production mode.

Data collected in the electronic database will undergo random audits to ensure accuracy. A data safety officer will perform quality control checks on the entered data.

13.0 Follow-up and Record Retention

Subjects will be followed for up to a total of 36 months following transplant. All records produced or collected in connection with this research project, including primary (e.g., laboratory, medical), financial, statistical, supporting, administrative, and regulatory documentation, shall be retained for a minimum period of seven (7) years.

References:

1. P De Simone, F Nevens, L De Carlis, *et al* (2012) "Everolimus With Reduced Tacrolimus improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial" *Am J Transplant*. 2012 Nov; 12(11): 3008–3020. doi: [10.1111/j.1600-6143.2012.04212.x](https://doi.org/10.1111/j.1600-6143.2012.04212.x)
2. Saliba F, De Simone P, Nevens F *et al* (2013) Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *Am J Transplant*. 2013 Jul;13(7):1734-45.
3. Fischer L, Saliba F, Kaiser GM *et al* (2015) Three-year Outcomes in De Novo Liver transplant Patients Receiving Everolimus With Reduced Tacrolimus: Follow-Up Results From a Randomized, Multicenter Study. *Transplantation*. 2015 Jul;99(7):1455-62.
4. Li L1, Wozniak LJ, Rodder S, Heish S, *et al*. (2012) A common peripheral blood gene set for diagnosis of operational tolerance in pediatric and adult liver transplantation. *Am J Transplant*. 2012; 12(5):1218-28